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Review

# Gender issues in the neurobiology of epilepsy: A clinical perspective

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ABSTRACT

A patient's hormonal milieu contributes to the timing of emergence of several epilepsy syndromes that are known to begin at puberty and recede with the end of reproductive potential.
One's hormonal balance at any particular moment contributes to seizure occurrence in both men and women. The best studied condition, catamenial epilepsy, refers to seizure clusters occurring in a cyclical pattern related to menses. Treatment of epilepsy using hormones complements standard antiepileptic therapy and its use will be reviewed, along with some other medications unique to catamenial epilepsy, such as diuretics.
Seizures and "silent" epileptiform discharges in turn affect the hypothalamic pituitary axis and can cause release of hormones at inappropriate times leading to sexual dysfunction, menstrual irregularity, infertility and premature termination of reproductive states. Combined with psychological consequences of epilepsy, this sexual dysfunction has deleterious effects on the quality of life in patients and their partners.


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## Introduction

Long known for their influence on mood and cognitive function, the sex hormones have also been known to affect seizure threshold since Locock's observations in 52 patients (Locock, 1857) and Gowers' in 46 women with menstrually-related attacks (Gowers, 1881). Based on patterns of seizure occurrence in catamenial epilepsy, and later confirmed by assays of hormone levels throughout the menstrual cycle, estrogen is considered to be excitatory (lowering seizure threshold), while progesterone is calming (antiepileptic) (Fig. 1). Clinical studies which contribute to understanding the pathophysiology of catamenial epilepsy will be reviewed, and the influence of sex hormones on epilepsy syndromes in general will be described, including experience gained from case reports.

Successes and limitations of hormonal treatment of epilepsy will be described.

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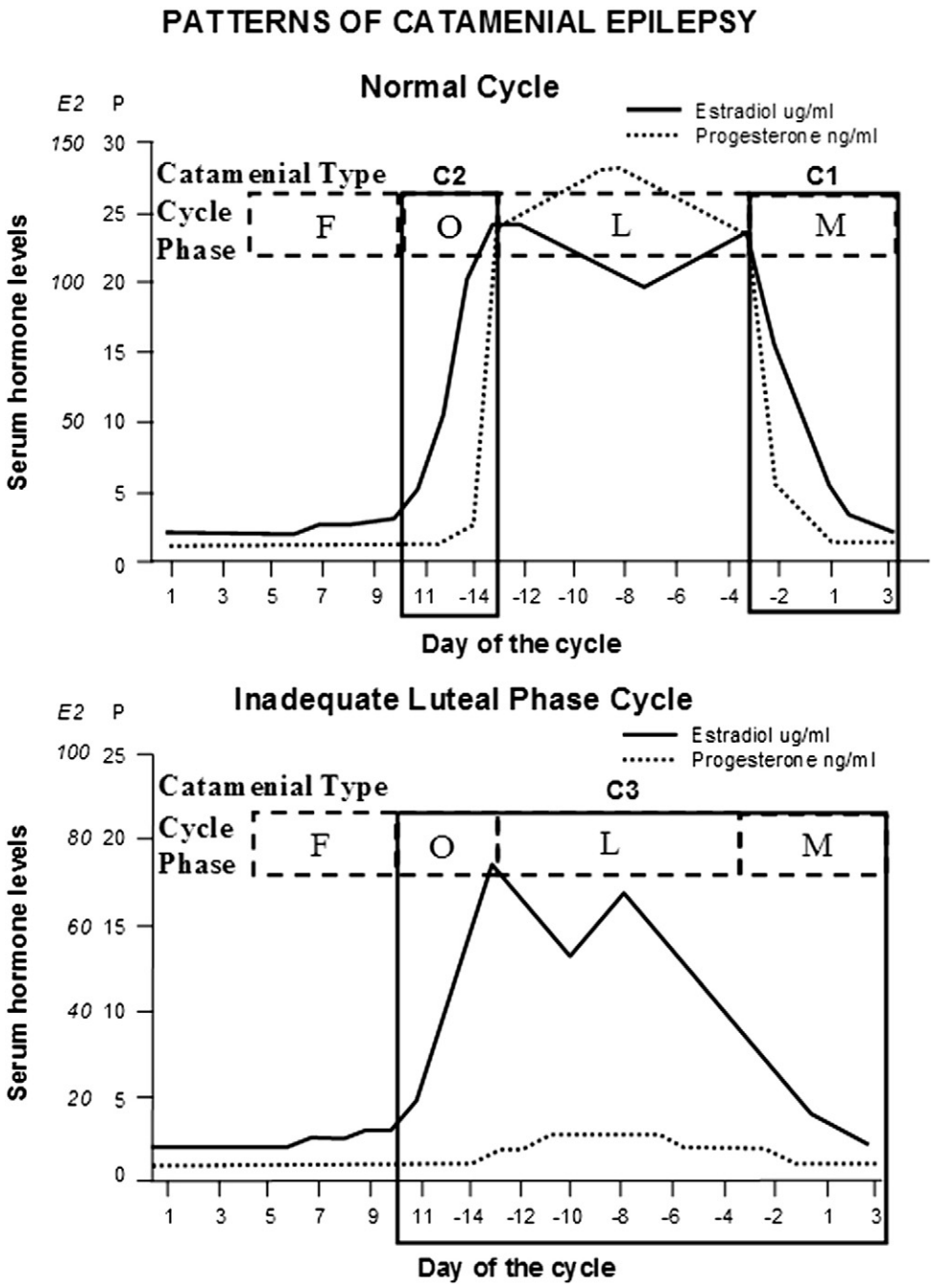


**Fig. 1.** Three patterns of catamenial epilepsy: perimenstrual (C1) and periovulatory (C2) exacerbations during normal ovulatory cycles and entire second half of the cycle (C3) exacerbation during inadequate luteal phase cycles where day 1 is the first day of menstrual flow and Day −14 is the day of ovulation. F = follicular phase; O = periovulatory; L = Luteal phase; M = perimenstrual. E2 = Estradiol; P = Progesterone.

Conversely, the effects of epilepsy and epileptiform activity on gonadotropin release and subsequent state of hormonal balance and related dysfunction will be reviewed.

### Relationships between hormonal states and seizure occurrence

Sex hormones such as estrogen, androgen and progesterone, along with their metabolites, play a role in brain development and network formation. During parturition female hormones may be neuroprotective for birth-related trauma and anoxia. Postnatally, estrogen promotes cognitive function and memory formation, through immediate gene transcription. Modulation of neurotransmitters, specifically NMDA and glutamate in the case of estrogens and $GABA_A$ in the case of progesterone, set a state of excitation or inhibition. Androgen is metabolized to 17β estradiol (by aromatization) or androstenedione (by glucuronidation) and these metabolites have opposite effects on the excitability of cortex (Sivaraaman and Mintzer, 2011). It has even been proposed that some of these hormone metabolites, such as androsterone, which, like progesterone metabolites, modulates GABA receptors, may be protective against seizures (Kaminski et al., 2005; Frye, 2010). However, this simple paradigm of hormonal influence on seizure threshold is difficult to confirm in patients. In fact, cortical excitability as measured using transcranial magnetic stimulation, admittedly of the motor cortex and not the limbic system, was not different in ovulatory or anovulatory cycles and was the same for women with epilepsy of all types, not just catamenial, displaying maximal excitability in the