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CRITICAL REVIEW AND INVITED COMMENTARY

Antiepileptic drugs, sex hormones, and PCOS

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Summary

Reproductive endocrine dysfunction in women with epilepsy is an important issue, and in recent years there is growing evidence to support the effect on sex hormones of both epilepsy per se and various antiepileptic drugs (AEDs). Focal epileptic discharges from the temporal lobe may have a direct influence on the function of the hypothalamic–pituitary axis, thereby altering the release of sex steroid hormones. The role of laterality and severity of epilepsy is still conflicting. The use of the liver enzyme–inducing AEDs—such as phenobarbital, phenytoin, and carbamazepine—can increase serum sex hormone–binding globulin concentrations, leading to diminished bioactivity of testosterone (T) and estradiol. Valproic acid, an enzyme inhibitor, has been associated with the occurrence of reproductive endocrine disorders characterized by high serum T, free androgen index, androstenedione, dehydroepiandrosterone sulfate concentrations, and with polycystic changes in ovaries and menstrual disorders. A better understanding of the effects of AEDs on sex hormones is key to selecting the appropriate AEDs and is crucial for reproductive health in female patients.

KEY WORDS: Epilepsy, Amenorrhea, Hirsutism, Sex hormone-binding globulin, Testosterone, Estradiol, Dehydroepiandrosterone sulfate.

Reproductive endocrine dysfunction is more common among women with epilepsy than in the healthy population (Bauer et al., 2002; Luef et al., 2002a; Luef & Rauchenzauner, 2009). It manifests itself as menstrual disorder, hirsutism, and polycystic changes in the ovaries (Herzog et al., 1986). However, it is difficult to determine whether hormonal abnormalities are due to epilepsy-related hypothalamic–pituitary axis (HPA) dysfunction or to side effects of antiepileptic drugs (AEDs). This review focuses on the effects both of epilepsy itself and of AEDs on the sex hormones and reproductive function.

Sex Hormones and Epilepsy

Reproductive endocrine disorders have frequently been reported in epileptic women. These abnormalities include polycystic ovary syndrome (PCOS) (Herzog et al., 1986; Webber et al., 1986; Bilo et al., 1988; Meo et al., 1993; Drislane et al., 1994; Herzog & Schachter, 2001; Isojärvi et al., 2001a; Herzog & Friedman, 2002; Herzog et al., 2003a,b; Sahota et al., 2008; Gorkemli et al., 2009) as well as isolated components of this syndrome such as polycystic ovaries (PCOs) (Isojärvi et al., 1993, 1996, 1998; Betts et al., 2003) or hyperandrogenism (Bilo et al., 1991; Luef et al., 2002a; Herzog et al., 2003b; Löfgren et al., 2007), hypothalamic amenorrhea (HA) (Herzog et al., 1986), and hyperprolactinemia (Bauer et al., 1989; Rao et al., 1989; Bauer, 1996; Bauer & Cooper-Mahkorn, 2008).

The function of the HPA, including the production of luteinizing hormone (LH), follicle-stimulating hormone (FSH), gonadotropin-releasing hormone (GnRH), and prolactin (PRL), and the concentrations and metabolism of its end-products, such as estrogen (E), testosterone (T), and dehydroepiandrosterone (DHEAS), is modified in many women with epilepsy (Morrell, 2003). Epilepsy itself may have effects on reproductive endocrine function (Herzog et al., 1986; Bilo et al., 1988; Isojärvi et al., 2005; Scharfman et al., 2008). Endocrinologic changes associated with epilepsy can reasonably be expected in view of the complex interconnections between the HPA and limbic system. Outputs to the HPA from the limbic cortex, including nuclear structures within the amygdala, can modify key factors in the release of sex hormones. The involvement of medial temporal lobe regions in epilepsy may cause changes in sex hormone secretion and reproductive function (Herzog et al., 1986; Herzog & Friedman, 2002). This hypothesis is suggested by the evidence from preclinical investigations showing that the induction of temporolimbic seizures in

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animals can cause changes in reproductive hormone levels (Edwards et al., 1999; Hum et al., 2009; Scharfman et al., 2009). However, the possible endocrine influence of epilepsy was increasingly noted when postictal elevations in serum concentrations of PRL were assumed to be a marker of retrospective evidence of epileptic seizures (Bauer, 1996). Epileptic activity in the frontal lobe exhibits propagation toward the temporal lobe and, thereby, influences the hormonal pathway of PRL, inducing abnormal elevation of this hormone (Sperling et al., 1986; Bauer et al., 1998). Limbic efferents seem to exhibit an impact on the HPA, even in the interictal phase of the disorder: In fact, some hormonal changes can show close temporal relationship with the occurrence of interictal epileptiform discharges (Herzog et al., 2003a). Moreover, menstrual disorders have been found to be significantly more common among women with interictal discharges as well as those with associated abnormal neuroendocrine regulation (Herzog et al., 2003a). The presence of increased LH pulse frequency in untreated or drug-free epileptic women with regular menstrual cycles supports the notion that epilepsy itself may contribute to reproductive abnormalities (Bilo et al., 2001). Indeed, high levels of LH and an altered LH-to-FSH ratio have been reported in women with epilepsy (Bauer et al., 2002; Morrell et al., 2002; Hamed et al., 2007). Some studies suggest that the pituitary release of LH in women with epilepsy is altered both spontaneously and in response to GnRH (Herzog et al., 1986; Drislane et al., 1994; Löfgren et al., 2007).

It is probable that in patients with epilepsy, the progression toward a specific reproductive disorder may depend on additional factors, those related to the characteristics of the seizure disorders, the endocrine susceptibility of the patient, and the use of different AEDs (Bilo et al., 2001).

Mechanisms by which epilepsy may induce reproductive disorders in women are presented in Fig. 1.

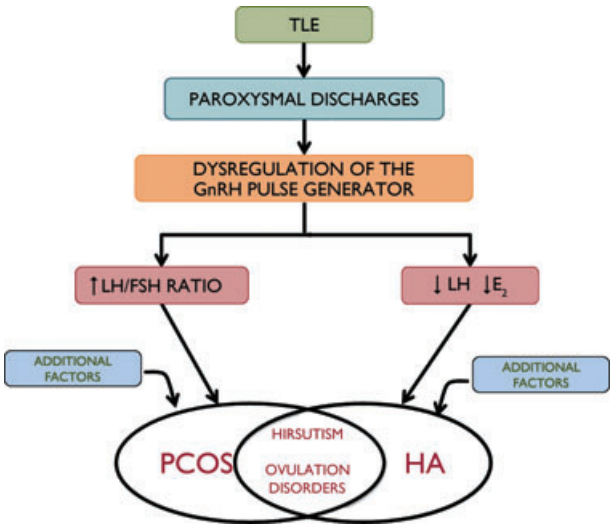

Figure 1.
Pathogenic mechanisms by which epilepsy itself may induce reproductive disorders in women. The involvement of temporal lobe regions in epilepsy may cause a propagation of paroxysmal discharges toward the hypothalamus and, thereby, disrupt the activity of the GnRH pulse generator. Increase of the pulse frequency of GnRH secretion and, consequently, of the LH/FSH ratio is associated with PCOS. In contrast, a lower GnRH pulse frequency causes a decrease of LH and E2 levels that is characteristic of HA. Furthermore, additional factors (laterality of epilepsy, severity of seizures, obesity, genetic factors, endocrine susceptibility, type of AED, and age that treatment is started) may contribute to the clinical expression of specific reproductive disorders (PCOS, HA, hirsutism, ovulation disorders).
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Seizure frequency and sex hormones

With regard to the real role of seizure frequency, we can tentatively acknowledge the existence of a possible relationship between sex steroids and seizure frequency. Interestingly, a recent study of Murialdo et al. (2009) evaluated this relationship in women with partial epilepsy who were receiving AED treatments. Estradiol (E2), free E2, and progesterone (Pg) levels were lower in both ovarian phases, whereas those of sex hormone–binding globulin (SHBG) were higher than in controls; luteal free E2 and Pg levels were chiefly impaired in women with more frequent seizures, mostly those taking AED polytherapies, but not in those with absent or rarer seizures. An inverse relationship was found between free E2 levels and seizure frequency scores during the follicular phase and with disease duration in the luteal one. Accordingly, previous studies (Svalheim et al., 2003; Galimberti et al., 2005) have indicated that menstrual disorders were more frequent in patients with high seizure frequency.

Probably the severity of epilepsy can have a role in the development of sex hormone abnormalities.

Reproductive endocrine disorders related to different types of epilepsy

Experimental and human studies (Edwards et al., 1999; Quigg et al., 2002; Baird et al., 2003; Herzog et al., 2003a) have demonstrated that reproductive endocrine and sexual dysfunction are more common in patients with partial epilepsy than in patients with generalized epilepsy, particularly that of temporal lobe origin. Interestingly, Herzog et al. (1986), examining 50 women with temporolimbic epilepsy, found 28 patients with amenorrhea, oligomenorrhea, or abnormally long or short menstrual cycle intervals; 19 of the 28 women with epilepsy and menstrual disorders had reproductive endocrine disorders: PCOS in 10, HA in 6, premature menopause in 2, and hyperprolactinemia in one patient. No significant relationship between the occurrence of menstrual disorders and the use of AEDs has been found, suggesting that epilepsy may have an independent effect on reproductive function. This is in agreement with a report of a previous study (Bilo et al., 2001) that describes a signifi-

cantly higher frequency of ovulatory dysfunction in female patients, not linked to the use of any specific AED.

Nevertheless, other studies (Bilo et al., 1988; Morrell et al., 2002; Löfgren et al., 2007) demonstrated that hyperandrogenemia, PCOs, and PCOS are more frequent in women with idiopathic generalized epilepsy than in location-related epilepsy.

There is no evidence to suggest whether reproductive disorders are more common in localization-related epilepsy or generalized epilepsy.

Reproductive dysfunctions related to the laterality of epilepsy

Laterality of epilepsy may be an important determinant of certain reproductive endocrine disorders (Herzog et al., 1986; Herzog, 1993; Baird et al., 2003; Herzog et al., 2003a,b): Unilateral temporal lobe discharges are associated with laterally differing changes in hormonal secretion at all levels of the neuroendocrine reproductive axis; consequently, different reproductive disorders may develop in relation to left- and right-sided temporolimbic epilepsy; particularly, left unilateral temporal lobe epilepsy (TLE) is associated with a higher occurrence of PCOS (Herzog & Schachter, 2001; Herzog et al., 2003a). Seizures on the left side of the limbic system increase the pulse frequencies of GnRH secretion which, in turn, increases the LH/FSH ratios and T levels. This combination of neuroendocrine changes characterizes PCOS. Ten percent to 20% of women with left unilateral TLE have been found to have PCOS, in comparison with about 5–6% in the general population (Herzog & Schachter, 2001) In contrast, right TLE is associated with lower GnRH pulse frequency, which causes a decrease in LH and E2 levels and, consequently, HA (Herzog et al., 1986, 2003a; Webber et al., 1986; Herzog, 1993; Kalinin & Zheleznova, 2007).

Nevertheless, the data from animal studies show conflicting results. In fact, in the amygdala kindling rat model, seizures originating in the left or right amygdala do not result in lateralized effects on the reproductive system (Hum et al., 2009). In contrast, Silveira et al. (2000) showed that unilateral amygdaloid seizures in female rats activated hypothalamic neurons regulating reproductive secretion in a laterally asymmetric fashion; this may explain the clinical association of different reproductive endocrine disorders with left and right TLE.

In conclusion, the evidence of association between laterality of epilepsy and reproductive disorders is inconsistent.

Epilepsy and sexual dysfunction

Epileptic discharges in limbic structures may contribute to sexual dysfunction in women such as lack of sexual interest; high rates of orgasmic dysfunction including anorgasmia, dyspareunia, vaginism; or insufficient vaginal lubrication (Crawford et al., 1999; Harden, 2008). Sexuality in people with epilepsy may be affected by alterations in the pituitary gonadotropins and PRL and in sex steroid hormones (Herzog et al., 1986; Morrell et al., 2002). However, the etiology of sexual dysfunction with epilepsy seems to be multiple; in addition to the effect of hormonal reproductive disorders on sexual dysfunction encountered in epilepsy, the disorder itself appears to have the potential to affect sexual function. The amygdala is a brain structure involved in sexuality, as shown by alterations in sexual functioning after temporal lobectomy (Baird et al., 2003). After surgery, the seizure-free group experienced a higher level of sexual satisfaction than non–seizure-free group (Christianson et al., 1995).

The different pattern of sexual dysfunction found in different seizure types is an important consideration. Women with primary generalized epilepsy experience anorgasmia and sexual dissatisfaction, whereas women with localization-related epilepsy experience more sexual anxiety, dyspareunia, and vaginism (Morrell & Guldner, 1996). Furthermore, it has been reported a lateralization asymmetry of the pattern of sexual dysfunction (Herzog et al., 1986; Murialdo et al., 1997); Herzog et al. (1986) found that right temporal epileptic discharges in women were associated with hypogonadotropic hypogonadism including decreased sexual interest. Accordingly, hyposexuality was more prominent in women with right TLE than in women with left TLE (Murialdo et al., 1997). In contrast, other studies (Jensen et al., 1990; Svalheim et al., 2009) found no difference in sexual satisfaction in male and female outpatients compared to healthy controls. It is important to consider that sexual function is not an easy parameter to measure, although few scales are available, for example, the Arizona Sexual Experience Scale. Moreover, sexuality is not only affected by the epileptic discharges and AEDs, but definitely also by many other factors: psychological (e.g., quality of intimate partner relationship, women sexual-self image), social (e.g., public health services), and cultural (e.g., religious practice, interest in sexual activity); and finally, neurologic factors such as seizure frequency and comorbidity (e.g., headache, mood disorders) are also important.

In conclusion, epilepsy itself, whether partial or generalized, could affect sexual function in women with epilepsy.

Sex Hormones and AEDs

Although women with epilepsy may already have a higher prevalence of reproductive endocrine disorders, the treatment with certain AEDs may increase this risk (Isojärvi, 2008; Luef & Rauchenzauner, 2009; Verrotti et al., 2009).

A large body of literature addresses the presence of alterations in sex hormone levels in women on AED therapy (Dana-Haeri et al., 1982; Beastall et al., 1985; Levesque et al., 1986; Isojärvi, 1990; Isojärvi et al., 1993; Murialdo et al., 1998; Bauer et al., 2002; Morrell et al., 2002; Isojärvi et al., 2005; Hamed et al., 2007; Herzog, 2008).

AEDs may have a variety of influences on the metabolism of some sex hormones and their binding proteins that may result in secondary complications (Bauer et al., 2002). In particular, enzyme-inducing AEDs (EIAEDs)—such as phenobarbital (PB), phenytoin (PHT), and carbamazepine (CBZ)—rather than non-EIAEDs (NEIAEDs) seem to be most clearly linked to altered metabolism of sex steroid hormones.

EIAEDs

The possibility that abnormal serum sex hormone levels in women with epilepsy can be caused by the enzyme-inducing properties of certain AEDs was suggested in the late 1970s and 1980s, when a reduction of sex steroid levels, such as estradiol (E2) and DHEAS, was reported in female patients treated with some EIAEDs (Dana-Haeri et al., 1982; Beastall et al., 1985; Levesque et al., 1986). A possible explanation for this alteration was suggested by Victor et al. (1977), who reported elevated serum concentrations of SHBG in women treated with PHT. EIAEDs can induce hepatic cytochrome P450–dependent steroid hormone breakdown and production of SHBG, reducing biologically active sex hormone serum concentrations, such as E2 and T (Bauer et al., 2002; Isojärvi et al., 2005; Herzog, 2008). The main hormonal effects induced by AED monotherapy are reported in Table 1.

Low DHEAS levels have been reported in women taking PHT (Levesque et al., 1986). Similarly, impaired steroid levels have also been shown in women with epilepsy treated with other EIAEDs (Murialdo et al., 1998; Galimberti et al., 2005, 2009). Galimberti et al. (2005) reported decreased DHEA levels and increased cortisol levels in women treated with CBZ, PHT, and PB in monotherapy or polytherapy, but not in those treated with NEIAEDs. Moreover, women with epilepsy who were taking EIAED polytherapies had lower levels E2 and free estrogen index (FEI) than patients treated with a single EIAED: The older patients and those with longer disease duration show higher levels of SHBG (Galimberti et al., 2009). This can be attributed to the physiologic increase in binding protein levels with aging and to the use of EIAEDs. These changes in serum SHBG levels, and the lowered total E2 levels, suggest a global decrease in biologically active free E2. Conversely, significant differences in E2 levels and in FEI were found between women on different AED regimens. Patients treated with EIAED polytherapies showed E2 and FEI values that were lower than those recorded both in patients treated with a single EIAED or NEIAED, and in those on combined (EIAED plus NEIAED) therapies.

Recently, the expression of androgen receptor (AR), estrogen receptor α (Erα), and cytochrome P450-3A (CYP3A) has been analyzed in the hippocampus of patients with TLE and in murine hippocampal cell line HN25.1. In both humans and cell lines, the expression of T metabolizing CYP3A4 (human) or CYP3A11 (mouse) and AR was upregulated when EIAEDs had been applied (Killer et al., 2009). These findings suggest that EIAEDs influence AR expression and signaling in hippocampus most likely via CYP3A4/11-induction.

To date, among EIAEDs (CBZ is the most studied drug), increased serum levels of SHBG and reduced serum concentrations of DHEAS, T, free androgen index (FAI), and E2 have been reported (Isojärvi, 1990; Isojärvi et al., 1993, 1995; Murialdo et al., 1997; Rättyä et al., 2001; Hamed et al., 2007; Löfgren et al., 2007; Lossius et al., 2007; Jacobsen et al., 2008). In particular, an increase in serum SHBG concentrations with low E2 levels and E2/SHBG ratio was noted during the first 5 years of CBZ treatment. Furthermore, menstrual disorders in patients with normal ovaries were associated with increased serum SHBG levels and low E2/SHBG ratio (Isojärvi et al., 1995). Increase in SHBG serum concentrations and resulting decreased serum free E2 may interfere with the feedback regulation of pituitary secretion, which may lead to anovulation and menstrual disorders.

Decrease of free serum T levels during CBZ treatment due to an induction of SHBG was also documented (Isojärvi, 1990; Isojärvi et al., 1995; Stoffel-Wagner et al., 1998), and free T serum concentrations rise when patients are switched from CBZ to oxcarbazepine (OXC), which causes less hepatic induction (Isojärvi et al., 1995). Recently, a double-blind, randomized, controlled withdrawal study (Lossius et al., 2007) reported that CBZ withdrawal was associated with a decrease in SHBG levels and an increase in serum T concentrations, FAI, and E/SHBG ratio, suggesting that potential changes in sex steroid levels are reversible.

Only two studies (Dana-Haeri et al., 1984; Hamed et al., 2007) have reported abnormalities in basal or stimulated serum gonadotropin or PRL levels in women taking CBZ. Dana-Haeri et al. (1984) observed that epileptic patients on CBZ had elevated baseline LH levels and exaggerated LH response to the GnRH and thyrotropin-releasing hormone (TRH) stimulation. This response may be related to a positive feedback mechanism. Furthermore, they reported slightly higher PRL levels 2 h after stimulation with GnRH and TRH. More recently, Hamed et al. (2007) reported increased levels of LH an FSH in 28.1% and 34.4% of CBZ-treated patients, respectively. These changes have not been confirmed by other studies (Bonuccelli et al., 1985; Isojärvi et al., 1989; Murialdo et al., 1998; Lossius et al., 2007).

NEIAEDs

Among NEIAEDs, valproate (VPA) appears to be associated with reproductive endocrine disorders, such as polycystic changes in the ovaries, high serum concentrations of T and androstenedione (A), increase in levels of LH and LH/FSH ratio, and amenorrhea (Isojärvi et al., 1993; Rättyä et al., 2001; Stephen et al., 2001; Svalheim et al., 2003; Morrell et al., 2005; Prabhakar et al., 2007; Cansu, 2010;

Table 1. Laboratory and clinical features in patients with epilepsy treated with AEDs

AED	Study	T	SHBG	FAI	A	DHEAS	E2	Other data
PB	Murialdo et al. (1997)	≠	≠	≠	NA	NA	↓	
	Murialdo et al. (1998)	≠	≠	≠	NA	NA	↓	
PHT	Victor et al. (1977)	NA	↑	NA	NA	NA	NA	
	Levesque et al. (1986)	NA	NA	NA	NA	↓	NA	
	Isojärvi (1990)	↓	↑	↓	NA	↓	≠	These hormonal changes are associated with low levels of circulating thyroxine and free thyroxine
CBZ	Isojärvi (1990)	↓	↑	↓	NA	↓	≠	
	Isojärvi et al. (1993)	≠	↑	NA	NA	NA	≠	
	Isojärvi et al. (1995)	↓	↑	NA	NA	NA	↓	Menstrual disorders are associated with increased serum SHBG levels and low E2/SHBG ratio
	Murialdo et al. (1998)	↓	≠	≠	NA	↓	↓	
	Isojärvi et al. (2001a)	≠	↑	≠	NA	NA	≠	Menstrual disorders are reported only in 6% of women
	Rättyä et al. (2001)	≠	↑	≠	NA	NA	≠	
	Löfgren et al. (2006)	↓	↑	↓	≠	≠	≠	Low E2/SHBG ratio is not associated with menstrual disorders
	Lossius et al. (2007)	↓	↑	↓	NA	NA	NA	CBZ withdrawal is associated with a significant decrease in SHBG levels and an increase in serum T concentrations, FAI, and E/SHBG ratio
VPA	Isojärvi et al. (1993)	↑	≠	NA	NA	NA	≠	43% of the women receiving VPA had PCO
	Isojärvi et al. (1996)	↑	↓	NA	≠	↑	NA	T concentration is more elevated in women initiating treatment at the age <20 years
	Murialdo et al. (1998)	↑	≠	↑	↑	NA	↓	63.6% of patients had luteal Pg levels consistent with impaired ovulation
	Vainionpää et al. (1999)	↑	≠	↑	NA	NA	≠	Hyperandrogenism in 38% of prepubertal, 36% of pubertal and 57% of postpubertal girls
	Isojärvi et al. (2001a,b)	↑	↑	↑	NA	NA	NA	8% of patients has amenorrhea, 41% oligomenorrhea, and 11% irregular cycles
	Rättyä et al. (2001)	↑	↑	≠	↑	NA	≠	LH and FSH are increased
	Stephen et al. (2001)	↑	≠	↑	≠	≠	NA	4 obese patients are hyperinsulinemic: 3 with abnormal menstrual cycles, 1 with raised T
	Morrell et al. (2003)	↑	NA	NA	↑	NA	NA	Mean weight increased by 3.7 kg
	Prabhakar et al. (2007)	↑	NA	NA	NA	↑	NA	Of the 25 women, 40% had weight gain, 20% hirsutism, 24% menstrual disorders, and 24% PCO
	Rauchenzauner et al. (2010)	≠	≠	NA	↑	≠	≠	

T, testosterone; SHBG, sex hormone-binding globulin; FAI, free androgen index; A, androstenedione; DHEAS, dehydroepiandrosterone sulfate; E2, estradiol; LH, luteinizing hormone; FSH, follicle-stimulating hormone; Pg, progesteron; PB, phenobarbital; PHT, phenytoin; CBZ, carbamazepine; VPA, valproic acid; NA, not available; ↑, increased; ↓, decreased; ≠, unchanged.

Rauchenzauner et al., 2010). These abnormalities are especially common among women who have gained weight during VPA therapy (Herzog, 2008). In 1993, Isojärvi et al. (1993) through a cross-sectional study showed that menstrual disorders were common among women taking VPA monotherapy for epilepsy, and that they were frequently associated with PCO and/or hyperandrogenism. PCO and hyperandrogenism seem to be common if VPA was started before the age of 20 years (see Newer EADs).

It is still impossible to predict the ovary dysfunction in VPA-treated women. In fact, Morrell et al. (2002) studied indicators of ovulatory failure in 94 women with VPA therapy: 38.1% had experienced at least one anovulatory cycle in contrast to 10.7% of women not using VPA within the preceding 3 years. It is interesting to note that women with idiopathic generalized epilepsy receiving VPA were at the highest risk of anovulatory cycles, PCO, elevated body mass index (BMI), and hyperandrogenism.

A significant increase in serum T concentrations was especially prominent in women who initiated treatment at an age <20 years, suggesting that young women with epilepsy seem to be especially vulnerable to the effects of VPA (Isojärvi et al., 1996).

Alterations in serum androgen levels have been detected already before and during pubertal development in young girls, 8–18 years old, taking VPA (Vainionpää et al., 1999). Serum T levels and FAI were high in all pubertal phases in girls on VPA, even if the frequency of hyperandrogenism

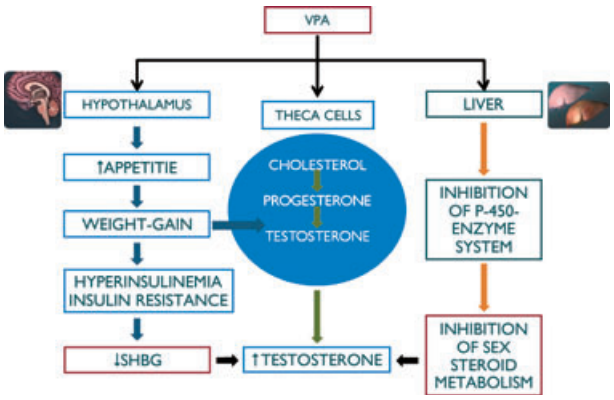

Figure 2.
Mechanisms of induced hyperandrogenism by VPA. VPA may induce hyperandrogenism through an indirect effect. VPA has a stimulating effect on the hypothalamus leading to increased appetite and, thereby, weight gain. This weight gain causes insulin resistance and related hyperinsulinemia; by suppressing the synthesis of SHBG, insulin increases free testosterone concentrations. Another hypothesis is that VPA leads to hyperandrogenism through direct effects on the ovary. VPA stimulates androgen biosynthesis in human theca cells in vitro. In addition, VPA has an inhibitory effect on the hepatic P450 enzyme system and, thereby, it may inhibit the metabolism of sex steroids such as T, hence provoking increased androgen levels.

increased with pubertal development; in fact, hyperandrogenism was found in 38% of prepubertal, 36% of pubertal, and 57% of postpubertal girls. Similar findings were noted by El-Khayat et al. (2004). VPA may affect steroid metabolism during the sensitive period, at the onset of puberty. Accordingly, hyperandrogenism observed in most adult women on VPA therapy can be induced already before clinical signs of puberty. Recently, VPA treatment has been associated with higher T levels only after menarche, suggesting that the sensitivity to VPA-induced hyperandrogenism is a function of sexual maturation (de Vries et al., 2007).

However, it is encouraging to note that the reproductive endocrine effects of VPA may be reversible after the medication is discontinued. In a 5-year follow-up study the 60% of the patients who were on VPA during the follow-up study had PCOS as compared to 5.5% of the girls whose medication had been discontinued (Mikkonen et al., 2004).

The mechanism by which VPA could cause hyperandrogenism and related reproductive disorders is still unclear. VPA can have a direct effect on ovarian androgen production or it may inhibit the metabolism of sex hormones and thereby lead to increased serum androgen levels (Dana-Haeri et al., 1982; Verrotti et al., 2006) (Fig. 2). Furthermore, VPA may cause inappropriate LH secretion through its effect on gonadotropin pulsatility with simultaneous reduction of FSH and E2 synthesis, hence increasing the levels of T (Drislane et al., 1994). Moreover, hyperinsulinemia associated with VPA-related weight gain may further stimulate T secretion from the ovaries, and high serum insulin levels in obese VPA-treated women reduce serum SHBG levels, which further increases the bioactivity of T (Hamed et al., 2007) (see subsequent text of this article).

Finally, VPA can block the AR and progesterone receptor (PgR), but not the ER (Lydon et al., 1996). The PgR antagonism by VPA suggests that some biologic effects in women may be at least partly due to impaired PgR-mediated Pg action on reproductive tissue, and may be a previously unrecognized factor contributing to the low fertility of women with epilepsy. Antiprogestin effects may contribute to the higher frequency of anovulation among VPA-treated women with epilepsy (Stephen et al., 2001).

Recently, Jacobsen et al. (2008) reported that VPA, PB, PHT, OXC, and lamotrigine (LTG), but not CBZ, inhibit the aromatase complex (CYP19) activity that converts T in E2 in vitro. Accordingly, VPA and LTG reduced CYP19 aromatase activity in human ovarian follicular cells, but only in FSH-stimulated cells and at higher concentrations (Taubøll et al., 2009). Additive enzyme inhibition has been observed in vivo, mainly when combined AED therapies were employed (Galimberti et al., 2009). Therefore, reduced E2 and Pg levels may be due, in large part, to AED therapies, which interfere with sex steroid synthesis and metabolism; however, a reduced conversion of androgens to E might also be involved.

Newer EADs

The reproductive endocrine effects of new AEDs have not been widely studied. OXC therapy is not associated with changes in reproductive function in patients with epilepsy (Rättyä et al., 1999; Vainionpää et al., 1999). One study (Löfgren et al., 2006) reported low serum T concentrations, low FAI, elevated levels of A and DHEAS, and increased prevalence of PCO in women during OXC treatment. As with OXC treatment, a low prevalence of reproductive disorders has been reported during LTG therapy (Isojärvi et al., 1998; Isojärvi et al., 2005).

Replacement of VPA with LTG normalized endocrine function in women with a previous endocrine disorders (PCO, hyperandrogenism, and increase in body weight) most likely related to VPA medication. Serum insulin and T levels returned to normal in 2 months after VPA replacement, and the levels remained normal thereafter; LTG treatment is not associated with changes in body weight or changes in endocrine functions (Isojärvi et al., 1998). In accordance with these findings, it has been reported that women taking LTG had lower serum T levels and or incidence of ovulatory dysfunction than women taking VPA (Morrell et al., 2003, 2005). Successively, the same authors (Morrell et al., 2008) showed that VPA and LTG appeared to have opposite effects on DHEAS and SHBG: DHEAS decreased and SHBG increased with VPA, whereas SHBG decreased and DHEAS increased with LTG treatment. The

clinical significance of these modest changes in SHBG and DHEAS levels remains unclear.

No reproductive endocrine effects of levetiracetam (LEV) have been described (Harden, 2001; Ben-Menachem, 2003; Briggs & French, 2004): in particular, in the first large cross-sectional study in women (Svalheim et al., 2009), no sex hormones abnormalities were observed during LEV treatment. This reassuring information of no drug-specific endocrine effect of LEV contrasts with data from animal studies (Taubøll et al., 2006; Svalheim et al., 2008). In a recent study (Rauchenzauner et al., 2010), no changes in reproductive endocrine hormones levels were found in prepubertal children treated with LEV.

To date, there are no data available for the other new AEDs (felbamate, gabapentin, tiagabine, topiramate, vigabatrin, and zonisamide).

In conclusion, EIAEDs can modify sex hormone metabolism via different mechanism; however, a common mechanism seems to be the increase of SHBG concentrations leading to diminished bioactivity of E2, which may result in menstrual disorders in some women and thus in reduced fertility. Among NEIAEDs, VPA is associated with more frequent changes in sex hormone serum concentrations that cause hyperandrogenism and polycystic changes, especially among women who have gained weight and in those who start VPA treatment at an age <20 years.

AEDs and PCOS

The incidence of PCO and PCOS appears to be more common among women with epilepsy than among women without epilepsy (Herzog et al., 1986; Bilo et al., 2001; Herzog & Friedman, 2002).

In particular, PCOS occurs in 10–25% of women with epilepsy, even if they are not treated with AEDs, compared with 5–6% of women in the general population (Webber et al., 1986; Isojärvi et al., 2001a; Herzog & Friedman, 2002; Herzog et al., 2003a).

Before analyzing the relationship between AEDs and PCOS, it is important to distinguish PCO from PCOS, because the morphologic appearance of PCO can exist without any clinical signs of the syndrome. PCO is a morphologic finding defined by ultrasonographic and anatomic criteria as the presence of multiple follicular cysts (10 or more) measuring 2–8 mm in diameter and usually distributed in the periphery, but sometimes disseminated, and increased ovarian stroma and/or size (Adams et al., 1985). PCO may not be associated with any hormonal or clinical abnormalities, but the most common feature is erratic or infrequent ovulation giving rise to menstrual irregularity (Adams et al., 1986). PCOS was defined at a National Institutes of Health (NIH) consensus conference as (1) the presence of ovulatory dysfunction (i.e., polymenorrhea, oligomenorrhea, or amenorrhea), (2) clinical evidence of hyperandrogenism or hyperandrogenemia, and (3) exclusion of other endocrinopathies (e.g., hyperprolactinemia, thyroid dysfunction, adrenal hyperplasia, or Cushing syndrome) (Zawadski & Dunaif, 1992). This, more restrictive, definition of PCOS excludes isolated findings of PCO, hyperandrogenism, or multifollicular ovaries.

Recently, the recognition of the wider range of symptomatic presentation of women with PCO prompted a reevaluation of the diagnostic criteria for PCOS at a joint meeting between the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) in Rotterdam (Hart et al., 2004; Franks et al., 2008a). Accordingly, PCOS is diagnosed in the presence of two of three following symptoms: (1) oligomenorrhea, anovulation, (2) hyperandrogenism, and (3) PCO at ultrasound scan. In essence, the Rotterdam criteria expanded the NIH criteria, including in the diagnosis of PCOS also ovulatory women with PCO and hyperandrogenism as well as normoandrogenic oligoanovulatory women with PCO. At the present time, the Rotterdam 2003 criteria are still debated and the NIH criteria continue to be widely accepted.

PCOS is the most common endocrine disorder in women of reproductive age. In its classic form, a combination of oligo/anovulation and hyperandrogenism, it is estimated to affect 5% of the female population (Asuncion et al., 2000; Azziz et al., 2004; Ehrmann, 2005). It is the major cause of anovulatory infertility, menstrual disturbances, and hirsutism. PCOS is also associated with a metabolic disturbance, with peripheral insulin resistance, and with compensatory hyperinsulinemia (Dunaif, 1997; Ehrmann, 2005). These metabolic abnormalities have implications both for reproductive function and for long-term health.

A large body of literature has suggested that treatment with certain AEDs, particularly VPA, increase the incidence of PCOS (Isojärvi et al., 1993, 1995, 1996, 1998, 2001a; Betts et al., 2003; Sahota et al., 2008). However, the analysis of studies evaluating the incidence of this syndrome reveals some discrepancies. The role of VPA in the pathogenesis of PCOS was first raised by Isojärvi et al. (1993), who showed that women using VPA were more likely to have PCO morphology or an elevated T level than those taking other AEDs (56% on VPA vs. 20% non-VPA). Furthermore, nine studies (Isojärvi et al., 1995, 1996, 2001a; Bilo et al., 2001; Morrell et al., 2002; Betts et al., 2003; Prabhakar et al., 2007; Morrell et al., 2008; Sahota et al., 2008) confirmed a significant association between VPA and PCOS. The most recent study of Sahota et al. (2008) reported that PCOS features are frequent and significantly higher (11.8% vs. 2.5%) in women with epilepsy receiving VPA than those taking other AEDs, independent of seizure type. In a trial (Morrell et al., 2008) 447 women without PCOS at baseline were randomized to VPA or LTG for 1 year: those randomized to VPA were significantly more likely to develop hyperandrogenemia or ovulatory dysfunction (indicated by low levels of Pg) than those randomized

to LTG (36% VPA vs. 23% LTG), with 9% of women on VPA (vs. 2% on LTG) developing new-onset PCOS after 1 year of treatment.

In contrast, other six studies have reported no significant association between VPA treatment and PCOS (Bilo et al., 1988; Murialdo et al., 1998; Bauer et al., 2000; Genton et al., 2001; Luef et al., 2002a,b).

Possible explanations for the discrepancy in these studies may be the small sample size of some studies, and the lack of randomization, which may result in differences in the distribution of characteristics that predispose the development of PCOS. Another possible explanation may be the differences in the way in which PCOS is defined. Indeed, this lack of distinction between PCO and PCOS may indicate a falsely high PCOS incidence.

It is important to underscore that in Isojärvi studies (Isojärvi et al., 1993, 1995, 2001a) the authors have not defined VPA-related reproductive endocrine problems as PCOS; in particular, in their first paper published in 1993, the authors conclude that menstrual disorders, PCO, or hyperandrogenism are often encountered in women taking VPA. This fact must be taken into consideration when we discuss the frequency of this complication in women with epilepsy.

In contrast, two comparative cross-sectional studies (Murialdo et al., 1998; Bauer et al., 2000) had the great virtue of using NIH criteria to define PCOS. The first (Murialdo et al., 1998) of these reported PCO in 0% of women taking VPA, 40% of women taking polytherapy including VPA, and 13% of women taking polytherapy that did not include VPA; none of the patients with PCO exhibited PCOS. The second study (Bauer et al., 2000) reported an incidence of PCOS of 10.5% in the untreated group, 10% in CBZ group, and 11.1% in VPA group. Therefore, by NIH criteria in the VPA group the incidences of PCOS are lower than those PCO alone. Therefore, the evidence of the association between VPA treatment and PCOS has led to much debate (Genton et al., 2001; Isojärvi et al., 2001b), and this evidence still remains controversial (Bauer & Cooper-Mahkorn, 2008; Hamed, 2008). Merit, in any case, is due to Isojärvi et al. (1993) for their initial discovery that VPA can induce changes in ovarian structure.

In contrast, the data related to CBZ are more homogeneous. None of the larger studies are showing an increased frequency of PCOS, or any other reproductive endocrine disorders, despite alterations in sex hormone concentrations (Beastall et al., 1985; Isojärvi et al., 1993; Murialdo et al., 1997; Bauer et al., 1998; Murialdo et al., 1998; Bauer et al., 2000; Isojärvi et al., 2001a; Betts et al., 2003; Jacobsen et al., 2008).

Among new AEDs, LTG is not associated with endocrine disorders in women with epilepsy (Betts et al., 2003; Morrell et al., 2003, 2008). Betts et al. (2003) found a low prevalence of PCOS (6%) among women taking either LTG or CBZ. A more recent prospective study (Morrell et al., 2008) demonstrated that more women in the VPA group than the LTG group developed PCOS (9% vs. 2%); no changes in ovarian morphology were observed after long-term LTG therapy in nonepileptic rats (Røste et al., 2001).

Etiology of the syndrome still remains unknown. Three major pathophysiologic hypotheses have been proposed to explain the clinical findings of PCOS related to three major laboratory findings: (1) the LH hypothesis, (2) ovarian hypothesis, and (3) the insulin hypothesis.

LH Hypothesis

PCOS represents failure of the ovarian follicle to complete normal maturation during the menstrual cycle or a series of cycles, a failure that is related to the presence of an altered LH/FSH ratio with inadequate levels of pituitary FSH, and abnormally high LH pulse frequency and amplitude. These conditions produce a failure of ovulation and the partially developed follicle is retained in the ovary in the form of a tiny cyst (Herzog & Schachter, 2001). This partially developed follicle is secretory but deficient in aromatase (the enzyme that converts T to E) and, therefore, it has T as its principal secretory product. T may increase the positive feedback of E on pituitary LH secretion, resulting in increased ovarian steroid secretion, and can result in hyperandrogenism. Androgen excess can be stimulated by excess LH, and the situation compounded if there is a relative reduction in FSH activity.

Ovarian Hypothesis

Impaired ovarian function can be a potential cause of PCOS. In fact, women with PCOS can have increased 17-hydroxyprogesterone levels, an androgen precursor, in theca cells (Ibañez et al., 1996). The increase of androgen synthesis in PCOS theca cells may be caused by a genetic defect leading to dysregulation of enzymes involved in androgen biosynthetic pathways (Gilling-Smith et al., 1997).

Insulin Hypothesis

The insulin hypothesis links the pathogenesis of PCOS with insulin resistance/hyperinsulinemia.

PCOS can be stimulated by decreased peripheral insulin sensitivity and hyperinsulinemia (Dunaif, 1997); insulin inhibits the production of insulin-like growth factor 1 (IGFBP-1) and SHBG levels in the liver (Hamilton-Fairley et al., 1993). Inhibition of insulin-like growth factor binding protein-1 (IGFBP-1) in the ovary would result in an increased concentration of free insulin-like growth factor 1 (IGF-1) (Cataldo, 1997). Both insulin and IGF-1 stimulate thecal androgen production (Bergh et al., 1993) and reduce SHBG levels, resulting in free T (Hopkinson et al., 1998). Therefore, hyperinsulinemia in women with PCOS increases the secretion of ovarian androgen bioavailability and promotes androgen bioavailability.

However, it is unlikely that a single mechanism could be applied to all cases of PCOS. The pathogenesis of PCOS is believed to be multifactorial, including the effects of multiple environmental factors, on a genetically predisposed individual (Franks et al., 1997; Bauer et al., 2000). Factors in favor of a genetic predisposition include the observation that women/girls with PCOS are found in family clusters along with other members with PCOS, infertility, insulin resistance, type 2 diabetes mellitus, and metabolic syndrome (Lunde et al., 1989). Weight gain is another important factor (Betts et al., 2001; Duncan, 2001; Rasgon, 2004; Martínez-Bermejo et al., 2007; Franks, 2008b).In fact, PCOS is commonly associated with weight gain, and it has been reported that up to 50% of women with PCOS are obese (Balen et al., 1995; Dunaif, 1995; Lobo & Carmina, 2000). Furthermore, obesity has a significant impact on the clinical and endocrine presentation of women with PCOS (Conway et al., 1989; Vrbikova & Hainer, 2009). Overweight women with PCOS are more likely to be anovulatory and to have symptoms of androgen excess (Balen et al., 2006).

The mechanism of the effects of obesity on reproductive function is complex, but hyperinsulinemia and/or insulin resistance appear to play an important part. There is a disadvantageous interaction between PCOS and obesity in that although obesity is associated with reduced insulin sensitivity in normal women, obese women with PCOS are relatively more insulin resistant than BMI-match subjects with normal ovaries (Ehrmann, 2005).

The positive correlation between insulin resistance and obesity means that in some women with PCO, the clinical manifestation of menstrual irregularity and hirsutism will become apparent only if there is an increase in weight (Polson, 2003).

An important risk factor for PCOS is weight gain and related insulin resistance, which is a common and undesirable effect of certain AEDs, notably VPA and, to a lesser extent, CBZ, vigabatrin, and gabapentin (Biton et al., 2001; Jallon & Picard, 2001; Wirrell, 2003; Mikkonen et al., 2004; Rauchenzauner et al., 2008a; Hamed et al., 2009; Sharpe et al., 2009; Verrotti et al., 2010). Weight gain may lead to the expression or exacerbation of PCOS, reducing insulin sensitivity in some genetically predisposed women. Therefore, AED-related weight increases could trigger the manifestation of clinically relevant endocrine disorders.

The pathogenetic mechanisms underlying weight gain during VPA treatment are still unclear (Egger & Brett, 1981; Dinesen et al., 1984; Gidal et al., 1996). The observation that VPA-treated epileptic patients, who have reported weight gain, developed increased appetite, thirst, and quenching with calorie-rich beverages supports the hypothesis of a stimulating effect of VPA on the hypothalamus (Covanis et al., 1982; Dinesen et al., 1984).

VPA-related obesity may be associated with elevated serum leptin levels in women with epilepsy (Verrotti et al., 1999; Rauchenzauner et al., 2008b), but it is unclear whether leptin behavior in VPA-induced obesity is similar to that of any other obesity situation (Pylvänen et al., 2002). VPA can modify leptin levels through the increase of body weight, and this modification is related to BMI. It is likely that obesity is the cause of insulin resistance and related hyperinsulinemia (Verrotti et al., 2009), which are often associated with PCOS (Dunaif & Thomas, 2000). By suppressing the synthesis of SHBG, insulin increases free androgen concentrations, subsequently increasing the degree of hirsutism. In some women with PCO, the clinical manifestation of menstrual irregularity and hirsutism will become apparent only if there is an increase in weight and associated metabolic changes (Polson, 2003).

It has been also proposed that weight gain is associated with low serum IGFBP-1 levels, which may lead to hyperandrogenism and PCO (Isojärvi et al., 1996). A significant weight gain was recorded in a retrospective analysis of hospital records of the women on VPA who also had PCO and hyperandrogenism; these women had higher insulin and lower IGFBP-1 levels.

Moreover, it is probable that VPA, as a branched chain fatty acid, is able to compete with free fatty acids for albumin binding, thereby increasing their local availability and thus their physiologic modulation of insulin secretion (Luef et al., 2002a). On the other side, VPA can directly stimulate pancreatic β-cells (Luef et al., 2003) and inhibit glucose transporter protein type 1 (GLUT-1) activity (Wong et al., 2005). Other proposed mechanisms include an inhibitory effect on sympathetic nervous system and an impairment of insulin signal transduction pathway through the inhibition of GLUT-1 activity (Wong et al., 2005).

Finally, recent evidence suggests that VPA leads to hyperandrogenemia and PCOS features through direct effects on the ovary. It has been suggested that, given that VPA inhibits the microsomal epoxide hydrolase enzyme activity (Hattori et al., 2000; McIntyre et al., 2003), it can suppress the aromatase activity in granulosa cells, so that T produced by theca interna cells is not converted to E2 in the follicles. This could lead to the androgen-dominant microenvironment in the ovary and then to polycystic change of the ovary. Moreover, VPA stimulates androgen biosynthesis in human theca cells at doses that represent therapeutic levels in the treatment of epilepsy: VPA-induced ovarian androgen biosynthesis results from changes in chromatin modifications (histone acetylation) that augment transcription of steroidogenic genes. These data establish a direct link between VPA and increased ovarian androgen biosynthesis (Nelson-DeGrave et al., 2004). Microarray data have also shown common gene expression profiles in PCOS and VPA-treated normal theca cells that are not seen in normal, untreated theca cells, suggesting that similarities in theca cells function may explain the features of PCOS that develop in some women treated with VPA (Wood et al., 2005). Furthermore, VPA has been shown to

alter steroidogenesis and increase T to E2 ratios in porcine ovarian follicles (Gregoraszczuk et al., 2000). VPA increased the number of follicular cysts and altered sex steroid hormone levels in rats (Taubøll et al., 1999; Røste et al., 2001). It remains to be proven that these direct gonadal VPA effects are relevant in humans; perhaps, the younger ovary may be more vulnerable to this effect. Indeed, several studies (Isojärvi et al., 1993; Joffe et al., 2006; Löfgren et al., 2007; Morrell et al., 2008) have demonstrated that the association between VPA and PCOS can be influenced by the age at which VPA is initiated: women are more likely to develop PCOS features on VPA if they are younger when their VPA therapy is started.

Finally, VPA is an AED with an inhibitory effect on the hepatic P450 enzyme system and, thereby, it may impair the metabolism of sex steroids such as T, hence provoking increased androgen levels (Isojärvi, 2008). EIAEDs, such as CBZ, PHT, or PB, may exert a protective effect against the development of PCOS, reducing biologically active T in the serum, by increasing the binding and metabolism of T (Herzog et al., 1984).

In conclusion, there are limited data suggesting that VPA is directly responsible for the development of PCOS; although it is possible that weight gain may alter the endocrine and biochemical features to produce PCOS, there is no conclusive evidence to support this hypothesis. For these reasons, to date, VPA could be considered as an option for the treatment of many types of epilepsy, also in young women. However, because VPA treatment is associated with greater disruption of reproductive endocrine functions than other AEDs, the length of the menstrual cycle and bodyweight should be monitored in women treated with VPA.

Clinical Implications

Physicians should be aware of reproductive endocrine dysfunction that may occur in women with epilepsy, especially in long-term therapy, and it may be associated both with epilepsy per se and AEDs.

If a reproductive endocrine disorder is found, AEDs should be reviewed in terms of their indication for the particular seizure type and their tolerability vis-à-vis their potential for contributing to these endocrine problems. Therefore, regular monitoring of reproductive function is recommended, including questioning about menstrual disorders, fertility, hirsutism, and galactorrhea.

Furthermore, a serum T assay is helpful in following the possible biochemical endocrine changes in order to detect the early presence of subclinical hyperandrogenemia. Moreover, examination of the ovaries, through ultrasonography, may be indicated if the menstrual cycles are prolonged and serum T levels are elevated, particularly if there is associated weight gain.

Finally, because younger women seem to be especially vulnerable to the effects of VPA on serum androgen levels, the age of patients should be also considered while prescribing AEDs.

It is important to reassure the patients that the AED-related adverse disorders are, in most cases, reversible if the medication is discontinued.

The effects of the new AEDs have not been widely studied; however, it seems that they may offer an alternative should reproductive endocrine problems emerge during the treatment with the older AEDs.

Disclosure

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The authors have no conflicts of interest to disclose.

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