REVIEW ARTICLE

Drugs 2003; 63 (12): 1185-1227
0012-6667/03/0012-1185/$33.00/0

Polycystic Ovary Syndrome and Epilepsy

A Review of the Evidence

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Contents

Abstract

Overrepresentation of polycystic ovary syndrome (PCOS) in women with epilepsy has been described since the early 1980s. While some authors attribute this association to an effect of the seizure disorder on the hypothalamic control of reproductive function, others have reported a relationship with the use of the antiepileptic drug valproic acid (VPA). In this article we review the literature on this complex issue, with a detailed analysis of the different reports which describe the reproductive endocrine assessment in women with epilepsy. In spite of the large number of patients assessed, a clear picture does not emerge, mostly because of the wide variability of methodology employed in the different study projects and of the small size of many patient samples especially when divided in subgroups. However, on the whole these studies suggest that women with epilepsy are at risk for developing reproductive endocrine disorders, even if there is not yet definite evidence that PCOS may be over-represented in these patients nor that VPA may be the cause of endocrine problems. It is likely that both the epileptic disorder and the antiepileptic treatment play different roles in the development of such disturbances. This hypothesis deserves further prospective study in large

samples of patients; consistency in methodology, diagnostic criteria and presentation of results should always be encouraged in the researchers dealing with these projects. In the meantime, women with epilepsy should be carefully monitored with regard to menstrual function, bodyweight and hyperandrogenism, and evaluation of these parameters should become part of the routine evaluation in baseline and follow-up consultations.

In 1984 Herzog and his group[1] first published a report describing a high frequency of polycystic ovary syndrome (PCOS) in women with temporal lobe epilepsy (TLE), followed in 1986 by a second report[2] describing similar results from a larger sample. This association was confirmed in 1988 by Bilo and co-workers[3] in a smaller sample of women with idiopathic generalised epilepsy (IGE). Neither group found any significant association between occurrence of reproductive endocrine disturbances and use of antiepileptic drugs (AEDs), and both suggested a possible deranging effect of epilepsy on the hypothalamus.

However, the possibility that women with epilepsy might be at risk for a reproductive endocrine disease known to affect fertility did not seem to raise much interest in the scientific world. In the years immediately following these publications, no other group evaluated the reproductive hormonal status of women with epilepsy, and the hypothesis of a disruptive effect of paroxysmal discharges on reproductive function was examined and discussed at length only by the original groups.[4-6]

In 1993, nearly 10 years after the first report on the subject, Isojarvi and co-workers[7] described a high occurrence of menstrual disorders and/or polycystic ovaries and/or hyperandrogenism in women with epilepsy, reporting a significant association with the use of the AED valproic acid (VPA). After this first report, this group published an impressive amount of data on the subject,[8-25] always confirming their earlier findings. These papers received growing attention in the scientific world and in particular the possible risks of using VPA in adolescent patients raised discussions beyond the group of epileptologists, involving paediatricians[26] and psychiatrists.[27-38] Contemporarily, a growing concern for specific women-related issues in epileptology gave rise to dedicated projects in which the possible increased frequency of reproductive endocrine disorders was discussed at length, without favouring any specific pathogenic hypotheses on the subject, and possible research guidelines were suggested.[39-43]

In more recent years the dispute on this subject has become particularly heated, additionally because the possible involvement of AEDs had raised interest and concern among pharmaceutical companies. The problem has been the subject of specific symposia[44-46] and of wide-ranging debates with contributions from different points of view, encompassing neurologists, pharmacologists and endocrinologists.[47-61] The long overdue attention to this subject was finally stimulated in clinical researchers, giving rise to a growing number of endocrinological studies in women with epilepsy coming from all over the world and describing conflicting results.[62-81] More recently the possible endocrine effects of VPA have also been studied in non-epileptic individuals receiving this drug long-term for psychiatric disturbances.[82-85]

In this article we review the literature on this subject, trying to analyse the conflicting results emerging from different reports. The fundamental questions: (i) is there an increased prevalence of PCOS in women with epilepsy; and (ii) is this related to the use of VPA, will be addressed and tentative conclusions will be drawn.

1. Polycystic Ovary Syndrome (PCOS): Still a Matter of Debate?

A clear and consistent definition of a disease or syndromic entity is fundamental if an estimation of its prevalence is to be evaluated. Unfortunately, for a long-time, the definition of PCOS has been a

debated issue among endocrinologists and gynaecologists, with the criteria employed for its diagnosis showing considerable differences between different reports. The uncertain and discussed pathogenesis of the syndrome contributed to further difficulties in terminology,[86,87] and so did the possibility of finding the echographic pattern of polycystic ovaries in a consistent sample of a 'normal' population, without any specific endocrine alteration. It is now universally accepted that the isolated finding of polycystic ovaries should not be considered as an abnormal feature,[88] since it is described on ultrasonography in nearly 20% of women without symptoms.[88-90]

While the 'classical' syndrome is usually easily recognised in women displaying hyperandrogenism, irregular menstruations, obesity and a polycystic ovarian morphology, the diagnosis of PCOS in women who present with fewer of the classic symptoms has caused considerable controversy.[88] However, in spite of these difficulties, in recent years a substantial uniformity for 'minimal' diagnostic criteria for PCOS has been reached, and a National Institutes of Health (NIH) Conference in 1990 has standardised them at least in the US.[91] The 'minimal' diagnostic criteria suggested in the 1990 NIH Conference include: (i) menstrual irregularity; (ii) evidence of hyperandrogenism either clinical or biochemical; or (iii) exclusion of other diseases (i.e. other known causes of female hyperandrogenism such as congenital adrenal hyperplasia, androgen-secreting tumours and hyperprolactinaemia).[88] In short, a diagnosis of hyperandrogenic anovulation is required, and differential diagnosis from other endocrine diseases which can also lead to this picture is necessary. It is worth noting that the 'typical' (echographic) finding of polycystic ovaries has not been included in these minimal criteria, having been considered insufficient and unnecessary to make the diagnosis of PCOS. Some authors, especially in Europe, have criticised this latter point and do still require the morphological polycystic changes findings to formulate the diagnosis.

In conclusion, nowadays a diagnosis of PCOS should require a relatively simple clinical and laboratory assessment in order to fulfil the above mentioned minimal diagnostic criteria. A clinical evaluation, with a detailed and possibly documented menstrual history, allows the assessment of hirsutism and of menstrual cyclicity; hormonal study, (including gonadotropins, testosterone, androstenedione, dehydroepiandrosterone sulfate [DHEAS], 17OH progesterone, sex hormone binding globulin [SHBG], prolactin and thyroid stimulating hormone) allows detection of laboratory hyperandrogenism and evaluation of a differential diagnosis with other causes of hyperandrogenic anovulation.[88] Possibly, but not necessarily, ovarian morphology may be evaluated – usually by means of ultrasound – and using specific, standardised criteria for the definition of polycystic ovaries.[92] Using these diagnostic criteria, recent population-based studies have estimated a 4–6.8% prevalence of PCOS in premenopausal women.[93-95]

Unfortunately, no consistency of diagnostic criteria and diagnostic tools is found in papers dealing with occurrence of PCOS in women with epilepsy, and consequently the results are very often difficult to interpret and virtually impossible to compare. Many authors still confuse the concept of PCOS with that of polycystic ovaries; others still prefer to use personal views on the basis of the supposed lack of uniformity of criteria for diagnosis, despite the results of the 1990 NIH Conference or other authoritative guidelines. Another frequent problem is presentation of results. Many authors, even when performing a complete evaluation of patients, present the results only as means of hormonal values or as percentages of abnormal findings observed in different groups, without giving any detail of the evaluation of the single patient and of the consequent diagnostic assessment in each individual. Although knowing that mean androgen values are significantly higher in a given group may be of interest, this information is of no help for the diagnosis of PCOS, for which an individual assessment of each patient is required. Similarly, knowing that a given percentage of women in a specific group has hyperandrogenism and that menstrual dysfunction is found in another percentage is of little use when it is not possible to

understand how many have both and could consequently be diagnosed as having PCOS.

Consistent diagnostic tools, diagnostic criteria and data presentation should be required in every study project that deals with prevalence of PCOS in women with epilepsy. Otherwise, it is very difficult for data coming from different sources to be compared and for a final conclusion to be reached, even if prospective studies are employed.

2. PCOS in Women with Seizures: the Epilepsy Theory

In 1984 Herzog and co-workers[1] presented a series of 20 consecutive patients with TLE, in which five were diagnosed with PCOS. All five patients had oligomenorrhoea and hirsutism; two of them had elevated testosterone levels while the other three had polycystic ovaries. However, three of the five patients presented galactorrhoea, and consequently a differential diagnosis with hyperprolactinaemia should have been considered. Actually, only one of these galattorrhoic patients had normal prolactin levels. Another galactorrhoeic patient presented elevated prolactin levels, and consequently should have been excluded from the diagnosis of PCOS according to 1990 NIH Conference criteria. It should be underlined, however, that women with 'true' hyperprolactinaemia usually have prominent menstrual dysfunction but subtle hyperandrogenism, together with elevated prolactin concentrations; on the other hand, hyperandrogenic women with PCOS may have mildly elevated serum prolactin level of uncertain significance.[88] The hyperprolactinaemic patient in this group had elevated prolactin in only one of two blood evaluations but was severely hyperandrogenic; it is consequently possible that she was not to be considered to have hyperprolactinaemia. Finally, in the remaining galactorrhoic patient, a prolactin evaluation was not performed: this patient could also have had hyperprolactinaema and not have 'true' PCOS. The authors underlined that the 25% occurrence of the syndrome was higher in women with TLE than in general population, in which a 3–7% prevalence was suggested. This prevalence may fall to 15% if we exclude the two patients in which hyperprolactinaemia can not be ruled out.

Results obtained from this small sample were successively confirmed in a report describing the endocrine assessment of 50 women with TLE.[2] In this larger sample ten women (20%) were diagnosed with PCOS. Once again, the authors give full details of the assessment of every single patient, so that it is possible to evaluate retrospectively the diagnosis using the 1990 NIH Conference criteria. Nine women do completely meet these criteria: they all have irregular menstrual cycles and clinical and/or laboratory hyperandrogenism; in addition, seven had elevated luteinising hormone (LH) and three had polycystic ovaries. Two of them had galactorrhoea with normal prolactin values. The tenth patient is slightly less convincing, since menstrual cyclicity was only slightly altered and she had only a minimal androgen elevation without clinical hirsutism. A more detailed evaluation of ovulatory function could have helped in the assessment of this patient.

Both in the first and in the second series no correlation between AED use and reproductive endocrine problems was observed. In fact, most of the patients with TLE and PCOS were not receiving any antiepileptic treatment at the time of the study (four of five in the first series and six of ten in the second were untreated). No specific information on therapy employed in the remaining patients is offered, but the authors conclude that no relationship was found between PCOS and the type or serum concentration of AEDs. Considering that most patients with PCOS were untreated, these conclusions seem sound even in absence of a detailed statistical analysis on the issue.

The high prevalence of PCOS in women with epilepsy was confirmed in 1988 by Bilo and co-workers[3] in a series of 20 random patients with IGE, three of whom were diagnosed with PCOS. Actually, the frequency of PCOS in women with IGE (15%) was lower than that reported in patients with TLE, but still higher than the prevalence reported in the general population. All three patients with IGE and PCOS fulfilled the consensus diagnostic

criteria, since severe menstrual irregularities, hirsutism and laboratory hyperandrogenism were found in all of them; moreover, all had polycystic ovaries, elevated LH/follicle stimulating hormone (FSH) ratio and exaggerated LH response to gonadotrophin releasing hormone (GnRH) stimulation. Study of ovulation, performed for three consecutive cycles with monitoring of basal body temperature and evaluation of progesterone levels 10, 8 and 5 days before the expected menstruation, showed chronic anovulation in all three patients. All of them had normal adrenal and thyroid function; none was hyperprolactinaemic. Once again, no relationship was found with the use of a specific AED: one of the epileptic patients with PCOS was untreated, and the other two had already reported menstrual irregularities before AED therapy was started. One of the treated patients with PCOS received phenobarbital, while the other was treated with phenobarbital and VPA. These drugs were also employed, alone or in association, in the majority of the remaining patients in this series. No statistical analysis was performed regarding AED treatment and occurrence of PCOS, possibly because of the very small number of patients with PCOS described in this series. However, considering the results, the conclusions of the authors seem sound, and no association between PCOS and use of AEDs seems to emerge from this report.

Considering these results, both groups[1-3] independently focused their attention on the possible pathogenic mechanisms linking the epileptic disorder with the development of PCOS, and hypothesised that epilepsy itself might be responsible for a derangement of hypothalamic function leading to reproductive dysfunction.[4-6,96]

How could epilepsy lead to PCOS? Abnormalities in hypothalamic function have been suggested as one of the possible pathogenic mechanisms in PCOS, which probably has a multifactorial basis;[86-88,97-99] and, on the other hand, epileptic disorders might lead to disruption of hypothalamic functioning. Medial temporal lobe structures have extensive, reciprocal, direct connections with hypothalamic regions that are involved in reproductive endocrine regulation, and it is consequently possible that epileptic paroxysmal discharges involving these areas may disrupt normal hypothalamic-pituitary function.[2,4,96] Moreover, the generalised epileptic discharges which characterise IGE may also derange the normal functioning of the GnRH pulse generator, as supported by several reports[100-102] which describe significant increases in plasma prolactin and, less consistently, in gonadotropins after complex partial seizures and after primarily generalised tonic-clonic seizures. These hormonal elevations are not due to a nonspecific stress effect nor to the intense motor activity which may occur during seizures, but are thought to result from spreading of paroxysmal discharges within the hypothalamic areas which control pituitary reproductive hormones.[100-102]

Animal data also support this possibility.[103] In female rodents, both chemical and electrically-induced seizures disrupt normal ovarian cyclicity.[104-106] Right amygdala-kindled seizures in both the male and female rat may increase pulsatile GnRH release, thereby favouring pituitary LH biosynthesis over FSH;[107,108] moreover, repeated kindled seizures in the right basolateral amygdala cause the cessation of regular oestrous cycles, the development of polycystic ovaries and premature reproductive ageing of the hypothalamic-pituitary neuroendocrine axis.[109] Furthermore, in addition to limbic seizures, generalised seizures also appear to cause reproductive dysfunction in rats, since repeated electroconvulsive shocks delay the onset of puberty and the initiation of ovarian cyclicity in juvenile female rats,[110,111] while in adult ovariectomised female rats electroshock treatment attenuates the positive feedback effect of progesterone on LH and FSH.[104,111] The substantial rearrangement of GnRH-containing efferents observed in the epileptic female rat brain also suggests that epileptic discharges may disrupt the normal modulation of GnRH neurons, thus resulting in reproductive endocrine disorders.[112]

Further support to this theory came from the finding of altered LH pulsatility in women with epilepsy, reported by Bilo and co-workers in 1991[113] and by Herzog and co-workers in 1994.[114]

Since none of the patients in the series described by Bilo was receiving AEDs nor presented any factors which could affect hypothalamic function, the authors suggested that the abnormal LH pulsatile pattern could be related to epilepsy itself, and that it might represent the first, subclinical change leading to endocrine dysfunction. Conversely, most patients in Herzog's series were treated with AEDs, and consequently a possible effect of these drugs in affecting LH pulsatility could not be ruled out; however, the relationships between the laterality of the epileptic focus and the alteration of LH pattern suggested a possible additional pathogenic role of the seizure disorder. Alterations in LH pulsatility in epileptic patients were successively described by other groups,[115-117] whose data also indicated a possible role of seizure disorders in disrupting LH pulsatile release. Interesting data come also from the 5-hour monitoring of gonadotropin secretion under continuous electroencephalographic (EEG) recording in untreated epileptic women and controls, reported by Meo and co-workers in 1993.[118] A significant rise of gonadotropin secretion was observed in epileptic patients contemporarily to the increase of paroxysmal activity, once again suggesting a possible spreading of epileptiform discharges within hypothalamic areas.

Finally, in a preliminary report in 1997[119] and successively in 2001,[120] Bilo and co-workers presented a detailed study of reproductive endocrine function and ovulation dynamics in a series of 50 consecutive patients with IGE and partial epilepsy; 32% of patients were untreated. All participants underwent an early follicular and luteal-phase hormonal evaluation in a basal cycle, in order to document the presence and timing of ovulation, and an ovarian scan. Individuals with menstrual, androgen and/or ovarian abnormalities in the basal cycle had an additional 1-cycle follow-up with frequent hormonal sampling, in order to document ovulation. PCOS was diagnosed in 13 participants (26%), all fulfilling the 1990 NIH Conference criteria; other possible causes of hyperandrogenic anovulation were ruled out. No correlation was observed with use of a specific AEDs or with epilepsy type: in particular, PCOS was observed in 23.5% of patients treated with any AED and in 31.2% of untreated patients. The possible pathogenic role of epilepsy was once again suggested.

The possibility that a seizure disorder may be the result of hypothalamic dysfunction is fascinating, but quite difficult to demonstrate. The spread of paroxysmal activity within hypothalamic areas with acute increases of hormonal levels may not necessarily lead to chronic dysfunction. Moreover, if intrahypothalamic spread of ictal/interictal paroxysmal activity is responsible for the hormonal dysfunction ultimately leading to clinical problems, there should be a correlation between epilepsy severity and occurrence of reproductive endocrine disorders, but this has not been observed in reports evaluating this parameter.[63] On the other hand, the impact of seizure disorders on the hypothalamus is probably very complex and not necessarily limited to the acute effects of the spread of paroxysmal activity. Seizure disorders are accompanied by, and in some cases probably caused by, neurotransmitter imbalance. Central neurotransmitters modulate brain susceptibility to seizures, and probably play also an important role in the pathogenesis of human epilepsies: catecholaminergic, serotoninergic, opioidergic, GABAergic and glutamatergic dysfunctions have been suggested.[121-128] Since some of these neurotransmitter systems are relevant neuroendocrine modulators for the release of GnRH, it is reasonable to suppose that a neurochemical imbalance might at the same time be responsible both of the lowering of seizure threshold and of the dysfunction of GnRH secretion.[3,5,113] This kind of imbalance is probably only in part related to seizure frequency, and consequently may be acting as a pathogenic factor independently from actual seizure control.

In conclusion, the reports from Herzog and Bilo have the merit of presenting a complete report of the specific diagnostic assessment performed in each individual patient, and of using up-to-date criteria for the diagnosis of PCOS. The most recent report by Bilo and co-workers[120] offers an interesting evaluation of ovulation dynamics as well. However, case-control series are quite limited in number; in

particular, the number of individuals receiving a given AED, especially as monotherapy, is too small to allow any significant conclusion to be drawn on the possible role of AEDs. The finding of endocrine disturbances in untreated patients is interesting and suggestive of a possible role of epilepsy itself, but should be tested in a wider sample; similarly, the possible role of type and severity of the seizure disorder should be evaluated on larger series.

3. PCOS in Women with Seizures: the Valproic Acid (VPA) Theory

In 1993 Isojarvi and co-workers[7] from Finland published their first report suggesting a possible relationship between use of VPA and occurrence of reproductive endocrine disturbances in women with epilepsy. Actually, the possible association between VPA use and menstrual dysfunction had already been suggested by several earlier anecdotal reports, describing menstrual problems in individual patients with epilepsy or in small series of epileptic women using VPA.[129-133] In some of these patients[132,133] discontinuation or dose reduction of VPA was accompanied by restoration of menstrual cyclicity, while in another series[130] menstrual problems disappeared in most patients without any change in VPA treatment. However, the report from Isojarvi and co-workers is the first to describe such problems in a large series of patients.

After their first paper in 1993, the Finnish authors published an impressive series of reports, all confirming their earlier data.[8-24] Endocrine disturbances (namely, polycystic ovaries, hyperandrogenism and menstrual irregularities, not necessarily associated in the same patient) were described with high frequency in epileptic female patients treated with VPA significantly more often than in controls or in patients treated with other AEDs. This pattern was most often associated with early exposure to the drug, since patients who had started VPA therapy before the age of 20 showed a higher frequency of endocrine disturbances,[7] and with obesity.[8] Actually, in their earlier reports the authors suggested that weight gain could be the main pathogenic factor leading to reproductive endocrine disturbances,[8] proposing that VPA-induced obesity might lead to insulin resistance which could in turn give rise to hyperinsulinaemia. Hyperinsulinaemia may result in hyperstimulation of the ovaries, through a direct effect or through indirect effects secondary to decreased levels of insulinlike growth factor binding protein-1 (IGFBP-1), and this would give rise to hyperandrogenism and finally to ovarian polycystic changes. Moreover, the inhibitory effect of insulin on SHBG synthesis would result in increased bioavailability of androgens with further enhancement of hyperandrogenism. However, further studies from the same group showed that, after VPA withdrawal, insulin and androgen levels reverted to normal quite early, while weight loss occurred more gradually and progressively,[11] and that hyperandrogenism could be observed as an early sign in young and adult patients treated with VPA before or in absence of weight gain.[17,21] These findings challenged the theory that VPA-induced obesity might have a primary role in inducing endocrine and metabolic changes and suggested that increase of androgen production might be the first abnormal finding originating from VPA use in epileptic women.

Several theories have been proposed to explain the possible pathogenic mechanism of VPA-induced hyperandrogenism. A possible effect on gonadotropin release, mediated by a VPA-induced increase of GABA levels affecting GnRH secretion, was considered unlikely since VPA-treated hyperandrogenic patients have normal LH levels.[7,19] Alternatively, a direct effect of VPA on androgen formation has been suggested.[7] Even if the evidence of an inhibitory effect of VPA on testosterone metabolism is indirect and only speculative at present, VPA is thought to inhibit the glucoronidation of several substances.[49] Consequently, a possible VPA-mediated inhibition of the conversion of testosterone to estradiol could be hypothesised, with consequent increase of testosterone concentrations, arrest of follicular maturation and development of polycystic changes in the ovaries.[19] However, VPA-related obesity is still considered to play a possible additional role in the development of endocrine disturbances, since polycystic ovaries, hyperandrogenism

and menstrual disorders were more common in obese than in lean women treated with VPA.[21]

The possibility of an unfavourable effect of VPA on reproductive status is also supported by several animal studies, performed by authors from the same group that described such findings in epileptic women.[134-139] These reports show significant changes in serum sex steroid hormone levels and ovarian structure after VPA treatment in female rats, with a significant increase in ovary weight, an increased number of ovarian follicular cysts, and reduced testosterone and oestrogen levels,[134,136] without any change in p53 protein expression which could indicate an oncogenic effect of VPA.[135] Conversely, the AED lamotrigine did not lead to any change in ovarian morphology in rats.[138] Other studies investigated a possible direct VPA effect on steroidogenesis in the ovary, by exposing to VPA cultures of isolated porcine ovarian follicular cells in different stages of follicular development.[137,139] The results of these studies suggested a direct effect of VPA on steroidogenesis, slightly different depending on the stage of follicular development, with reduction of both testosterone and oestrogen secretion, increased testosterone/oestrogen ratio (suggesting inhibited conversion of testosterone to estradiol), early inhibition of progesterone secretion with subsequent gradual increase during long-term VPA exposure. The authors stress that, since these findings are observed in nonepileptic animals, this argues against the hypothesis of epileptic activity as the primary cause of endocrine and morphological changes in these animals.[58] This is quite obvious, but the reverse is true when considering endocrine and morphological changes observed in epileptic animals not exposed to VPA, such as those discussed in section 2. It is worth noting that the endocrine changes observed in VPA-exposed animals are not identical to those observed in humans, since insulin levels are unchanged and testosterone levels are decreased.

The results of all these studies are very interesting and surely raise a very important point. The possibility that an effective, widely used AED may give rise to unwanted endocrine side effects, possibly evolving in reduced fertility and increased cardiovascular risk, deserves full consideration both from researchers and clinical epileptologists, and may suggest caution in prescribing VPA in women with epilepsy, particularly in the peripubertal period. Accordingly, increasing concern has been shown by paediatricians and psychiatrists before prescribing VPA to female patients, and the appropriateness of using VPA in young female patients has been questioned.[26-38] Consequently, given their wide impact in the literature and the possible consequences of their dramatic conclusions on the use of a otherwise highly effective AED, the results of Isojarvi and co-workers deserve a careful and critical reading, in order to fully understand their meaning. We review their main reports and underline the possible methodological problems which warrant caution in the interpretation of their conclusions (table I).

3.1 Studies on Prevalence

The first report from Isojarvi and co-workers,[7] usually quoted as describing the endocrine study of 238 women with epilepsy, actually presents endocrine findings coming from a much smaller sample of 98; only data about menstrual history and AED therapy are obtained from the whole sample of 238. Because the authors only provide results as percentages of 'abnormal' findings (polycystic ovaries or hyperandrogenism) as found in separate subgroups of patients, divided according to AED therapy and menstrual regularity, there is no way of understanding if and how these findings are associated in individual patients, and how many of these patients do actually have PCOS, since each one of the findings of menstrual irregularities, hyperandrogenism and polycystic ovaries is not by itself indicative of such a diagnosis. If the 1990 NIH Conference criteria are applied, the percentage of women with PCOS can be assessed as 3% (3/98) of patients in whom hyperandrogenism is associated with menstrual irregularities. There is mention of four patients presenting hirsutism, but since no information on their menstrual cycles is given it is not possibly to accurately assess a diagnosis.

Table I. Reports by Isojarvi and co-workers: prevalence data on endocrine disturbances in adult female patients with epilepsy

Treatment	Patients (n)			Menstrual dysfunction (%)			Hyperandrogenism (%)			PCO (%)			PCOS (%)			'1990 NIH Conference' PCOS (%)		
	total	mono	poly	total	mono	poly	total	mono	poly	total	mono	poly	total	mono	poly	total	mono	poly
Isojarvi et al. 1993[7][a]																		
Total	238			19.7			7.1[a]			27.6[a]						3.1[a]		
VPA	41	29	12[b]	39.0	44.8	25.0	22.6	17.4	37.5	45.2	43.5	50.0	NA	NA	NA	9.7	13.0	0
CBZ		120			19.2			0			22.4			NA			0	
Other AEDs		62			12.9			0			11.1						0	
Drug free		15			0			NS			NS						NS	
Isojarvi et al. 1996[8]																		
Total	65[c]			NA			6.2			29.2			NA			NA		
VPA		22			NA			18.2			45.4			NA			NA	
CBZ		43			NA			0			20.9			NA			NA	
Isojarvi et al. 1997[9]																		
Total	62			NA			NA			41.9			NA			NA		
VPA		34			NA			NA			61.8			NA			NA	
CBZ		28			NA			NA			17.9[d]			NA			NA	
Isojarvi et al. 2001[21]																		
Total	72			36.1			22.2			38.9			27.8			12.5		
VPA		37			59.5			27.0			62.2			48.6			21.6	
CBZ		35			11.4			17.1			14.3			5.7			2.9	
Lofgren et al. 2001[22]																		
Total	31			32.3			NA			NA			NA			NA		
VPA		15			40.0			NA			NA			NA			NA	
OxCBZ		16			25.0			NA			NA			NA			NA	

a Data on hyperandrogenism, PCO and '1990 NIH Conference' PCOS do not come from the original series of 238, but from 98 patients, mostly selected because of the presence of menstrual irregularities. For this reason, these prevalence data can not be compared with data coming from an unselected population. The 98 patient sample includes 31 of 41 total VPA recipients (75.6%), 49 of 120 CBZ recipients (40.8%), 18 of 62 other AEDs recipients (29.0%) and 0% of drug-free patients.

b These patients received VPA and CBZ but are analysed by the authors receiving VPA polytherapy

c This group of patients includes monotherapy patients coming from the previous study of 1993. For this reason, this population is mostly selected because of menstrual irregularities.

d In the abstract publication, the authors give a prevalence of 21.7%, but since they also state that PCO is observed in 5/28 CBZ recipients, the actual prevalence is 17.9%

AEDs = antiepileptic drugs; **CBZ** = carbamazepine; **mono** = monotherapy; **NA** = not available; **NIH** = US National Institutes of Health; **NS** = not studied; **OxCBZ** = oxcarbazepine; **PCO** = polycystic ovaries; **PCOS** = polycystic ovary syndrome; **poly** = polytherapy; **VPA** = valproate (valproic acid).

Independently from their diagnostic significance, however, in this study the findings of menstrual irregularities, elevated testosterone and polycystic ovaries are more commonly found in women receiving VPA than in women receiving other AEDs. In fact, comparing patients on VPA monotherapy to patients on carbamazepine monotherapy, we find menstrual irregularities in 44.8 versus 19.2%, polycystic ovaries in 43.5 versus 22.4%, and hyperandrogenism in 17.4 versus 0%. These data strongly suggest the possibility that VPA treatment in females with epilepsy might be associated with unfavourable changes in the reproductive balance. However, prevalence data as reported in the study may be misleading. First, the findings described in this report do not reflect the evaluation of a random population of epileptic women treated with VPA, but are actually derived from a selected sample of patients who were enrolled in the study because they had menstrual abnormalities. From the original series of 238 in whom menstrual history was evaluated, hormonal and ultrasound investigations were performed in 41 of 47 (87.2%) patients who had reported menstrual problems and in 57 of 191 (29.8%) patients with normal menstrual cyclicity, giving rise to a final sample which was preferably composed of women with abnormal cycles. In our opinion, this is an important observation that was not sufficiently stressed in the original report. Moreover, the high prevalence (68%) of 'abnormal endocrine findings' in VPA recipients stressed in the conclusive remarks is actually obtained by summing the prevalence of hyperandrogenism to the prevalence of isolated polycystic ovaries, which should not be considered an abnormal finding on their own.

The presentation of results is somewhat inaccurate also in the second report from this group,[8] in which a more detailed hormonal investigation, including evaluation of insulin metabolism, is employed in the same patients studied in the first study, selecting only women receiving monotherapy (22 with VPA and 43 with carbamazepine). The authors state that polycystic ovaries, hyperandrogenism or both are found in 14 (64%) of the 22 women receiving VPA, without giving further details. However, looking at the individual data of these same patients as given in the previous report, ten patients receiving VPA monotherapy had polycystic ovaries and four had hyperandrogenism. In the first report, it was not possible to understand if any of the women with polycystic ovaries also had hyperandrogenism. However, if the total sum of such patients with these findings is 14, as reported in the second paper, then it appears that this group originates from the union of 10 women with isolated polycystic ovaries and four with isolated hyperandrogenism. None of these patients may present both findings as the authors imply, because in that case the total sum should have been less than 14; consequently, the actual prevalence data in VPA recipients are that 45% have isolated polycystic ovaries and 18% isolated hyperandrogenism. Such data may have a clinical relevance, if considered together with data on menstrual cycles, which are not presented in this paper. In fact, when we integrate data from the two reports, we learn that six women (27% of the VPA group) had menstrual irregularities and polycystic ovaries: even if the diagnostic criteria for PCOS are not satisfied, these women surely deserve further investigation for possible endocrine problems. Moreover, three women (14% of the VPA group) have menstrual irregularities and hyperandrogenism, and consequently satisfy the diagnostic criteria for PCOS. These figures may be interesting and worth reporting, but are clearly much less dramatic than the 64% of abnormal findings presented in the results and which are usually quoted in the literature, resulting in a lot of misquoted information, as underlined elsewhere.[51] Only a careful comparison of information reported in different papers (not the standard approach for the average reader) may help to clarify the truth.

After these two papers were published, epidemiological data regarding the prevalence of endocrine disturbances in women receiving VPA for epilepsy were presented by the Finnish group at several congresses.[9,15,18,22] As the authors stated elsewhere,[58] it is difficult to give all details in the limited space of a short congress abstract. However, the ambiguous parameter of 'polycystic ovaries and/or hyperan-

drogenism', employed in the 1996 report,[8] is still largely used and often used as a synonym for endocrine disease, with a prevalence ranging from 60% in a study evaluating 15 patients on VPA monotherapy[22] to 72% in a multicenter study in which 39 VPA patients coming from three different epilepsy centres are described.[15] Another study[18] summarises the endocrine assessment obtained in 139 women with epilepsy during the years 1990–1997, reporting a 70% prevalence of polycystic ovaries and/or hyperandrogenism in VPA recipients. It is not possible to understand how many of the patients grouped together under this common definition might actually have only polycystic ovaries and consequently be considered as 'normal'. However, when in a more recent congress abstract[22] the finding of polycystic ovaries and/or hyperandrogenism is coupled to menstrual irregularities, the prevalence in the 15 VPA-treated women falls to 33%. It would be interesting to know how many of them did actually have the association of hyperandrogenism and menstrual disorders, i.e. PCOS.

The most detailed paper from this group reporting prevalence data was published in 2001.[21] In this report, the frequency of VPA-related metabolic and endocrine disorders was assessed in 72 women with epilepsy coming from three different epilepsy centres in Finland, Norway and The Netherlands, with the aim of evaluating the possible increased risk for coronary artery disease associated with these metabolic changes. In total, 37 women receiving VPA and 35 receiving carbamazepine were evaluated, together with 52 controls. Detailed information is given in this paper regarding the distribution of isolated hyperandrogenism, isolated polycystic ovaries and association of both in the different groups. However, in the evaluation of results the authors once again group together all these findings, considering the presence of 'polycystic ovaries and/or hyperandrogenism' as an abnormal feature. This way of presenting results is not inconsequential. When the group of 'women with any abnormality' also includes (incorrectly) patients with isolated polycystic ovaries, the distribution of 'abnormal women' is 70% in the VPA group, 20% in the carbamazepine group and 19% in controls. Accordingly, the authors conclude that, 'these results confirm … that polycystic ovaries and related hyperandrogenism are common among women taking VPA for epilepsy. Approximately two thirds of the women treated with VPA had these disorders, a frequency that was more than threefold greater than that of control subjects and women treated with carbamazepine'. It is not clear how the authors may consider the 16 women with polycystic ovaries and normal androgen levels as also affected by 'polycystic ovaries and related hyperandrogenism'. If these women were not included in the group of abnormal patients, and only elevation of androgens (with or without polycystic ovaries) is considered as a marker of endocrine abnormality, the distribution of 'abnormal' women is not significantly different between VPA (27%) and carbamazepine recipients (17%). According to these 'corrected' data, hyperandrogenism is quite common in women with epilepsy with no definite relationship to AED treatment. Once again the finding of polycystic ovaries is far more common in VPA-treated women than in carbamazepine recipients and controls, with prevalences of 62, 14 and 17%, respectively.

In this paper,[21] data on the association of menstrual irregularities with hyperandrogenism are shown only in a figure, according to which about 22% of women in the VPA group and about 6% in the carbamazepine group present with the association of hyperandrogenism and menstrual irregularities that allows a diagnosis of PCOS. The prevalence of this disorder in the VPA group is consequently much higher than in the carbamazepine group and higher than that reported in the general population. This result is highly interesting and raises valid concerns about the possible side effects of VPA on reproductive health. However, the authors' conclusions on these data appear quite misleading. Their statement 'approximately 2/3 (70%) of women treated with VPA had polycystic ovaries or hyperandrogenism … and most of them had menstrual disorders, suggesting hyperandrogenic chronic anovulation' is incorrect, since women with polycystic ovaries and normal androgens could not have such a

condition. In fact, only 22% of VPA-treated women in this particular series had hyperandrogenic anovulation.

3.2 Studies on Adolescent Patients

One of the most interesting study projects from this group is devoted to evaluation of the possible endocrine effects of VPA in adolescent patients, presented in reports[14,17] describing clinical and endocrine assessment of 41 young female patients with epilepsy treated with VPA monotherapy and compared to 54 age-matched controls. Patients and controls were divided in subgroups according to the stage of their sexual development (prepubertal, pubertal and postpubertal); hyperandrogenism was defined as testosterone values exceeding the mean ± 2SD in controls of the same pubertal stage. For patients versus controls: 16 versus 20 were prepubertal, 11 versus 13 were pubertal and 14 versus 21 were postpubertal. Results showed that the frequency of menstrual irregularities was not significantly different between menstruating patients and controls, and that the occurrence of polycystic ovaries was not significantly increased in pubertal and postpubertal patients compared with matched controls. However, in the prepubertal group, polycystic ovaries were observed only in two (14.3%) patients and not in the controls. Mean testosterone levels were significantly raised in all three patient groups compared with control groups; 38.0% of prepubertal, 36.4% of pubertal and 57.1% of postpubertal patients were hyperandrogenic. Since hyperandrogenism was observed in prepubertal patients without concomitant signs of obesity or hyperinsulinism, the authors conclude that hyperandrogenism may be the first abnormal sign induced by VPA use, being observed as early as after 0.8 years of VPA use, while development of weight gain may need a longer period of treatment. Moreover, they underline that the prevalence of hyperandrogenic patients in their series increases with pubertal development, suggesting that the sensitivity to manifest hyperandrogenism increases as a function of sexual maturation.

These findings are very interesting and might suggest caution in the use of VPA in young female patients. However, since individual hyperandrogenism in these individuals is deduced only from the comparison with small subgroups of controls, these results need to be confirmed after comparison with much larger samples of normative data from matched controls.

3.3 Studies on Selected Groups of Patients

The reversibility of VPA-associated endocrine effects is described in a report[10,11] of a switch from VPA to lamotrigine therapy in a group of 12 patients with epilepsy 'who had a previously identified endocrine disorder (polycystic ovaries or hyperandrogenism) likely related to VPA medication'. Clinical data from these patients are presented in detail, with body mass index (BMI) data reported before, during and after VPA therapy, and menstrual cycle/ovarian data reported only for the period of VPA treatment and after its withdrawal. No individual data on plasma androgen levels are given. All patients were switched from VPA to lamotrigine treatment and studied before withdrawal and after 2, 6 and 12 months of treatment with lamotrigine. The authors conclude that the metabolic/endocrine syndrome induced by VPA treatment is reversible after VPA withdrawal, since, after replacing VPA with lamotrigine, BMI, insulin and testosterone levels decreased, the high-density lipoprotein (HDL) cholesterol/total cholesterol ratio increased, and the total number of polycystic ovaries decreased.

However, individual data offer a better insight. First, the possibility that all 12 patients may actually have an 'endocrine disorder likely related to VPA therapy' does not seem so obvious. In fact, 4 of 12 patients have actually only isolated polycystic ovaries with regular menstrual cycles; two of these four patients are obese but, in one, obesity was present before VPA use. The ovarian cysts disappear after VPA withdrawal in two of four. It is not possible to be sure that these four participants had any endocrine disease. It is not clear if any of them may have been hyperandrogenic, since the authors do not give this information in an otherwise very detailed table.

However, as none of them had menstrual irregularities and there is no proof that they may be anovulating, they do not have PCOS. Disappearance of polycystic ovaries in two of four is not necessarily related to withdrawal of VPA, since we have no information on ovarian findings before VPA treatment. A fifth patient had normal weight and polycystic ovaries both during VPA therapy and after VPA withdrawal; she had long (34 days), but not necessarily irregular, menstrual cycles which showed a slight improvement after VPA withdrawal, being reported as 30 days thereafter. Also in this patient, no clear VPA-related endocrine disorder is observed, and the slight improvement of menstrual cycle length, if even were caused by VPA withdrawal, could not be considered as a recovery of any sort. A sixth patient had amenorrhoea, which persisted after VPA withdrawal, and normal ovarian findings; there is no way of attributing her endocrine problems to VPA as no information on her menstrual cycles before VPA treatment is given and the menstrual problems persist more than 1 year after withdrawal. She showed a considerable weight gain during VPA treatment, which greatly improved after withdrawal, but without any effect on the menstrual picture, which consequently did not seem to be obesity related. Finally, the remaining six patients had menstrual irregularities which disappeared or improved after VPA withdrawal, and polycystic ovaries which disappeared in two patients and became unilateral in two. Four of them had weight gain during VPA treatment, with reduction after withdrawal. These are the only patients in whom, in our opinion, a definite, possibly VPA-related endocrine disorder is actually observed.

In total, only 50% of patients in this series showed the VPA-related reproductive endocrine disorder which should have characterised the whole group. This confirms the suspicion that the elevated prevalence of these disorders as reported by the Finnish group may actually be overestimated as a result of the inclusion of otherwise normal women with polycystic ovaries; moreover, endocrine disturbances not necessarily related to VPA use may have been considered as such. Androgen data in this paper are shown only as mean values in a bar graph, which shows a clear significant reduction of mean testosterone after VPA withdrawal and switch to lamotrigine therapy. Since no individual androgen data are given, it is not possible to know how many patients decreased from abnormal to normal testosterone levels and in how many, conversely, testosterone changes occurred inside the range of normal values.

In conclusion, all the six women who presented definite menstrual irregularities and polycystic ovaries during VPA therapy had restoration or improvement of menstrual cyclicity after VPA withdrawal, accompanied by disappearance of polycystic ovaries in two women, in two women bilateral polycystic ovaries became unilateral, while in the remaining two polycystic ovaries showed no changes. The authors report the results on ovarian findings as a comparison between the total number of polycystic ovaries before and after VPA withdrawal, stressing how they decrease from 20 to 11; however, individual data of abnormal patients give a better understanding, since it is doubtful if changes in ovarian morphology in otherwise healthy women might have any importance. In summary, four of six women (66.7%) who showed improvement of menstrual cyclicity after VPA withdrawal still had polycystic ovaries 1 year after VPA discontinuation; the fact that in some women polycystic changes were unilateral rather than bilateral is rather questionable as a sign of improvement.

Although the report describing the switch from VPA to lamotrigine therapy shows interesting data about the reversibility of menstrual abnormalities, reduction of bodyweight and of ovarian cysts in individual epileptic women,[10,11] several shortcomings must be stressed. A possible effect on androgens can not be completely evaluated from this report, since individual testosterone levels are not shown and the reduction of mean testosterone values is of dubious clinical significance. Moreover, despite the significant reduction of the total number of polycystic ovaries, 7 of 12 women still had uni- or bilateral ovarian cysts 1 year after VPA withdrawal. The role of obesity and weight reduction on the

improvement of the metabolic syndrome is not evaluated in individual patients. However, even if it is doubtful that all women included in this study did actually have an endocrine problem, and there is no clear proof that in all of them it might be VPA related to begin with, there is no doubt that VPA withdrawal and switch to lamotrigine is temporally accompanied by changes of several parameters both in women with an endocrine problem and those without. The actual clinical importance of these changes should probably re-evaluated after a longer follow up.

These conclusions seem to be supported by another interesting report from this group[19] which reviews the detailed clinical history of three women with epilepsy who experienced 'VPA related endocrine disorders'. The aim of the paper is to describe the progressive development of these disturbances over time during VPA treatment and their regression after VPA discontinuation. However, a clear cause/effect relationship between the use of VPA and the endocrine disturbance is far from being certain in this study as well. The first two patients developed a relevant weight gain during use of VPA and, somewhat later, important menstrual disturbances. Elevated testosterone levels and polycystic ovaries were documented. However, while still receiving VPA treatment, both patients presented a spontaneous decrease of testosterone levels, which in one (patient 1) nearly reached normal values. After VPA discontinuation, both patients showed improvement of menstrual cyclicity, from amenorrhoea to 30-day menstrual cycles (patient 1) or from amenorrhoea to oligomenorrhoea with 4 cycles in 1 year (patient 2). Testosterone levels decreased to normal levels; polycystic ovaries disappeared only in patient 1. It must be stressed that while the anamnestic/laboratory data regarding the time period of VPA treatment are collected over a long period of time (9 years for patient 1 and 4 years for patient 2), follow up after VPA discontinuation is offered for only 1 year.

There is no doubt that both patients have PCOS, but the pathogenic relationship of this picture with VPA is far from being definite. Testosterone levels show spontaneous reductions during VPA treatment, so there is no proof that its increase had been caused by VPA – it is possible that we could just be witnessing the natural history of PCOS, in which changes in laboratory and clinical findings occur over time. The improvement of the clinical picture observed after VPA discontinuation – which is only partial in patient 2, who is severely oligomenorrheic and shows an unmodified ovarian picture after switch to lamotrigine – is documented only for 1 year. Surely a longer lasting improvement would be necessary to conclude that these patients have definitely recovered from their previous endocrine problem, especially considering that we are dealing with a clinical picture that shows considerable changes over time, in relation to multiple possible cofactors. In our opinion, the possibility that VPA had only an additional, even if quite relevant, role in the expression of PCOS in these patients must be taken into consideration, and no definite conclusions should be reached before a longer follow up has been obtained.

Patient 3 in this series always had normal menstruations, and was accidentally discovered to have elevated testosterone (7.5 nmol/L) with normal ovaries after 18 months of VPA use. Two years after this assessment, still under VPA treatment, she was still menstruating regularly, had normal testosterone levels (2.5 nmol/L) and polycystic ovaries. VPA was withdrawn, and during the first year after withdrawal her ovaries reverted to normal. Menstrual cyclicity and bodyweight did not change; testosterone levels (already in the normal range) showed a further decrease. The endocrine problem of this patient is not known, since no further assessment was made to discover the causes of her hyperandrogenism and to evaluate her ovulatory dynamics. However, both the hormonal and the echographic pattern showed spontaneous changes during VPA therapy, and menstrual cyclicity and bodyweight were consistently normal. The further decrease in testosterone levels after VPA discontinuation seems of little relevance, since levels were already reverted to normal during VPA treatment. Similarly, she had showed normal ovaries even when treated with VPA, so the disappearance of polycystic changes after VPA discontinuation does not seem necessari-

ly related to therapy changes. Once again, a longer follow up might have helped to clarify if the changes in ovarian morphology and androgens were VPA related or just part of the natural history of a non-VPA related situation. This would be particularly necessary considering that pre-treatment data regarding testosterone levels and ovarian morphology are not available for any of these patients.

The authors are aware of such inconsistencies, since they state that 'interestingly, serum testosterone levels seemed to decrease in all 3 patients before VPA therapy was discontinued. Therefore, a relationship between discontinuation of VPA therapy and the decrease of serum testosterone concentrations cannot be clearly established in these 3 patients'. The fact that, in the absence of pre-VPA testosterone levels, this may also imply that the increase in testosterone levels was not VPA related in the first place is not commented on. However, this possibility should have been taken into consideration, especially because it undermines the authors' theory about the relevant role of VPA-induced hyperandrogenism as the first pathogenic step towards endocrine disturbances, independently from hyperinsulinism and weight gain.

There are three further studies from this group in which endocrine changes under VPA treatment are studied in a prospective fashion, with evaluation of clinical, laboratory and echographic parameters both before and shortly after starting of VPA treatment.[20,23,24] In the first report,[20] ten women are examined before starting VPA therapy and then 1 and 3 months thereafter. This study also includes women started on carbamazepine therapy and men started on VPA or carbamazepine treatment. In the group of female VPA recipients no changes in menstrual cyclicity or bodyweight were observed during 3 months of treatment. Mean testosterone values were significantly raised after 1 month, but after 3 months this increase was no longer significant (p values are reported as ≤0.1). However, the authors report that five patients (50%) had an individual increase in testosterone levels after 3 months and could consequently represent a subset of VPA recipients who are at high risk of developing hyperandrogenism on long-term use. It is unfortunate that individual testosterone levels over time are not given and that testosterone increases in individual patients are only described as 'a change exceeding 1 SD of the mean serum hormone level of all participants of the same sex before the medication was initiated'. It is questionable that such small hormonal changes, with a doubtful statistical significance, are clinically relevant over the long term.

Another report,[23] presented as a congress abstract, describes the 2-year prospective follow-up in four consecutive women with epilepsy, assessed before and after starting VPA therapy (another two women had not completed the 2-year study when the abstract was published). One of the four women had polycystic ovaries before starting VPA therapy; one was taking oral contraceptives before starting VPA, and another one was started on them after 3 months of VPA usage. After 24 months, all showed polycystic ovaries, regardless of oral contraceptive use; a nonsignificant increase of mean testosterone and an increase of mean androstenedione ($p = 0.021$) was observed in the group. According to the authors, individual increases of serum androgens were observed regardless of weight gain and of use of oral contraceptives. No pathogenic hypothesis is offered in the abstract to explain these unusual findings – apparently the hyperandrogenic activity of VPA must be exceptionally strong to be effective even in presence of oral contraceptives, which usually decrease androgen secretion both in women with and without PCOS.[140] On the other hand, mean androgen changes are once again of very small magnitude and their clinical importance may once again be questioned.

Finally, a third study[24] presents preliminary data about weight gain, androgen levels and menstrual cyclicity evaluated over time in patients on monotherapy with VPA (n = 103) or lamotrigine (n = 119). Patients receiving VPA showed higher levels of testosterone and androstenedione, longer and more variable cycle length, and an increase of bodyweight over time. The actual impact of these findings on the reproductive status needs to be evaluated

with time but preliminary results are very interesting.

3.4 Studies Focusing on Hyperinsulinism, Insulin Resistance Syndrome and Increased Cardiovascular Risk

The possibility that the altered endocrine balance associated with the use of VPA in females with epilepsy may also result in a metabolic syndrome giving rise to an increased cardiovascular risk has been examined in many of the studies by Isojarvi and co-workers, especially in the most recent ones. An increased risk of cardiovascular mortality is reported in women with insulin resistance syndrome,[141,142] a picture which includes hyperinsulinaemia, reduced insulin-like growth factor binding protein (IGFBP)-1, and altered lipid profile with elevated levels of serum triglycerides and a low serum HDL cholesterol/total cholesterol ratio.[143] The association of this metabolic picture with obesity is well established,[99,141,144] and it is known that adipose tissue plays a significant role in the pathogenesis of insulin resistance, as shown by the high correlation between obesity and insulin resistance.[144] However, insulin resistance is also a common feature in spontaneous PCOS independent of obesity, since it may be encountered in both lean and obese patients with this condition, even if in different degrees.[88,99] Because of this possible association with PCOS, metabolic parameters correlated to insulin resistance have been repeatedly investigated in VPA-treated patients by Isojarvi and co-workers.

In their first reports[7,8] the authors underlined how the laboratory features of insulin resistance (hyperinsulinaemia and low IGFBP-1) were significantly associated with obesity in VPA-treated patients, and proposed that obesity may be the first step in the pathogenic mechanism of VPA-induced endocrine unbalance, leading to hyperinsulinaemia which could in turn result in ovarian hyperstimulation. However, despite the significant findings that emerged from their earlier series, the authors later dismissed this theory[11] on the basis of further evidence coming from successive studies: in particular, the authors underlined how, after VPA withdrawal, reduction of insulin levels could be observed before weight loss, suggesting that the alterations in insulin metabolism were not mediated by weight gain but directly caused by VPA usage. This phenomenon was observed in the 12-women series switched from VPA to lamotrigine therapy, whose endocrine findings we have discussed in section 3.3.[11]

In this report,[11] the evaluation of parameters related to the metabolic syndrome associated with insulin resistance showed that mean BMI, waist/hip ratio, insulin and triglycerides were significantly raised in VPA-treated patients compared with controls, while HDL cholesterol **:** total cholesterol was significantly lower. Individual levels of insulin and lipid profiles are not given. All these parameters reverted to normal after the switch to lamotrigine, with a reduction of mean insulin levels already relevant 2 months after VPA withdrawal, and a more gradual and progressive decrease in mean BMI. However, in the absence of individual data on insulin and lipid profile, it is not possible to know if hyperinsulinism and unfavourable lipid changes were present both in lean and in obese VPA-treated women described in these series, or in how many, if any, women the reduction of insulin levels did actually precede weight reduction. Presentation of mean data does not seem the ideal way to find out if the metabolic syndrome should be considered a direct effect of a supposed VPA-induced hyperinsulinaemia or an indirect effect linked to VPA-induced weight gain.

A later report from this group,[21] which we discussed in section 3.1, does actually show that insulin resistance syndrome is encountered only in obese, but not in lean, VPA-treated women. In this study, a specific investigation on metabolic parameters related to the insulin resistance syndrome was conducted in the 37 VPA-treated, 35 carbamazepine-treated and 52 control women. When all VPA recipients are compared with all carbamazepine recipients and with all controls for the parameters related to insulin resistance, we observe that insulin is significantly raised in both the VPA and carbamazepine groups, that IGFBP-1 is normal in both patient groups, that triglycerides are normal in both patient groups, and

that HDL cholesterol **:** total cholesterol is lower only in VPA recipients. Therefore, as far as the insulin resistance syndrome is concerned, VPA recipients differ from the carbamazepine recipients only in their cholesterol profile; otherwise, both patients groups present hyperinsulinaemia with normal IGFBP-1 and normal triglycerides.

However, these are not the conclusions of the authors who dismiss any possible significance of the raised insulin levels in the carbamazepine recipients, stating that normal IGFBP-1 levels and normal serum lipid profile in this group rule out insulin resistance. The fact that the VPA-treated patients also have normal IGFBP-1 levels, and that they only have cholesterol but not triglycerides alterations is not discussed. Conversely, much discussion involves the finding of the complete picture of insulin resistance (hyperinsulinaemia, low IGFBP-1 and unfavourable lipid serum profile) in obese VPA-treated women with polycystic ovaries and/or hyperandrogenism, implying that long-term VPA use could be associated with increased cardiovascular risk. However, only when VPA recipients are divided in subgroups does the complete picture of hyperinsulinaemia, low IGFBP-1 and altered lipid profile observed, and only in the highly selected group of obese women with hyperandrogenism and/or polycystic ovaries.

It is not clear why such a subdivision was not employed in the carbamazepine group, in which 37% women were obese (vs 38% of VPA-treated patients) and 17% were hyperandrogenic (vs 27% of VPA-treated patients). Even if these two parameters were apparently never associated in carbamazepine patients, it is possible that also these patients, if studied in separated subgroups similarly to the VPA-treated patients, could show an altered metabolic profile as well. This may be true especially for obese carbamazepine recipients, since obesity *per se* is a disease entity, and its association with insulin resistance/hyperinsulinaemia is well established.[99,141,144]

In conclusion, in our opinion the definite relationship between obesity and insulin resistance syndrome emerging from this study clearly suggests that the 'metabolic syndrome' observed in VPA-treated epileptic women might actually be a consequence of a VPA-mediated increase in bodyweight rather than a direct effect of VPA on insulin secretion. However, in a very recent report[25] the same authors again disagree with their previous conclusions because of new evidence coming from a different study.

In this last report,[25] specifically devoted to investigate the relationships between insulin metabolism and obesity in VPA-treated patients with epilepsy, insulin levels are evaluated separately in obese and lean patients, and compared to controls similarly subdivided according to their BMI. In the total group of female VPA recipients, insulin levels are significantly raised when compared to the total control group. A significant difference is also observed when patients and controls are subdivided according to their BMI, so that an increase of insulin levels can be observed not only in obese, but also in lean VPA-treated patients, suggesting that hyperinsulinaemia in VPA recipients may develop independently of weight gain.

However, a closer look to the actual data raises some doubts on the appropriateness of such conclusions. In fact, in the previous paper[21] which showed a relationship between an increase in insulin levels and obesity, mean insulin values for lean VPA-treated women were 7.3 ± 3.4 mU/L (in patients who also presented polycystic ovaries and/or hyperandrogenism) and 7.7 ± 3.9 (in patients with normal ovaries): these values did not differ significantly from those of the control group (6.4 ± 4.6), which consisted of 52 participants whose BMI was not reported. In the most recent paper,[25] however, insulin values of lean VPA-treated women are consistently lower than previously reported, being 6.7 ± 2.9, but they are nevertheless significantly higher than the control group. However, this control group, which does not seem to be any more representative than the one employed in the previous paper[25] (27 controls vs 52 in the previous paper), had insulin values that were considerably lower than those seen in the controls in the previous paper (4.5 ± 2.6 in the total control group and 5.4 ± 2.4 in the group of

obese controls). In conclusion, the different results in the two reports investigating insulin levels in obese and lean VPA-treated patients seem to depend mostly on the characteristics of the control groups, which show considerable differences between the two reports, and consequently their apparently contrasting conclusions must be considered with caution. In our opinion, at present there is no consistent evidence that might challenge the hypothesis that the metabolic syndrome observed in VPA-treated patients may be related to an increase in bodyweight. The contradictory results coming from the Finnish group probably reflect shortcomings in the presentation of findings.

4. Polycystic Ovary Syndrome in Women with Seizures: Other Voices

After the interest and debate raised by results from Isojarvi and co-workers, in recent years several other groups have investigated the prevalence of PCOS in women with epilepsy. Results are often contrasting and a clear picture does not emerge. Much responsibility for this can probably be attributed to the different methods used in the evaluation of patients.

Some of these reports are available only as congress abstracts and for this reason they are particularly difficult to evaluate. This is the case with the interesting report from Kasradze et al.,[65] who assessed the endocrine picture in 323 women with epilepsy ranging in age from 10–40 years, reporting a diagnosis of PCOS in 17.6%. No information is given on AED treatment or on diagnostic criteria, and so it is difficult to comment on these data, which have the merit of coming from a large sample of patients. Similarly, Morrell and co-workers[62] have evaluated the reproductive endocrine picture of 28 women with epilepsy by assessing hormonal levels and ovarian echographic findings, but since a complete investigation was performed only in a limited sample and results were not given for individual patients, we can only quote the authors' statement that 'women with epilepsy are at risk for polycystic ovaries, anovulatory cycles and abnormal menstrual cycle length' – the prevalence of the complete picture of PCOS and its distribution according to different AED therapy can not be estimated from the abstract.

More detailed data can be obtained from the congress abstract by Khatami et al.[71] in which the prevalence of polycystic ovaries and PCOS is evaluated in a sample of 26 women with epilepsy, some of whom are successively followed up after 2 and 6 months. Fifteen patients were treated with VPA, six with carbamazepine and five with lamotrigine. The isolated finding of polycystic ovaries was found in 12 patients (46.2% of the whole group) and, specifically, in four patients receiving carbamazepine, one patient receiving lamotrigine and seven receiving VPA. According to these data, isolated polycystic ovaries are more frequent among women with epilepsy than in the general population, but these findings are not linked to the use of VPA, since they are described in 66.7% of women treated with carbamazepine, 20% of women treated with lamotrigine and 46.7% of women treated with VPA. Women with isolated polycystic ovaries did not differ from those with normal ovaries as to BMI, insulin, lipid profile, hip/waist ratio or fasting glucose levels; higher but not significantly different LH/FSH ratio and free testosterone were observed. Moreover, PCOS was diagnosed in 19.2% (five patients); once again this prevalence is higher than that reported in the general population. However, this abnormal picture was more frequent among VPA-treated (26.7%) than in carbamazepine-treated patients (16.7%) even if the difference was not significant. No lamotrigine-treated patient had a picture of PCOS. Diagnostic criteria employed for definition of PCOS are not given in the abstract. Follow up at 2 and 6 months on a partial sample showed that the echographic ovarian picture of polycystic ovaries disappeared in two women (one VPA and one carbamazepine recipient), that none of the women with normal ovaries developed polycystic ovaries and that none of the women with isolated polycystic ovaries developed PCOS. On the whole these data show a high prevalence both of polycystic ovaries and of PCOS among women with epilepsy, with a nonsignificant clustering of PCOS among VPA-treated patients. The picture of isolated

polycystic ovaries is not accompanied by changes in mean metabolic or endocrine parameters, apart from a nonsignificant increase in testosterone and LH, which do not show a progressive trend over time. A longer follow up will probably be reported in the future, since these results are reported as preliminary. For the moment, the lack of diagnostic criteria for PCOS and the small size of the study sample do not allow a definitive comment on the results.

Another interesting study, which is so far available only in congress abstracts, is the one from Betts and co-workers on women with epilepsy whose preliminary results have been presented on several occasions.[53,70,73] Women with epilepsy are consecutively recruited as they attend a preconception clinic in the Epilepsy Unit, and submitted to magnetic resonance imaging (MRI) investigation of the ovaries and to a basic hormonal evaluation, which includes LH, FSH and testosterone. So far, preliminary data from 56 women with IGE and who had only ever taken either VPA, carbamazepine or lamotrigine have been presented in comparison to data from 50 controls; results from a group who have switched from VPA and lamotrigine are also commented upon.[53] Preliminary results show that the prevalence of isolated polycystic ovaries is high among women with epilepsy (which is only represented by the idiopathic generalised type in this study) compared with the general population, since they are found in 35% of VPA-treated patients and in 45% of the lamotrigine/carbamazepine group, compared with 5% in the controls.[73] No differences in the distribution of this finding are observed in the different AED groups. However, 'hormonal evidence of PCOS' (which appears to be defined as raised testosterone and/or LH levels) can be found only in the VPA group, where PCOS is reported in 28%, versus 10% in controls and 0% in the carbamazepine/lamotrigine group. Hormonal alterations are more likely to occur in women who start taking VPA around puberty. Substitution of lamotrigine for VPA leads to an immediate drop in testosterone and/or LH levels, before VPA is withdrawn; after VPA withdrawal there was some evidence of a reduction in ovarian volume and cyst size.

The authors comment that women with epilepsy seem more prone to have polycystic ovaries independently of specific AED treatment, and that consequently it is unlikely that VPA induces the ovarian finding, which is more probably attributable to epilepsy itself; in any case, the significance of the isolated finding of polycystic ovaries is unclear. Moreover, the authors suggest that VPA use seems to 'push women, already predisposed by having polycystic ovaries, down the metabolic pathway towards PCOS, possibly by raising insulin resistance, but this effect is reversible'. It is hypothesised that carbamazepine and lamotrigine may have a protective effect against the development of hormonal alterations consistent with PCOS; carbamazepine might exert this effect through its enzyme-inducing proprieties which reduce levels of unbound testosterone, while the possible mechanism of lamotrigine protection is unknown, since this drug is not enzyme-inducing.

Several comments are suggested by these very interesting findings. It is noteworthy that results from Betts' and Khatami's groups are very similar, and that they come from similar samples of epileptic women treated only with VPA, carbamazepine or lamotrigine. Both groups report a high prevalence of polycystic ovaries in all epileptic women independently from AED treatment, and a higher distribution of PCOS only in VPA-treated patients. The possibility that this different distribution may be due to a protective effect of carbamazepine and lamotrigine, rather than (or in addition to) a disruptive action of VPA, must surely be considered. Indeed, this concept has already been suggested some time ago for carbamazepine.[47,114] In 1994 and in 1996, Herzog and co-workers suggested that carbamazepine, and other AEDs with enzyme-inducing effects, may treat hyperandrogenism and PCOS in epileptic women, while VPA may not; consequently, while VPA is not the primary cause for PCOS in epileptic women, its selection as treatment may be an important factor in the distribution of PCOS among epileptic females.[47] It is now possible to hypothesise that lamotrigine may have a protective effect as

well, even if the mechanism by which this effect might be exerted is presently unknown.

The possibility that a 'favourable carbamazepine/lamotrigine effect' rather than an 'unfavourable VPA effect' might be the cause of the different distribution of PCOS among different therapy groups is also suggested by other findings reported by Betts' group. To begin with, the distribution of 'hormonal evidence of PCOS' is actually higher in controls than in patients receiving carbamazepine or lamotrigine even if not significant.[73] Consequently, epileptic women receiving carbamazepine or lamotrigine seem to have a decreased risk of developing PCOS than the general population, even if they more frequently have isolated polycystic ovaries. Moreover, the authors report an immediate restoration of normal hormonal levels as soon as lamotrigine is added and independently from VPA withdrawal,[53] which could also suggest a favourable effect of lamotrigine on hormonal parameters. This hypothesis is very interesting but needs to be tested on larger samples of patients.

Some methodological problems must also be underlined in the reports from Betts and co-workers. First of all, it is not clear if all patients in Betts' series with 'hormonal evidence of PCOS' may be actually have PCOS. No data on menstrual cycles are given in these reports; the presence of menstrual dysfunction is necessary for diagnosis of PCOS according to the 1990 NIH Conference criteria, and even if such criteria are somehow questioned by the authors in relation to their possible difference with criteria employed in Europe,[53] these differences in approach are mostly related to the opportunity of making such a diagnosis without recourse to evaluation of ovarian morphology, which is not the issue here. Data of menstrual cyclicity would surely be necessary to support the diagnosis, especially if we consider that the authors have also considered as 'hormonal evidence of PCOS' an isolated elevation of LH. It is questionable if a diagnosis of PCOS may be suggested without hyperandrogenism and without information on menstrual cyclicity, and only based on elevation of LH values; moreover, unless the authors have obtained individual LH levels by averaging the values of two samples drawn 30 minutes apart, it is possible that a single finding of LH above the normal levels may be of limited significance, because of the pulsatility of LH levels.[99] On the other hand, since the authors do not apparently evaluate other androgens nor clinical hirsutism, it is also possible that patients actually presenting laboratory or clinical hyperandrogenism may have missed the diagnosis of 'hormonal evidence of PCOS'. It is likely that when these data are published in full, these issues will be clarified.

More detailed data are available from the reports of authors who have published their data in full. This is the case of reports from Stephen et al.[72,77,78] Since there are some differences in study population and results among the data reported in full extensively and those described in the abstracts, we will only comment here results emerging from the full report,[77] and in particular only those coming from female patients. In total, 44 women with epilepsy are described, of whom 23 had been treated exclusively with VPA and 21 with lamotrigine for a period ≥2 years. Menstrual cycle length was recorded, BMI calculated, and sex hormones, insulin, SHBG, glucose and lipid profile evaluated. However, clinical evaluation of hirsutism was not performed; this might lead to underestimation of PCOS patients, in whom clinical hyperandrogenism is considered a diagnostic criterion also in absence of laboratory hyperandrogenism.[88]

The results showed that VPA-treated patients had significantly higher triglyceride and testosterone levels and free androgen index (FAI) with respect to lamotrigine patients, whereas no differences were observed in BMI, insulin, DHEAS, androstenedione, LH : FSH or cholesterol profile. Menstrual irregularities were found in 21.7% of VPA recipients and 33.3% of lamotrigine recipients, and 73% of VPA recipients and 48% lamotrigine recipients were overweight. Abnormal individual hormone levels were found only in VPA recipients, and precisely in five, of whom four had hyperinsulinaemia (17.4%) and two elevated testosterone (8.7%); one of the hyperinsulinaemic women was also hyperandrogenic. (Curiously, in the table showing individu-

al data for abnormal VPA recipients, the authors give normal values of testosterone as ranging from 1.0–3.2 nmol/L, and display abnormal values for the two hyperandrogenic patients as 3.4 and 3.7 nmol/L. However, in the table showing mean hormone values for all patients, testosterone levels in VPA recipients range from 0.2–7.0 nmol/L: consequently, at least one VPA recipient must have testosterone values of 7.0 and, therefore, there should be at least three hyperandrogenic VPA-treated patients).

Individual data are given for these five women, four of whom the authors consider to have PCOS. The criteria used for this diagnosis are not given, but they do not appear to include hyperandrogenism as a necessary finding, in spite of the importance given to androgen levels for the diagnosis by the authors themselves. In fact, only one of these patients fulfilled 1990 NIH Conference criteria for PCOS, having irregular menstrual cycles and elevated testosterone; she was also hyperinsulinaemic and obese. The other hyperandrogenic patient had regular menstrual cycles, normal weight and normal insulin levels; a more detailed investigation, including study of ovulatory dynamics, would be needed for a diagnostic assessment of her hyperandrogenism. The other three patients have normal testosterone and are hyperinsulinaemic and obese; two have irregular menstruations. In these patients, obesity seems to be the key factor that can lead to hyperinsulinism and to menstrual irregularities; there is no evidence of PCOS. The authors attribute the difference between PCOS prevalence in their sample of VPA recipients (which they consider as 17.3% but which drops to 4.3% if 1990 NIH Conference criteria are applied) and prevalence described by Isojarvi and co-workers to genetic and/or phenotypic factors. Their concluding remarks underline that in women, a subclinical increase of insulin and testosterone is associated with VPA-treated patients compared with lamotrigine-treated patients, but that these alterations lead to clinical problems only in a minority of patients. However, an elevated insulin level, in particular, is only observed in obese VPA recipients compared with obese lamotrigine recipients, but not in the total group of VPA recipients versus the total group of lamotrigine recipients; this would suggest that weight gain might have an additional role in insulin changes. However, since this finding is also observed in male VPA recipients compared with lamotrigine recipients, the authors conclude that VPA may have an effect on insulin resistance independently from weight gain.

Murialdo et al.[63,66] have studied in two different reports the endocrine profile of women with epilepsy. In the first report[63] a sample of 101 women with epilepsy were evaluated; the hormonal profile (both in follicular and in luteal phase), menstrual status, BMI and hirsutism score was investigated in all patients, whereas ultrasonographic ovarian findings were obtained in 83. Fifty-four patients were receiving AED monotherapy, which consisted of VPA in 11, carbamazepine in 20, phenobarbital in 19, phenytoin in three and primidone in one. Polytherapy with two or three AEDs was employed in the remaining 47; 16 of this latter group received VPA, while in the remaining 31 VPA was not included in the therapy regimen.

Results showed menstrual abnormalities in 21.8% of the whole group, a prevalence that the authors underline as being only slightly higher than in the normal population. Menstrual irregularities were seen in 29.6% of patients whose AED regimen included VPA versus 18.9% in patients not treated with VPA; this difference was not significant.

Polycystic ovaries were observed in 14 of the 83 women who had an ovarian scan, with a prevalence of 16.9% in the whole group; this was, once again, not different from numbers reported in the general population. None of the patients receiving VPA monotherapy had polycystic ovaries, which were conversely found in 3 of 14 women receiving carbamazepine monotherapy (21.4%) and in 2 of 16 women receiving phenobarbital monotherapy (12.5%). However, the authors do not comment on this finding, while reporting that ‘polycystic ovaries were found in 40.0% of patients on AED polytherapy including VPA’. Since it is likely that polytherapy in most of these patients also included carbamazepine and/or phenobarbital, it is not clear why a ‘VPA effect’ should be implicitly suggested in this

group, considering that data on monotherapy patients show polycystic ovaries in all AED groups but not in the VPA group. However, if all VPA-treated patients (mono- and polytherapy) are considered, the prevalence of polycystic ovaries in these participants is 24%, which is not significantly different from patients not receiving VPA.

The prevalence of PCOS is not given nor are specific criteria for this diagnosis offered. However, information on this issue can be obtained from luteal phase hormonal data. Luteal progesterone values below 2 μg/L were found in 30 patients who were considered to be anovulating (in three of them, however, an LH surge suggested that ovulation, probably delayed, had occurred). The real significance of the blunted luteal progesterone values is difficult to ascertain, since it is obtained from a single determination, without information of cycle length and without other data on luteal function. The authors are aware of such inconsistencies, but suggest that because of the large number of patients studied this information may allow them to infer information on luteal function. However, 15 of these possibly anovulating 30 patients were reported as hyperandrogenic and were consequently considered to have hyperandrogenic anovulation. The prevalence of PCOS in the whole sample could consequently be estimated as 14.9%. The authors underline that most of these 15 patients (12 or 80%) received VPA, which supports the possibility of adverse effects of VPA on reproductive function. The prevalence of PCOS in VPA recipients could be estimated as 44.4% in this series.

Data detailed in tables show indeed a higher prevalence of impaired luteal function in VPA-treated women than in the other therapy groups. However, the prevalence of menstrual irregularities did not differ between the different therapy groups and hirsutism score (which is the only information on androgen status, since androgen levels are not provided) was actually highest in the carbamazepine group, followed by the 'polytherapy with VPA' group, the 'polytherapy without VPA' group and finally the VPA monotherapy group. The possibility that many of the hyperandrogenic anovulating VPA recipients may actually have received polytherapy with VPA and that a VPA effect might have been uncritically considered the cause of their disturbances despite the observation that the carbamazepine recipients seem to be the most hyperandrogenic, should be considered. Considering the high prevalence of polycystic ovaries and the high hirsutism score of patients receiving carbamazepine monotherapy, a clear account of the specific percentage of carbamazepine recipients in polytherapy groups should have been provided; however, this was only done for VPA recipients.

The possibility that a polytherapy confounding factor might have influenced the interpretation of results in this study is also suggested by the findings reported in the second study by this group. In the second study,[66] a similar clinical, hormonal and echographic investigation was performed in 65 women with epilepsy receiving monotherapy and in 20 controls. Participants were divided into three groups according to AED therapy (21 patients treated with VPA, 21 with phenobarbital and 23 with carbamazepine). Menstrual irregularities were observed in seven patients (10.8%), five of who received carbamazepine. Patients receiving VPA had a higher BMI, but no significant differences in hirsutism score or in polycystic ovary prevalence were noted. In fact, polycystic ovaries were observed in seven (10.8%) patients who were equally distributed among different therapy groups and, specifically, three in the carbamazepine group (13.0%), two in the VPA group (9.5%) and two in the phenobarbital group (9.5%). The comparison of mean hormonal values between the different groups showed a significantly higher FAI, and testosterone and androstenedione levels, in VPA-treated patients compared with the other patient groups and controls; however, the actual meaning of the difference in testosterone values between VPA and carbamazepine recipients is difficult to interpret – it is not necessarily due to abnormal elevation in VPA group, since testosterone levels in carbamazepine treated patients were lower than in controls, possibly because of the enzyme-inducing properties of carbamazepine. Luteal progesterone values below 4 μg/L were seen in

63.6% of VPA-treated patients; this percentage was significantly higher than that observed in carbamazepine- and phenobarbital-treated patients (23.0 and 23.8%, respectively). With the limitations suggested above, the low progesterone values in VPA recipients might be suggestive of impaired ovulation or corpus luteum dysfunction. Individual data or prevalence of abnormal hormonal findings in the different therapy groups are not presented. Since it is not possible to ascertain how many, if any, women were hyperandrogenic in the different therapy groups and if this finding, if present, was associated with menstrual irregularities, prevalence of PCOS in this study can not be evaluated.

Bauer et al.[67,69] have investigated the prevalence of PCOS in women with epilepsy in two different studies. The first one, which was published as a congress abstract,[67] describes the endocrine assessment in 23 females with epilepsy who had reported weight gain, with the aim of evaluating 'the frequency of PCOS in female obese patients with epilepsy'. 1990 NIH Conference criteria are employed for the diagnosis of PCOS; sex hormone and insulin levels are obtained, hirsutism and BMI are evaluated, and ovulation is investigated by means of basal body temperature and or progesterone levels. Since the inclusion criterion is obesity, it is quite surprising to discover that only 69.5% of patients have a BMI >25. No detail is given of androgen levels; seven patients (30.4%) had menstrual irregularities (including anovulatory cycles in two) and 12 (52.2%) had hirsutism. However, these findings were apparently associated only in two women (8.7%) who were considered to fulfil the diagnostic criteria for PCOS. Both received VPA as co-medication with nonenzyme-inducing AEDs; consequently, PCOS, diagnosed according to 1990 NIH Conference criteria as hyperandrogenic anovulation, was found in 2 of 11 (18.2%) epileptic women treated with VPA as mono- or polytherapy, and in none of the remaining 12 patients whose treatment did not include VPA. However, this population of patients was apparently pre-selected because of obesity and consequently these prevalence data can not be compared with data from other reports in which unselected patient series were described.

The second study from this group[69] investigated 93 women with temporal lobe epilepsy; 19 of them were drug free, 18 received VPA monotherapy, 20 carbamazepine monotherapy and 36 polytherapy which included VPA in 16. Hirsutism and BMI were evaluated, and menstrual cyclicity was followed up for 6 months. Sex hormone levels were evaluated, apparently in the follicular and luteal phase, but information on ovulation is not given. The authors discuss diagnostic criteria for PCOS in the introductory section of their report, and positively comment on 1990 NIH Conference criteria of 'ovulatory dysfunction with clinical evidence of hyperandrogenism and/or hyperandrogenaemia and exclusion of related disorders, such as those affecting adrenal or thyroid function'. However, the criteria used for diagnosing PCOS in their report are slightly different from 1990 NIH Conference criteria, and may actually result in an underestimation of affected patients. In fact, the authors diagnose PCOS in patients presenting with 'a combination of raised testosterone and oligomenorrhoea or amenorrhoea'. This leaves out all women in who other androgens, but not necessarily testosterone, may be raised (elevation of androstenedione, in particular, is quite frequent in patients with PCOS) and all hirsute patients with normal androgen levels, who also should be included in the diagnosis.

The report from Fox et al.,[145] quoted by the authors to support the appropriateness of their diagnostic criteria, actually discusses the predictive power of tests in the diagnosis of PCOS: diagnostic accuracy of testosterone evaluation in patients with functional oligo-amenorrhoea is reported as being100% for a positive test and 49% for a negative test, with an overall diagnostic accuracy of 71%. In the same report, androstenedione and FAI have a higher overall diagnostic accuracy (74 and 94%, respectively). Surely in a prevalence study the diagnostic accuracy of both positive and negative tests is equally important, and the best overall accuracy should be aimed for when establishing the diagnos-

tic criteria. The results of this study are consequently prone to the risk of underestimation.

The authors report irregular cycles in 35.5% of participants, with an even distribution across the different therapy groups. Specifically, irregular cycles were observed in 29.4% of the 34 treated patients whose regimen included VPA, in 37.5% of the 40 treated patients whose regimen did not include VPA, and in 42.1% of the 19 untreated patients. Individual androgen levels are not reported; the authors state that when the finding of irregular menstruation was coupled with elevated testosterone levels, a diagnosis of PCOS was made in six patients, giving a prevalence of 6.5% in the whole group. The distribution of patients with PCOS according to therapy showed once again no significant differences between groups. Two patients with PCOS were untreated (10.5% prevalence). Of the four treated patients with PCOS, two were receiving VPA monotherapy and two were receiving carbamazepine monotherapy. Consequently, the prevalence of PCOS in monotherapy groups was 11.1% for VPA and 10.0% for carbamazepine. These figures are not significantly different from prevalence reported in the general population, and consequently the association of PCOS with epilepsy and with VPA use is not confirmed in this report, in agreement with that reported by Stephen et al.;[77] however, underestimation of diagnosis might lead to exclusion of some patients with PCOS.

However, an interesting finding in this report is the high prevalence of hyperinsulinaemic women which is not commented on. Thirty patients (32.3%) had raised insulin levels, which in three patients is associated with PCOS. No explanation is offered for the hyperinsulinaemia of the remaining 27 patients, of whom only eight were obese. A 20.4% prevalence (19 of 93) of nonobese, hyperinsulinaemic, non-PCOS women can consequently be observed in this sample of epileptic patients, which seems to be quite unusual and to deserve further diagnostic investigations. It would be interesting to know if any of these women were hirsute or if they had elevated androstenedione and/or DHEAS levels, and to have information about their ovulatory status. Unfortunately, no information about therapy status of the hyperinsulinaemic patients is given and, consequently it is not possible to ascertain if this condition was related to VPA use as suggested by Isojarvi and co-workers.

Luef et al.[79] also present a detailed report which follows a congress presentation,[68] of an interesting study. A total of 45 patients agreed to enter the study from an initial sample of 104 random patients fulfilling the selection criteria but a complete evaluation was obtained only in 43. Menstrual history, BMI, hirsutism and virilisation were evaluated; data about sex hormones, insulin, glucose and lipid profile, and echographic ovarian findings were collected. Women were divided in two groups according to AED therapy: the first group included 22 women with IGE and treated with VPA, and the second (control) group included 21 women receiving carbamazepine (15), lamotrigine (5) or primidone (1); most of them (19) had partial epilepsy. Menstrual irregularities were observed in 12 patients (27.9%), of whom five (22.7%) received VPA and seven were in the 'control group' (33.3%). Polycystic ovaries were observed in 11 (25.6%) women with a distribution of five in the VPA group (22.7%) and six in the carbamazepine/lamotrigine/primidone group (28.6%). Finally, hirsutism was observed in four women (9.3%), three of whom were in the VPA group (13.6%) and one was in the 'control group' (4.8%). No individual data on laboratory hyperandrogenism are given but mean DHEAS levels were elevated in VPA recipients (androstenedione was not evaluated). The association of menstrual disturbances and polycystic ovaries (six patients) was similar in both groups (13.6% in VPA and 14.3% in the 'control group'). A final diagnosis of PCOS, based on 1990 NIH Conference criteria, was obtained only in three participants (7.0%), two (9.1%) VPA recipients and one (4.8%) from the 'control group'. No significant differences in weight parameters were observed between VPA recipients and controls. Glucose metabolism parameters (glucose, insulin, pro-insulin and C-peptide) did not differ between the two groups when examined in the fasting state, but postprandial pro-insulin and C-peptide

levels were higher in the VPA group. Finally, VPA recipients had lower levels of total and low-density lipoprotein (LDL) cholesterol than the control group. A further subanalysis of patients showed that VPA recipients with polycystic ovaries had higher testosterone levels and higher BMI than 'control' patients with polycystic ovaries, but the small numbers of patients involved in these analyses warrant caution in the interpretation of these data, as suggested by the authors themselves.

Once again, while menstrual disturbances and polycystic ovaries are randomly distributed within different AED treatment groups, and their prevalence is (slightly) higher than that described in the general population, PCOS prevalence is higher among VPA recipients than patients receiving enzyme-inducing AEDs or with lamotrigine, even if the difference is not statistically significant. Also in this series, similarly to the studies by Stephens and Bauer, the observed frequency of PCOS (diagnosed with 1990 NIH Conference criteria) is within the range reported in the general population, both in the global group of epileptic women and in the subset of patients treated with VPA. In this report there is no evaluation of androstenedione, so it is possible that hyperandrogenic patients may have been missed the correct diagnosis with underestimation of the prevalence of PCOS. Apart from PCOS prevalence, VPA treated patients differed from 'control' patients only in DHEAS levels; no differences in BMI and glucose metabolism were observed, at least in the fasting state, and total and LDL cholesterol levels were actually lower than in patients treated with other AEDs.

This group has recently presented additional data in a more consistent sample of patients, published in full[80] after a congress presentation;[75] it is not clear if this included some of the patients described in the previous report.[79] In the most recent study,[80] a sample of 105 patients was investigated, 52 of whom were treated with VPA and 53 with carbamazepine. Also in this report all VPA recipients had IGE while most of carbamazepine recipients had partial epilepsy. A clinical endocrinological and gynaecological assessment was conducted, with evaluation of menstrual function, bodyweight and hirsutism; glucose and lipid metabolism were studied, and ovarian echography was performed. Hormonal data were not evaluated in this study. Menstrual disturbances (oligomenorrhoea or, more rarely, amenorrhoea) were found in 29 (27.6%) patients and, specifically, in 12 of 52 VPA recipients (23.1%) and 17 of 53 carbamazepine recipients (32.1%). Polycystic ovaries were found in 28 patients (26.7%), of whom 13 received VPA (25.0%) and 15 received carbamazepine (28.3%). Hirsutism was observed in four patients (3.8%), three of whom received VPA (5.8%) and one received carbamazepine (1.9%).

Since no information is given on androgen data or about the possible association of hirsutism with menstrual disturbances, it is not possible to ascertain the prevalence of PCOS according to 1990 NIH Conference criteria. However, the authors seem to imply that PCOS may be considered in patients with both polycystic ovaries and menstrual disturbances, and report this association in eight women (7.6%), including four treated with VPA (7.7%) and four with carbamazepine (7.5%). VPA-treated women had a significantly higher BMI than carbamazepine treated-women, but the authors seem to be quite critical on this finding, since they underline that nearly as many patients treated with carbamazepine tended to be obese. Similarly to the previous study, no differences in fasting glucose and insulin metabolism were observed between the two groups, and total and LDL cholesterol levels were significantly higher in carbamazepine recipients than VPA recipients.

In conclusion, this study reports a prevalence of polycystic ovaries in epileptic women that is similar to or only slightly higher than the general population, without any apparent relationship with AED therapy. Regrettably, it is not possible to evaluate the prevalence of PCOS, since the criteria employed by the authors do not include clinical or laboratory hyperandrogenism. In contrast to Isojarvi's data, VPA-treated patients in this series do not have an increased frequency of menstrual disturbances, polycystic ovaries or a combination of these two

parameters. In addition, hirsutism is more common in VPA recipients but not significantly; insulin levels do not differ between treatment groups and cholesterol levels are actually lower in the VPA group.

In a recent short report presented as a 'letter to editor', Chakravarti[81] describes a 35% prevalence of 'definite/probable' PCOS in a sample of 14 epileptic patients treated with VPA. All patients had undergone pelvic ultrasound examination; no details on clinical data are given and apparently no hormonal study was carried out. The diagnosis of PCOS seems to be based on the association of cystic changes in the ovaries – not necessarily fulfilling the criteria for polycystic ovaries – with unspecified 'clinical stigmata'. No control group is present and, consequently, it is not possible to compare findings obtained in VPA-treated patients with those obtained in patients receiving other therapy. These data must be interpreted with extreme caution and at the present time no significant conclusions can be drawn from this report.

5. Polycystic Ovary Syndrome in Non-Epileptic Women Treated with VPA: Settling the Controversy?

Of value in settling the issue about the pathogenic mechanisms of reproductive endocrine disturbances in women with epilepsy, i.e. whether the seizure disorder or therapy with VPA should be considered as primarily responsible for these problems, may come from researchers who have examined the problem in a different context. Besides being an effective drug in the treatment of epilepsy, VPA is also used by psychiatrists for treatment of bipolar disorder. Several reports suggest that the use of VPA in such patients appears to be increasing and that this medication is becoming a widespread treatment for these conditions, both in the acute treatment and in long-term use, in adult and in child/adolescent populations.[35] The report of possible adverse effects of such treatment on the reproductive health of epileptic female patients has caused a debate among psychiatrists, with some authors expressing concern about the possible risks of VPA use in women and suggesting caution in its use, especially in young patients,[28,33,35,37] and others underlining the lack of specific evidence of such risks in the psychiatric population.[30,31,36]

Currently, there are a very limited number of reported studies of female patients receiving VPA for psychiatric disturbances investigated for reproductive endocrine function. Rasgon et al.[83] have recently reported preliminary data of a study of 22 women with bipolar disorders. Ten patients were treated with lithium, ten with VPA and two were co-medicated with both lithium and VPA. No lithium recipients had been treated with VPA in the past. Menstrual history was obtained and physical examination with evaluation of hirsutism and BMI was performed in all patients. Menorrhagia and dysmenorrhoea were included in the definition of menstrual disturbances. Hormonal screening for assessment of total testosterone, free testosterone, estradiol, estrone, LH, FSH, DHEA and DHEAS was performed in 19 patients, as three (one from each therapy group) refused the blood draw; one of them (from the co-medicated group) also refused the pelvic scan, which was consequently performed only in 21 patients.

Results showed a high prevalence of menstrual disturbances in all therapy groups, with 20% oligomenorrhoea and 10% amenorrhoea in the lithium group, 30% oligomenorrhoea and 20% amenorrhoea in the VPA group, and one amenorrhoeic patient in the co-medicated group. However, in all patients amenorrhoea preceded the use of mood stabilisers, and only one oligomenorrhoeic woman (treated with VPA) reported the onset of this disturbance after the use of the mood stabiliser. The authors stress that the high incidence of menstrual disturbances in this series may derive from a selection bias, with women with menstrual problems preferentially electing to participate (26% of the eligible sample population declined to enter the study). No patient was hirsute and apparently none was hyperandrogenic - no individual data for androgens are given, but mean androgen values always fall in the normal range and the authors, who apparently use 1990 NIH Conference criteria, state that no

patient met diagnostic criteria for PCOS. Fifty percent of VPA-treated patients versus 30% of lithium patients were obese; all mean hormonal values were within the normal ranges and did not significantly differ between groups. Only one patient, treated with lithium, had polycystic ovaries. Although these preliminary results are severely limited by the small sample size, they suggest that long-term use of VPA in non-epileptic patients is not accompanied by hyperandrogenic anovulation. Despite the high prevalence of menstrual irregularities in this sample, possibly due to a selection bias, no patient meets the criteria for PCOS; this is, as the authors suggest, even more reassuring as far as the possible risks of VPA use are concerned. Isolated hyperandrogenism or isolated polycystic ovaries are not encountered.

Another study in psychiatric patients, first presented as a congress abstract[82] and successively as a full report,[85] describes the results of a survey on self-reported menstrual abnormalities and clinical hyperandrogenism in women with bipolar mood disorders treated either with VPA or with other mood stabilisers/no treatment; a more detailed evaluation is performed only in VPA patients with menstrual problems. Several shortcomings warrant caution in the interpretation of results from this interesting report. To begin with, there are several differences between the results displayed in the congress presentation and those given in the full report, up to the point that the conclusions are completely contrasting. This might be due to changes in the studied population: it is conceivable that some of the patients originally included in the preliminary study and reported in the congress abstract may have been successively excluded because of a more restrictive selection in the final study, since the population of eligible patients decreases from 35 in the preliminary report to 32 in the final one. However, the loss of three patients does not seem to be the only reason for the contrasting conclusions between the two reports, and it is possible that the composition of groups was relevantly changed in the final report, even if this is not indicated anywhere, despite the fact that the preliminary presentation of data as a congress poster is clearly mentioned in the final report.

All this considered, we discuss in detail only data coming from the full report, which conveys the most detailed information. In this report, a questionnaire regarding medical history, menstrual history and possible occurrence of hirsutism, acne or lactation was sent to 140 women meeting the criteria for bipolar disorder. Of the 60 patients who returned the completed questionnaire, 32 were considered eligible for the study, and their data analysed. This sample included 17 women receiving VPA (eight of whom also received other psychiatric medications) and 15 women not receiving VPA (ten received other medications, and five were drug free). A control group of 22 healthy volunteers was also investigated. Self-reported menstrual abnormalities (including amenorrhoea, oligomenorrhoea, prolonged or irregular menstrual cycles) were considered 'current' if they were present at the time of the questionnaire and had been present for at least 6 months, and 'lifetime' if they were either current or had been present in the past, i.e. more than 6 months before the completion of the questionnaire.

Current menstrual abnormalities were significantly more often reported in the VPA group (8/17; 47%) than in the non-VPA (2/15; 13%) and than in the control group (0%); when lifetime abnormalities were considered, however, no significant difference could be observed between the occurrence of menstrual abnormalities in VPA recipients (13/17; 76%) and in non-VPA recipients (9/15; 60%), while both groups showed a significantly higher occurrence than controls (6/22; 27%). The authors explain the different results obtained in current and lifetime menstrual abnormalities on the basis that five of the women in the non-VPA group had been taking VPA in the past, and that consequently past menstrual abnormalities (which were reported by four of these five women) could be actually be related to the use of VPA. To prove their point, they put together VPA-treated women (17 patients) and non-VPA-treated women who had received VPA in the past (five patients), comparing lifelong menstrual abnormalities in this group ('past/present VPA' group, 22

patients) to those found in the 10 non-VPA-treated women who had never received VPA in the past ('never VPA' group). In this way, lifelong menstrual abnormalities appear significantly more frequent in the past/present VPA group (17/22; 77%) than in the 'never VPA' group (5/10; 50%).

However, this explanation is far from being convincing. Clearly, in order to attribute menstrual abnormalities observed in the past to previous use of VPA, some kind of temporal relationship between the use of the drug and the occurrence of the abnormalities should be depicted. The authors comment on this point underlining that, of 17 'past/present VPA' women who reported menstrual abnormalities, 10 (59%) reported the onset of such problems after starting VPA. This obviously means that in the remaining seven patients menstrual abnormalities were temporally unrelated to the use of VPA. Consequently, when evaluating lifelong menstrual abnormalities, if the presentation of results had also considered the temporal association, the reader should have been told that of 22 patients who currently receive or had received VPA, ten (45%) reported menstrual abnormalities after the use of this drug, which is not significantly different from what observed in the 'never-VPA' group, in which 50% of women reported such problems. It is possible that, if the temporal association between VPA therapy and menstrual disturbances had also been taken into consideration for the analysis of current menstrual abnormalities, different results might have been observed.

Hirsutism (by self-evaluation) was seen in 4/17 (24%) VPA recipients, 2/15 (13%) non-VPA recipients and 2/22 (9%) controls. The authors do not perform a chi-square analysis due to the small number (<5) in some subgroups, and only comment about a trend for more women in the VPA group presenting with this problem. However, if the Fisher test is performed (as customary with small subgroups), no statistical difference is observed between these three groups. Moreover, if the temporal association between hirsutism and VPA use is taken into consideration, only two of the four VPA recipients who reported hirsutism observed the onset of this phenomenon after VPA use.

After evaluation of the completed questionnaire, a more detailed study was proposed to women who had been receiving VPA for at least 6 months, did not receive other medications and had current menstrual abnormalities. Eight patients met these criteria and seven of them volunteered to participate. In these patients, a clinical assessment for features of hyperandrogenism was carried out, hormonal and lipid profiles were evaluated, and a transvaginal ovarian scan was performed. Hirsutism was seen in five patients, two of whom reported that this problem had started after VPA use. All the seven patients had laboratory hyperandrogenism and five had polycystic ovaries. In conclusion, all these seven women had PCOS according to 1990 NIH Conference criteria, and the authors consequently conclude that at least 41% of the 17 women with bipolar disorders receiving VPA had PCOS. While this is true, the pathogenic relationship between the endocrinological disturbance and the use of VPA remains to be proved, since the authors themselves underline that a temporal association between VPA use and clinical disturbances is not present in all patients. The high prevalence of hyperandrogenism and polycystic ovaries in bipolar VPA users is surprising, considering the contrast with data coming from the report of Rasgon et al.[83] However, since in the present study no comparison is possible on this point with non-VPA bipolar patients, who were not submitted to the examination study, it is not possible to know if the high prevalence of these features is actually related to VPA use or might be found also in the remaining bipolar patients, possibly depending on demographic factors in this specific sample.

VPA effects in psychiatric patients were also examined in a study reported as a congress abstract by McIntyre et al.,[84] in which 38 bipolar female patients were examined with regard to menstrual history and hormonal assessment. Menstrual irregularities were significantly more frequent in VPA recipients (50%) than lithium recipients (15%); hyperandrogenism was also apparently more represented in VPA-treated women. From the abstract it

is not possible to learn how many VPA recipients presented with the association of menstrual irregularities and hyperandrogenism, and consequently how many had PCOS.

Finally, several authors[38,146] report unpublished data from Sachs (November 2001) whose retrospective review of charts from 189 bipolar women (106 treated with VPA) found a 0% prevalence of PCOS. No comment is possible on this issue since we have no access to these data and it is not possible to know what parameters were used to evaluate the prevalence of PCOS.

At the present time the evidence coming from a psychiatric female population using VPA is insufficient to allow any definite conclusion. Contradictory results may depend on methodological problems and/or on the small size of patient samples. Further studies describing the investigation of these patients will be extremely useful in clarifying the possible risks of VPA use in female patients. Women with bipolar illness, like women with epilepsy, are likely to be treated for long periods of time, often encompassing most of their reproductive life. The possibility of evaluating the endocrine effects of the same drug without the confounding effects due to the specific pathophysiological characteristics of the disease will probably be of great help.

6. Conclusions

In spite of the large amount of data reporting endocrine assessment in women with epilepsy, a clear picture does not emerge (tables II and III). While the differences in the prevalence of PCOS (which ranges from 6.5[69] to 27.8%[21]) may be attributed to the different diagnostic criteria employed for the diagnosis, the wide variability of findings such as menstrual irregularities or androgen levels is more difficult to explain.

There is no doubt that methodological problems do play a relevant role (table IV). Collection of menstrual history from patients may give quite different results in patients keeping menstrual diaries or in patients just recalling their menstrual pattern without a written record. Prospective study of patients with direct recording of menstrual cyclicity over time surely gives the best results; however, the time period in which menstrual patterns are studied may also be relevant, that is, the longer the period of observation, the more accurate the results will be. Definition of menstrual irregularities is not given in all studies, and may vary between different series so that results are actually not comparable. Ovulation patterns, which are investigated in some studies,[63,66,75,120] surely give a better picture of reproductive function than menstrual patterns but accuracy in their evaluation is critical – a single luteal progesterone sample is of very limited value in ascertaining ovulation and this method may in fact give rise to questionable results as observed in the series from Murialdo et al.[66] in which the prevalence of 'anovulating' subjects is strikingly higher than the prevalence of menstrual irregularities (35.4 vs10.8%). Definition of hyperandrogenism varies from series to series, since the complete androgen pattern is not evaluated in all reports and some authors only evaluate total testosterone levels, which are not as accurate as free testosterone levels or FAI in the assessment of hyperandrogenism.[88] Finally, the remarkable variability in the prevalence of polycystic ovaries (ranging from 10.8[66] to 46.1%[71] in reports employing ultrasonography) may surely be related to problems in methodology. Even if the definition of polycystic changes is presently quite standardised due to the wide use of criteria of Adams et al.,[92] the full interpretation of an ovarian scan requires a great deal of experience, as underlined elsewhere,[53] and the use of transabdominal or transvaginal scanning may have different degrees of accuracy. Consequently, appropriate 'gold standards' as those identified in authoritative guidelines[147] should be followed during performance and interpretation of ovarian ultrasound examinations. Recently, MRI scanning of the pelvis has been proposed as a more accurate, even if more expensive, diagnostic tool for evaluation of polycystic ovaries.[148,149] So far, only Betts and coworkers[53,70,73] have employed MRI in the evaluation of ovaries of women with epilepsy: the fact that their series presents the highest prevalence of polycystic ovaries in epileptic women (59 vs 5% in controls) is surely dependant on this, even if the fact

Table II. Prevalence data on endocrine dysfunction from different series of patients with epilepsy[a]

Study	Patients (n)	MD (%)	HA (%)	PCO (%)	PCOS (%)	Authors' criteria for PCOS	'1990 NIH conference' PCOS (%)	Comments
Herzog et al.[1] (only TLE)	20	NA	NA	NA	25.0	1990 NIH conference	15.0	Hyperprolactinemia not ruled out in 2 galattorrhoic patients
Herzog et al.[2] (only TLE)	50	56.0	28.0	6.0[b]	20.0	1990 NIH conference	20.0	
Bilo et al.[3] (only IGE)	20	30.0	15.0	15.0	15.0	1990 NIH conference	15.0	
Bilo et al.[120]	50	36.0	26.0	32.0	26.0	1990 NIH conference	26.0	
Isojarvi et al.[21]	72	36.1	22.2	38.9	27.8	HA and/or PCO + MD	12.5	Overestimation of PCOS (inclusion of normoandrogenic patients)
Murialdo et al.[63]	101	21.8 MD 29.7 AN	NA	16.9[c]	14.9	1990 NIH conference	14.9	Diagnosis of anovulation based on single progesterone luteal samples
Murialdo et al.[66]	65	10.8 MD 35.4 AN	NA	10.8	NA	NA	NA	Diagnosis of anovulation based on single progesterone luteal samples
Betts et al.[53,73] (only IGE)	56	NA	NA	39.0 59.0[d]	16.1	Elevated LH and/or T + PCO	NA	Both underestimation and overestimation of PCOS are possible
Khatami et al.[71]	26	NA	NA	46.1[e]	19.2	NA	NA	
Stephen et al.[77]	44	27.3	4.5	NA	9.1	HA and/or HI + MD	2.3	Possible underestimation of PCOS
Bauer et al.[69] (only TLE)	93	35.5	NA	NA	6.5	MD + elevated T	NA	Possible underestimation of PCOS
Luef et al.[79]	43	27.9	8.9[f]	25.6	7.0	1990 NIH conference	NA	Possible underestimation of PCOS
Luef et al.[80]	105	27.6	3.8[f]	26.7	7.6	MD + PCO	NA	Both underestimation and overestimation of PCOS are possible

a Reports by Isojarvi et al.,[7] 1993 and Isojarvi et al.,[8] 1996 are not included in this table because most data come from patients specifically selected because of menstrual irregularities. Reports by Isojarvi et al.,[9] 1997 and Lofgren et al.,[22] 2001 are not included because a diagnosis of PCOS is not possible from reported data.

b It is not possible to ascertain if all patients were submitted to ovarian scan.

c On 83 patients.

d 39.0% are isolated PCO as given in Betts et al.[73] 2001; 59.0% is the total number of PCO, including both isolated PCO and PCO associated to hormone abnormalities, as given in Betts et al.,[53] 2001. Ovaries are evaluated by MRI.

e Isolated PCO.

f Only data on hirsutism are given.

AN = anovulation; **HA** = hyperandrogenism; **HI** = hyperinsulinaemia; **IGE** = idiopathic generalised epilepsy; **LH** = luteinising hormone; **MD** = menstrual dysfunction; **MRI** = magnetic resonance imaging; **NA** = not available; **NIH** = US National Institutes of Health; **PCO** = polycystic ovaries; **PCOS** = polycystic ovarian syndrome; **T** = testosterone; **TLE** = temporal lobe epilepsy.

Table III. Prevalence data on endocrine function from different series of patients, divided by AED therapy[a]

Treatment	Patients (n)			MD (%)			HA (%)			PCO (%)			PCOS (%)			'1990 NIH Conference' PCOS (%)		
	total	mono	poly	total	mono	poly	total	mono	poly	total	mono	poly	total	mono	poly	total	mono	poly
Bilo et al.[3]																		
VPA	11	2	9	27.3	0	33.3	9.1	0	11.1	9.1	0	11.1	9.1	0	11.1	9.1	0	11.1
Mono PB and drug free	9			33.3			22.2			22.2			22.2			22.2		
Bilo et al.[120]																		
VPA	13	3	10	38.5	NA	NA	23.1	NA	NA	38.5	NA	NA	23.1	NA	NA	23.1	NA	NA
Other AEDs and poly w/o VPA	21			42.8			28.6			28.6			23.8			23.8		
Drug free	16			25.0			25.0			31.2			31.2			31.2		
Isojarvi et al.[21]																		
VPA		37			59.5			27.0			62.2			48.6			21.6	
Mono CBZ		35			11.4			17.1			14.3			5.7			2.9	
Murialdo et al.[63]																		
VPA	27	11	16	29.6	NA	NA	NA	NA	NA	24.0[b]	0	40.0	44.4	NA	NA	44.4	NA	NA
Mono CBZ		20			NA			NA			21.4			NA			NA	
Mono PB		16			NA			NA			12.5			NA			NA	
Other AEDs and poly w/o VPA	38			18.9[c]			NA			10.7			NA			NA		
Murialdo et al.[66]																		
VPA		21			0–9.5 as MD[d] 63.6 as AN			NA			9.5			NA			NA	
Mono CBZ		23			21.7 as MD; 23.0 as AN			NA			13.0			NA			NA	
Mono PB		21			0–9.5 as MD[e]; 23.8 as AN			NA			9.5			NA			NA	
Betts et al.[53,73] **(only IGE)**																		
VPA		32			NA			NA			35.0[f]			28.0			NA	
Mono CBZ or LTG	24			NA			NA			45.0[f]			0			NA		

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Table III. Contd

Treatment	Patients (n)			MD (%)			HA (%)			PCO (%)			PCOS (%)			'1990 NIH Conference' PCOS (%)		
	total	mono	poly	total	mono	poly	total	mono	poly	total	mono	poly	total	mono	poly	total	mono	poly
Khatami et al.[71]																		
VPA		15			NA			NA			46.7[f]			26.7			NA	
Mono CBZ		6			NA			NA			66.7			16.7			NA	
Mono LTG		5			NA			NA			20.0			0			NA	
Stephen et al.[77]																		
VPA		23			21.7			8.7			NA			17.3			4.3	
Mono LTG		21			33.3			0			NA			0			NA	
Bauer et al.[69] **(only TLE)**																		
VPA	34	18	16	29.4	NA	NA	NA	NA	NA	NA	NA	NA	5.9	11.1	0	NA	NA	NA
Mono CBZ		20						NA			NA			10.0			NA	
Poly w/o VPA	20			37.5[g]			NA			NA			0			NA		
Drug free	19			42.1			NA			NA			10.5			NA		
Luef et al.[79]																		
VPA		22			22.7			13.6[h]			22.7			9.1			NA	
Mono CBZ or LTG or PRI	21			33.3			4.8[h]			28.6			4.8			NA		
Luef et al.[80]																		
VPA		52			23.1			5.8[h]			25.0			7.7			NA	
Mono CBZ		53			32.1			1.9[h]			28.3			7.5			NA	

a Reports from Herzog et al.[1] 1984, and Herzog et al.[2] 1986, are not included in this table because individual data on AED therapy are not given.

b Ovarian scan performed on 25 on 27 VPA patients.

c This prevalence value includes also patients on CBZ monotherapy and patients on PB monotherapy.

d A range is given since, in absence of numeric data, we only know that VPA patients with menstrual irregularities may be a minimum of 0 or a maximum of 2.

e A range is given since, in absence of numeric data, we only know that PB patients with menstrual irregularities may be a minimum of 0 or a maximum of 2.

f Isolated PCO.

g This includes also patients from mono CBZ group.

h Only data on hirsutism are given.

AED = antiepileptic drug; **AN** = anovulation; **CBZ** = carbamazepine; **HA** = hyperandrogenism; **IGE** = idiopathic generalised epilepsy; **LTG** = lamotrigine; **MD** = menstrual dysfunctions; **mono** = monotherapy; **NA** = not available; **NIH** = US National Institute of Health; **PB** = phenobarbital; **PCO** = polycystic ovaries; **PCOS** = polycystic ovarian syndrome; **poly** = polytherapy; **PRI** = primidone; **TLE** = temporal lobe epilepsy; **VPA** = valproate (valproic acid); **w/o** = without.

Table IV. Materials and methods used in different series investigating endocrine dysfunction in patients with epilepsy

Study	Materials			Methods				
	patient selection	epilepsy type	AED therapy	menstrual history: collection of data	menstrual irregularities: definition of irregular cycles	androgen profile	free androgens	ovarian evaluation
Herzog et al.[1]	Consecutive	PE (TLE)	Untreated and treated (treatment not specified)	NS	NS	T	Free T	NA
Herzog et al.[2]	Consecutive	PE (TLE)	Untreated and treated (treatment not specified): separate evaluation of results	NS	a) Amenorrhoea (no menses >6m) b) Oligomenorrhoea (<8 periods/y) c) Frequently prolonged (>32d) cycles d) Frequently shortened (<26d) cycles	T, DHEAS	Free T	US or laparoscopic[a]
Bilo et al.[3]	Random	IGE	Untreated, mono and poly	NS	a) Amenorrhoea (undefined) b) Oligomenorrhoea >40d c) Polymenorrhoea <24d	T in all participants; A and DHEAS only in pts with menstrual irregularities	NP	Transabdominal US
Bilo et al.[120]	Consecutive	IGE (50.0%) and PE (50.0%): separate evaluation of results	Untreated, mono and poly: separate evaluation of results for untreated, treated w VPA, treated w/o VPA	Retrospective (from charts?) for 3m and prospective for 1 or 2m	Regular cycles defined as 21–35d with no more than 4d variation from cycle to cycle	T, A, DHEAS	NP	Transabdominal US
Isojarvi et al.[21]	NS	IGE (45.8%) and PE (54.2%)	VPA mono and CBZ mono: separate evaluation of results	Retrospective (from charts?) for 6m	a) Amenorrhoea (no menses 6m) b) Oligomenorrhoea (>35d) c) Irregular cycles (cycle interval varying >4d)	T, SHBG	FAI	Transvaginal US
Murialdo et al.[63]	Consecutive	IGE (35.6%) and PE (64.4%): separate evaluation of results	Mono and poly: separate evaluation for mono groups, poly w VPA and poly w/o VPA	NS	a) Amenorrhoea (no menses >6m) b) Oligomenorrhoea (>35d) c) Polymenorrhoea (>21d)	T, A, SHBG	NP	Transabdominal US

Continued next page

Table IV. Contd

Study	Materials			Methods				
	patient selection	epilepsy type	AED therapy	menstrual history: collection of data	menstrual irregularities: definition of irregular cycles	androgen profile	free androgens	ovarian evaluation
Murialdo et al.[66]	NS	IGE (44.6%), PE (52.3%) and undetermined (3.1%)	VPA mono, CBZ mono, PB mono: separate evaluation of results	NS	Oligomenorrhoea >35d	T, A, DHEAS, SHBG	FAI	Transabdominal US
Betts et al.[53,73]	Consecutive?	IGE	VPA mono, CBZ mono, LTG mono: separate evaluation of results for VPA group and CBZ/LTG group. All patients had only ever taken 1 AED	NA	NA	T	NA	MRI
Khatami et al.[71]	Consecutive	NA	NA	NA	NA	NA	Free T	Transvaginal US
Stephen et al.[77]	NS	IGE and PE (proportions in female patients not specified)	VPA mono and LTG mono: separate evaluation of results	(Retrospective?) written record for 6m	a) >35d b) Varying from <35 to >35d c) 22–35d but varying >4d	T, DHEA, A, SHBG	FAI	NP
Bauer et al.[69]	NS	PE (TLE)	Untreated, mono and poly: separate evaluation for untreated, mono groups, poly w VPA and poly w/o VPA	Prospective follow up for 6m	a) Amenorrhoea (undefined) b) Oligomenorrhoea >35d	T, DHEAS, A[b]	NP	NP
Luef et al.[79]	Random	IGE (55.8%) and PE (44.2%)	VPA mono, CBZ mono, LTG mono and PRI mono: separate evaluation for VPA group and CBZ/LTG/PRI group	NA	a) Amenorrhoea (undefined) b) Oligomenorrhoea (undefined)	T, DHEAS, SHBG	NP	Transvaginal or transabdominal US
Luef et al.[80]	Consecutive	IGE (61.9%) and PE (38.1%)	VPA mono and CBZ mono: separate evaluation of results	NS	a) Amenorrhoea (undefined) b) Oligomenorrhoea (undefined) c) Other (undefined)	NP	NP	Transvaginal or transabdominal US

a Not performed in all participants.

b Only T elevations considered for diagnosis of PCOS.

A = androstenedione; **AED** = antiepileptic drug; **CBZ** = carbamazepine; **DHEAS** = dehydroepiandrosterone; **FAI** = free androgen index; **IGE** = idiopathic generalised epilepsy; **LTG** = lamotrigine; **mono** = monotherapy; **MRI** = magnetic resonance imaging; **NA** = not available; **NP** = not performed; **NS** = not specified; **PB** = phenobarbital; **PCOS** = polycystic ovarian syndrome; **PE** = partial epilepsy; **poly** = polytherapy; **PRI** = primidone; **SHBG** = sex hormone binding protein; **T** = testosterone; **TLE** = temporal lobe epilepsy; **US** = ultrasonography; **VPA** = valproate (valproic acid); **w** = with; **w/o** = without.

that they only report women with IGE may be a confounding factor.

A wide variability may also be observed in the characteristics of the patient series investigated in the different studies. In only some of the studies were patients enrolled consecutively, while this is probably the best way to avoid selection bias in a prevalence study. Patient groups in different reports differ widely as to the percentage of participants with different epilepsy types or different AED therapy; most authors do evaluate results separately according to therapy groups but not according to epilepsy types, which might also be a relevant factor in influencing the endocrine status. For example, there is evidence suggesting that in TLE with unilateral focus the laterality of EEG epileptiform discharges might influence the altered patterns of reproductive hormonal secretion from the hypothalamus, so that left-sided TLE would be associated with PCOS and right-sided TLE with hypothalamic amenorrhoea.[150] Moreover, because of the concern about possible adverse effects of VPA on reproductive health, patients on AED polytherapy are usually divided into subgroups depending on the presence or absence of VPA in their therapeutic regimen; this choice may lead to other possible problems induced by other AEDs, whose respective influence on the endocrine status is not investigated, being overlooked. Duration of therapy regimens, age at which therapy was started, type of AEDs used in the past, epilepsy severity and location of seizure focus, are all factors that may have a relevant influence on reproductive endocrine status and that vary greatly between patients within the same series and between different series. Personal characteristics of patients, like those related to ethnicity and bodyweight, and their different proportion within subgroups, might also influence the results. Finally, the small size of most patient series, especially when divided in subgroups, is a critical factor. This point has been specifically underlined in other review articles dealing with this issue,[60] which stressed how the relatively small size of patient samples permitted chance observations and selection bias to exert substantial effects, while other authors[57] estimated that, considering the relatively low frequencies of PCOS in women with epilepsy and in the general population, a sample size of 88–160 in each group of epileptic patients and controls would be optimal to demonstrate a significant difference between the two, but that much larger samples would be necessary to take into consideration all the epilepsy-related and therapy-related variables.

All this considered, the inconsistency of results in the different series is not surprising. Some of the problems will hopefully be taken care of in future studies, since authors are becoming increasingly aware of the need for prospective studies to be carried out in large series of patients recruited consecutively, and possibly only ever treated with the same AED. However, given the large number of variables and confounding factors, interpretation of results will always need caution.

With these limitations in mind, however, some tentative conclusions can be proposed, as an answer to the questions that we addressed in the introduction. As a result of the marked differences in material and methods among the different series our conclusions are only speculative, but might be of help in suggesting future lines of research.

6.1 Is There an Increased Prevalence of PCOS in Women with Epilepsy? Is this Related to the Use of VPA?

According to the results displayed in table II, women with epilepsy seem to have a high prevalence of menstrual disturbances. With the exception of the report of Murialdo et al.[66] which describes a 10.8% prevalence of menstrual irregularities (for which no specific definition is given in the method section), in all the other series in which such information is offered the prevalence of irregular menstruations, ranging from 21.8 to 56.0%, is much higher than the 7% prevalence described in the general population in a recent epidemiological study[151] and is observed also in drug-free patients, with values of 25.0 and 42.1% in different series[69,120] (table III). Even if comparisons with the general population must be evaluated with caution, it must be stressed that a high occurrence of men-

strual dysfunctions in women with epilepsy has long been reported.[152-158] A high prevalence of polycystic ovaries (>30%) is reported in about half of the studies[21,71,73,120] in which this finding was systematically evaluated, most of which employed transvaginal scanning or MRI rather than transabdominal scanning, which is associated with a lower prevalence.[3,63,66,79,80] Hyperandrogenism has a high prevalence in most reports offering laboratory data,[2,3,21,120] with a single report describing a 4.5% prevalence[77] and all the others ranging from 15 to 26% (table II).[2,3,21,120] Finally, the prevalence of PCOS is highly variable: when 1990 NIH Conference criteria are used, it ranges from 2.3[77] to 26.0%.[120] The report with the highest prevalence,[120] however, performs the most careful evaluation of patients, documenting presence and timing of ovulation in all participants, performing a careful assessment of clinical hyperandrogenism, including hirsutism and acne, and considering this parameter in the diagnostic assessment as requested by 1990 NIH Conference criteria. Since in most of the other reports a 1990 NIH Conference criteria diagnosis can not be obtained because critical individual findings are not offered to the reader,[66,69,71,73,80] and the ones in which such data are presented have methodological problems which could lead to over- or underestimation of prevalence,[21,63,77,79] we should actually rely only on this report[120] which is, however, of a relatively small sample. In conclusion, the first question does not have yet a definite answer, but we suspect that, with careful and complete evaluation of patients, the prevalence of PCOS in epileptic women will be found to be significantly elevated.

The possible role of VPA in inducing endocrine changes (table III) is more difficult to evaluate, since in some reports the subanalyses of patients according to AED therapy results in very small samples.[3,71,120] However, speculative conclusions can be attempted. While the series from Isojarvi et al.[21] reports a striking and significant difference in the prevalence of menstrual dysfunctions between VPA recipients (59.5%) and carbamazepine recipients (11.4%), in the majority of the other reports distribution of menstrual irregularities is quite similar in different therapy groups,[3,66,69,77,79,80,120] with prevalence in VPA recipients usually being slightly lower. Besides the studies of Isojarvi et al., the only other series describing a higher, but not significant, prevalence of menstrual disturbances in VPA recipients is the one reported by Murialdo et al.[63] in which the VPA group also includes carbamazepine-treated patients and the prevalence of menstrual disturbances for VPA monotherapy is not given. Polycystic ovaries are more frequently reported in VPA recipients only in a minority of reports[21,63,120] in which a significant difference with non-VPA recipients is once again observed only in the series by Isojarvi et al.[21] Most reports describe a non-significantly higher prevalence of polycystic ovaries in non-VPA users.[3,66,71,73,79,80] Prevalence of hyperandrogenism is not significantly different between VPA and non-VPA groups in any of the reports in which such findings are examined,[3,21,77,79,80,120] even if it is higher in VPA recipients in most reports.[21,77,79,80] Finally, the prevalence of PCOS is higher in VPA-treated patients in most reports,[21,73,77,79] but only in the series by Isojarvi et al. is this difference statistically significant. The groups of non-VPA users are highly heterogeneous in the different series, and consequently difficult to compare; however, in four reports[69,71,73,77] a 0% prevalence of PCOS is reported in specific groups of non-VPA users, including most lamotrigine recipients.[71,73,77] Untreated patients with epilepsy are separately described only in two reports,[69,120] with the prevalence of PCOS varying greatly, being 31.2% in the report from Bilo et al.[120] and 10.5% in the report form Bauer et al.[69] Quite intriguingly, the reports in which drug-free patients are included are the only ones in which prevalence of PCOS is not higher in VPA-treated patients.[3,69,120]

In summary, we can conclude that women with epilepsy have menstrual dysfunctions significantly more often than those in the general population; this finding, which has been known for 50 years, does not seem related to the use of any AED and can also be observed in drug-free patients. Aspecific stress, caused by a chronic disease with a strong impact on quality of life, could play a relevant role the patho-

genesis of menstrual irregularities; however, women with epilepsy have also a high prevalence of polycystic ovaries and of hyperandrogenism. As we have repeatedly underlined when commenting data from Isojarvi and co-workers, the finding of isolated polycystic ovaries is not *per se* abnormal and, in the absence of large prospective studies monitoring reproductive health in epileptic women with isolated ovarian changes, there is no reason to consider it as a marker of endocrine abnormalities. However, its elevated prevalence in women with epilepsy is intriguing and its possible meaning is worth speculating about. Polycystic changes are not specifically linked to the use of VPA in most series describing epileptic women, and are frequently observed in drug-free patients with epilepsy. For this reason, they seem to be related to the epileptic disorder rather than to AED therapy. However, the specific endocrine disorder of PCOS, with its well-known impact on fertility and on cardiovascular health, is more frequently observed in epileptic women using VPA.

On the basis of the finding of abnormal LH pulsatility in drug-free women with epilepsy with a normal endocrinological profile reported in our previous studies,[113] we have already proposed[5,113] that a derangement of the GnRH pulse generator might be observed in women with epilepsy, caused by spreading of paroxysmal activity within the hypothalamus and/or by neurotransmitter dysfunctions which accompany seizure disorders. This abnormal finding is independent from AED use, may be observed in normally ovulating epileptic women and does not necessarily lead to clinical reproductive endocrine disturbances. The possible evolution towards a clinical dysfunction is probably dependent on several different factors, whose relative weight may be difficult to evaluate: seizure frequency, seizure distribution within the menstrual cycle, duration of epilepsy, age at onset of seizures and its temporal relation with puberty, and abundance of interictal paroxysmal activity, are all factors which may possibly contribute to the clinical expression of the reproductive disorder.[5] However, as a result of this increased susceptibility to hypothalamic dysfunction, a high percentage of women with epilepsy will present menstrual disorders; it is also possible to hypothesise that the higher prevalence of polycystic ovaries in these women may result from an altered hypothalamic control. The further possible evolution towards a definite clinical disease, on the other hand, seems to be more often related to the use of AEDs and, in particular, of VPA.

The 'specific' role of VPA in increasing the probability of the clinical expression of an endocrine disorder may be caused by several different factors. Weight gain, which is frequently reported in children[159-161] and adult patients[162-166] during VPA treatment, may be a contributing factor: even if obesity is not considered as a prerequisite in the development of PCOS and, conversely, absence of obesity in PCOS has been viewed as the 'authentic PCOS syndrome', weight gain may act as a modifier which might contribute to the genesis and maintenance of hyperandrogenic chronic anovulation.[167] It is in fact known that some women with PCOS may develop menstrual irregularities in association with weight gain and resume more regular menstrual cycles after relatively small amounts of weight loss.[88,168] Incidentally, weight gain is probably responsible for the metabolic syndrome with increased cardiovascular risk observed in obese VPA-treated epileptic women,[21] since this is not observed in lean VPA-treated epileptic women in the same report,[21] conversely to that reported in spontaneous PCOS, where both lean and obese women present insulin resistance.[88,99]

However, weight gain is probably not the only VPA-related mechanism leading to endocrine problems in epileptic women, since these findings have also been described in lean VPA-treated epileptic females and hyperandrogenism, in particular, has been reported in VPA-treated epileptic patients also in the absence of or before weight gain.[17,21] As we have underlined above (in sections 3.2 and 3.3), evidence supporting development of hyperandrogenism during VPA use in epileptic patients needs to be confirmed in larger samples since their statistical significance is minimal and control groups are quite small.[17,20] However, in different

reports an increased prevalence of hyperandrogenism/hirsutism is observed in VPA recipients compared with carbamazepine-[21,79] and/or lamotrigine-[77,79] treated patients, but not compared with drug-free epileptic women.[120]

This leads to the hypothesis that actually this difference might originate from a protective effect of carbamazepine and lamotrigine on the development of hyperandrogenism and PCOS in epileptic women predisposed to endocrine disturbances, rather than, or in addition to, a hyperandrogenic effect of VPA in such patients. This hypothesis, originally suggested by Herzog and co-workers with regard to carbamazepine and other enzyme-inducing AEDs,[47,114] has been successively been re-proposed by our group[120] and, more recently, by Betts.[53] However, while the possible mechanism of a carbamazepine-mediated protection on hyperandrogenism may be recognised in its enzyme-inducing action, which may lower androgen levels, the possible mechanism of a supposed lamotrigine action is not known yet, since this drug does not possess enzyme-inducing activities. Even if scanty, evidence that suggest a possible protective role of lamotrigine on the development of PCOS in epileptic patients is highly interesting: (i) a 0% prevalence of PCOS is often observed in lamotrigine-treated patients,[71,73,77] while this prevalence is higher in controls in the same study[73] and still higher in untreated epileptic women in another series;[69,120] (ii) the highest prevalence of PCOS among non-VPA recipients is observed in a series which does not include any patients treated with lamotrigine;[120] and (iii) Betts reported an immediate restoration of normal hormone levels in patients who switched from VPA to lamotrigine, this effect being observed as soon as lamotrigine is added and independently from VPA withdrawal.[53]

In this light, the modifications of the some endocrine parameters observed in one of the studies by Isojarvi et al.[10] after switching from VPA to lamotrigine could be related not necessarily or not only to VPA withdrawal, but also to lamotrigine use. This possibility requires further investigation in larger series of epileptic, and may be also in nonepileptic, women with PCOS.

6.2 Suggested Guidelines in Clinical Practice

In conclusion, much work still needs to be done in order to clarify the issue of relationships between epilepsy and PCOS. In the meantime, when treating female patients with epilepsy, what should we do?

This problem has been addressed in several review articles[34,49,52,55-57,61] from which a substantial uniformity of management strategies emerge. In agreement with most authors, we therefore suggest the following.

- Women with epilepsy may represent a group at risk for reproductive health, independently from the use of AEDs, and this possibility must be always kept in mind in the general assessment of patients. Therefore, investigation of reproductive health should become part of the routine evaluation both in baseline and follow-up consultations. Accordingly, an initial menstrual history including age at menarche, cycle length and previous menstrual dysfunctions should be possibly obtained before starting any AED therapy, and follow-up on these issues should be performed regularly. Similarly, signs of clinical hyperandrogenism, such as hirsutism and acne, should be evaluated, and weight and height measurements should be included in baseline visit and in follow-up consultations.
- When findings suggestive of reproductive endocrine dysfunction are encountered (such as menstrual irregularities, hyperandrogenism, infertility, obesity, etc.) patients must be referred to a gynaecologist/endocrinologist, possibly familiar with the complexities of these specific issues in women with epilepsy and used to working in a team with the epileptologist. A definite nosological diagnosis of the reproductive endocrine disease must be obtained, employing the appropriate tools and following up-to-date diagnostic criteria. Only after these goals have been achieved, can the possible role of AEDs and/or of the epileptic disorder be considered.

- Currently, there is no clear evidence contraindicating the use of VPA in women with epilepsy. However, since it is possible that such treatment may be associated with an increased risk of developing reproductive endocrine disturbances, an alternative treatment should be considered if the patient presents with obesity, menstrual irregularities or signs of hyperandrogenism. In this context, the possibility that some AEDs might have a favourable effect on hyperandrogenism should also be taken into consideration.
- Female patients treated with VPA should be frequently monitored with regard to bodyweight; they should be informed of the possibility of gaining weight during VPA therapy and be encouraged to use healthy weight maintenance strategies. In these patients, lipid and glucose metabolism should be evaluated at least once a year. If a significant weight gain is observed over time, and no result is obtained with dietetic measures and exercise, the possibility of VPA withdrawal and switch to another appropriate AED must be considered.
- Female patients treated with VPA should be investigated at least once a year for polycystic ovaries and laboratory hyperandrogenism, and more often if they present changes in their menstrual patterns during VPA use. In the presence of menstrual dysfunction and/or hyperandrogenism occurring during VPA therapy, the possibility of VPA withdrawal and switch to another appropriate AED must be considered.
- However, any decision concerning the choice or the change of VPA therapy must clearly take into careful consideration both the results obtained with this drug in the individual patient and the possible risks of its discontinuation (and/or of the use of an alternative AED). These should then be balanced against the risks on reproductive health in the specific setting of the individual patient's lifestyle. This is particularly important in patients with severe epileptic disorders in which VPA usage may have given a consistent contribution to seizure control.

Acknowledgements

No sources of funding were used to assist in the preparation of this manuscript. The authors have no conflicts of interest that are directly relevant to the content of this manuscript.

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