Reproductive disturbances in patients with epilepsy

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ABSTRACT

In persons with epilepsy, both seizures and antiepileptic drugs can disturb reproductive health. For example, seizures can alter the release of hypothalamic and pituitary hormones, while some antiepileptic drugs alter concentrations of sex steroid hormones. Women with epilepsy are at increased risk for polycystic ovary syndrome and disorders of the menstrual cycle. Studies have found reduced fertility rates among men and women with epilepsy. The reasons for this reduction in fertility are likely to be both psychosocial and physiologic, and again, both epilepsy itself and antiepileptic drugs are implicated. Sexual dysfunction is common among patients with epilepsy and can have a somatic, psychological, or social basis. To provide the best care for patients with epilepsy, particularly women of reproductive age, clinicians must consider both the gender-based biology of epilepsy and the effects of antiepileptic drugs on reproductive health.

Epilepsy has wide-ranging physiologic consequences that arise from seizures and from the use of antiepileptic drugs. Women with epilepsy face a host of challenges, including reproductive health disturbances.[1,2] They also have lower birthrates and a greater risk for syndromes associated with infertility, such as hypothalamic-pituitary axis disruption, polycystic ovary–like syndrome, and anovulatory cycles. A growing body of research and heightened concern about the overall health of women with epilepsy have brought these risks to the attention of health care providers.

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HORMONE DISTURBANCES

Epilepsy and seizures alter hypothalamic and pituitary hormones,[3] and some antiepileptic drugs alter concentrations of sex steroid hormones produced by the ovaries and adrenal glands.

As depicted in **Figure 1**, the hypothalamus regulates secretion of anterior pituitary gonadotropins through the release of gonadotropin-releasing hormone (GnRH). GnRH is released episodically to stimulate the pulsatile release of the pituitary gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

Input to the hypothalamic-pituitary-gonadal axis from the cerebral cortex and from the amygdala and hippocampus (limbic cortex) is altered during seizures. Depending on the brain region disrupted by the epileptic discharge, the hypothalamus may be stimulated or inhibited. For example, the amygdala contains two distinct nuclear groups—the corticomedial nuclear group, which stimulates hypothalamic GnRH release, and the basolateral nuclear group, which inhibits GnRH release.[4] Depending on the nuclear group affected, excitation of the amygdala either inhibits or stimulates release of hypothalamic hormones such as GnRH, which ultimately alters release of the corresponding pituitary hormones.[5] Release of excitatory and inhibitory neurochemicals such as γ-aminobutyric acid (GABA) and glutamate during and after seizures may also influence hypothalamic and pituitary hormone release.[6]

The location of the ictal or interictal discharge also influences the specific type of input to the hypothala-

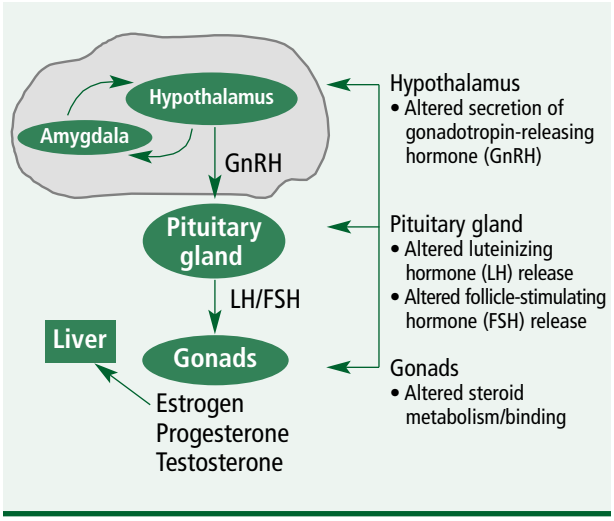

FIGURE 1. Disturbances in the hypothalamic-pituitary-gonadal axis in women with epilepsy receiving antiepileptic drugs. Input to this axis from the amygdala is altered during seizures.

mus. The laterality of limbic epileptiform discharges differentially alters hypothalamic hormone release.[7] Pulsatile secretion of LH in men with temporal lobe epilepsy has been shown to be altered interictally and with seizures.[8] Interictally, these men had lower mean LH concentrations, slower pulse rates, and higher peak amplitudes compared with nonepileptic male controls. Ictal changes were principally characterized as irregularities in secretion. These observations suggest that women with epilepsy are more likely to experience disturbances in hypothalamic hormone release, but the nature of the hormone disruption will vary depending on the focality and laterality of the epileptiform discharge and the relative frequency of ictal versus interictal epileptiform discharges.

Pituitary hormone abnormalities are observed in persons with epilepsy. LH concentration and pulsatile release are abnormal in some men and women with epilepsy,[9–11] probably because of derangement of the hypothalamic GnRH pulse generator.[12] Women with epilepsy not treated with antiepileptic drugs have a significant increase in gonadotropin basal secretion when interictal epileptiform activity is more frequent. LH release may be affected differently in different epilepsy syndromes and according to the antiepileptic drug taken. An increase in LH pulsatility was observed in one study of women with a variety of epilepsies not treated with antiepileptic drugs,[10] although another study of women with temporal lobe epilepsy treated with antiepileptic drugs found that LH pulse frequency diminished.[9]

Prolactin is also elevated interictally in some men and women with epilepsy.[13–15] Pituitary prolactin increases more than twofold after generalized convulsive seizures, most complex partial seizures, and simple partial seizures involving limbic structures, but not after nonepileptic seizures.[16–18] The increase occurs within 5 minutes, is maximal by 15 minutes, and persists for 1 hour.[19]

Sex steroid hormone levels are also abnormal in some men and women with epilepsy, as a result of antiepileptic drug–induced changes in steroid metabolism. Antiepileptic drugs that induce the hepatic microsomal enzyme system (the cytochrome P450 system) increase metabolism of gonadal and adrenal steroid hormones and induce the synthesis of sex hormone–binding globulin, a binding protein for steroid hormones. Increased protein binding decreases the free, biologically active fraction of hormone. Men and women with epilepsy who are taking drugs that induce cytochrome P450 have lower levels of sex steroid hormones.[20–25] Women taking valproate (which does not induce liver cytochrome enzymes) have higher gonadal and adrenal androgen levels.[26] These alterations in steroid hormones are associated with reproductive endocrine disorders and ovulatory dysfunction, conditions that will be discussed below.

REDUCED FERTILITY

Most studies find that fertility rates are reduced in men and women with epilepsy. Although a population-based incidence cohort of patients with epilepsy in Iceland showed no differences in live birth-rates compared with controls,[27,28] other studies have reported that fertility rates are reduced by one third[29–31] to as much as two thirds.[32]

Psychosocial and physiologic causes

This reduction in fertility rates is multifactorial. A study in Finland found that persons with epilepsy were less likely to marry and to have offspring.[33] In part, this reflects a choice. Much of that choice comes from faulty information suggesting that women with epilepsy are not fit parents, that the risk for transmission of epilepsy is high, or that the risk for birth defects in children born to mothers with epilepsy is higher than it really is. A recent survey of health care professionals likely to encounter women with epilepsy found that there is a marked lack of knowledge about pregnancy and fetal risks associated with maternal epilepsy and that many physicians would not support the decision of a

woman with epilepsy to become pregnant.[34]

Another basis for infertility is physiologic. Reproductive health disturbances in women with epilepsy include menstrual cycle abnormalities, anovulatory menstrual cycles, reproductive endocrine disorders, and sexual dysfunction. About one third of menstrual cycles in women with epilepsy are anovulatory, compared with about 10% in women without epilepsy.[35] Women with primary generalized epilepsy are more likely than women with localization-related epilepsy to have anovulatory cycles. The antiepileptic medication valproate, but not carbamazepine, gabapentin, lamotrigine, phenobarbital, or phenytoin, was significantly associated with anovulatory cycles. Women with primary generalized epilepsy receiving valproate were at highest risk. In fact, 55% of menstrual cycles were anovulatory in this group.[35]

Ovulatory failure associated with epilepsy and some antiepileptic drugs may be a result of endocrine disturbances and ovarian dysfunction. Hypothalamic-pituitary axis dysfunction is suggested by observations that pituitary release of LH in women with epilepsy is altered spontaneously and in response to GnRH.[9] Women receiving cytochrome P450 enzyme–inducing antiepileptic drugs have significant reductions in serum concentrations of estradiol, testosterone, and dihydroepiandrostenedione, as well as elevations in sex hormone–binding globulin.[20,25] Enhanced steroid metabolism and binding reduces the concentration of biologically active steroid. In contrast, adrenal and gonadal androgens are significantly elevated in women receiving the cytochrome P450 enzyme inhibitor valproate.[26] However, women with epilepsy who take gabapentin or lamotrigine, two antiepileptic drugs that do not alter cytochrome P450 enzymes, have sex steroid hormone levels that do not differ from those in nonepileptic controls not taking medications.[25]

Increased risk of polycystic ovary–like syndrome

The polycystic ovary syndrome is a gynecologic disorder affecting approximately 7% of women of reproductive age. The phenotype includes signs of excess androgen sensitivity, such as hirsutism, truncal obesity, and acne. Women with this syndrome have frequent anovulatory cycles and may have elevated androgen levels, elevated cholesterol levels with abnormal lipid profiles, an abnormal ratio of pituitary LH to FSH, elevated insulin levels, and glucose intolerance. The requirement for a diagnosis of polycystic ovary syndrome is phenotypic or serologic evidence of androgen excess, as well as anovulatory cycles. Polycystic ovaries, while often present in women with this syndrome, are not required for diagnosis. In fact, asymptomatic polycystic ovaries may be relatively common in normal women of reproductive age, occurring in 21% to 23%.[36,37] The health consequences of polycystic ovary syndrome include infertility, accelerated atherosclerosis, diabetes, and endometrial carcinoma, underscoring the importance of detection and treatment.

Women with epilepsy appear to be at risk for developing features of this syndrome, although there is no study in a cohort of women with epilepsy that is adequately designed to permit an accurate diagnosis of this syndrome. An study of 50 women with partial seizures arising from the temporal lobe found that 28 had menstrual cycle disturbances and 19 had reproductive endocrine disorders and polycystic ovaries.[11] Another assessment of 40 women with epilepsy with a variety of seizure types found reproductive endocrine disorders in 32%; the disorders were polycystic ovaries, hypothalamic amenorrhea, and luteal phase deficiency.[38] Polycystic-appearing ovaries and hyperandrogenism are reported to arise in as many as 40% of women with epilepsy receiving valproate,[26] and may be more likely to occur in women who receive valproate at puberty.[39] Polycystic ovaries were detected in 26% of a sample of 94 women with localization-related epilepsy and in 16% of nonepileptic controls. The women most likely to have multiple ovarian cysts were those with primary generalized epilepsy (41%) and those receiving valproate currently or recently (38%).[35] Polycystic ovaries in women receiving valproate may be reversible when the women are switched to other antiepileptic drugs.[35,40]

Polycystic ovary syndrome, obesity, and valproate

Obesity is associated with a higher rate of polycystic ovaries. The higher prevalence of polycystic ovaries in women receiving valproate may be related to a higher rate of obesity.[40] Valproate alters carbohydrate metabolism. Adolescent girls who gained weight after 1 year of valproic acid therapy had significantly higher insulin levels than girls who did not gain weight.[41] Postprandial insulin, C-peptide, and proinsulin levels were significantly elevated in 53 women treated for 2 or more years with valproate relative to 52 women treated for 2 or more years with carbamazepine.[42] There was no difference between the two groups in the fasting state.

Valproate is a fatty acid derivative that competes

with free fatty acids for protein binding and increases GABA-mediated inhibition. These mechanisms also increase pancreatic beta-cell regulation and insulin secretion. Glucose-stimulated increases in pancreatic secretion of insulin may be the cause of valproate-associated obesity.[43]

Impact of epilepsy vs antiepileptic drugs on reproductive health

The relative effect of epilepsy versus antiepileptic therapy on reproductive function can be considered by examining reproductive physiology in animal models of epilepsy, in nonepileptic animals treated with antiepileptic drugs, and in persons receiving antiepileptic drugs for conditions other than epilepsy.

Evidence that these reproductive health disturbances are a consequence of epilepsy as well as antiepileptic drug treatment comes from a study in female primates. Nonepileptic, regularly cycling rhesus monkeys were treated with valproate for 1 year, achieving serum concentrations of valproate similar to those of adult humans with epilepsy. Over the prospective 1-year assessment, the animals did not develop abnormalities in menstrual cycle length, ovarian morphology, or response to GnRH stimulation.[44]

A study of male gonadectomized rats with partial seizures induced by kindling or with generalized seizures induced by maximal electroshock found that partial seizures were associated with elevations in steroid hormone levels and an increase in the weight of the testes, epididymides, and prostate, whereas generalized seizures caused short-term reductions in testosterone and in the weight of the testes, epididymides, and prostate.[45] Seizures in female kindled rats arrested ovarian cyclicity and caused elevations in estradiol, prolactin, and pituitary weight and polycystic ovaries.[46] These results strongly suggest that different types of seizures cause specific types of disruptions in the hypothalamic-pituitary-gonadal axis.

Two studies have evaluated menstrual cycle regularity and ovarian morphology in women with bipolar disorder. One study found no difference in length of the menstrual cycle or appearance of polycystic ovaries in women treated with either lithium or valproate for bipolar disorder, although both groups had a high prevalence of abnormal menstrual cycle length.[47] Another study assessed women treated with valproate for bipolar disorder and reported that 47% had abnormal menstrual cycle length and 16% had polycystic ovaries, in contrast to women with bipolar disorder not receiving valproate, of whom only 13% had abnormal menstrual cycles and none had polycystic ovaries.[48] These findings are similar to those described for women with epilepsy.

Data such as these suggest that both epilepsy and some antiepileptic drugs can affect fertility and that these effects may be additive. This implies that the most sophisticated therapy for epilepsy is that which considers the effects of both the disease and its treatment on reproductive health.

SEXUAL DYSFUNCTION

Another cause of lower birthrates, and an area of clinical concern, is epilepsy-associated sexual dysfunction. Men and women with epilepsy appear to have a higher incidence of sexual dysfunction than persons with other chronic neurologic illnesses, with the dysfunction being manifested primarily as diminished sexual desire and potency. Sexual dysfunction affects 30% to 66% of men with epilepsy[49,50] and 14% to 50% of women with epilepsy.[49,51,52] Men with epilepsy have sexual complaints that include lack of spontaneous morning penile tumescence, anorgasmia, and erectile difficulties.[53,54] More than one third of women with epilepsy report dyspareunia, vaginismus, and lack of vaginal lubrication, with normal sexual desire and experience.[55]

Both men and women with localization-related epilepsy arising from the temporal lobe have been found to have significantly lower increases in genital blood flow in response to an erotic audiovisual stimulus compared with control subjects, even given normal subjective sexual arousal.[56]

Sexual dysfunction in persons with epilepsy is probably multifactorial.[57] Social development is impaired in some patients with epilepsy. Poor self-esteem as a result of having seizures may lead to feelings of sexual unattractiveness. Sexual arousal may be negatively reinforced, especially when sexual activity precipitates seizures or when sexual sensations or behaviors become identified as part of the seizure or postictal period. Realistic acceptance of the psychosomatic aspects of a chronic illness is positively correlated with sexual function, whereas poor disease acceptance is often associated with sexual dysfunction.[58] Epileptic discharges in brain regions mediating sexual behavior may also contribute to sexual dysfunction.

Alterations in pituitary and gonadal hormones are associated with sexual dysfunction. Elevated prolactin, low estrogen and progesterone, and low testosterone levels are correlated with sexual dysfunction

in women with epilepsy.[15,59,60] Impotent men with epilepsy have higher estradiol levels.[61] Some antiepileptic drugs contribute to sexual dysfunction by direct cortical effects or secondarily through alterations in the hormones supporting sexual behavior.[62,63]

Evaluating for sexual dysfunction

Sexual complaints can have a somatic, psychological, or social basis.[58] The frequency with which patients volunteer sexual complaints may depend to a great extent on the attitude of the physician. Patients with epilepsy should be questioned about precipitating factors, such as acute or chronic life stresses, seizure control, antiepileptic drugs, illnesses, or symptoms of depression. A recommended evaluation strategy includes the following:

- Thorough physical and neurologic examination
- Thyroid function tests
- Assessment of testosterone, estrogen, prolactin, and LH levels
- Complete blood cell count
- Assessment of fasting glucose level
- Urologic or gynecologic consultation.

POSSIBLE LINK TO PREMATURE MENOPAUSE?

Menopause marks the end of reproductive life. Women with epilepsy may be more likely to experience premature menopause, according to one study.[64] Seven (14%) of 50 women with epilepsy had nonsurgical premature menopause as compared with 3 (4%) of 82 nonepileptic controls. No correlation was seen between premature menopause and seizure duration, seizure severity, or age at seizure onset. Further research is needed to determine more precisely whether seizures, antiepileptic drugs, or both alter the length of the reproductive life.

Many menopausal women will be on hormone replacement therapy. The results of a study analyzing the characteristics and temporal relationship of seizures to menopause found that of 15 women taking hormone replacement therapy, the 6 who were taking progestin were significantly less likely to report a worsening of their seizures.[65] This suggests that unopposed estrogen may exacerbate seizures in menopausal women with epilepsy and that opposed estrogen replacement should be considered if hormone replacement therapy is required.

CONCLUSIONS

Epilepsy raises special concerns for women, particularly during the reproductive years. Fertility rates are reduced as a result of psychosocial pressures facing the person with epilepsy and because of disruption of physiologic systems supporting reproductive health. Ultimately, the health care provider must consider the physiologic effects of seizures and of antiepileptic drugs. The challenge is to provide the woman with epilepsy the opportunity for seizure freedom, overall good health, and enhanced well-being. This goal can be achieved when the health care provider appreciates the gender-based biology of epilepsy.

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