



Review

Female issues in epilepsy: A critical review

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ABSTRACT

The focus on gender-related issues for women with epilepsy has heightened in recent years. The emphasis, however, has been on the childbearing years. Epilepsy and antiepileptic drug treatment affect sexual development, the menstrual cycle, and aspects of contraception, fertility, and reproduction. Female patients with epilepsy at a reproductive age face a unique set of reproductive issues, ranging from descriptions of disorders of reproduction in epilepsy and its causes, to contraception, pregnancy, sexuality, menopause, and osteoporosis. Conditions and diseases that specifically affect women are discussed. The role of hormones across the life cycle—endogenous and exogenous hormones and their effects on drug interactions, drug metabolism, and therapeutic outcomes—is described. Contraception and pregnancy issues for women with epilepsy have received the appropriate attention.

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1. Introduction

People with epilepsy experience several gender-related physical and social problems, and the last decade has seen a focus on gender issues in epilepsy. Being a woman with epilepsy is not the same as being a man with epilepsy [1]. Sexual dysfunction in women with epilepsy (WWE) is an important comorbidity. A significant minority of WWE have markedly decreased sexual interest, and it appears that orgasmic dysfunction occurs more frequently in WWE than in control women [2].

Reproductive dysfunction is unusually common among women and men who have epilepsy. It generally manifests as menstrual disorder, hirsutism, and infertility in women [3]. Both epilepsy and antiepileptic drugs (AEDs) have been causally implicated [3,4].

The temporolimbic system has integral roles in reproductive endocrine regulation and feedback as well as in sexual and reproductive function [5]. Consequently, the development of epileptiform discharges in medial temporal lobe structures may disrupt hypothalamic regulation of pituitary secretion and, hence, alter gonadal function and reproductive function. It is evident that AEDs may also alter endocrine function in women with epilepsy and that this alteration may lead to clinically significant reproductive endocrine disorders in certain cases [6]. The underlying mechanisms, clinical significance, and incidence of the AED-related reproductive changes differ between various AEDs. However, it is well established that AEDs with liver enzyme-inducing properties decrease the serum concentrations of bioactive sex steroids, whereas VPA increases the serum concentrations of androgens [7]. It is impor-

tant to acknowledge that the reproductive effects of AEDs may differ depending on age. Young women with epilepsy seem to be especially vulnerable to the effects of VPA on ovarian function. It is encouraging to note that most of the reproductive effects of the AEDs appear to be reversible, if the medication is discontinued before adulthood. The endocrine effects of the new antiepileptic drugs have not been widely studied. However, it seems they may offer an alternative if reproductive endocrine problems emerge during treatment with the older AEDs.

The occurrence of bidirectional drug interactions between AEDs and combined oral contraceptives (OCs) poses the potential risks of unintended pregnancy and seizure deterioration [8]. The contraceptive regimen that is optimal for an individual WWE is one of the most challenging clinical decisions when taking care of women with epilepsy [9].

Childbirth rates are lower in both men and women with epilepsy [10]. Childbearing rates are 16.9–22.5 per 1000 in WWE compared with 67.6 per 1000 in women without epilepsy. The lower marriage rate of WWE does not fully explain this difference.

During pregnancy, the use of older-generation AEDs is known to be associated with a two- to threefold increased risk of birth defects in the offspring and possibly other adverse outcomes for the exposed infant. Much less is known about newer-generation AEDs in this respect [11]. Risk of spontaneous abortion is significantly increased in pregnancies of women with localization-related epilepsy, and the risk is greatest in women with a family history of epilepsy [12]; folic acid supplementation seems to have a prophylactic effect [13]. Recent studies based on national registries as well as specific epilepsy and pregnancy registries are beginning to provide information on the comparative teratogenic effects of different AEDs [14].

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2. Sexual dysfunction in women with epilepsy

Many WWE have normal sexuality, but there is a significant fraction who have markedly decreased sexual desire, and this fraction is not present in the general population.

Bergen et al. evaluated 50 WWE in a tertiary epilepsy care center; 32 of 50 women had partial epilepsy, and 28 of 50 were taking only one AED. WWE and a comparison group of women of similar age were asked how often they had the desire for sex and how often they actually had intercourse. A much greater proportion of WWE than comparators had very infrequent sexual desire, with about 20% reporting that they almost “never” had sexual desire; very few women in the comparison group reported this low level of sexual desire [2]. Several reports suggest that orgasmic dysfunction is overrepresented among WWE. Jensen et al. [15,16] and Morrell et al. [17] reported on genital blood flow (GBF) measured by vaginal plethysmography in women with temporal lobe epilepsy as they watched either erotic or sexually neutral videos. GBF was significantly decreased in WWE compared with controls during erotic visual stimulation. There was no difference in mood scales between the patient and control groups; however, subjects with epilepsy were less sexually experienced than the controls and reported more anxiety on imagining sexual situations than did controls. The authors proposed a central mechanism for this effect: disruption of relevant regions of cortex by epileptic activity, specifically limbic and frontal areas, could be the cause of sexual dysfunction. The occurrence of decreased GBF in WWE could, at least in part, contribute to inadequate orgasm [18]. AEDs that induce the cytochrome P450 isoenzyme 3A4 and therefore decrease free testosterone are also associated with sexual dysfunction. Right temporal lobe epilepsy also appears to be associated with sexual dysfunction compared with left temporal lobe epilepsy. Lack of seizure freedom could adversely impact psychosocial aspects of living with epilepsy, including sexuality [18].

3. Reproductive endocrine disorders in women with epilepsy

Hospital- and community-based studies have shown that menstrual disorders are more common among women with epilepsy than in the general population [3]. The most common reproductive endocrine disorder in women with epilepsy, as well as women in the general population, is polycystic ovary syndrome (PCOS) [3,19,20]. PCOS occurs in 10 to 20% of women with epilepsy compared with 5 to 6% of women in the general population [21,22]. 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 [3,22] or to the use of AEDs, most notably valproate [4,23]. 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 [7,24].

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 [25]. 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 [26]. 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 [22]. 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 gonatrophin-releasing hormone (GnRH) secretion [22,24]. Higher GnRH pulse frequency, in turn, is associated with higher luteinizing hormone (LH)/follicle-stimulating hormone (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 valproate (VPA) for epilepsy was published in 1993 [4]. Changes in serum androgen levels have been detected before and during pubertal development in young girls taking VPA for epilepsy [27].

Studies by Murialdo et al. have also reported a high prevalence of menstrual disorders and hyperandrogenic anovulation in VPA-treated women with epilepsy [28]. However, the study by Bauer et al. did not show any differences between carbamazepine- and VPA-treated women with epilepsy with respect to reproductive endocrine parameters [29], but 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 [6]. Other studies have also addressed the issue of reproductive endocrine function in women with epilepsy. Luef et al. reported similar frequencies of menstrual disorders and PCOS in women taking carbamazepine and VPA for epilepsy [30]. 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 [6].

Several studies have suggested that the reproductive endocrine effects of AEDs may be reversible if the medication is discontinued. In a prospective study, 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 [6].

4. Oral contraceptives and antiepileptic drugs

Combined oral contraceptive steroids (OCs) are prescribed for 17% of fertile women with epilepsy, which is almost as frequent as for the general population (25%) [31]. Co-administration of OCs and AEDs is therefore a common clinical situation that calls for specific consideration of possible drug interactions.

Among women with epilepsy there has been observed a higher incidence of breakthrough bleeding and contraceptive failure that is correlated with the time when the ethinyl estradiol fraction of OCs decreases from 50–100 μg to <50 μg to diminish the risk of thromboembolic side effects. The contraceptive failure, therefore, was regarded as mainly dependent on the concentration of the estrogen fraction of the OC. Modern available combined OC preparations contain 20–35 μg of ethinylestradiol and less than 1 mg of progestogen. The major part of the estrogen compound is hydroxylated to inactive metabolites by hepatic cytochrome P450 (CYP)

3A4 or directly conjugated. AEDs that induce the CYP 3A4 isoenzyme (carbamazepine [32], oxcarbazepine [33], phenobarbital [34], phenytoin [32], and topiramate) may therefore accelerate the hepatic elimination of OCs. A recent study of topiramate with an OC containing 35 µg ethinyl estradiol demonstrated that topiramate monotherapy at doses <200 mg did not significantly affect the clinical efficacy of OCs [35].

OCs can increase the metabolism of glucuronidated drugs by induction of the uridine diphosphate glucuronosyltransferase system. This has been most intensively studied for lamotrigine, which is hepatically metabolized primarily by glucuronic acid conjugation. Several studies have demonstrated that the clearance of lamotrigine is significantly and substantially (>50%) increased by combined OCs [36,37] and that interaction is associated with increased seizure frequency in most of the cases [22].

The contraceptive-induced pharmacokinetic alteration shows considerable interindividual variability based on probably both genetic factors and co-administration with other AEDs. This can be exemplified by the results of a recent study that revealed that OC induction of lamotrigine elimination was almost eliminated when it was co-administered with valproate [38,39].

If combined OCs are used in combination with enzyme-inducing AEDs, it is recommended that a combined OC containing a high progestin dose, well above the dose needed to inhibit ovulation, is chosen and that the combined OC be taken continuously (“long cycle therapy”). But even with the continuous intake of a combined OC containing a higher progestin dose, contraceptive safety cannot be guaranteed; thus, additional contraceptive protection may be recommended. Progestin-only pills (POPs) are likely to be ineffective if used in combination with enzyme-inducing AEDs. Subdermal progestogen implants are not recommended in patients on enzyme-inducing AEDs because of published high failure rates. Depot medroxyprogesterone acetate (MPA) injections appear to be effective; however, they may not be the first choice because of the serious side effects (delayed return to fertility, impaired bone health). Intrauterine devices are an alternative method of contraception in the majority of women, with the advantage of no relevant drug–drug interactions. The levonorgestrel intrauterine system appears to be effective, even in women taking enzyme-inducing AEDs. Likelihood of serious side effects is low in users of the levonorgestrel intrauterine system [9].

5. Teratogenicity and antiepileptic drugs

Despite differences in study design and populations, most reports have confirmed an increased risk of adverse pregnancy outcome with exposure to the older-generation AEDs such as phenobarbital, phenytoin, carbamazepine, and valproate. Potential adverse fetal effects of these drugs include intrauterine growth retardation, dysmorphisms, major congenital malformations, and delay in postnatal cognitive development. Although it is evident that the vast majority of women with epilepsy who are on treatment with these AEDs during pregnancy give birth to perfectly normal children, these potential teratogenic effects are a major concern for all women with epilepsy of childbearing potential. The risks associated with uncontrolled seizures thus have to be balanced against the teratogenic risks imposed by the AEDs. Epilepsy and pregnancy registries have been established in different regions of the world. These are prospective observational studies aiming to enroll large numbers of AED-exposed pregnancies and providing outcome assessment in terms of birth defects in the offspring. Using slightly different methodologies such registries have been established in North America, the United Kingdom, Australia, and Europe. The European registry (EURAP) has been enlarged to include collaborators in Asia, Oceania, South America, and Australia

[40]. Malformation rates with carbamazepine exposure have ranged from 2.2 to 7.9%, with lamotrigine from 0 to 4.4%, with phenobarbital from 2.9 to 10.4%, with phenytoin from 0.7 to 9.1%, and with valproate from 5.7 to 16.8%. The wide ranges in malformation rates reflect differences in study populations, but probably most importantly differences in methodology. The largest cohort so far with data on different AEDs is the report from the UK Register, which demonstrated a greater risk for malformations with valproate than with carbamazepine [41]. However, even within-study comparisons should be interpreted with caution considering the possible effects of confounding factors.

The UK Register has published separately on outcome in association with levetiracetam exposure [42]. Three of 117 infants of women treated with levetiracetam during pregnancy had major congenital malformations, 2.7% (95% CI = 0.9–7.7%). There were none among the 39 exposed to levetiracetam in monotherapy. These studies are clearly too small to allow firm conclusions as to the teratogenic potential of levetiracetam, oxcarbazepine, or gabapentin.

The possibility that AED exposure during pregnancy may adversely affect postnatal development of the offspring has previously been assessed in several small-scale studies. In a Cochrane Review, Adab concluded that the majority of these studies are of limited quality and that there is little evidence about which drugs carry more risks than others to the development of children exposed [43]. A retrospective study from the United Kingdom measured significantly lower Verbal IQ scores in 41 children exposed to valproate monotherapy than in unexposed children and children exposed to carbamazepine ($n = 52$) or phenytoin ($n = 21$). Multiple regression analysis identified exposure to valproate, five or more tonic–clonic seizures in pregnancy, and low maternal IQ to be associated with lower Verbal IQ, even after adjustment for confounding factors. Valproate doses above 800 mg/day were associated with lower Verbal IQ than lower doses. These important signals still have to be interpreted with some caution given the small numbers, the retrospective nature of the study, and the fact that only 40% of eligible mothers agreed to participate.

Data are insufficient to assess the human teratogenic potential of other newer-generation AEDs. Although the observations of potential differences between AEDs in teratogenic potential are relevant for treatment decisions, these must be weighed against possible differences in effectiveness against the seizure disorder. The overall aim of the treatment should be to use the AED that can control tonic-clonic seizures with minimized risks to the mother as well as the fetus [44,45].

6. Catamenial epilepsy

Physiological endocrine secretion during the menstrual cycle influences the occurrence of seizures. In ovulatory cycles, seizure frequency shows a statistically significant positive correlation with serum estradiol/progesterone ratio [46]. This ratio is highest during the days prior to ovulation and menstruation and is lowest during the early and midluteal phase [46]. The premenstrual exacerbation of seizures has been attributed to the rapid withdrawal of the antiseizure effects of progesterone [47]. Although the precise definition of catamenial epilepsy remains arbitrary, one may maximize the efficiency of distinguishing between women whose seizure occurrence shows a high versus those whose seizures show a low degree of hormonal sensitivity by using the points of inflection of the S-shaped distribution curves that define the relationship between the severity of seizure exacerbation and the number of women who have exacerbations [47,48]. These points are calculated to be in the vicinity of a twofold increase in average daily seizure frequency during the phases of exacerbation

relative to the baseline phases for all three types of catamenial exacerbation.

Herzog et al. [47] presented statistical evidence to support the concept of catamenial epilepsy and the existence of at least three distinct patterns of seizure exacerbation in relation to the menstrual cycle: (1) perimenstrual (C1: Days –3 to 3) and (2) periovulatory (C2: Days 10 to –13) in normal cycles, and (3) luteal (C3: Days 10 to 3) in inadequate luteal phase cycles. In these cycles, Day 1 is the first day of menstrual flow and ovulation is presumed to occur 14 days before the subsequent onset of menses (Day –14). These three patterns can be demonstrated by (1) charting menses and seizures and (2) obtaining a midluteal phase serum levels. Two open-label trials of adjunctive progesterone therapy for women with catamenial epilepsy did result in clinically important and statistically significant reductions in seizure occurrence [49,50]. Progesterone treatment has taken two forms: (1) cyclic progesterone therapy that supplements progesterone during the luteal phase and withdraws it gradually premenstrually, and (2) suppressive therapy in which the goal is to suppress the menstrual cycle which is generally accomplished using injectable progestins or GnRH analogs [51]. Oral synthetic progestins administered cyclically or continuously have not proven to be an effective therapy for seizures in clinical investigations [52], although individual successes with continuous daily oral use of norethistrone and combination pills have been reported [53].

7. Menopause and epilepsy

Epilepsy can interfere with the time of menopause. Herzog et al. [3] were the first to report an association between partial epilepsy and premature menopause. Harden et al. [54] found a relationship between seizure frequency and age at menopause, and Klein and co-workers [55] found an increased frequency of premature ovarian failure in women with epilepsy. The normal hormonal fluctuations before the menopausal transition and the known effects of hormones on seizures might also be of importance in the evaluation of the hormonal changes in the menopausal transition and its effect on the epilepsy [56]. Rosciszewska et al. [57] were the first to report an increased risk for seizure onset or epilepsy during perimenopause. The results indicated that seizure frequency was more likely to improve during menopause if there was a catamenial relationship, if seizures began later in life, and if seizures were well controlled. The marked hormonal changes in the menopausal transition seem to have an effect on seizure susceptibility. Women with catamenial epilepsy might experience an increase in seizure frequency in perimenopause and decrease after menopause. Other patients may experience either an increase or decrease in seizure activity. There is limited knowledge of the impact of menopause on the different forms of epilepsy. However, the probability of a change in seizure frequency in the menopausal transition is high and medical adjustments may be necessary. The numbers of women with epilepsy in older age groups are steadily increasing, and they deserve increased awareness and attention around the time of perimenopause and menopause [58].

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