Epilepsia, 32(Suppl. 6):S27–S33, 1991
Raven Press, Ltd., New York

Reproductive Endocrine Considerations and Hormonal Therapy for Women with Epilepsy

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Summary: Animal experimental and human clinical investigations show that estrogens lower and progestins raise many seizure thresholds. In women, seizure frequency varies with the serum estradiol to progesterone ratio. The fluctuation of this ratio during the menstrual cycle is a major factor in catamenial epilepsy. A decline in serum antiseizure medication levels premenstrually may be another factor. Estradiol to progesterone ratios are elevated in anovulatory or inadequate luteal phase cycles. This may explain a propensity for seizure onset at the time of menarche and the exacerbation of seizures during the months or years leading up to menopause. It may also be an important factor in the association between reproductive endocrine disorders and epilepsy. Specifically, polycystic ovarian syndrome and hypogonadotropic hypogonadism are significantly overrepresented among women with epilepsy. Epilepsy may promote the development of these disorders. These disorders, in turn, are characterized by inadequate luteal phase cycles that may promote the development or occurrence of seizures. In the setting of catamenial epilepsy or reproductive endocrine disorders, progestins, such as natural progesterone and parenteral medroxyprogesterone, or antiestrogenic agents, such as clomiphene, constitute rational and effective adjuncts to therapy.
Key Words: Epilepsy—Hormones—Reproduction—Endocrine—Menstrual cycle—Female—Estrogens—Anticonvulsants—Drug-induced abnormalities.

There is considerable experimental animal and clinical evidence that gonadal steroids influence the occurrence of seizures (cf. Longo and Saldana, 1966; Holmes and Donaldson, 1987). The reproductive endocrine environment of a woman with epilepsy can undergo physiological, pathological, and pharmacological changes. Menarche (Turner, 1907; Lennox and Lennox, 1960), menstruation (Laidlaw, 1956; Newmark and Penry, 1980), pregnancy (Knight and Rhind, 1975; Schmidt et al., 1985), and the process of menopause (Turner, 1907; Sallusto and Pozzi, 1964) can be associated with altered seizure frequency. Reproductive endocrine disorders are overrepresented among women with epilepsy (Herzog et al., 1986; Bilo et al., 1988). The anovulatory and inadequate luteal phase cycles associated with them often exacerbate seizures (Backstrom, 1976; Mattson et al., 1981). Oral contraceptives (cf. Mattson and Cramer, 1985) and menopausal hormonal replacement (cf. Herzog, 1984) can exacerbate or benefit a seizure disorder, depending on the particular circumstances of the treatment. A knowledge of some interactions among hormones, epilepsy, and antiepileptic drugs (AEDs), therefore, may provide the clinician with a more comprehensive basis for the effective treatment of women with epilepsy.

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HORMONAL EFFECTS ON SEIZURES

In many experimental animal models, estrogen lowers the thresholds of seizures induced by electroshock, kindling, pentylenetetrazol, kainic acid, ethyl chloride, and other agents and procedures (Spiegel and Wycis, 1945; Logothetis and Harner, 1960; Woolley and Timiras, 1962; Nicoletti et al., 1985; Hom and Buterbaugh, 1986). The topical brain application or intravenous systemic administration of estradiol in rabbits produces a significant increase in spontaneous electrically recorded paroxysmal spike discharges (Logothetis and Harner, 1960). The increase is more dramatic in animals with pre-existent cortical lesions (Marcus et al., 1966). Progesterone, on the other hand, lessens spontaneous and induced epileptiform discharges

(Spiegel and Wycis, 1945; Landgren et al., 1978; Nicoletti et al., 1985).

Hormones also influence human electrical brain wave activity and epilepsy. Logothetis et al. (1958) showed that intravenously administered conjugated estrogen clearly activated epileptiform discharges in 11 of 16 women and was associated with clinical seizures in 4. Backstrom et al. (1984) found that intravenous infusion of progesterone, sufficient to produce luteal phase serum levels, was associated with a significant decrease in interictal spike frequency in four of seven women with partial epilepsy.

MENARCHE

Seizures do not occur entirely randomly in relation to physiological reproductive endocrine events. An influence of menarche on the onset of seizure disorders was postulated by a number of investigators who observed that late childhood and adolescence were peak periods for the first clinical manifestations of epilepsy (Turner, 1907; Lennox and Lennox, 1960). This tendency was noted by others, in particular among women who had catamenial epilepsy (Logothetis et al., 1958; Longo and Saldana, 1966). Logothetis et al. (1958), for example, reported that 16 of 25 women with catamenial epilepsy had the onset of their seizures within 3 years of menarche. Pre-existent seizures, however, were not found to be exacerbated by menarche in a recent investigation by Diamontopoulos and Crumrine (1986). This issue needs to be evaluated further with due consideration not only of possible differences in seizure frequency or brain wave findings in relation to the first menstrual period but also in relation to the more extensive adrenarchal and menarchal patterns of reproductive hormone secretion during the late childhood years leading up to the onset of menstruation.

CATAMENIAL EPILEPSY

Catamenial epilepsy refers to seizure exacerbation in relation to the menstrual cycle (Spiegel and Wycis, 1945; Woolley and Timiras, 1962). Three patterns exist (Herzog, 1986): (a) One-quarter to three-quarters of women with epilepsy describe an increase in seizures during the few days prior to menstruation and the first 2 or 3 days of menstruation. (b) A predilection for seizure exacerbation may also occur near the middle of the cycle, prior to ovulation between days 8 and 14. The onset of menstruation is considered day 1. (c) A more difficult pattern to discern is one in which seizures are frequent between day 8 of one cycle and day 2 of the next, relative to the interval between days 2 and 8.

Physiological endocrine secretion during the menstrual cycle influences the occurrence of seizures. In ovulatory cycles, seizure frequency shows a statistically significant positive correlation with the serum estradiol/progesterone ratio (Backstrom, 1976). This ratio is highest during the days prior to ovulation and menstruation and is lowest during the early and midluteal phase (Backstrom, 1976) (Fig. 1). The premenstrual exacerbation of seizures has been attributed to the withdrawal of the antiseizure effects of progesterone (Laidlaw, 1956). Midcycle exacerbations may be due to the preovulatory surge of estrogen unaccompanied by any rise in progesterone until ovulation occurs (Backstrom, 1976). Seizures are least common during the midluteal phase when progesterone levels are highest (Strott et al., 1970; Backstrom, 1976; Mattson et al., 1981).

Inadequate luteal phase refers to less than normal progesterone secretion during the second half of the cycle, regardless of whether ovulation does or does not occur (Berman and Korenman, 1974; Jones, 1976). It can be documented by one or preferably more findings, including (a) a failure of the basal body temperature to rise by 0.7°F for at least 10 days during the second half of the menstrual cycle; (b) a serum progesterone level of less than 5.0 ng/ml during the midluteal phase, generally measured between days 20 and 22 of a 28-day cycle; and (c) a biopsy that shows underdeveloped secretory endometrium, 8–10 days after ovulation. Serum estradiol/progesterone ratios and seizure frequencies tend to be higher than in normal ovulatory cycles during the second half of these cycles (Backstrom, 1976; Mattson et al., 1981) and seizure exacerbation may extend from day 8 of one cycle to day 2 of the next cycle (Herzog, 1986).

The premenstrual exacerbation of seizures may be related to a decline in serum AED levels as well as to withdrawal of the anticonvulsant effects of progesterone (Shavit et al., 1984; Roscizewska et al., 1986). Serum

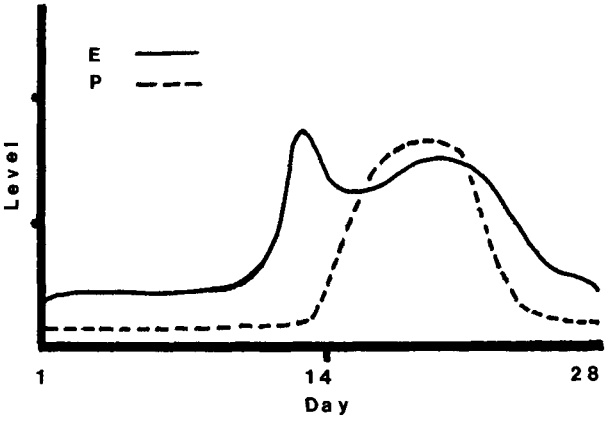

FIG. 1. Schematic illustration of relative variation in serum estradiol and progesterone levels during the menstrual cycle. E = estradiol; P = progesterone.

AED levels generally decrease in the days prior to menstruation (Shavit et al., 1984; Roscizewska et al., 1986). This decline is significantly more marked in women who experience premenstrual worsening of seizures (Shavit et al., 1984; Roscizewska et al., 1986). Hepatic mechanisms are implicated (Shavit et al., 1984; Roscizewska et al., 1986). Specifically, AEDs and gonadal steroids are metabolized by the same microsomal enzyme systems in hepatic cells. The premenstrual decline in gonadal steroid secretion, therefore, may permit increased metabolism of AEDs, resulting in lower serum levels.

PREGNANCY

Pregnancy may have variable effects on epilepsy. A very small number of women experience seizures for the first time during pregnancy and have seizures only during pregnancy (Knight and Rhind, 1975). Most large investigations agree that pregnancy does not affect seizure frequency in about one-half of women (Knight and Rhind, 1975; Schmidt et al., 1985). In about one-third of women, seizure frequency will increase during pregnancy (Knight and Rhind, 1975; Schmidt et al., 1985). Recent studies (Schmidt et al., 1985) suggest that this can be attributed in the majority of cases to a decrease in serum levels of AED. In some, this is due to diminished patient compliance. In others, it may be related to a greater volume of distribution and a higher rate of clearance. The latter may result from the increased circulatory rate during pregnancy, altered drug pharmacokinetics, and increased hepatic metabolism. In about one-sixth of women, seizure frequency will decrease (Knight and Rhind, 1975; Schmidt et al., 1985). This may be related, in some, to increased patient compliance with the use of AEDs. In the remainder, the mechanism is not known.

MENOPAUSE

There are differences of opinion regarding the effects of menopause on epilepsy. Turner (1907) stated that while menopause generally has little influence on epileptic attacks, there are a few cases in which seizures may become arrested. The beneficial results of ovariectomy in animal experiments was subsequently cited in support of the notion that clinical improvement occurs at the time of menopause (Woolley and Timiras, 1962). Other reports (Sallusto and Pozzi, 1964), however, described exacerbation of seizures at the time of the climacteric. It is important to be aware that the term "menopause" refers to a complex process and a variable end point that may differ significantly among individuals. Early during menopause, for example, anovulatory cycles may develop and lead to increased estrogen to progesterone ratios that would be expected to promote the occurrence of seizures. At the end of the process, estrogen production by the ovary may become essentially undetectable and potentially lead to a beneficial effect. Adrenal steroid secretion, however, continues beyond menopause. Some adrenal androgens are converted to estrogens by adipose tissue. The resulting estrogen to androgen ratio may exert a significant influence on seizures in the absence of gonadal secretion. Prospective investigations to correlate changes in seizure and brain wave patterns with ovarian and adrenal endocrine profiles during menopause need to be carried out to clarify these issues.

REPRODUCTIVE ENDOCRINE DISORDERS AND EPILEPSY

Reproductive dysfunction and endocrine disorders are unusually common among women who have epilepsy (Herzog et al., 1986). Amenorrhea occurs in 14–20% (Trampuz et al., 1975; Jensen and Vaernet, 1977; Cogen et al., 1979). Menorrhagia or metrorrhagia occurs in 43% (Jensen and Vaernet, 1977). Fertility is reduced to 69% of the expected number of offspring among married couples (Dansky et al., 1980). Luteinizing hormone (LH) responses to gonadotropin-releasing hormone stimulation may be abnormally high or low (Herzog et al., 1982), likely reflecting the association between left temporal lobe seizures and polycystic ovarian syndrome, on the one hand, and right temporal lobe seizures and hypogonadotropic hypogonadism, on the other (Herzog, 1991). The pulse frequency of LH secretion among drug-free epileptic women with regular menstrual cycles has been noted to be significantly higher than among normal controls (Bilo et al., 1991). The pulse frequency among treated women with complex partial seizures, regardless of menstrual characteristics, has a bimodal distribution with peaks below and above the normal mode (Herzog, unpublished results). Reproductive endocrine disorders, including polycystic ovarian syndrome and hypogonadotropic hypogonadism, as well as possibly premature menopause and functional hyperprolactinemia, appear to be overrepresented among women with partial seizures of temporal lobe origin (Herzog et al., 1986). Polycystic ovarian syndrome and hypogonadotropic hypogonadism are also unusually common in association with primary generalized epilepsy (Bilo et al., 1988). All are known to contribute to reproductive dysfunction. These reproductive endocrine disorders, moreover, may also promote the occurrence of seizures by their effects on medial temporal lobe limbic structures that bind gonadal steroids and show sensitive electrophysiological responses to hormonal influence

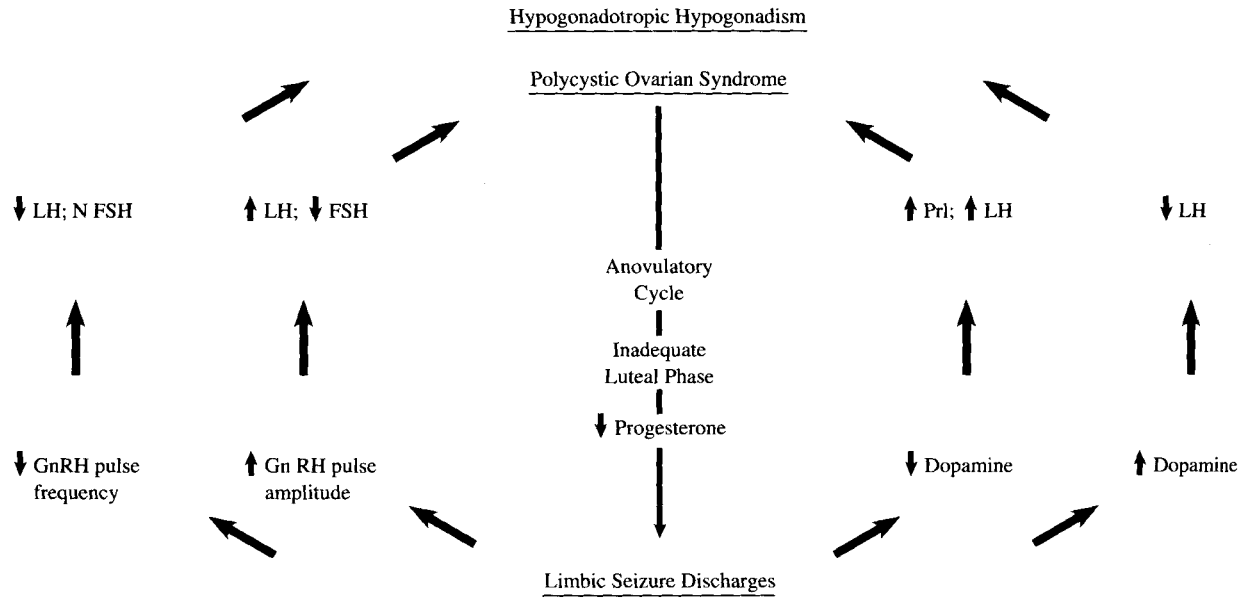

FIG. 2. Possible mechanisms of interaction between limbic epileptiform discharges and reproductive endocrine disorders. LH = luteinizing hormone; FSH = follicle-stimulating hormone; Prl = prolactin; GnRH = gonadotropin-releasing hormone; N = normal.

(Fig. 2). Specifically, reproductive endocrine disorders associated with temporal lobe epilepsy and primary generalized epilepsy are characterized by anovulatory cycles or inadequate luteal phase (Herzog et al., 1986). Such cycles expose temporal lobe limbic structures to a constant estrogen effect without the normal luteal phase elevations of progesterone and thereby tend to heighten interictal epileptiform activity (Fig. 2). In this regard, Sharf et al. (1969) found that 56.5% of women with anovulatory cycles or amenorrhea had EEG abnormalities, including some with focal paroxysmal epileptogenic discharges. Treatment with an antiestrogenic agent, clomiphene citrate, restored normal EEG findings in 54% (Sharf et al., 1969). There was, moreover, an association between restoration of ovulatory cycles and normalization of the EEG.

PROGESTERONE THERAPY

Progesterone therapy may benefit some women with catamenial epilepsy (Herzog, 1986). In the absence of an adequate response to classical antiseizure therapy, treatment may be considered in two settings: (a) women with catamenial epilepsy who have a documented inadequate luteal phase and (b) women with catamenial epilepsy who have no demonstrable reproductive endocrine abnormality. The former group may show any of the three previously described patterns of seizure exacerbation, while the latter generally experiences worsening of seizures premenstrually. The pattern should be documented during three cycles using charts that include the days of the month, cycle days, and seizure occurrence. Progesterone may be administered throughout the period of seizure exacerbation during the second half of the cycle and then tapered and discontinued over 3 days at the end of the cycle.

There are no definite absolute clinical contraindications to the intermittent use of natural progesterone to achieve physiological luteal range serum levels in a cyclic fashion. It is considered by some to be the treatment of choice for an inadequate luteal phase and is regularly used to help induce fertility (Jones, 1976). It is yet to be recognized, however, as an approved form of therapy for neurological purposes. Therefore, classical forms of AED therapy should be considered first and its status should be described carefully prior to prescription. Progesterone should be avoided (a) during or in anticipation of pregnancy unless it is used specifically in conjunction with a gynecologist as part of a fertility program and (b) in the absence of adequate birth control measures. It should also be used cautiously in the presence of undiagnosed breast lumps since synthetic progestin administration in experimental animals has been associated with mammary nodule development and, in high doses, malignancy.

Natural progesterone is available as an extract of soy in suppository and lozenge forms. The usual daily regimen to achieve physiological luteal range serum levels, as measured 4 h after administration, ranges from 100–200 mg, taken three or four times daily, with the average daily dose being 600 mg (Herzog, 1986). The

maintenance dosage and regimen should be individualized and based on a combination of clinical response and serum progesterone levels between 5 and 25 ng/ml. Adverse effects occur with overdosage and include sedation, mental depression, and asthenia (Herzog, 1986). Progesterone use may also be associated occasionally with breast tenderness, weight gain, and irregular vaginal bleeding. The vehicle used to dissolve progesterone for suppository use may rarely be responsible for the development of an allergic rash. Discontinuation of the hormone or lowering of the dosage resolves these side effects (Herzog, 1986).

Drug interactions are an important consideration. Higher progesterone dosages may be required to achieve luteal range levels in women who take AEDs because carbamazepine, phenytoin, and barbiturates are known to enhance the hepatic metabolism of gonadal and adrenal steroid hormones as well as to increase hormonal binding to serum proteins (Christiansen et al., 1975; Ludhorf et al., 1977). Progesterone use has been associated with changes in antiseizure medication levels in some cases, but this effect has been sporadic in occurrence and not readily predictable in direction. Therefore, total and free serum AED levels should be checked during concomitant hormonal therapy.

Synthetic progestin therapy has also benefitted some women with epilepsy (Zimmerman et al., 1973; Mattson et al., 1984). Parenteral medroxyprogesterone significantly lessens seizure frequency when it is given in sufficient dosage to induce amenorrhea (Zimmerman et al., 1973; Mattson et al., 1984). A regimen of approximately 120–150 mg given intramuscularly every 6–12 weeks generally achieves this goal (Mattson et al., 1984). Side effects include those encountered with natural progesterone. Depot administration, however, is also commonly associated with hot flashes, irregular breakthrough vaginal bleeding, and a lengthy delay of 6–12 months in the return of regular ovulatory cycles (Mattson et al., 1984). Long-term hypoestrogenic effects on bone density and cardiovascular status need to be considered with chronic use. In our own experience, the weekly intramuscular administration of 400 mg of depot medroxyprogesterone to a 44-year-old woman with polycystic ovarian syndrome and intractible complex partial seizures of left temporal and right frontal lobe origin despite extensive AED trials was associated with a reduction in average monthly seizure frequency from 22.5 to 2.4. Lower dosages or frequency of administration were less effective.

Oral synthetic progestins administered cyclically or continuously have not proven to be an effective therapy in clinical investigations (Dana Haeri and Richens, 1983; Mattson et al., 1984), although individual successes with continuous daily oral use of norethistrone and combination pills have been reported (Livingston, 1966; Hall, 1977).

CLOMIPHENE THERAPY

Clomiphene acts as an estrogen antagonist to increase gonadotropin secretion and induce ovulatory cycles in estrogen-secreting anovulatory women who do not have primary pituitary or ovarian failure (Cantor, 1984). Normalization of reproductive endocrine functions and menstrual cycles among women who have both partial seizures and menstrual disorders with a documented inadequate luteal phase has been demonstrated to lessen significantly and sometimes dramatically the seizure frequency (Login and Dreifuss, 1983; Herzog, 1988). In one investigation of 12 women, 10 improved and seizure frequency declined by 87% (Herzog, 1988). Clomiphene, however, is a drug with considerable pharmacological potency and potentially disturbing side effects. Therefore, it should be used only after potential risks and benefits are weighed carefully and treatment with AEDs and progesterone prove inadequate to control seizures. Clomiphene should not be administered in cases of suspected pregnancy or in the absence of adequate birth control measures unless it is used in conjunction with a gynecologist as part of a fertility program. Endometrial carcinoma should be ruled out prior to institution of therapy if abnormal uterine bleeding is present and normal liver function should be assured since clomiphene is excreted in the feces via the enterohepatic circulation.

Clomiphene is available in 50-mg tablets and can be administered in dosages ranging from 25 to 100 mg daily on days 5–9 of each cycle. Treatment should be initiated with the lowest dose and the daily dose may be raised by increments of 25–50 mg monthly as required to induce ovulatory cycles with normal luteal phase. Improved seizure control has been related to normalization of the reproductive endocrine cycle but, as yet, has not been recognized as an approved indication for continued clomiphene use.

In the one published investigation of clomiphene use in a series of 12 women with complex partial seizures, 6 experienced some side effects ranging from minor breast tenderness and pelvic cramps in 3 to severe lower abdominal pain with ultrasound documented ovarian cycts due to overstimulation of follicular development in 2, and 1 unwanted pregnancy (Herzog, 1988). Women with polycystic ovarian syndrome, which constituted the majority of the epileptic women in this investigation, appeared to be particularly sensitive to the development of overstimulation of follicular development and painful cyst formation (Her-

zog, 1988). Discontinuation of clomiphene was associated with a return of ovarian size to normal in both cases encountered in this series (Herzog, 1988).

Clomiphene therapy has not significantly altered total or free serum AED levels in the few cases that have been studied but a well-controlled investigation of possible drug interactions remains to be carried out (Herzog, 1988).

GONADOTROPIN-RELEASING HORMONE ANALOGUE THERAPY

Long-acting gonadotropin-releasing hormone analogues are used principally for the management of endometriosis. After a 3- to 4-week initial phase of reproductive endocrine stimulation, there develops a long-term suppression of gonadotropin and ovarian steroid secretion. Investigations into the possible use of these synthetic analogues for the management of catamenial epilepsy and disabling premenstrual syndromes are currently under way. Their use may provide valuable information concerning hormonal influences on epilepsy by assessing seizure frequency prior to their administration, during the two phases of their actions, and during hormonal supplementation with estrogens and/or progestins after the suppression of gonadal secretion. Our preliminary experience with a few cases suggests that gonadal suppression may improve seizure control but exacerbations of seizures and auras during the first month stimulation phase may be sufficiently marked to preclude their use in some cases. Moreover, the immediate and long-term effects of hypoestrogenism need to be considered, as in the use of depot progestins.

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