

Effects of Epilepsy on Women's Reproductive Health

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Summary: Reproductive dysfunctions are common and wide-ranging in women with epilepsy. Menstrual cycle disruption, anovulatory cycles, disturbances in hypothalamic and/or pituitary hormones, and disturbances in gonadal steroids are more common among women with epilepsy. Sexual dysfunction can present as either disorders of desire or physiologic arousal, but the most common dysfunction appears to be an inadequate initial physiologic arousal response. Reproductive dysfunctions may be due to psychologic, pharmacologic, or physi-

ologic factors. Physicians should routinely question all women with epilepsy regarding their reproductive and sexual health. A full history, a complete physical, and laboratory evaluations with endocrinologic work-up should be performed in any woman who reports a reproductive dysfunction. Treatment and/or referral to a gynecologist or endocrinologist should be initiated as appropriate. **Key Words:** Epilepsy—Women—Sexual function—Fertility—Hormones.

Steroid hormones of the reproductive system alter the excitability of central nervous system neurons. In some individuals these hormone effects may be sufficient to influence the phenotypic expression of epilepsy syndromes. In turn, epilepsy syndromes, seizures, or antiepileptic drugs (AEDs) may alter reproductive endocrine systems. For the woman with epilepsy, the interactions between seizures and hormones may complicate seizure management and create challenges to reproductive health.

Alterations in levels of sex steroid hormones during puberty, menarche, and menstruation have all been implicated in the onset and exacerbation of seizure disorders in women (1-4). The influence of hormones on seizures is discussed further in the articles by Drs. Woolley and Schwartzkroin (page S2), and Drs. Herzog and Klein (page S9).

Disorders of reproductive function in women with epilepsy are fairly common and include endocrine abnormalities, infertility, and sexual dysfunction. This article reviews the range of reproductive dysfunctions in women with epilepsy, discusses potential mechanisms, and offers diagnostic strategies.

ENDOCRINE ABNORMALITIES

Epilepsy is associated with neuroendocrine dysfunction (Fig. 1) (5). In the normally functioning hypothalamic-pituitary axis, the hypothalamus releases a number of trophic hormones, which act on the pituitary to regulate the synthesis and circadian/ultradian release of hormones of the anterior pituitary. Gonadotrophin-releasing hormone (GnRH) is a hypothalamic hormone that controls the cyclic release and concentration of the pituitary gonadotrophins follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH stimulate the gonads to synthesize and release sex steroid hormones which, in turn, provide positive and negative feedback at the hypothalamus and pituitary (5).

Seizures can disrupt cortical regulation of hypothalamic hormone release and therefore can disturb the entire hypothalamic-pituitary axis (6). Endocrine abnormalities described in women with epilepsy include an abnormal pituitary response to GnRH (7,8), altered pulsatile release of pituitary LH (9-11), abnormal concentrations of pituitary LH, and elevated pituitary prolactin (PRL) (12,13).

There are several potential mechanisms for these endocrine abnormalities. Ictal discharges may directly and episodically alter the hypothalamic-pituitary axis, and epileptogenic lesions may predispose to chronic alter-

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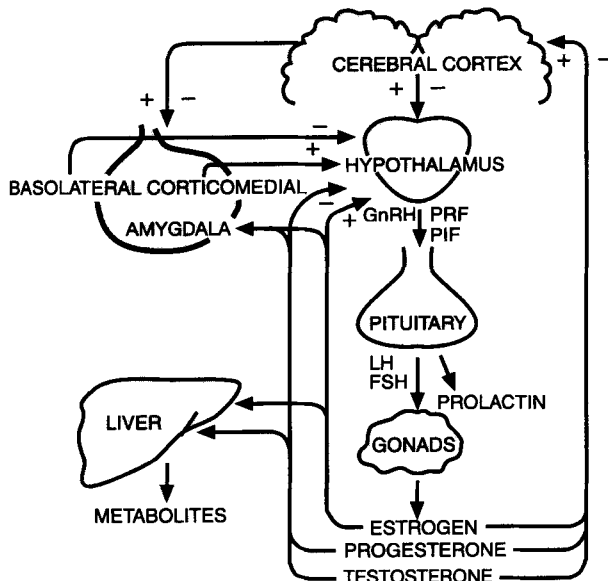


FIG. 1. Schematic of the hypothalamic-pituitary-gonadal axis illustrates modulation of the axis by cortical centers and by two functionally distinct regions of the amygdala. Reciprocal connections are designated as predominantly excitatory (+) or inhibitory (-). PIF, prolactin-releasing factor; PIF, prolactin inhibitory factor; GnRH, gonadotropin-releasing hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

ations in axis functioning. AEDs may alter hypothalamic-pituitary axis functioning by direct effects on CNS input to the axis and by affecting feedback regulation by gonadal steroid hormones (5).

Generalized seizures are associated with significant increases in PRL. PRL increases three- to fivefold after generalized tonic-clonic seizures (14) and may also increase after partial seizures associated with hippocampal ictal discharges (15). Postictal increases in ACTH and in growth hormone (GH) have also been described in humans (11,16). The limbic cortex, especially the amygdala, is extensively interconnected with the hypothalamus. Stimulation of the limbic cortex, whether experimentally or ictally, is associated with immediate alterations in the release of hypothalamic trophic hormones (17-19) and hormones of the anterior pituitary (20,21).

AEDs influence the hypothalamic-pituitary axis by direct effects on cortical input to the axis and by altering feedback modulation provided by gonadal steroid hormones. AEDs alter neurochemicals involved in regulating the hypothalamic-pituitary axis, including γ -aminobutyric acid (GABA), glutamate, serotonin, and endogenous opioids (22). Some AEDs also alter the metabolism of steroid hormones, which affects feedback excitation and inhibition to the hypothalamus and the pituitary. AEDs that induce the cytochrome P450 enzyme system enhance steroid metabolism and increase binding to steroid hormones (23), effectively reducing the concentration of hormones available to the CNS. AEDs that have been shown to reduce the concentration

of steroid hormones include carbamazepine, oxcarbazepine, phenytoin, phenobarbital, and topiramate (24). In addition, the AED valproate inhibits this enzyme system and increases the concentration of some steroid hormones (25). In one recent study, gonadal and adrenal steroids in women receiving gabapentin or lamotrigine in monotherapy showed no difference from nonepileptic controls (26). As discussed in the articles by Dr. El-Sayed (page S17) and Dr. Zahn (page S26), altered metabolism of steroid hormones by AEDs also reduces the effectiveness of oral contraception.

MENSTRUAL CYCLE IRREGULARITY, ANOVULATION, AND POLYCYSTIC OVARIES

Women with epilepsy are more likely to experience abnormalities in menstrual cycle length, including abnormally short cycles (<23 days) and abnormally long cycles (>35 days). Significantly abnormal cycles affected 18% of women with epilepsy in one recent study (27). Irregular cycles may be a consequence of anovulatory menstrual cycles and/or luteal phase deficiency. Anovulatory cycles were reported to affect more than 30% of menstrual cycles in one group of women with localization-related epilepsy of mesial temporal lobe origin, but were not more likely to arise in a group of women with idiopathic (genetic) primary generalized epilepsy than in nonepileptic controls (28). Another study reported that ovulation was delayed in women with epilepsy (29). Although these observations suggest that anovulatory cycles may be more likely to occur in women with epilepsy arising from limbic structures, further study is needed to establish the neuroanatomic basis for ovulatory failure in women with epilepsy.

Irregular menstrual cycles and anovulation may also occur in association with polycystic ovaries. Although the frequency with which polycystic ovaries occur in healthy women is not established, several recent reports suggest that women with epilepsy are more likely to develop multiple ovarian cysts and, in some cases, to present with a clinical picture very similar to polycystic ovary syndrome (30). Isojarvi et al. (25) evaluated a group of women with epilepsy and found that 43% had polycystic ovaries and/or elevated androgens. The majority of these women were receiving valproate, suggesting that this AED is more associated with these findings, perhaps as a consequence of valproate's inhibition of steroid hormone metabolism. Other studies have also found polycystic ovaries in women with epilepsy receiving a variety of AEDs (26,31).

The significance of an isolated finding of polycystic ovaries is not known. Polycystic ovary syndrome is characterized by polycystic ovaries, hirsutism, acne, obesity, elevated androgens, an elevated LH:FSH ratio, chronic anovulation, and insulin resistance (32). This syndrome

is associated with infertility and an elevated lifetime risk for cardiovascular disease, dyslipidemia, insulin resistance, diabetes, and endometrial and possibly breast carcinoma (33).

Although most detections of polycystic ovaries in women with epilepsy have not included an evaluation for other components of this syndrome, there is an indication that some, if not all, of the diagnostic criteria may be present and that the syndrome may be AED-related (34). Valproate was replaced with lamotrigine in a small group of women who exhibited symptoms compatible with polycystic ovary syndrome, including polycystic ovaries, hyperandrogenism, and dyslipidemia manifested as an elevated low-density lipoprotein (LDL) cholesterol level and a low high-density lipoprotein (HDL) cholesterol level. The switch from valproate to lamotrigine resulted in reversal of hyperandrogenism, normalization of ovarian morphology, and improvement in the lipid profile, including an increase in the HDL level (35).

FERTILITY IN WOMEN WITH EPILEPSY

Epidemiologic studies have found that women and men with epilepsy are less likely to have children (36–39). Schupf and Ottman (36) compared 1,558 adults with epilepsy with 318 of their siblings who did not have epilepsy. Women with epilepsy were 37% as likely to have been pregnant, and men with epilepsy were 36% as likely to have fathered a pregnancy, compared with their siblings (36). In men, this reduction in fertility was associated with partial-onset seizures, early age at onset, a negative family history of epilepsy, and reduced marriage rates. However, these factors did not appear to play a role in reduced pregnancy rates in women (36).

To better identify predictors of reduced fertility, 863 married or previously married adults with epilepsy were compared with their nonepileptic same-sex siblings who were or had been married. Fertility rates appeared to decline after the onset of epilepsy. Partial seizures were more likely than generalized seizures to be associated with reduced fertility. Finally, there was an association between reduced fertility and prepubertal onset of epilepsy, suggesting that early-onset epilepsy may predispose to a persistent deficit in fertility (37).

SEXUAL DYSFUNCTION

Prevalence

Compared with other chronic neurologic disorders, epilepsy is associated with a higher incidence of sexual dysfunction (40). Most of the literature regarding the effect of epilepsy on sexual function has focused on men. This literature has described a global hyposexuality in 30–66% of men that manifests as reduced libido/desire and impotence (41–44). Studies on sexual function in women with epilepsy are more limited and are colored

by cultural biases about what constitutes appropriate sexuality. This has led to reports of widely variable frequencies of sexual dysfunction: 14% in Egypt (41), 29% in Scandinavia (45), and 36–50% in the United States (42,46).

Sexual function was evaluated in 116 women with epilepsy who presented to an outpatient epilepsy center (26). Women were excluded if they had a concomitant gynecologic, psychiatric, or other medical illness. Standardized inventories were used to assess various parameters of sexual functioning, including sexual arousability, anxiety, and behavior. Depression was also assessed. These women with epilepsy did not have reduced sexual desire/libido or reduced frequency or type of sexual encounters. Women with epilepsy did report less arousal to imagined sexual situations and also described sexual activities as significantly more anxiety-provoking. In addition, women with epilepsy were statistically significantly ($p < 0.001$) more likely to experience physiologic sexual dysfunctions, which included vaginismus, dyspareunia, and arousal insufficiency (Table 1), suggesting an inadequate initial physiologic sexual arousal response. Sexual symptoms were not associated with seizure frequency, AED exposure, sexual experience, depression, or prepubertal seizure onset.

These symptoms were subjectively important to the affected women. When asked to classify their overall sexual satisfaction, more than half of the women with epilepsy reported dissatisfaction with sexual functioning and almost one-third reported very significant dissatisfaction that impaired the quality of their relationship. In contrast, three-quarters of nonepileptic patients report overall satisfaction with their sexual functioning.

In another study, vaginal blood flow was measured before and after presentation of erotic visual stimuli (videotapes) in nine women with temporal lobe epilepsy and in 12 nonepileptic women (47). Nonepileptic controls had a significant increase in genital blood flow within 1.5 min of viewing the erotic videotapes, whereas the women with epilepsy had an insignificant response. However, women in both groups reported feeling sub-

TABLE 1. Frequency of self-reported sexual dysfunctions in women with localization-related epilepsy (LRE) and primary generalized epilepsy (PGE)

Dysfunction	LRE (%)	PGE (%)	Controls (%)
Low desire disorder	15.9	11	16
Global anorgasmia	17.9	31.3	9
Vaginismus	27.8 ^a	13.3	6.8
Dyspareunia	38.5 ^a	18.8	8
Arousal insufficiency	42.3 ^a	33.3	14

^a Significant compared with controls at $p < 0.001$.
From Morrell et al., ref. 47.

jectively aroused by the videos. These results further support the hypothesis that the sexual dysfunction in women with epilepsy is largely a result of physiologic rather than psychologic deficits.

Mechanisms

The mechanisms of sexual dysfunction in women with epilepsy are probably multifactorial. Although women with epilepsy are at risk for psychosocial disabilities that may affect sexual function, physiologic and pharmacologic factors appear to play a greater role in producing sexual dysfunction.

Included among the psychologic factors that may be at play are depression, low self-esteem and, until recently, lower marriage rates. Recent reports indicated that marriage rates among persons with epilepsy are now on a par with rates in the general population (36). Disease acceptance may also play a role. It has been shown in other chronic illnesses that sexual functioning is improved when the individual and her partner have a realistic understanding of the limitations imposed by the disease, neither overestimating nor underestimating the disease impact (45). Anxiety surrounding seizures may provoke sexual anxiety. In particular, there may be concern on the part of the patient or her partner that sexual activity will precipitate a seizure.

Physiologic factors are probably the basis of most sexual dysfunction associated with epilepsy. Sexuality is mediated in multiple locations within the CNS, including the frontal lobe, limbic cortex, and hypothalamus. Functional or structural disruption of these regions is associated with disturbance in sexual function. In animal models, lesions in the preoptic area of the hypothalamus, dorsolateral tegmentum of the midbrain, or medial forebrain bundle dramatically curtail mating behavior (17,48). Removal of both temporal lobes (including the amygdala and hippocampus) produces uninhibited sexual behavior (Klüver-Bucy syndrome) in nonhuman primates (49). Although studies in humans have been limited, direct stimulation of the circuit of Papez elicited erections in two men with chronically implanted depth electrodes (50). In addition, two patients with partial epilepsy experienced orgasms associated with hippocampal discharges, and electrical and chemical stimulation of the same area of the brain produced pleasurable sexual sensations (51). Therefore, the areas of the brain that are commonly affected by epilepsy are also those that mediate sexual behavior.

Neurochemical events associated with seizures are also likely to disrupt sexual behavior. Postictal elevations in GABA, serotonin, and endogenous opioids may be sufficient to produce transient disturbances in sexual desire and arousal (52-54).

Sexual dysfunction associated with epilepsy may have an endocrinologic basis as well (Fig. 1). GnRH, pro-

duced by the hypothalamus, supports mating behavior in nonhuman mammals, as do pituitary LH and FSH (55). Excessive release of pituitary PRL reduces sexual desire in both men and women (56). Of the gonadal hormones, testosterone supports sexual desire in both women and men and sexual arousal in men (57,58), estrogen supports sexual arousal in women (59), and progesterone inhibits sexual desire and promotes parental behavior in nonhuman mammals (60).

Finally, sexual dysfunction may be an adverse effect of therapy with AEDs, particularly the depressants, benzodiazepines, and barbiturates. Barbiturates produced sexual dysfunction in about one-third of male users (61). Additional studies are needed to determine the prevalence of sexual dysfunction with other AEDs and to identify the individuals who are most at risk for experiencing this adverse effect. It should be remembered that other classes of drugs (e.g., selective serotonin reuptake inhibitors, antipsychotics, and antihypertensives) may also cause sexual dysfunction, as can substance abuse.

EVALUATION AND MANAGEMENT

Health-care providers should include questions regarding reproductive cycles and sexual function in the routine history. Women (and men) with epilepsy may be uncomfortable initiating discussions on this subject, especially as it pertains to sex, or may not make the connection between their reproductive dysfunction and their epilepsy. Evaluation of patients who report sexual or reproductive dysfunction (Table 2) should begin with a careful and thorough history and physical examination, including neurologic assessment. Laboratory measurements should include serum levels of PRL, LH/FSH, estrogen, testosterone, adrenal dehydroepiandrosterone sulfate (DHEAS), and thyroid hormones. It may also be useful to provide ovulation test kits that detect the ovulatory LH surge to women with irregular menstrual

TABLE 2. Directed strategy for the evaluation of sexual dysfunction

Evaluation	Comments
Medical and sexual history	Explore duration of symptoms, situational anxieties, affective symptoms, medication, substance use, and menstrual history
Physical and neurologic examination	
Laboratory studies	Estrogen, testosterone, DHEAS, prolactin, LH/FSH, thyroid hormones, routine hematology, routine chemistries, triglycerides/cholesterol, glucose tolerance test
Gynecologic examination	Ovarian ultrasound if menstrual cycles are irregular and/or androgens are elevated

cycles and to instruct patients on how to chart the menstrual cycle with basal body temperature. An ovarian ultrasound to screen for polycystic ovaries is warranted if the patient's menstrual cycles are irregular or if androgen levels are elevated. Results of the ultrasound and endocrine measurements should be considered together in assessing for polycystic ovary syndrome.

Women with abnormally elevated androgens or abnormal ovarian morphology may be considered for further evaluation and treatment by a gynecologist or endocrinologist.

CONCLUSIONS

Reproductive health problems associated with epilepsy are common and are of great personal importance to our patients. Reproductive and sexual dysfunction has important negative effects on patients' overall health and quality of life. Therefore, it is important not to overlook this aspect of care in women with epilepsy.

Further study is needed, particularly to confirm the effects of hormones on seizure activity and vice versa, to assess the effects of AEDs on sexual behavior, and to evaluate endocrinologic function in women with epilepsy.

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