Reproductive Hormones in Epilepsy Therapy: From Old Promises to New Hopes

Alberto Verrotti, Giovanni Prezioso, Claudia D'Egidio and Vincenzo Belcastro

Abstract A significant mutual interaction between sex hormones and the central nervous system has been reported by several studies in the past years.

This paper aims to discuss the genomic and electrophysiological effects of androgens, estrogens and progestogens on neurons, their influence on seizure frequency and antiepileptic drugs metabolism, and, conversely, the hormonal changes and reproductive dysfunction in patients with epilepsy.

In conclusion, the correlations between Polycystic Ovary Syndrome (PCOS), reduced effectiveness of contraceptives and antiepileptic drugs have also been mentioned.

Epilepsy represents one of the most frequent neurological diseases worldwide, affecting nearly 1 % of the population. It is characterized by the chronic recurrence of seizures in an unpredictable fashion. The prevention of seizures is the primary goal of epilepsy treatment. This requires the use of anti-epileptic drugs (AEDs) for the majority of patients.

Biological, experimental, and clinical studies for a number of years reported a noticeable interaction between epilepsy, AEDs and sex hormones.

Not only seizures and AEDs can induce significant changes in sex hormones regulation, sexual development, and reproductive functions, but also seizures and AEDs metabolism are strongly influenced by steroid hormones and their derivatives.

A. Verrotti (✉)
Department of Pediatrics, University of Perugia, Perugia, Italy
e-mail: averrotti@unich.it

G. Prezioso · C. D'Egidio
Department of Pediatrics, University of Chieti, Chieti, Italy

V. Belcastro
Neurology Unit, Department of Medicine, S. Anna Hospital, Como, Italy

P. Striano (ed.), *Epilepsy Towards the Next Decade,*
Contemporary Clinical Neuroscience, DOI 10.1007/978-3-319-12283-0_11

Sex Hormones Role on CNS

Androgens, estrogens, and progestogens play a key role in shaping neural activity since prenatal life, moreover they exert a regulatory action on neurotransmitters and their receptors in neurons. Sex hormones interact with tissues, like the brain, by means of both receptor mediated and receptor-independent pathways. The first mechanism starts with nuclear receptor dimerization after hormone binding, thereafter the steroid-receptor complex in turn binds to and regulates the transcription of sex steroid responsive genes or post-transcriptional proteins. (Keefe 2002; Reddy 2009; Finocchi and Ferrari 2011) Each steroid receptor isoform is linked with different adapter protein and different response elements. Non-genomic effects of sex steroids have also been reported. (Keefe 2002) These effects are usually faster than nuclear receptor-mediated ones. Indeed, some steroids seem to conditioning electrophysiologic neuronal activity by interacting with high affinity on specific binding sites of the main neurotransmitter receptors, like GABA-A and NMDA receptors, effectively acting as neural stimulants or depressant. For instance, some of these hormones exert an agonist action on the GABA-A receptor even more potent than benzodiazepines and barbiturates, clearly affecting the epileptogenic activity. (Keefe 2002; Reddy 2009)

Estrogens show evident proconvulsant and epileptogenic properties, even if in sometimes they may exhert protective and anticonvulsant effects. Several studies have found estradiol (E2) both to enhance NMDA receptor activity and to temporarily decrease GABA inhibition. Moreover it appears to decrease GABA synthesis. There is also emerging evidence of hippocampus hyperexcitability due to estrogen and brain derived neurotrophic factor interactions (Foldvary-Schaefer et al. 2004; Erel and Guralp 2011; Finocchi and Ferrari 2011; Guille et al. 2008)

In contrast, clinical studies reported marked anticonvulsant qualities of progesterone, in particular of its 5α-reduced metabolites, like allopregnanolone. It has been demonstrated that glial and neuronal cells of the cerebral cortex and subcortical white matter are even able to synthesize by themselves from cholesterol these metabolites (neurosteroids). (Finocchi and Ferrari 2011; Reddy 2009; Guille et al. 2008). Neurosteroids activate the GABA receptor both directly, by binding two distinct sites different from the benzodiazepine or barbiturate sites, and indirectly, through a longer-term action on progesterone nuclear receptors. (Reddy 2009)

Nevertheless, proconvulsant neurosteroid acting as NMDA receptor agonists and GABA-A receptor antagonists have been identified (i.e. pregnenolone sulfate). (Reddy 2009)

In regards to androgens, testosterone affects neural activity depending on its conversion to androstanediol, which has anticonvulsant and GABA-A agonist property, and E2 with the aforementioned proconvulsant activity. (Reddy 2009; Keefe 2002; Hamed 2008)

Table 1 Three types of catamenial epilepsy. (modified from Reddy 2009)

Subcategories of catamenial epilepsy	Main characteristics
C1—perimenstrual	Due to the rapid decrease in anticonvulsant progesterone and neurosteroids blood level during days −3 to +3 which lead to descreased GABA inhibition
	Incidence: 71% of women with regular ovulatory cycles
C2—periovulatory	Due to the proconvulsant estrogen peak not balanced by an adequate level of neurosteroids in days 10–13. This requires a decrease in GABA inhibition and a marked excitation
	Incidence: 71% of women with regular ovulatory cycles
C3—inadequate luteal	Due to the insufficient brain levels of neurosteroids resulting from progesterone metabolism in anovulatory cycles. The final result is both a marked estradiol excitation and a persistent low GABA inhibition during days
	Incidence: 78% of women with anovulatory cycles (luteal phase)

Effects on Seizures-Catamenial Epilepsy

There is clinical evidence that interaction between steroid hormones and the CNS influences seizure susceptibility in epileptic patients. Being this especially evident in women, whose remarkable hormonal changes during puberty as well as pregnancy and menopause affect seizure frequency and AED metabolism. Moreover menopausal transition seems to have an effect on seizure susceptibility with a seizure increase of about 30% in women with epilepsy in perimenopause and a tendency to decrease after menopause, but there is no consensus on these findings (Erel and Guralp 2011; Røste et al. 2008).

Another clear proof of the role of sex hormones in seizure exacerbation is the catamenial epilepsy phenomenon in women. Catamenial epilepsy (CE) derives from the Greek word *katamenios*, which means "monthly", and it refers to a cyclical variation in seizures frequency in relation to menstrual cycle phases in women affected by epilepsy (genetic, structural, metabolic or of unknown cause), especially temporal-lobe epilepsy (Foldvary-Schaefer et al. 2004; Guille et al. 2008; Reddy and Rogawski, 2009; Pennell 2009; Pack 2010; Finocchi and Ferrari 2011). The incidence varies from 10 to 70% due to the lack of an unambiguous definition and to methodological differences among studies (Reddy 2009). A significant contribution to the study of CE was made by Herzog et al. (Herzog et al. 1997), who proposed the most accepted definition: a twofold increase in average daily frequency during a phase of menstrual cycle. They also described three subcategories of CE: C1 during the perimenstrual period, probably due to the withdrawal of allopregnanolone and other inibitory neurosteroids at the time of menstruation, C2 in the periovulatory phase, owing to an increase in estrogen concentration, defined above as proconvulsant, and C3, typical of the inadequate luteal phase of women with anovulatory cycles (see Table 1 and Fig. 1). A concurrent involvement in CE of AEDs blood level fluctuations and of the possible changes in water, pH, and electrolyte cannot

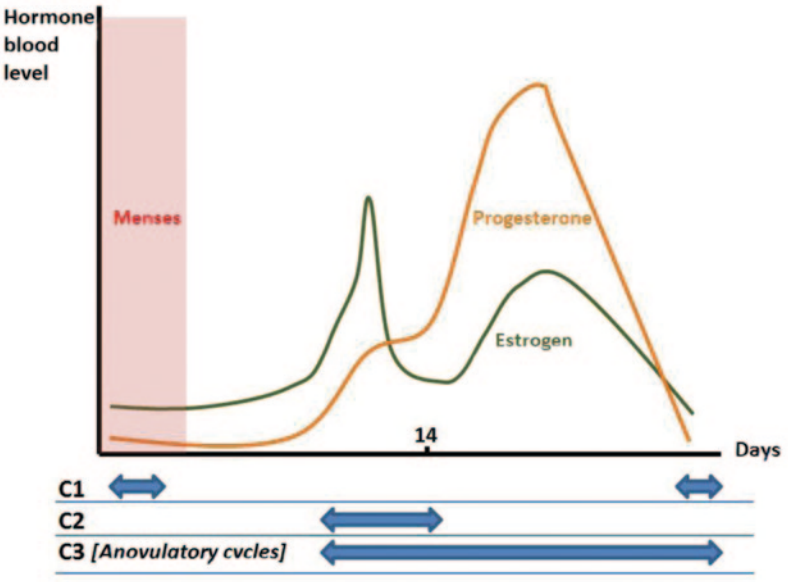

Fig. 1 Seizures distribution within the three patterns of catamenial epilepsy

be definitely ruled out, although hormonal oscillation maintains a key etiologic role (Pack 2010). A correct diagnosis of CE requires both careful compilation and evaluation of menstrual and seizure diaries as well as characterization of cycle type and duration (Reddy 2009; Foldvary-Schaefer et al. 2004). It is not rare to find women with CE presenting with state-dependant pharmacoresistance or intractable seizures (Reddy and Rogawski 2009). The first-line therapy includes the AEDs and usually requires cyclic dosage adjustments or supplement with other AEDs. Adjunctive hormonal treatment with progesterone or estrogen antagonists has been reported to augment seizure control in appropriate CE patients (Pack 2010; Herzog 1995, 1999). Natural progesterone, mainly converted to the anticonvulsant allopregnanolone, has been demonstrated to be effective in women with focal epilepsy and CE, even though it showed endocrine and CNS side effects (Herzog 1986, 1995, 1999; Pack 2010; Reddy 2009). Synthetic progestogen like Medroxyprogesterone is only partially converted to active neurosteroids, resulting in moderate improvement in seizure frequency (Zimmerman et al. 1973; Mattson et al. 1984). Nonetheless it provokes menses interruption and consequently reproductive disturbances in long-term therapy. On the contrary the use of combined oral contraceptives has a questionable effectiveness (Guille et al. 2008). Antiestrogens (clomiphene citrate), androgen, or synthetic gonadotropin-releasing hormone therapies have a limited utility as they show several adverse events (Foldvary-Schaefer et al. 2004). Great interest has been recently engendered about the use of Ganaxolone in CE. Ganaxolone is a synthetic analogue of allopregnanolone with potent positive action on GABA-A receptors resulting in anticonvulsant effect (Reddy 2009; Pack 2010; Guille et al.

2008; McAuley et al. 2001). Non-hormonal therapy of CE includes Acetazolamide, a carbonic anhydrase inhibitor with a broad spectrum of efficacy on seizures. The mechanism of action on seizure reduction is unclear, maybe a diuretic effect is implied. Since Acetazolamide is subject to tolerance as much as significant adverse events, it is usually administered intermittently (Reddy 2009; Ross 1958; Lim et al. 2001; Pack 2010).

Anyway, further investigation is needed in the matter of CE therapy given that data currently available largely belong to small non randomized studies and empirical evidence (Reddy 2009).

Effects of Seizures on Sex Functions

Epilepsy itself may directly influence the hypothalamic-pituitary axis (Herzog et al. 1986; Isojärvi et al. 2005; Scharfman et al. 2008) Preclinical investigations suggested that the involvement of medial temporal lobe regions in epilepsy may alter sex hormone secretion and reproductive functions. A dysregulation of GnRH pulsatility and therefore of LH/FSH ratio in epileptic women and of testosterone/LH ratio in epileptic men has been described (Verrotti et al. 2011; Drislane et al. 1994; Ciampani et al. 2005; Morell 2003; Herzog 2008; Hamed 2008; Fawley et al. 2006). Experimental studies reported an interesting correlation with laterality, even though datas are not univocal (Pack 2010; Quigg et al. 2009). Unilateral left-sided temporolimbic discharges seem to increase the pulse frequencies of GnRH secretion, resulting in a higher occurrence with PCOS, while right-sided temporolimbic discharges may decrease GnRH pulse frequency and are more commonly associated with sexual dysfunction (hypotalamic amenorrhea, functional hyperprolactinemia, infertility and premature menopause in women; decreased libido, abnormal semen analysis and reduced fertility in men with epilepsy) (Verrotti et al. 2011; Herzog et al. 1986; Morrell et al. 2005; Quigg et al. 2009; Harden 2008; Duncan et al. 2009).

Furthermore, some studies draw attention to the increased risk of premature ovarian failure and perimenopausal symptoms in women with epilepsy (Klein et al. 2001; Harden 2003).

Mutual Interactions Between Sex Hormones and AEDs

There is increasing evidence of AEDs contribution to sex dysfunction in epileptic patients. Indeed, studies suggest that AEDs may variably influence both the steroid hormones metabolism and their binding proteins (Hamed 2008; Bauer et al. 2002). Enzyme-inducing AEDs (EIAEDs)—such as phenobarbital (PB), phenytoin (PHT), and carbamazepine (CBZ)—rather than non-EIAEDs (NEIAEDs) have been known to play a critical role in steroid hormones abnormalities (see Table 2). EIAEDs can

Table 2 EIAEDs and NEIAEDs. (modified from Reddy 2009)

EIAEDs	NEIAEDs
Carbamazepine	Clobazam
Oxcarbazepine	Clonazepam
Phenobaribatal	Ethosuximide
Methylphenobarbital	Mesuximide
Phenobarbital sodium	Valproic Acid[a]
Phenytoin	Lamotrigine
Fosphenytoin sodium	Gabapentin
Felbamate	Pregabalin
Topiramate	Vigabatrin
Primidone	Tiagabine
	Zonisamide
	Sultiame
	Beclamide
	Levetriacetam
	Rufinamide
	Stripentol

[a] weak CYP inducer

induce hepatic cytochrome P450 (CYP450), a system of mixed oxidative enzymes which metabolizes AEDs to a more water-soluble form. As the CYP450 is involved in steroids metabolism, its induction implies a faster hormone clearance (Isojärvi et al. 2005). In addition, EIAEDs were found to increase serum sex hormone-binding globulin (SHBG) levels in patients with epilepsy, reducing biologically active steroid hormones like DHEAS, T, free androgen index, and E2 (Pennell 2009; Erel and Guralp 2011; Verrotti et al. 2011). This may result in impotence and decreased fertility in men, hyperandrogenism and menstrual disorders in women. EIAEDs may also correlate with hypogonadotropic hypogonadism, by inhibiting LH secretion, and with decreasing libido and potency, by increasing the conversion of testosterone to E2 (Hamed 2008).

Anyway also NEIAEDs have been found to be involved in hormonal dysregulation. Valproate (VPA), in particular, seems to be associated with high serum concentrations of T, androstenedione and DHEAS, and with increase in levels of LH and LH/FSH ratio, leading to polycystic ovary syndrome, hyperandrogenism and amenorrhea in women, reduced feritlity and sperm abnormalities in morphology, count and motility in men (Verrotti et al. 2011; Isojärvi et al. 1993; Prabhakar et al. 2007; Rauchenzauner et al. 2010; Xiaotian et al. 2013; Morrell et al. 2005; Chen et al. 1992). Even if not yet clear, VPA may directly alter androgen production in ovaries or it may act indirectly, by inhibiting steroid hormones metabolism and thereby increasing serum androgen levels. It is noticeable that hyperandrogenism has been evidenced more frequently in women who have gained weight during VPA therapy and in those who started treatment before the age of twenty.

Low prevalence of reproductive disorders has been reported during therapy with new AEDs like oxcarbazepine and lamotrigine (LTG), but no data are available for a number of other new AEDs. Besides, women on LTG, previously treated with VPA, seems to show a marked improvement in reproductive dysfunction (Isojärvi et al. 1998).

PCOS and AEDs

Among reproductive dysfunctions, PCO and PCOS appears to be particularly common in epileptic women (10–25 versus 5–6% of health women) (Herzog et al. 2003). Even though PCOS has been detected in non-treated epileptic patients, several studies highlighted an increased incidence during AED treatment, in particular with VPA, but the evidence still remains controversial (Isojärvi et al. 1993, 1995, 1996, 2001; Morrell et al. 2002, 2008; Betts et al. 2003; Prabhakar et al. 2007). Special attention should be directed to weight gain and insulin resistance, which can be common adverse effects of vigabatrin, carbamazepine and gabapentin other than VPA, because they have been reported as important risk factors for PCOS (Verrotti et al. 2011). Elevated serum leptin, impaired adipokine regulation, and low serum IGFBP-1 levels have been linked to VPA-related obesity in women with epilepsy (Belcastro et al. 2013; Greco et al. 2005; Gungor et al. 2007; Verrotti et al. 2011, 1999; Rauchenzauner et al. 2008). Moreover, VPA seems also able to stimulate insulin secretion both indirectly, by increasing free fatty acids levels in blood through albumin binding competition and directly by stimulating pancreatic b-cells and inhibiting glucose transporter protein type 1 (GLUT-1) activity (Luef et al. 2002, 2009, 2003; Wong et al. 2005; Belcastro et al. 2013; Evans et al. 2003). Finally, the inhibition of sympathetic nervous system, the impairment of insulin signal transduction pathway and the direct influence on the ovary via aromatase inhibition are other proposed mechanism of action of VPA (Verrotti et al. 2011). It has been demonstrated that all of these metabolic abnormalities predispose also to metabolic syndrome, which is frequently detected among VPA overweight patients as a consequence of the excess fat mass (Belcastro et al. 2013; Verrotti et al. 2010; see Fig. 2).

On the other hand, EIAEDs like phenitoine and CBZ may prevent from the development of PCOS, by reducing free T levels.

Contraceptive and AEDs

EIAEDs may also interfere with oral contraceptive pills (OCPs) efficacy similarly by reducing the biological active hormone concentrations and allowing ovulations. In order to reduce the risk of unplanned pregnancies it is recommended to

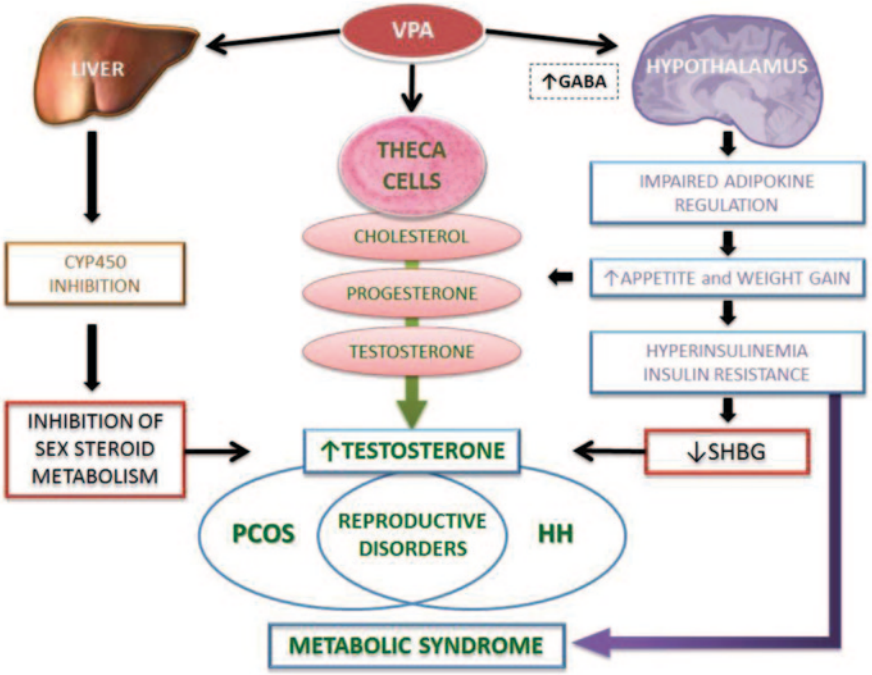

Fig. 2 Hormonal and metabolic alterations in VPA therapy. (modified from Verrotti et al.2011)

prescribe an OCP with higher doses of ethinyl estradiol (≥ 50 micrograms) and to use additional non-hormonal forms of contraception (Erel and Guralp 2011; Bartoli et al. 1997; Pennell 2009; Guberman 1999).

Refrences

Bartoli A, Gatti G, Cipolla G, Barzaghi N, Veliz G, Fattore C, Mumford J, Perucca E (1997) A double-blind, placebo-controlled study on the effect of vigabatrin on in vivo parameters of hepatic microsomal enzyme induction and on the kinetics of steroid oral contraceptives in healthy female volunteers. Epilepsia 38:702–707

Bauer J, Isojärvi JI, Herzo AG, Reuber M, Polson D, Taubøll E, Genton P, van der Ven H, Roesing B, Luef GJ, Galimberti CA, van Parys J, Flügel D, Bergmann A, Elger CE (2002) Reproductive dysfunction in women with epilepsy: recommendations for evaluation and management. J Neurol Neurosurg Psychiatry 73:121–125

Belcastro V, D'Egidio C, Striano P, Verrotti A (2013) Metabolic and endocrine effects of valproic acid chronic treatment. Epilepsy Res 107:1–8

Betts T, Yarrow H, Dutton N, Greenhill L, Rolfe T (2003) A study of anticonvulsant medication on ovarian function in a group of women with epilepsy who have only ever taken one anticonvulsant compared with a group of women without epilepsy. Seizure 12:323–329

Chen SS, Shen MR, Chen TJ, Lai SL (1992) Effects of antiepileptic drugs on sperm motility of normal controls and epileptic patients with long-term therapy. Epilepsia 33:149–153
Ciampani M, Verrotti A, Chiarelli F (2005) Sex hormones in patients with epilepsy-hormonal changes in epileptic men and women taking antiepileptics. Horm Metab Res 37:184–188
Drislane FW, Coleman AE, Schomer DL, Ives J, Levesque LA, Seibel MM, Herzog AG (1994) Altered pulsatile secretion of luteinizing hormone in women with epilepsy. Neurology 44:306–310
Duncan S, Talbot A, Sheldrick R, Caswell H (2009) Erectile function, sexual desire, and psychological well-being in men with epilepsy. Epilepsy Behav 15:351–357
Erel T, Guralp O (2011) Epilepsy and menopause. Arch Gynecol Obstet 284:749–755
Evans JL, Goldfine ID, Maddux BA, Grodsky GM. (2003) Are oxidative stress-activated signaling pathways mediators ofinsulin resistance and beta-cell dysfunction? Diabetes 52:1–8
Fawley JA, Pouliot WA, Dudek FE (2006) Epilepsy and reproductive disorders: the role of the gonadotropin-releasing hormone network. Epilepsy Behav 8:477–482
Finocchi C, Ferrari M (2011) Female reproductive steroids and neuronal excitability. Neurol Sci 32(Suppl 1):S31–35
Foldvary-Schaefer N, Harden C, Herzog A, Falcone T (2004) Hormones and seizures. Cleve Clin J Med 71(Suppl 2):S11–18
Greco R, Latini G, Chiarelli F, Iannetti P, Verrotti A (2005) Leptin, ghrelin, and adiponectin in epileptic patients treatedwith valproic acid. Neurology 65:1808–1809
Guberman A (1999) Hormonal contraception and epilepsy. Neurology 53:S38–40
Guille C, Spencer S, Cavus I, Epperson CN (2008) The role of sex steroids in catamenial epilepsy and premenstrual dysphoric disorder: implications for diagnosis and treatment. Epilepsy Behav 13:12–24
Gungor S, Yücel G, Akinci A, Tabel Y, Ozerol IH, Yologlu S (2007) The role of ghrelin in weight gain and growth in epileptic children using valproate. J Child Neurol 22:1384–1388
Hamed SA (2008) Neuroendocrine hormonal conditions in epilepsy: relationship to reproductive and sexual functions. Neurologist 14:157–169
Harden CL (2003) Menopause and bone density issues for women with epilepsy. Neurology 61:S16–S22
Harden CL (2008) Sexual dysfunction in women with epilepsy. Seizure 17:131–135
Herzog AG (1986) Intermittent progesterone therapy of partial complex seizures in women with menstrual disorders. Neurology 36:1607–1610
Herzog AG (1995) Progesterone therapy in women with complex partial and secondary generalized seizures. Neurology 45:1660–1662
Herzog AG (1999) Progesterone therapy in women with epilepsy: a 3-year follow-up. Neurology 52:1917–1918
Herzog AG (2008) Disorders of reproduction in patients with epilepsy: primary neurological mechanisms. Seizure 17:101–110
Herzog AG, Seibel MM, Schomer DL Vaitukaitis JL, Geschwind N (1986) Reproductive endocrine disorders in women with partial seizures of temporal lobe origin. Arch Neurol 43:341–346
Herzog AG, Klein P, Ransil BJ (1997) Three patterns of catamenial. Epilepsia 38:1082–1088
Herzog AG, Coleman AE, Jacobs AR, Klein P, Friedman MN, Drislane FW, Ransil BJ, Schomer DL (2003) Interictal EEG discharges, reproductive hormones, and menstrual disorders in epilepsy. Ann Neurol 54:625–637
Isojärvi JI, Laatikainen TJ, Pakarinen AJ, Juntunen KT, Myllylä VV (1993) Polycystic ovaries and hyperandrogenism in women taking valproate for epilepsy. N Engl J Med 329:1383–1388
Isojärvi JI, Laatikainen TJ, Pakarinen AJ, Juntunen KT, Myllylä VV (1995) Menstrual disorders in women with epilepsy receiving carbamazepine. Epilepsia 36:676–681
Isojärvi JI, Laatikainen TJ, Knip M, Pakarinen AJ, Juntunen KT, Myllylä VV (1996) Obesity and endocrine disorders in women taking valproate for epilepsy. Ann Neurol 39:579–584

Isojärvi JI, Rättyä J, Myllylä VV, Knip M, Koivunen R, Pakarinen AJ, Tekay A, Tapanainen JS (1998) Valproate, lamotrigine, and insulinmediated risks in women with epilepsy. Ann Neurol 43:446–451

Isojärvi JI, Taubøll E, Pakarinen AJ, van Parys J, Rättyä J, Harbo HF, Dale PO, Fauser BC, Gjerstad L, Koivunen R, Knip M, Tapanainen JS (2001) Altered ovarian function and cardiovascular risk factors in valproate-treated women. Am J Med 111:290–296

Isojärvi JI, Taubøll E, Herzog AG (2005) Effect of antiepileptic drugs on eproductive endocrine function in individuals with epilepsy. CNS Drugs 19:207–223

Keefe DL (2002) Sex hormones and neural mechanisms. Arch Sex Behav 31:401–403

Klein P, Serje A, Pezzullo JC (2001) Premature ovarian failure in women with epilepsy. Epilepsia 42:1584–1589

Lim LL, Foldvary N, Mascha E, Lee J (2001) Acetazolamide in women with catamenial epilepsy. Epilepsia 42:746–749

Luef G, Abraham I, Trinka E, Alge A, Windisch J, Daxenbichler G, Unterberger I, Seppi K, Lechleitner M, Krämer G, Bauer G. (2002) Hyperandrogenism, postprandial hyperinsulinism and the risk of PCOS in a cross sectional study of women with epilepsy treated with valproate. Epilepsy Res 48:91–102

Luef G, Lechleitner M, Bauer G, Trinka E, Hengster P (2003) Valproic acid modulates islet cell insulin secretion: a possible mechanism of weight gain in epilepsy patients. Epilepsy Res 55:53–58

Luef G, Rauchenzauner M, Waldmann M, Sturm W, Sandhofer A, Seppi K, Trinka E, Unterberger I, Ebenbichler CF, Joannidis M, Walser G, Bauer G, Hoppichler F, Lechleitner M (2009) Non-alcoholic fatty liver disease (NAFLD), insulin resistance and lipid profile in antiepileptic drug-treatment. Epilepsy Res 86:42–47

Mattson RH, Cramer JA, Caldwell BV, Siconolfi BC (1984) Treatment of seizures with medroxyprogesterone acetate: preliminary report. Neurology 34:1255–1258

McAuley JW, Moore JL, Reeves AL, Flyak J, Monaghan EP, Data J (2001) A pilot study of the neurosteroid ganaxolone in catamenial epilepsy: clinical experience in two patients. Epilepsia 42:85–85

Morell MJ (2003) Reproductive and metabolic disorders in women with epilepsy. Epilepsia 44:11–20

Morrell MJ, Giudice L, Flynn KL, Seale CG, Paulson AJ, Doñe S, Flaster E, Ferin M, Sauer MV (2002) Predictors of ovulatory failure in women with epilepsy. Ann Neurol 52:704–711

Morrell MJ, Flynn KL, Doñe S, Flaster E, Kalayjian L, Pack AM (2005) Sexual dysfunction, sex steroid hormone abnormalities, and depression in women with epilepsy treated with antiepileptic drugs. Epilepsy Behav 6:360–365

Morrell MJ, Hayes FJ, Sluss PM, Adams JM, Bhatt M, Ozkara C, Warnock CR, Isojärvi J (2008) Hyperandrogenism, ovulatory dysfunction, and polycystic ovary syndrome with valproate versus lamotrigine. Ann Neurol 64:200–211

Pack AM (2010) Implications of hormonal and neuroendocrine changes associated with seizures and antiepileptic drugs: a clinical perspective. Epilepsia 51(Suppl 3):150–153

Pennell PB (2009) Hormonal aspects of epilepsy. Neurol Clin 27:941–965

Prabhakar S, Sahota P, Kharbanda PS, Siali R, Jain V, Lal V, Khurana D (2007) Sodium valproate, hyperandrogenism and altered ovarian function in Indian women with epilepsy: a prospective study. Epilepsia 48:1371–1377

Quigg M, Smithson SD, Fowler KM, Sursal T, Herzog AG (2009) Laterality and location influence catamenial seizure expression in women with partial epilepsy. Neurology 73:223–227

Rauchenzauner M, Haberlandt E, Scholl-Bürgi S, Karall D, Schoenherr E, Tatarczyk T, Engl J, Laimer M, Luef G, Ebenbichler CF (2008) Effect of valproic acid treatment on body composition, leptin and the soluble leptin receptor in epileptic children. Epilepsy Res 80:142–149

Rauchenzauner M, Bitsche G, Svalheim S, Tauboll E, Haberlandt E, Wildt L, Rostasy K, Luef G (2010) Effects of levetiracetam and valproic acid monotherapy on sex-steroid hormones in prepubertal children—results from a pilot study. Epilepsy Res 88:264–268

Reddy DS (2009) The role of neurosteroids in the pathophysiology and treatment of catamenial epilepsy. Epilepsy Res 85:1–30
Reddy DS, Rogawski MA (2009) Neurosteroid replacement therapy for catamenial epilepsy. Neurotherapeutics 6:392–401
Ross IP (1958) Acetazolamide therapy in epilepsy. Lancet 2:1308–1309
Røste LS, Taubøll E, Svalheim S, Gjerstad L (2008) Does menopause affect the epilepsy? Seizure 17:172–175
Scharfman HE, Kim MK, Hintz TM, MacLusky NJ (2008) Seizures and reproductive function: insights from female rats with epilepsy. Ann Neurol 64:687–697
Verrotti A, Basciani F, Morresi S, de Martino M, Morgese G, Chiarelli F (1999) Serum leptin changes in epileptic patients who gain weight after therapy with valproic acid. Neurology 53:230–232
Verrotti A, Manco R, Agostinelli S, Coppola G, Chiarelli F (2010) The metabolic syndrome in overweight epileptic patients treated with valproic acid. Epilepsia 51:268–273
Verrotti A, D'Egidio C, Mohn A, Coppola G, Parisi P, Chiarelli F (2011) Antiepileptic drugs, sex hormones, and PCOS. Epilepsia 52:199–211
Wong HY, Chu TS, Lai JC, Fung KP, Fok TF, Fujii T (2005) Sodium valproate inhibits glucose transport and exacerbates Glut1-deficiency in vitro. J Cell Biochem 96:775–785
Xiaotian X, Hengzhong Z, Yao X, Zhipan Z, Daoliang X, Yumei W (2013) Effects of antiepileptic drugs on reproductive endocrine function, sexual function and sperm parameters in Chinese Han men with epilepsy. J Clin Neurosci 20:1492–1497
Zimmerman AW, Holder DT, Reiter EO, Dekaban AS (1973) Medroxyprogesterone acetate in the treatment of seizures associated with menstruation. J Pediatr 83:959–963