ABSTRACT

Women with epilepsy face unique challenges, some of which arise from the interaction between epilepsy and endocrine hormones. Epilepsy and endocrine hormones reciprocally influence one another such that hormonal changes impact epilepsy and epilepsy impacts hormonal functioning. In this article, the effect of that interaction on the lifelong health of epileptic women is examined. Fluctuations in sex hormones can increase the vulnerability to seizures in many epileptic women. One third to one half of women with epilepsy experience catamenial seizures (changes in seizure frequency at specific times during the menstrual cycle). Seizures can result in endocrine abnormalities that can affect menstrual irregularities, fertility, and sexual dysfunction and have been linked to polycystic ovary syndrome. The mechanisms of seizure-associated abnormalities have not been determined, but some theories include seizure-related disruption of hormones or brain regions mediating reproduction; antiepileptic drugs; and structural or functional central nervous system dysfunction associated with the disease of epilepsy (but not with seizure activity per se). By being aware of how endocrine hormones and epilepsy interact throughout the patient's life span, the healthcare provider is better equipped to manage endocrine-associated changes in seizure frequency and epilepsy-associated changes in neuroendocrine function.


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in the midbrain (Figure 1). The hypothalamus and the anterior pituitary gland regulate the endocrine system by modulating the secretion of hormones from a variety of glands throughout the body. The hypothalamus produces releasing hormones that stimulate the anterior pituitary gland to produce and release stimulating or inhibiting hormones. The stimulating or inhibiting hormones affect target organs throughout the body to influence their function—usually by causing the target organs themselves to release hormones. Via negative feedback loops, the target organs in turn modulate release of releasing hormones from the hypothalamus and stimulating or inhibiting hormones from the anterior pituitary.

The ovary is one of the target organs for hormones secreted by the hypothalamus and anterior pituitary gland. Together, the hypothalamus, the anterior pituitary gland, and the ovary control the menstrual cycle, which culminates either in pregnancy (when a fertilized ovum attaches to the lining of the uterus and begins to grow) or in shedding of the uterine lining (when fertilization does not occur).

The menstrual cycle, which begins during female puberty, repeats approximately every 28 days unless pregnancy occurs (Figure 2). Each cycle is divided into 2 phases:

- **During the follicular phase**, which constitutes the first half of the 28-day cycle and begins on the first day of menstruation, the ovum develops and matures in the ovarian follicle, in which it is housed during the follicular phase.
- **The luteal phase**, which constitutes the second half of the 28-day cycle, begins with ovulation (the release of the ovum from the ovarian follicle) and lasts until the first day of menstruation. During the luteal phase, the ovum travels through the fallopian tubes to the uterus. If the egg is fertilized with sperm, it implants in the uterine lining and menstruation does not occur. If the egg is not fertilized with sperm, the egg is discharged, and menstruation (ie, shedding of the uterine lining) occurs.

The events occurring during the follicular and luteal phases are controlled by hormones released from the hypothalamus, the anterior pituitary gland, and the ovaries (Figures 1 and 2). Estrogen and progesterone play key roles in the events of ovulation, proliferation of the uterine lining, and menstruation:

- An estrogen surge late in the follicular phase causes the anterior pituitary to release a pulse of luteinizing hormone, which causes ovulation.
- The decidualization of the uterine lining to prepare it for implantation of a fertilized ovum is mediated by progesterone.
- A rapid decline in estrogen and progesterone is responsible for menstruation.

Hormones released from the hypothalamus and anterior pituitary affect the release of estrogen and progesterone from the ovary. Estrogen and progesterone, in turn, modulate release of hypothalamic and pituitary hormones via negative feedback loops. Data from Morrell.

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**Figure 1. The Hypothalamic-Pituitary-Ovarian Axis**
Many other endocrine hormones in addition to those produced by the ovaries are modulated by the hypothalamus and the anterior pituitary. Although estrogen and progesterone are the best studied of the hormones in patients with epilepsy, the effects of other endocrine hormones may also be important. Given the interconnection of the endocrine system and the range of ways in which the endocrine system and epilepsy can interact (see below) most neuroendocrine pathways will probably be shown to affect and be affected by epilepsy.

**Effects of Hormones on Epilepsy**

Hormonal fluctuations—particularly fluctuations in estrogen and progesterone—coincide with changes in seizure patterns. These sex hormones are not thought to be the primary cause of seizures, but they alter the vulnerability to seizures. One third to one half of women with epilepsy experience catamenial seizures (changes in seizure frequency at specific times during the menstrual cycle). Some women experience these changes in seizure frequency just before the start of their menstrual period. Changes in seizure frequency may also occur around the time of ovulation.

The causes of catamenial seizures are not fully understood but are hypothesized to involve fluctuations in estrogen or progesterone, or changes in the estrogen-progesterone ratio. Both estrogen and progesterone can influence brain function by interacting with specific hormone receptors on neurons. High concentrations of these hormone receptors are found in brain regions thought to be important in generating epileptic seizures. By interacting with hormone receptors on brain cells, estrogen can increase the likelihood of seizures, and progesterone can decrease the likelihood of seizures.

In addition to influencing seizure frequency via a direct effect on brain cells, hormones can affect seizure frequency by changing the blood level of antiepileptic drugs, many of which are metabolized by the same enzymes that metabolize hormones such as estrogen and progesterone. It is hypothesized that the characteristic decline in estrogen and progesterone that immediately precedes menstruation may make enzymes usually involved in breaking down estrogen and progesterone available to break down antiepileptic drugs. As a result, antiepileptic drugs are degraded to a greater extent than they are at other times during the menstrual cycle, and blood levels of the drugs decrease. Some studies have confirmed a decline in blood levels of antiepileptic drugs around the time of menstruation whereas the results of other studies are inconclusive.

**Figure 2. Hormonal Fluctuations During the Menstrual Cycle**

**FOLLCULAR PHASE**
- Ovarian follicle (growing)
- Estrogen

**LUTEAL PHASE**
- Corpus luteum

- Progesterone (+ estrogen)

- E2 = estrogen; FSH = follicle-stimulating hormone; LH = luteinizing hormone.

**Effects of Epilepsy on Hormones**

As hormones can affect epilepsy by altering the likelihood of seizures, so can epilepsy affect bodily functions dependent on hormones (Table 1).1-4 Women with epilepsy are more likely than those without epilepsy to experience menstrual dysfunction, including abnormalities in cycle length (i.e., polymenorrhea characterized by cycle length of fewer than 23 days or oligomenorrhea characterized by cycle length of more than 35 days), irregular cycles, amenorrhea (absence of menstruation), and anovulation (failure to ovulate).

Women with epilepsy are more likely than those without epilepsy to have ovaries that appear polycystic as well as polycystic ovary syndrome (PCOS), which is characterized by enlarged, cystic ovaries and is accompanied by clinical features such as obesity, high blood insulin levels (hyperinsulinemia), high blood lipid levels (dyslipidemia), and amenorrhea or oligomenorrhea.12-14 Hyperinsulinemia, obesity, and poor lipid profiles are independent risk factors for coronary artery disease.15 Ovarian abnormalities in the absence of PCOS have also been found more often in women with epilepsy compared with nonepileptic women. In a recent study, ovaries appearing polycystic were described in 16% of nonepileptic women (controls), 26% of women with localization-related epilepsy, and 41% of women with generalized epilepsy.16

Some research suggests that women with epilepsy have lower fertility rates compared with women without epilepsy, but the evidence of infertility in epilepsy is not strong.2,3,17 In epidemiologic studies, women with epilepsy are approximately two thirds less likely to have children compared with women without epilepsy.2 However, other research did not find a decreased rate of live births to women with epilepsy compared with a population control.17 The reasons for the possible lower fertility rates in women with epilepsy have not been definitively established. Social factors probably play an important role, and it is postulated that epilepsy-associated disruption of the menstrual cycle may be responsible.3 Other possible reasons for the lower fertility rates among women with epilepsy include a reluctance to become pregnant because of fear of complicating the outcome of pregnancy or fear of having a child with epilepsy.

Women with epilepsy may also be more likely to experience sexual dysfunction than women without epilepsy.18,19 They experience not only reduced desire but also impaired sexual function, both of which are mediated at least in part by endocrine hormones.

The reasons for the reproductive abnormalities described in this article have not been determined, but several possible mechanisms have been suggested (Table 2).3 Some evidence suggests that reproductive dysfunction in women with epilepsy may be caused by seizure-induced disruptions of hormonal functioning. The activation of brain circuits that occurs during seizures may disrupt the brain's regulation of hormone release from the hypothalamus.2 Because the release of hormones by the anterior pituitary gland and the ovary is controlled by hormones released from the hypothalamus, the hypothalamic disruption in turn disrupts hormone release from the anterior pituitary and the ovary. Studies in patients with epilepsy confirm that seizures alter circulating levels of endocrine hormones such as prolactin, luteinizing hormone, and growth hormone.

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**Table 1. Endocrine Abnormalities in Women with Epilepsy**

- Menstrual dysfunction
- Polycystic-appearing ovaries
- Low fertility rates
- Sexual dysfunction

**Table 2. Potential Mechanisms of Reproductive Dysfunction in Women with Epilepsy**

- Seizure-related disruption of hormones or brain regions that mediate reproduction
- Antiepileptic drugs
- Structural or functional disruption of brain regions that mediate reproduction

Data from Morell.3
It is postulated that antiepileptic drugs may alter hormonal functioning and cause reproductive endocrine abnormalities in women with epilepsy. For example, PCOS has been attributed to valproate-associated increases in circulating testosterone although available data has not yet confirmed this hypothesis.21

Finally, structural or functional central nervous system dysfunction associated with the disease of epilepsy (but not with seizure activity per se) may also explain reproductive dysfunction in women with epilepsy.3 Epilepsy is a disease of altered central nervous system structure and function. Independent of the neural activity associated with seizures, the altered structure and function of brain regions may affect reproductive function when areas of the brain that are affected by epilepsy are also involved in reproduction.

HORMONES AND EPILEPSY THROUGHOUT THE LIFE SPAN

PUBERTY

Puberty relative to childhood is a time of marked hormonal fluctuations.1 Some seizure disorders become evident for the first time during puberty, whereas others remit, perhaps due to the hormonal changes occurring during puberty. For example, juvenile myoclonic epilepsy typically develops around the onset of puberty, whereas childhood absence seizures often remit during puberty. In studies conducted to date, the frequency of seizures in preexisting seizure disorders is not markedly altered during puberty, but some types of seizures begin or remit during puberty.1,3

The potential interaction of antiepileptic drugs with hormonal contraception during puberty and continuing into later years is a growing concern.31 Interactions with some antiepileptic drugs can reduce the effectiveness of hormonal contraception, the birth-control pill being one such example. The incidence of oral contraceptive failure is higher among women taking antiepileptic drugs compared with those who are not.18 This finding is attributed to increased metabolism of exogenous hormones stimulated by enzyme-inducing medications, including phenytoin, carbamazepine, and oxcarbazepine.

Changes in reproductive hormones can also affect the anticonvulsant efficacy of antiepileptic drugs. For example, preliminary evidence shows that birth-control pills and pregnancy may lead to lowered levels of lamotrigine, which may hypothetically affect seizure control.22

Menarche

A seizure disorder may first become evident around the time of menarche (ie, the first menstrual period), particularly among women who develop catamenial epilepsy. However, in studies conducted to date, preexisting seizure disorders have not been found to respond predictably to menarche.1

Pregnancy

Pregnancy is associated with marked increases in estrogen and progesterone levels as well as alterations in the metabolism of hormones and antiepileptic drugs. Both factors may be expected to influence seizure frequency. Up to one third of women have been reported to experience increased seizure frequency during pregnancy.23,24 More research is needed to characterize the relationship between seizures and pregnancy.

Menopause

Estrogen can increase the likelihood of seizures by interacting with hormone receptors on neurons. The estrogen deficiency that characterizes menopause might be expected to result in a reduction in seizure frequency.1 Seizures and menopause show a variable relationship in which some women experience decreases in seizure frequency, some experience increases, and some experience no change.25 Women who suffered from catamenial epilepsy were more likely to experience remission of seizures during menopause compared with women who did not suffer from catamenial epilepsy.

Conclusions

The interaction between endocrine hormones and epilepsy poses unique challenges for women with epilepsy and the physicians who treat them. Fluctuations in sex hormones can increase vulnerability to seizures in many women. Conversely, seizures can cause endocrine abnormalities that can result in menstrual irregularities, altered fertility, and sexual dysfunction that have been linked to PCOS. The healthcare provider is better equipped to manage endocrine-associated changes in seizure frequency and epilepsy-associated changes in neuroendocrine function by being aware of how endocrine hormones and epilepsy interact throughout the patient's life span.
REFERENCES