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ScienceDirect
Epilepsy & Behavior 11 (2007) 160–178
Epilepsy & Behavior
www.elsevier.com/locate/yebeh

Review

Women with epilepsy: Hormonal issues from menarche through menopause ☆

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Received 6 March 2007; accepted 10 March 2007
Available online 26 July 2007

Abstract

Epilepsy is a multilayered disorder complicated by numerous comorbid conditions and hormonal changes. More than 1.5 million girls and women with epilepsy face side effects that are compounded at different ages by menstruation, fertility, pregnancy, fetal health, bone health, and other health issues. Changes in hormonal balance during maturation, from menarche through menopause, affect seizure thresholds and antiepileptic drugs, and vice versa. This overview provides physicians with a background on the multiple issues relevant to women of all ages in the reproductive years, including those planning to conceive and those who are pregnant, and beyond the childbearing years.

Keywords: Epilepsy; Women's health; Pregnancy; Teratogenicity; Reproductive health; Antiepileptic drugs; Menopause

1. Introduction

Epilepsy is a neurological disorder that causes seizures. These seizures can range from very mild, with disruption in attention for a few seconds, to severe, with muscle spasms and loss of consciousness. There are an estimated 50 million people with epilepsy worldwide [1]. The relationship between epilepsy and the endocrine system has been investigated by neurologists, endocrinologists, and basic scientists. Seizures as well as antiepileptic medications have been found to compromise sexual development, with impairment of libido and sexual potency in some patients with epilepsy. Women with epilepsy have a greater risk of infertility than the general population [2–6]. This review discusses the issues concerning women with epilepsy, beginning with the onset of the menarche and continuing through the postmenopausal years.

2. Overview of the relationship between hormones and epilepsy

Women with epilepsy have particular challenges that are related to ovarian steroid hormones [7]. The ways in which hormones affect their seizure activity begin to be evident at the start of menstruation [8,9]. Women may have changes in seizure threshold related to their menstrual cycle, as well as at other times in their reproductive life including puberty, pregnancy, and menopause, all times when there are changes in the estrogen and progesterone levels in the body [10]. Fertility and reproductive capacity may be affected in some women with epilepsy [11]. In many ways, hormones influence epilepsy, and epilepsy influences hormones. Estrogen can be a very potent proconvulsant, whereas progesterone can be anticonvulsant [12–14]. The relationships are complex [15,16]. Research into this complex interaction

☆ Presented in part on www.professionals.epilepsy.com; September 2006 (http://professionals.epilepsy.com/pdfs/discussion_guide.pdf).

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doi:10.1016/j.yebeh.2007.03.007

is ongoing, but much is known that can help physicians as they manage the care of female patients through all of the phases of their reproductive life while maintaining optimal control of their epilepsy.

Ovarian sex steroid hormones affect the excitability of the central nervous system (CNS) and alter the frequency and severity of seizures. The principal ovarian steroid hormones are estrogens (estradiol, estrone, and estriol) and progesterone, with their secretion controlled by the hypothalamus and pituitary. Estradiol is the most potent estrogen [17–19]. A complex neuroendocrinological feedback system, the hypothalamic–pituitary–ovarian axis (see Fig. 1), regulates the menstrual cycle [20]. Gonadotropin-releasing hormone (GnRH) secreted by the hypothalamus stimulates the release of follicle-stimulating hormone (FSH) by the pituitary. FSH stimulates formation of the ovarian follicles, which secrete estradiol as they develop. FSH is inhibited whereas GnRH is stimulated by estrogen. One result is a surge of luteinizing hormone (LH), which induces oocyte maturation, ovulation, and conversion of the follicle into the corpus luteum. This marks the end of the follicular phase of the cycle, preceding ovulation by about 36 h. Following ovulation is the luteal phase, when the corpus luteum secretes progesterone. The progesterone inhibits secretion of GnRH, FSH, and LH. If there is no pregnancy, the corpus luteum regresses, and production of progesterone and estradiol declines. When progesterone secretion tapers off and GnRH inhibition decreases, the cycle repeats, forming a loop [21].

Estradiol and progesterone are highly lipophilic and easily cross the blood–brain barrier and diffuse through cell membranes, binding to intracellular receptors and forming hormone–receptor complexes. The fluctuations in ovarian steroids and peptides directly affect the brain. Hormones from the hypothalamus and pituitary gland regulate the amounts of estrogen and progesterone circulating in the body. The hypothalamus, in turn, receives many direct connections from those parts of the temporal lobe that are involved in the generation of seizures. Alteration of normal LH pulsatile secretion has been documented in women with epilepsy [22,23]. Chronic epilepsy and the seizure event itself have different effects on LH pulsatility. Research has shown that seizure discharges can disrupt the output of hormones such as FSH and LH, which, in turn, can alter the balance of estrogen and progesterone and affect seizure control. In other words, seizures can affect hormones, and hormone levels can also affect seizures.

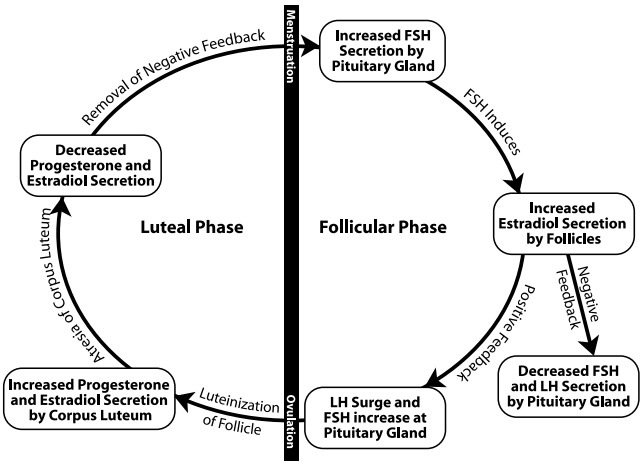

Fig. 1. Reproductive endocrine axis disturbances.

Experimental models of epilepsy demonstrate a change in seizure susceptibility provoked by the ovarian steroid hormones. These hormones alter the excitability of neurons in the brain, particularly in the temporal and frontal lobes.

Animal models have demonstrated the proconvulsant effects of estrogen and anticonvulsant effects of progesterone [17–19]. Estrogen increases excitatory neurotransmitters and also alters dopamine, which is an inhibitory neurotransmitter. Estrogen may also alter the structure of the synaptic area of neurons, increasing the number of dendritic spines and the number of spine synapses, thereby increasing cell-to-cell contacts.

Because the antiseizure effect of progesterone is present in progesterone-receptor knockout mice, it can be assumed that progesterone exerts its seizure-inhibitory effects through its metabolites. Those metabolites are sometimes referred to as neuroactive steroids. Allopregnanolone is a GABA-A receptor-modulating neurosteroid progesterone metabolite. Metabolites of progesterone regulate hippocampal neuronal excitability, with a positive allosteric effect on GABA-A receptors [24,25]. In animal models of epilepsy, progesterone raises the seizure threshold [26–28]. Progesterone metabolites produce anticonvulsant, antianxiety, and sedative effects similar to, but in a narrower range than those of, benzodiazepines. For this reason, researchers are working on developing progesterone-based antiepileptic medications that may have fewer adverse effects than current antiepileptic drugs (AEDs) [14,29].

The effects of estrogen and progesterone demonstrated in experimental models of epilepsy have also been seen clinically [12,30]. Women with epilepsy have exhibited a variety of endocrine disturbances [31,32]. These have been attributed to a combination of factors, including the epilepsy syndrome and the effect of interictal and ictal epileptic discharges in the brain. The risk is exacerbated by the effects of some AEDs [32]. The relationship between a particular AED and the endocrine system appears to result from the drug's effect on hepatic microsomal enzymes of the cytochrome P450 system. For example, AEDs that induce hepatic microsomal enzymes (EIAEDs) also interact with hormonal contraceptives to increase estrogen's metabolism and progesterone's protein binding, thereby decreasing concentrations of both hormones and thus reducing contraceptive efficacy [33,34].

Normally, estrogen levels are higher than progesterone levels in the days leading up to ovulation and immediately before menstrual bleeding. These are the times in the menstrual cycle during which many women notice more fre-