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The Impact of Epilepsy on Reproductive Functions

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1. Introduction

1.1 Regulation of female reproductive system

Regulation of female reproductive system consists of very complex interactions between the hypothalamus, neurohypophysis and ovaries. Beginning from the embryologic stage, female reproductive system is regulated by the brain. Ovarian hormone production is suppressed by the hypothalamo-hypophyseal control mechanism till the end of the childhood period when the puberty begins. During puberty, menstrual cyclicity and timely ovulation, which are the result of the precise integration within different components of the reproductive system, are achieved. After puberty, comes the reproductive period which generally lasts about 30-35 years. During reproductive period, from daily social behavior to sexual life and reproduction, many important issues depend on normal ovarian folliculogenesis and hormonogenesis. Menopause refers to the final menstrual period accompanying the permanent cessation of ovarian function and menstruation.

Gonadotropin releasing hormone receptor (GnRHR) is secreted from hypothalamus and delivered to the anterior pituitary via the hypophyseal portal circulation where it binds to the GnRHR on the surface of gonadotropes triggering the synthesis and secretion of the gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (LH). In the female, LH stimulates the production of androgens by the thecal cells that surround the growing ovarian follicle. During the terminal stages of follicular growth, LH also drives the production of progesterone from the granulosa cells of the preovulatory follicle. FSH binds to receptors on the surface of ovarian granulosa cells stimulating the expression of aromatase enzymes that convert thecal androgens to estradiol. The Hypothalamus-hypophysis-gonadal (HPG) axis is subject to both positive feed-forward and negative feedback regulation at several levels. At the level of the hypothalamus, early recognition of the pulsatile nature of gonadotropin releasing hormone secretion led to the notion of a central "pulse generator", the inherent oscillatory activity of which controls the secretory rhythm of GnRH neurons (Knobil, 1980). Hypothalamic pulse generator is extensively modulated by a multitude of higher level inputs including photoperiod, environmental stress, metabolic state and nutritional status, as well as various endocrine mediators. (Bliss, 2010)

1.2 Impact of epilepsy on female reproductive system

Epilepsy is a neurological disorder clinically characterized by recurrent seizures ranging from a very mild form of disruption in attention for a few seconds, to a severe form of muscle spasms and loss of consciousness. Epilepsy is a major public health problem worldwide. The prevalence of epilepsy increases with age (Brodie et al, 2009; Wallace et al, 1998) from 90 per 100,000 people of age 65–70 years, to 150 per 100,000 in those older than 80 years. The treatment goals are suppression and prevention of the seizures. For these purposes, antiepileptic drugs (AED) are used.

Epilepsy has a gender-related pathophysiology and consequences. Therefore, being a woman with epilepsy is not the same as being a man with epilepsy (Taubøll et al, 2008); in fact, the frequency and severity of seizures can increase on certain days of the menstrual cycle (Herzog et al, 1997). Seizures generally exacerbate during the 3 different periods of the menstrual cycle: in perimenstrual and periovulatory periods in normal cycles, and in inadequate luteal phase in abnormal cycles (Figure 1). This type of epilepsy is defined as catamenial epilepsy and is under the influence of estrogen and progesterone. Estrogen has been shown to increase seizure activity, while progesterone decreases it by raising the seizure threshold level (Frye, 2008). Progesterone is converted to allopregnanolone in the brain. Allopregnanolone has been suggested as a primary compound responsible for decreased seizure susceptibility (Scharfman and MacLusky, 2006).

Estrogen acts as a proconvulsant in several animal models of epilepsy, including amygdala kindling and pentylenetetrazol administration in ovariectomized rats (Hom and Buterbaugh, 1986). Estrogen induces the formation of new excitatory synapses in the CA1 region of the hippocampus; and further, this estrogenic induction involves activation of N-methyl-D-aspartate (NMDA) receptors (McEwen, 2002). Increasing the complexity of hippocampal synaptic density is likely a mechanism for the proconvulsant activity of estrogen. Standard hormone replacement in postmenopausal women with epilepsy, which includes estrogen and a progestin, can be postulated to have an effect on seizures that is more evident than that of oral contraceptives in cycling women with epilepsy. This is because reproductive hormone levels during menopause are low and unchanging. Therefore, the brain hormonal milieu in which exogenous hormones are introduced is markedly different in menopause from that in menstruating women.

In the ovariectomized animals, however, the hormonal changes in the animals are abrupt in contrast to the gradual hormonal changes found in the menopausal transition. It might be the concerted lack of estradiol and progesterone that facilitate the seizure susceptibility. Both estradiol and progesterone affect γ -amino butyric acid (GABA)ergic function (Scharfman et al, 2005; Nakumura et al, 2005; Kokate et al, 1994). The simultaneous decrease of estrogen and progesterone may thereby lead to a decrease in GABAergic inhibition, facilitating seizures. Recently published results by Lavaque et al (2006) suggest age-related focal production of sex hormones especially prominent in the hippocampus and cerebral cortex. The expression of the steroidogenic acute regulatory protein was found to increase particularly in these areas. The hippocampus and cerebral cortex are areas associated with seizure initiation and propagation. It is therefore discussed how pathological disturbances in the local estrogen production after menopause may contribute to an increase in seizures in some women (Veliskova, 2007).

Estrone is the primary estrogen after menopause, and its main source is subcutaneous fat. This might be of importance for overweight women with epilepsy. Little is known on the influence of estrone on epilepsy. An altered ratio of estradiol/estrone might be of importance; however, this has not been investigated. Most likely, however, the hormonal changes in menopause may not affect the different types of epilepsy in the same way.

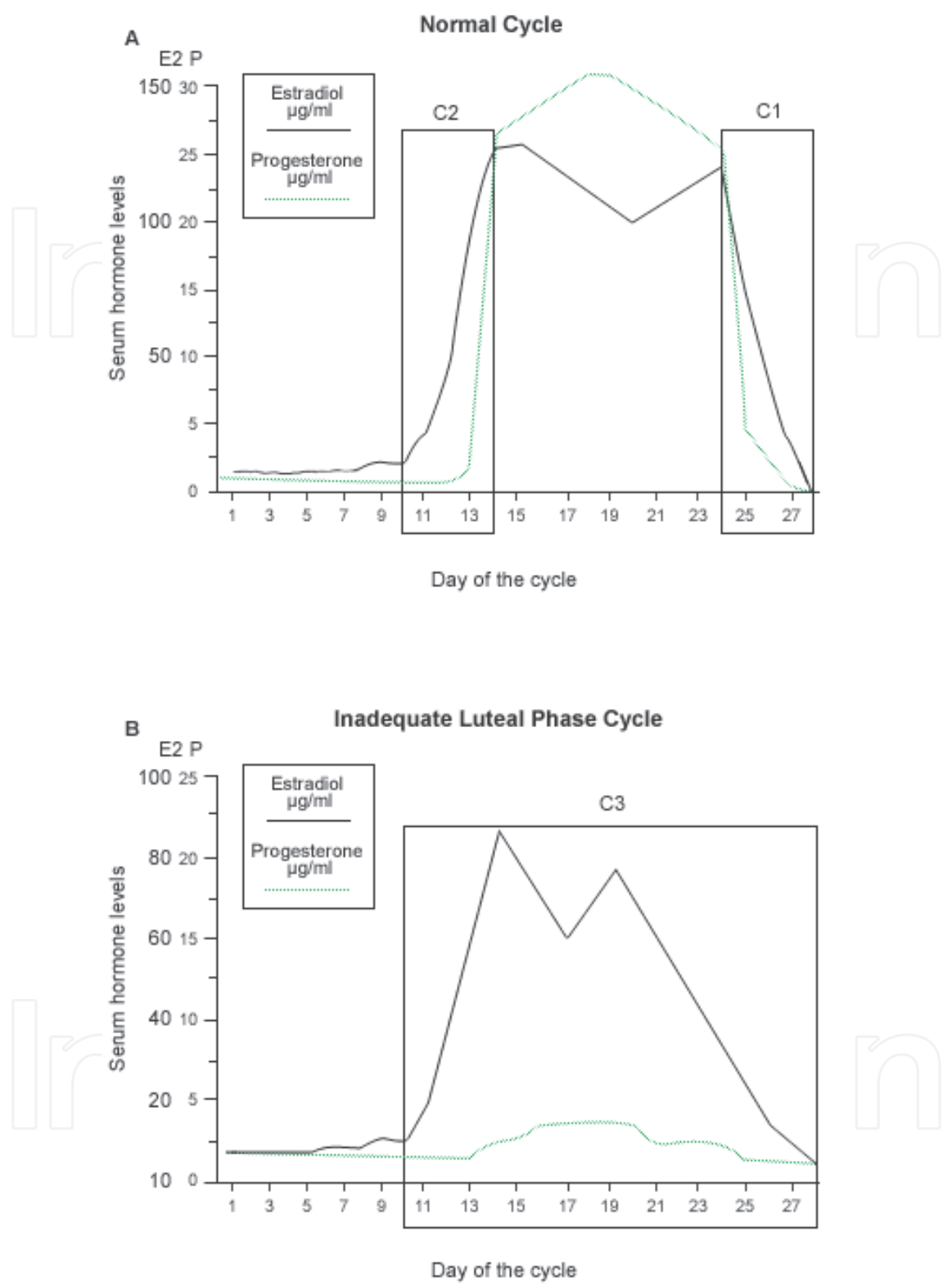


Fig. 1. Three patterns of catamenial epilepsy. During normal ovulatory cycles, both perimenstrual (C1) and periovulatory (C2) patterns can occur in isolation or together. During inadequate luteal phase cycles, the (C3) pattern can occur with increased seizures during the entire second half of the cycle. (Herzog AG. Catamenial epilepsy: definition, prevalence pathophysiology and treatment. *Seizure* 2008;17:151)

Reproductive dysfunction is common among women with epilepsy primarily due to the dysfunction in the temporolimbic system. This system has integral roles in reproductive endocrine regulation and feedback as well as in sexual and reproductive function (Herzog, 1989). Consequently, the development of epileptiform discharges in medial temporal lobe structures may disrupt hypothalamic regulation of pituitary secretion and, hence, alter gonadal function.

In addition, most of the AEDs (carbamazepine, oxcarbazepine, phenobarbital, phenytoin, and topiramate) may also alter endocrine function by inducing the cytochrome P450 isoenzyme 3A4 in women with epilepsy (Luef, 2009). Therefore, certain AEDs may accelerate hepatic elimination of hormonal preparations and decrease the serum concentrations of bioactive sex steroids.

Epileptic women have increased risk of polycystic ovary syndrome (PCOS), premature ovarian failure (POF), and hormonal contraceptive failure; as well as osteoporosis (Figure 2).

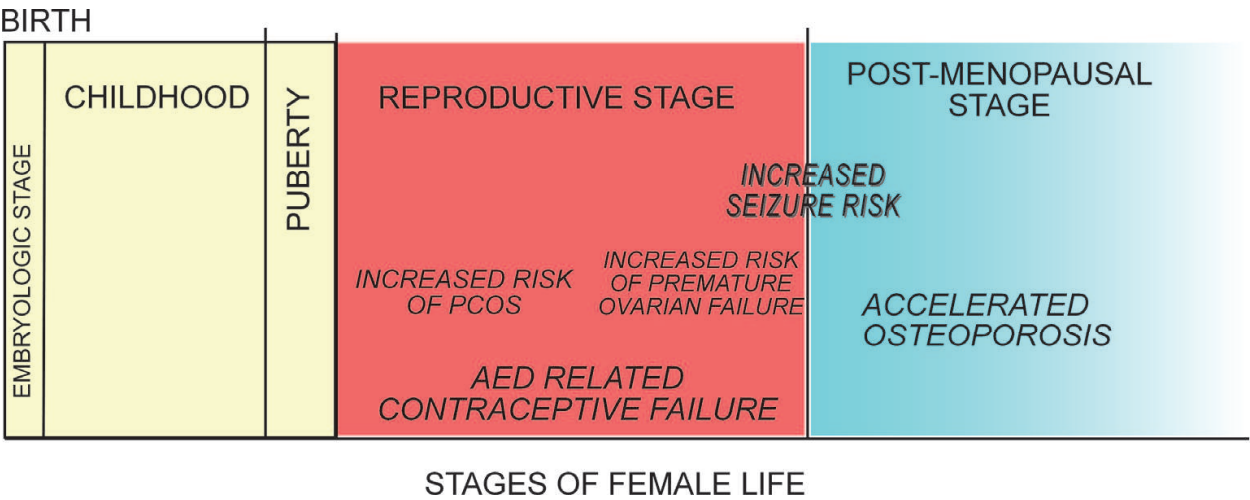


Fig. 2. Possible changes in epileptic women according to different stages of female life AED, anti-epileptic drug; PCOS, polycystic ovary syndrome.

2. Epilepsy and polycystic ovary syndrome

PCOS is characterized by enlarged ovaries with multiple small cysts and a hypervascularized, androgen-secreting stroma leading to the associated signs of androgen excess (hirsutism, alopecia, acne), obesity, and menstrual-cycle disturbance (oligo or amenorrhea) (Balen, 1999). The most common reproductive endocrine disorder in women with epilepsy, as well as in women in the general population, is PCOS. PCOS occurs in 10-20% of women with epilepsy compared to 5-6% of women in the general population (Bauer et al, 2008; Knochenhauer et al, 1998; Herzog, 2002; Herzog et al, 2003). The prevalence of PCOS in women with epilepsy is greater, even if they are not taking AEDs; and it is more frequent in women who take valproic acid (VPA), primarily if initiated before the age of 20. PCOS is probably not a single nosological entity, but rather the common endpoint for a number of pathophysiological mechanisms, some of which may be attributable to epilepsy itself (Herzog et al, 1986, 2003) or to the use of AEDs, most notably valproate. PCOS represents the failure of the ovarian follicle to complete normal maturation during the menstrual cycle or a series of cycles -- a failure that is perhaps related to the presence of

inadequate levels of pituitary follicle-stimulating hormone (FSH); whereas levels of luteinizing hormone (LH) are normal or elevated (Isojärvi, 2008; Herzog, 2008).

The brain controls reproductive function primarily through hypothalamic regulation of pituitary secretion. The left and right vagus nerves exert different modulatory influences on ovarian structure and function (Gerendai & Halasz, 1997). The reproductive neuroendocrine system, like many other brain systems, shows a lateralized asymmetry that might, by virtue of ipsilaterally predominating effects, contribute to the development of distinct reproductive endocrine disorders in association with unilateral left- and right-sided epileptic foci (Herzog, 2007). Unilateral temporolimbic discharges are associated with laterally differing, consistent, predictable, stochastic directional changes in hormonal secretion at all levels of the reproductive neuroendocrine axis, that is, hypothalamus, pituitary, and ovary (Herzog et al, 2003). These directional changes are consistent with the finding that different reproductive disorders may develop in relation to left- and right-sided temporolimbic epilepsy. Specifically, left temporal lobe epilepsy (LTLE) is associated with significantly higher pulse frequencies of GnRH secretion (Herzog et al, 2003; Herzog, 2008). Higher GnRH pulse frequency, in turn, is associated with higher LH/FSH ratios and higher serum testosterone levels. This combination of neuroendocrine changes characterizes PCOS and is consistent with the previously suggested association between left unilateral TLE and PCOS.

Antiepileptic drugs, on the other hand, also have substantial and differential effects on reproductive hormone levels. The first report suggesting a high incidence of menstrual disorders linked to obesity, hyperandrogenism, and polycystic ovaries in women taking VPA for epilepsy was published in 1993 (Isojärvi). Changes in serum androgen levels have been detected before and during pubertal development in young girls taking VPA for epilepsy (Vainionpää, 1999).

Studies by Murialdo et al (1997) have also reported a high prevalence of menstrual disorders and hyperandrogenic anovulation in VPA treated women with epilepsy. However, the study by Bauer et al (2008) did not show any differences between carbamazepine- and VPA-treated women with epilepsy with respect to reproductive endocrine parameters. Although the interpretation of the results of this study is difficult, because the age of the patients, the duration of medication, and seizure frequency in the different treatment groups were not given (Isojärvi, 2005). Other studies have also addressed the issue of reproductive endocrine function in women with epilepsy. Luef et al (2002) reported similar frequencies of menstrual disorders and PCOS in women taking carbamazepine and VPA for epilepsy. It has been suggested that obesity and associated hyperinsulinemia could be implicated in the development of PCOS and hyperandrogenism in women taking VPA. It seems that obesity and related hyperinsulinemia may exacerbate the VPA-related reproductive endocrine disorders in women with epilepsy. It seems likely that VPA has a direct effect on ovarian androgen production, or as an enzyme inhibitor, it may inhibit the metabolism of sex steroids and thereby lead to increased serum androgen levels (Isojärvi et al, 2005).

Several studies have suggested that the reproductive endocrine effects of AEDs may be reversible if the medication is discontinued. In a prospective study, the replacement of VPA with lamotrigine resulted in normalization of endocrine function during a 1-year follow-up in 12 women with a previously identified endocrine disorder (PCOS or hyperandrogenism, or both) likely to be related to VPA. Serum insulin and testosterone levels returned to normal 2 months after VPA was discontinued, and the levels remained normal thereafter (Isojärvi et al, 2005).

3. Epilepsy and premature ovarian failure

POF is characterized by amenorrhea, cessation of ovarian function, and elevated gonadotropin levels before 35 years of age and younger. Ovarian failure due to POF may not be absolute; hence, this condition needs to be differentiated from premature menopause because the latter reflects a “permanency” of the ovarian failure.

Indeed, women with POF often continue to have some residual ovarian function for many years after diagnosis (Kodaman, 2010, Kalantaridou&Nelson 2000). Both sporadic ovulation and occasional pregnancy are possible with POF; (Nelson et al, 1994, Alper et al, 1986) in fact; up to half of women affected by POF have intermittent follicular development, 25% may occasionally ovulate, and 5 to 10% will conceive and deliver (Nelson et al, 1994, Rebar&Connolly, 1990, Rebar, 2009). The term menopause thus should be avoided in the context of counseling these patients, and more recently, the term POF has also fallen into disfavor because it implies finality and gives a further negative connotation to an already devastating diagnosis for a young woman to come to terms with. POF, the term first coined by the endocrinologist Fuller Albright almost 70 years ago, is now the preferred nomenclature for this entity. (Albright et al, 1942, Welt, 2008, Nelson, 2009) The incidence of POF increases with age, affecting 0.01%, 0.1%, and 1% of women <20, 30, and 40 years of age, respectively (Coulam, 1986). Given the association of chemoradiation therapy with subsequent ovarian insufficiency and the increasing successes with childhood and early adulthood malignancy treatments, it has been predicted that the number of cases of POF will increase significantly in the future (Sklar, 2006, Panay&Fenton, 2008). Etiologies for POF are heterogeneous and, for the most part, poorly understood. The etiology for up to 90% of cases of POF remains elusive (Kodaman, 2010).

POF occurs more commonly in women with epilepsy. Klein et al (2001) evaluated the incidence of POF in 50 women with epilepsy, aged 38 to 64, compared with control women. Premature menopause was defined as amenorrhea for greater than 1 year with elevated day 3 FSH levels in women younger than 42 years. Premature perimenopause was defined by the presence of perimenopausal symptoms. Of the women with epilepsy, 14% had premature perimenopause or menopause, compared with only 3.7% of the control women ($P = 0.042$). They did not find an association with epilepsy duration, seizure severity, or AEDs; although women with premature menopause were more likely to have had catamenial exacerbation of their seizures than women without POF ($P = 0.02$). Harden et al (2003) also found in their multicentric cohort study that premature menopause was associated with epilepsy. In another study, the median age at menopause in the group of women with epilepsy was 47 years, compared with the median age of 51.4 years in the general US population (Gold, et al, 2001). When the investigators divided the patients into low, intermediate, and high seizure frequency groups, there was an increasingly lower age at menopause with a negative correlation between the age at menopause and seizure group based on estimated lifetime seizures ($P = 0.014$). They also found no influence of enzyme-inducing AEDs. The authors concluded that the association of lifetime number of seizures with the timing of cessation of reproductive cycling may occur as a result of direct disruption of hypothalamic and pituitary function by the seizures.

Women with epilepsy have an increased risk of experiencing an early onset of perimenopausal symptoms. Some studies draw attention to the increased frequency of POF in women with epilepsy. However, no association has been detected so far between the POF and epilepsy duration, seizure severity, or use of enzyme-inducing AEDs. POF may occur as

a result of direct disruption of hypothalamic and pituitary function by the seizures. It has been suggested that women with POF were more likely to have catamenial exacerbation of their seizures than women without POF.

4. Contraception and epilepsy

Contraceptive methods can be divided into two subgroups as hormonal and non-hormonal. Hormonal contraceptives include combined-oral contraceptives, progestin only pills, hormonal implants, progestin releasing intrauterine systems, depomedroxyprogesterone acetate injections, and vaginal rings. Non-hormonal contraceptive methods include male and female condoms, copper intrauterine device, tubal ligation and vasectomy of the companion. Combined oral contraceptives are a widely used and well accepted form of contraception. Combined-oral contraceptives are highly effective when used consistently and correctly, and are well tolerated by most women. Combined-oral contraceptives contain a combination of an estrogen and a progestin. Since their introduction, several progestins have been developed for use in combined-oral contraceptives. Conversely, the estrogen component has remained largely unchanged, with the vast majority of combined-oral contraceptives containing ethinylestradiol (EE) or, more commonly in the past, mestranol, the 3-methyl ether of EE. The estrogen component of combined-oral contraceptives is responsible for suppressing FSH, providing endometrial stability, and potentiating the activity of the progestin component, e.g., by increasing progestin receptor concentrations. However synthetic progestins may directly influence ovarian function by a direct inhibition of the ovarian steroid biosynthesis. Modern combined-oral contraceptives have two components: EE and a progestin. Both are on their own able to inhibit ovulation. In modern combined-oral contraceptives ovulation inhibition is mainly achieved by the progestin and not by ethinylestradiol. The typical daily progestin dose in today's combined-oral contraceptives is about 1.5–2 times the ovulation-inhibiting dose (Schwenkhagen&Stodieck, 2008).

The choice of a contraceptive drug can be challenging for women with epilepsy due to possible interactions between AEDs and hormonal contraception. Enzyme-inducing AEDs can cause hormonal contraception to fail and can increase the risk of teratogenicity. Higher doses of oral contraceptives can overcome pharmacologic failure but may create additional risks (Burakgazi et al, 2009).

In women with epilepsy failure rates of oral contraceptives may increase to 6% depending on the antiepileptic drug they are taking (Morell, 1996). Drugs such as phenobarbital (PB), primidone (PRM), phenytoin (PHT), carbamazepine (CBZ), oxcarbazepine (OXC) at doses above 600 mg daily and topiramate (TPM) at doses above 200 mg (Doose et al, 2003) may cause induction of hepatic cytochrome P450, reducing the effects of contraceptives to block ovulation. VPA and felbamate (FBM) inhibit the hepatic microsomal system and do not reduce, and can even increase, the levels of the steroid hormones of oral contraceptives. Other drugs such as gabapentin (GBP), lamotrigine (LTG), tiagabine (TGB), pregabalin (PGB), vigabatrin (VGB), and levetiracetam (LEV) do not affect the serum concentrations of contraceptives (Tatum et al, 2004) (Table 1). To avoid lack of efficacy of contraception used in a patient that is on therapy with enzyme-inducing AEDs when the “morning-after pill” is used at the same time, the first dose of levonogestrel should be 1.5 mg (twice the usual dose of 750 µg), and after 12 hours the recommended 750 µg are reinstated (Mayor, 2004; Perruca, 2004). Moreover, oral contraceptives can reduce levels of LTG by 25% to 70%. If the woman

is taking AEDs, which reduce steroid hormone levels, oral contraceptives must contain a minimum of 50 µg of EE. If there is a hemorrhage, the dose should be raised to 75 or 100 µg. During the first months of oral contraceptive use, and once ovulation has been eliminated, complementary contraceptive methods are recommended. To improve contraceptive efficacy, the use of a combined-oral contraceptives that contains a progestin well above the dose needed to inhibit ovulation may be recommended. Ovulation-inhibiting doses of progestins are given in table 1.

Progestin	mg/day
Chlormadinone acetate	1.7
Cyproterone acetate	1.0
Desogestrel/3-keto-desogestrel	0.06
Dienogest	1.0
Drospirenone	2.0
Gestodene	0.04
Levonorgestrel	0.06
Norethisterone	0.4
Norethisterone acetate	0.5
Nomegestrol acetate	5.0

Table 1. Ovulation-inhibiting doses of progestins (without additional estrogen) (Kuhl, 2005)

Commonly used AEDs which do and do not interact with oral contraceptives are given in Table 2.

Drugs which do not reduce the effects of oral contraceptives	Drugs which reduce the effects of oral contraceptives
Clonazepam	Barbiturates
Ethosuximide	Carbamazepine
Felbamate	Oxcarbazepine
Gabapentin	Phenytoin
Levetiracetam	Primidone
Lamotrigine	Topiramate (>200 mg/day)
Tiagabine	
Valproate	

Table 2. Commonly used AEDs which do and do not interact with oral contraceptives

Most drug–drug interaction studies have focused on the effect of AEDs on oral contraceptive safety. Much less is known about the result of a co-prescription of hormonal contraceptives on AEDs, which is surprising, since it is known for a long time that oral contraceptives have a strong influence on drug metabolizing enzymes. (Schwenkhagen&Stodieck, 2008).

In combined oral contraceptives, during the period “on the pill” lamotrigine levels decrease by approximately 50%, followed by an increase of lamotrigine levels in the contraceptive-free week up to 80– 100% of the baseline lamotrigine level. This is often clinically relevant and may result in an increased risk of seizure recurrence especially in week 2 and 3 on the pill or in concentration-dependent adverse effects at the end of the pill-free interval (Sabers

et al, 2001, 2003; Stodieck &Schwenkhagen, 2004; Christensen, 2007). These fluctuations are most likely due to an induction of UGT1A4, the enzyme responsible for the glucoronidation of lamotrigine, by EE. VPA levels also seem to be reduced by the concomitant use of hormonal contraceptives (Herzog et al, 2005; Galimberti, 2006). Just as with lamotrigine the magnitude of observed fluctuations of the VPA levels appear to vary interindividually. Hormonal contraceptives which are adversely affected by hepatic cytochrome P450 enzyme-inducing AEDs are given in Table 3.

Oral
Various combined estrogen/progesterone preparations
Progestin only pill
Morning after pill
Transdermal patch (norelgestromin and ethinyl estradiol)
Vaginal ring (etonorgestrel/ethinyl estradiol ring)
Implants (etonorgestrel)

Table 3. Hormonal contraceptives which are adversely affected by hepatic cytochrome P450 enzyme-inducing AEDs

In addition to induction of cytochrome P450 enzyme system, several AEDs induce the production of sex hormone binding globulin (SHBG) to which the progestins are tightly bound, resulting in lower concentrations of free progestin that may also lead to combined-oral contraceptive failure (Dutton C, Foldvary-Schaefer, 2008). While higher dose combined-oral contraceptives are one contraceptive option for women on enzyme-inducing AEDs, a variety of other options are available. Injectable contraception (depot medroxyprogesterone acetate) appears effective with AED use, but the potential for bone mineral density loss is a concern. (Dutton C, Foldvary-Schaefer, 2008) Non-hormonal contraceptive methods are not contraindicated in women with epilepsy. If contraception is addressed as a permanent measure, the safest method is tubal ligation or vasectomy of the companion. Intrauterine devices are an alternative to pharmacologic approaches because they lack drug-drug interactions and side effects (Burakgazi et al, 2009). There is no evidence that combined-oral contraceptives increase seizures in women with epilepsy (Dutton C, Foldvary-Schaefer, 2008).

5. Epilepsy and menopause

Ovarian reserve shrinks throughout life and reaches a critical threshold level at the inception of the menopause. At this point, a woman notes her first skipped menstrual period. The menopausal transition begins with the onset of first menstrual irregularity, or skipped menses, and ends with the final menstrual period. Progressive loss of ovarian follicles results in decreased production of inhibin and a loss of restraint on FSH secretion. The monotropic increase in FSH leads to variable hormonal patterns, depending on the available ovarian follicles and their degree of responsiveness. Once follicles reach a critically low level, ovulation becomes progressively less likely and prolonged amenorrhea ensues. In addition to ovarian factors that contribute to reproductive senescence in women, there is accumulating evidence that as in rodents, hypothalamic-pituitary dysfunction accompanies reproductive aging and contributes to the process. As knowledge about the menopausal

transition increases, it may turn out that the ovary is not the only area that should be studied – the brain may undergo changes as well (Santoro, 2005).

During the perimenopausal period, the frequency of catamenial epileptic seizures may increase (probably due to hyperestrogenism) and then decrease after menopause. According to current data, hormone replacement therapy (HRT) may increase the frequency of epileptic seizures. Changes in serum concentrations of sex steroid hormones are frequently observed when enzyme-modulating AEDs (VPA, CBZ, phenytoin, or phenobarbital) are used. It is generally accepted that long-term treatment with VPA and CBZ may lead to reproductive endocrine disorders in patients with epilepsy. VPA can increase biologically active sex hormone levels (e.g., hyperandrogenism) independent of associated weight gain, more commonly seen in women before the age of 20. In contrast, CBZ may decrease free serum testosterone concentrations through the induction of SHBG. If the woman is taking AEDs, which reduce steroid hormone levels, OCs must contain a minimum of 50 µg of EE. If there is a hemorrhage, the dose should be raised to 75 or 100 µg.

Indications for HRT are dealing with menopausal symptoms and conservation of bone mass and fracture prevention. As epilepsy is affected by sex steroids, careful consideration must be given to the regimen used. However, the data are extremely limited (Harden et al, 2006; Shen & Stearns 2009). The details of the only randomized trial double-blind, placebo-controlled trial are now described (Harden et al, 2006). This was undertaken in postmenopausal women with epilepsy who are taking stable doses of AEDs and are within 10 years of their last menses. After a 3-month prospective baseline, subjects were randomized to placebo, Prempro (0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate or CEE/MPA) daily, or double-dose CEE/MPA daily for a 3-month treatment period. Twenty-one subjects were randomized after completing baseline. The subjects' ages ranged from 45 to 62 years (mean, 53 years), and the number of AEDs used ranged from none to three (median, one). Five (71%) of seven subjects taking double-dose CEE/MPA had a worsening seizure frequency of at least one seizure type, compared with four (50%) of eight taking single-dose CEE/MPA, and one (17%) of six taking placebo ($p = 0.05$). An increase in seizure frequency of the subject's most severe seizure type was associated with increasing CEE/MPA dose ($p = 0.008$). An increase in complex partial seizure frequency also was associated with increasing CEE/MPA dose ($p = 0.05$). Two subjects taking lamotrigine had a decrease in lamotrigine levels of 25–30% while taking CEE/MPA. The authors concluded that CEE/MPA is associated with a dose-related increase in seizure frequency in postmenopausal women with epilepsy. CEE/MPA may decrease lamotrigine levels. There are no data with other regimens with different estrogens and progestogens or transdermal or vaginal administration. It is not known whether women with epilepsy need higher doses of estrogen or whether transdermal rather than oral therapy is preferred depending on their AED use. Based on the randomized trial, it would be prudent to closely monitor women who start HT as their AED needs may change (Erel et al, 2010).

Non-estrogen based treatments are used to treat hot flushes and symptoms of urogenital atrophy (Erel et al, 2010). Drug interactions need to be carefully assessed before using pharmacotherapy. Interventions to consider include clonidine, selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs), gabapentin, and vaginal lubricants and moisturizers (Shen et al, 2009). While bisphosphonates will conserve bone mass, there are little data in women with epilepsy and there are concerns about the safety of long term use (Drezner, 2004).

As vitamin D and calcium metabolism can be affected by AEDs, supplements should be considered. Herbal preparations should be avoided as their efficacy is uncertain and they may interact with AEDs (Erel et al, 2010).

6. Epilepsy and osteoporosis

The cessation of ovarian function at the menopause is associated with a phase of rapid bone loss which probably lasts from 5 to 10 years (Genant et al, 1982; Recker et al, 2000). This rapid bone loss results from an increase in bone turnover in association with a negative remodelling imbalance (Compston, 2001); whilst reduced bone formation undoubtedly contributes to the latter, there is evidence that increased osteoclastic activity also plays a role, particularly in the earlier stages of menopausal bone loss (Compston et al, 1995). The combination of increased bone turnover and increased resorption depth results in disruption of bone microarchitecture, with loss of connectivity of cancellous bone and thinning of the cortices, which also show increased porosity.

Osteoporosis and fractures may increase due to hypoestrogenism in menopause and cytochrome P450 inducing AEDs. Recent studies suggest lower bone mineral density (BMD) in adults and children with epilepsy, irrespective of AED treatment.

Both idiopathic epilepsy and symptomatic epilepsy are associated with reduced BMD, with the greatest reduction in symptomatic generalized epilepsy (Sheth & Hermann, 2008). However, the pathophysiological underlying mechanisms are far from understood and likely multifactorial. Potential risk or predisposing factors include physical impairment, genetic factors, AED treatment with enzyme-inducing drugs, AED polytherapy, impact of seizures on the hypothalamus-hypophysis-adrenal (HPA) axis, and vitamin D deficiency/insufficiency. As growth and sexual maturation in adolescence are regulated by a complex neuroendocrine system including the HPA axis, potential AED-related abnormalities may be reflected in growth and bone metabolism in childhood epilepsy. In adults and children treated with enzyme-inducing AEDs, vitamin D deficiency/insufficiency (up to 50% of patients) and low BMD have been reported in most, but not all, studies (Petty et al, 2007; Farhat et al, 2002; Pack et al, 2005; Verrotti et al, 2000).

However, and in particular in children, it is unclear whether non-enzyme-inducing AED monotherapy (lamotrigine, sulthiame) or minimal enzyme-inducing AED monotherapy (oxcarbazepine) seem to have any adverse effects on linear growth or to cause vitamin D deficiency in otherwise healthy children with epilepsy (Luef & Rauchenzauner, 2008). In contrast to adults, there is controversy over the association of chronic AED use with an increased incidence of fractures in children (Souverein et al, 2005; Petty, et al, 2007). Recent studies suggest lower BMD in adults and children with epilepsy, irrespective of AED treatment (Pack, 2008; Sheth et al, 2008a, 2008b; Pack & Walczak, 2008; Sheth & Hermann, 2008).

7. Conclusion

In conclusion, in gynecological practice, women with epilepsy deserve special care with a multidisciplinary approach. Women with epilepsy should be questioned routinely about menstrual cycles, infertility, excessive weight gain, hirsutism, galactorrhea, and changes in sexual life. If abnormalities are detected, hormone determinations, pelvic ultrasound, and neuroimaging of pituitary gland should be assessed. If the cause of the problem is AED-

related, a therapeutic alternative should be addressed, taking into account seizure control possibilities versus side effects.

Seizures generally exacerbate during the 3 different periods of the menstrual cycle: in perimenstrual and periovulatory periods in normal cycles, and in inadequate luteal phase in abnormal cycles. This type of epilepsy is defined as catamenial epilepsy and is under the influence of estrogen and progesterone. Estrogen has been shown to increase seizure activity, while progesterone decreases it by raising the seizure threshold level.

The prevalence of PCOS in women with epilepsy is 10-20%, which is greater than the normal population, even if epileptic women are not taking AEDs. PCOS is more frequent in women who take VPA, primarily if initiated before the age of 20.

Women with epilepsy have an increased risk of experiencing an early onset of perimenopausal symptoms. Some studies draw attention to the increased frequency of POF in women with epilepsy, although this relationship needs to be further investigated.

In women with epilepsy, failure of oral contraceptives may increase to 6% depending on the antiepileptic drug they are taking. Barbiturates, Carbamazepine, Oxcarbazepine, Phenytoin, Primidone, and Topiramate (>200 mg/day) may reduce the efficacy of oral contraceptives. Clonazepam, Ethosuximide, Felbamate, Gabapentin, Levetiracetam, Lamotrigine, Tiagabine, and VPA do not seem to interact with oral contraceptives. During the first months of oral contraceptive use, and once ovulation has been eliminated, complementary contraceptive methods are recommended. Non-hormonal contraceptive methods are not contraindicated in women with epilepsy. There is no evidence that combined-oral contraceptives increase seizures in women with epilepsy.

During menopause, 27% of the epileptic women had improvement, 33% did not modify their seizure pattern, and 40% worsened. Monitoring for osteoporosis is recommended, particularly if treatment is with AEDs which reduce steroid hormone levels. According to the The European Menopause and Andropause Society (EMAS) position statement, epileptic women starting hormone therapy should be closely monitored as their AED needs may change; calcium and vitamin D supplements should be considered, and herbal preparations should be avoided as their efficacy is uncertain and they may interact with AEDs (Erel et al, 2010).

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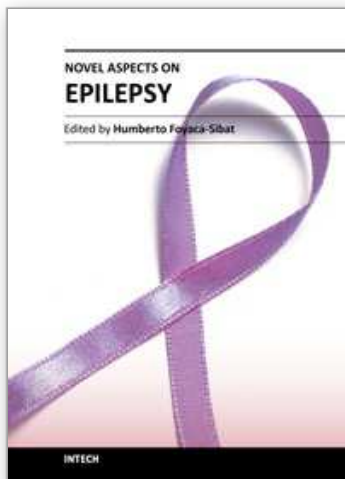
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This book covers novel aspects of epilepsy without ignoring its foundation and therefore, apart from the classic issues that cannot be missing in any book about epilepsy, we introduced novel aspects related with epilepsy and neurocysticercosis as a leading cause of epilepsy in developing countries. We are looking forward with confidence and pride in the vital role that this book has to play for a new vision and mission. Therefore, we introduce novel aspects of epilepsy related to its impact on reproductive functions, oral health and epilepsy secondary to tuberous sclerosis, mitochondrial disorders and lisosomal storage disorders.

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