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Drug Treatment of Catamenial Epilepsy

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Summary

Catamenial seizures are defined as seizures occurring at or related to the menses. They may occur in up to 70% of women with continuing epileptic seizures.

Therapies aimed at reducing menstrually related seizures have focused on several possible pathophysiological mechanisms. Water retention that occurs perimenstrually has prompted the use of diuretic therapies, with some limited success. Hormonal changes, especially the correlation between increased estrogen and reduced progesterone levels and the occurrence of seizures, has led to the use of progesterone or clomifene (clomiphene) in highly selected patients. Intermittent anticonvulsant treatment in the days prior to menstrual flow, or increased daily drug dosage over these days, was prompted by the observation of a decrease in some antiepileptic drug concentrations premenstrually.

Rational treatment regimens and therapeutic trials in catamenial epilepsy are hindered by methodological difficulties, the complexities of interactions between antiepileptic drugs, hormones and seizures, and the high frequency of abnormal menstrual cycles in women with epilepsy.

An association between the stage of the menstrual cycle and epileptic seizure occurrence has been noted in the medical literature for more than a century. Catamenial seizures refer to an increase in seizure activity around the time of menstrual flow. Recent reports, however, suggest that there may be 2 peaks of seizure occurrence in hormonally related seizures: at the midcycle and perimenstrually in ovulatory cycles (but only in the perimenstrual phase in anovulatory cycles).[1]

Any treatment of hormonally related seizures should take into account changes in the levels of

sex hormones over the menstrual cycle and possible fluctuations in the concentrations of antiepileptic drugs in various phases of the cycle. This review discusses treatment regimens based on these changes and on other putative factors in catamenial epilepsy.

1. Historical Perspectives

Cyclic increases in the frequency of epileptic seizures have been observed since antiquity and were felt by early observers to be related to the phases of the moon.[2] The influence of the moon on epilepsy, originally described by Arateus, and on human behaviour in general was held through the nineteenth century. A possible association between the menstrual cycle and cyclic fluctuations in seizure frequency was first noted by Locock in 1857.[3] He wrote that seizures were 'often related to hysteria or the menses'. The observation that seizures were strongly related to the onset of menstruation was made by Gowers in 1885.[4] He analysed the frequency of seizures in 1222 personally observed cases and noted 'in more than one half the attacks were worse at the monthly periods. Most frequently they were worse before the period, and much less frequent after the period.'

Few statistical surveys of the relationship between seizure incidence and the menstrual cycle were performed until 1904, when Spratling[5] analysed the seizure frequency in 1374 patients with epilepsy of both sexes and found the second most common frequency of seizures was once every 4 weeks. He concluded that this pattern was related to menstruation. Further clinical reports early this century supported the apparent relationship between seizures and menses.[6-8] Lennox and Lennox[9] performed a statistical survey of 686 women with epilepsy and reported that 49% of those surveyed noted some relationship between menstrual function and the frequency of attacks.

Laidlaw[10] performed a detailed retrospective study of 50 women with epilepsy with a total of 33 468 seizures over 25 years. He found unequivocal evidence to support the existence of catamenial epilepsy. His observation that more seizures occurred around the time of menstrual flow, i.e. the perimenstrual phase of the cycle, and fewest in the luteal phase lead to the suggestion that progesterone may play a significant anticonvulsant role. In addition, he was one of the first authors to use the term 'catamenial' epilepsy in relation to seizures occurring at the time of menstrual flow or on the days preceding it.

Other large studies have also suggested that a catamenial exacerbation of epilepsy may be seen in a majority of women with epilepsy: 63% of patients in 1 study[11] and 66% of 1200 menstrual cycles in another.[12]

There is, however, a wide variation in the findings of the frequency of a menstrually related change in seizure frequency. This may be due to several factors, including the highly selected nature of the patients studied, the lack of consistent definition of days of the cycle, marked variation in the length of follow-up, and the possible effect of anovulatory cycles on seizure frequency. In addition, the definition of catamenial epilepsy varies between authors: some hold that the seizures should occur exclusively at or around menses, others that the seizures should be predominantly at, or exacerbated by, menstruation. We[1,13] favour the latter definition.

2. Possible Causes of Catamenial Epilepsy and Treatment Approaches

The putative cause of a cyclic increase in seizures at the time of menstrual flow has been as disputed as the frequency of the association. Research, and subsequent attempts at therapy, has followed 4 main lines of inquiry (see table I).

Table I. Possible causes of catamenial epilepsy and approaches to therapy

Cause	Therapy
Water retention	Diuretics
Psychological factors	Unknown
Hormonal factors	Hormones
Changes in drug metabolism	Increase in dosage of antiepileptic agents

2.1 Water Retention

Water retention is common in the premenstrual phase of the cycle, and indeed the possible epileptogenic effect of water retention was used by Blyth[14] as a provocative test for diagnosing doubtful cases of epilepsy. The observation lead to the treatment of seizures by the restriction of fluids.[15] However, Ansell and Clarke[11] compared body water measurements and the water metabolism of 7 females with epilepsy, of whom 3 experienced an increase in seizures at menstruation, with that of 5 nonepileptic individuals. No significant difference in the handling of water was found between the 2 groups. This finding suggested that water retention is not primarily responsible for an increase in seizures at the time of menstrual flow, but may be contributory to precipitating seizures in some patients.[2,16]

The observation that water retention may play a possible role in catamenial epilepsy has lead to the use of the diuretic acetazolamide (an inhibitor of carbonic anhydrase) around the time of menses. Some authors[17] recommend the addition of acetazolamide, 250 to 500 mg/day, to pre-existing antiepileptic drugs beginning 10 days prior to the expected onset of menses and continued until after bleeding stops. The drug is usually well tolerated, with drowsiness and parasthesias the major adverse effects. However, no controlled trials of its efficacy could be traced.

2.2 Psychological Factors

Some investigators have suggested that premenstrual psychic disturbances and emotional instability contribute to an increase in seizures at the time of menstruation.[18] However, many investigators give little credence to this theory.[10,16] The role of psychological factors in the genesis of menstrually related epilepsy becomes less likely after the observation[19] that the greatest psychic disturbance appears during the luteal phase of the cycle, which is the time of lowest seizure frequency. It is possible that sleep disturbance, anxiety and fatigue may contribute to an increase in seizures at the time of menstruation.[20] However, no drugs or psychotherapeutic techniques aimed at psychiatric symptoms have been shown to be of proven clinical benefit.

2.3 Hormonal Factors

There is currently a considerable body of clinical, animal experimental and basic scientific data indicating that sex steroid hormones, especially estrogens and progesterones, have a significant effect on neural excitability.

2.3.1 Clinical Evidence

Laidlaw[10] suggested that progesterone may have an anticonvulsant effect after demonstrating a consistent midluteal reduction, and perimenstrual increase, in seizures in his patients. Progesterone levels are high in the midluteal phase, and they decrease rapidly in the perimenstrual phase. Laidlaw[10] proposed that the rapid withdrawal of progesterone precipitated seizures in some women. Conjugated estrogens, if given intravenously, increase epileptiform activity during electroencephalograms.[16]

No specific and consistent pattern of abnormality has emerged in the excretion of hormones in women with catamenial epilepsy.[2]

There appears to be an association between seizure occurrence and hormone level (unpublished personal observations). Backstrom[21] showed that during ovulatory cycles there is a positive correlation between the number of secondarily generalised seizures and the mean estrogen to progesterone ratio, and a negative correlation between the seizures and the progesterone levels. In anovulatory cycles, there was an overall increase in the number of seizures and these appeared to be associated with increased estrogen levels. There were decreased numbers of seizures in the luteal phase and an increased number of seizures in the follicular phase, when levels of estrogen are high. These findings have been confirmed and expanded by others (unpublished personal observations).[22]

2.3.2 Animal Experiments

Estrogens increase the susceptibility of experimental animals to seizures using a variety of seizure models.[23] Estrogen has been used as a potent cerebral irritant for the induction of seizure activity, and its local application to the surface of both cerebral hemispheres produces a bilaterally synchronous 2 to 4Hz spike-and-wave pattern in monkeys and cats.[23] Seizure threshold is lowest during oestrus in mature rats.[24] In addition, exogenously administered estrogen decreases the minimal electroshock threshold in mice, rabbits, cats and rats.[23,24] Intravenously administered estrogen activated epileptiform discharges in rabbits with focal cortical lesions.[25]

The effects of progesterone on seizure discharges are not as striking as those of estrogen. Progesterone has little effect on seizures in a variety of animal models, including rats subjected to electroshock and in audiogenic seizure-sensitive and seizure-resistant rats.[24] The abilities of various progesterones to alter the seizure threshold are quite different.[2]

2.3.3 Hormonal Treatments

The combined evidence from experimental and clinical studies has lead to several attempts to use hormonal therapy in women with seizure disorders. Zimmermann et al.[26] added medroxyprogesterone, administered by a depot injection, to the treatment of a patient with precocious puberty and reported a significant reduction in the number of seizures. Hall[27] prescribed a progestrogen-only oral contraceptive (norethisterone, a synthetic progesterone) to a woman with catamenial epilepsy and achieved control of seizures for 7 months.

On the basis of these observations, several larger trials have been performed.[28-30] In the study by Mattson et al.,[29] oral medroxyprogesterone, a synthetic progestrogen, was added to the antiepileptic drug regimens of 14 women with uncontrolled seizures. 11 women developed amenorrhoea and, of these, 7 reported fewer seizures during therapy, with an average reduction in seizure frequency of 30%. No effect on the plasma concentrations of antiepileptic drugs was observed. The investigators noted that patients treated with parenteral medroxyprogesterone were more likely to show a decrease in seizures than those taking oral therapy, even though the concentrations of medroxyprogesterone were lower with parenteral than with oral therapy. Dana-Haeri and Richens[28] performed a placebo-controlled trial of norethisterone in women with catamenial epilepsy and failed to show any antiepileptic effect of the hormone treatment. The lack of a significant effect may be due to the fact that norethisterone is a testosterone-derived synthetic hormone, rather than a hydroxyprogesterone, and has weaker anticonvulsant effects.[31] Natural progesterone has a metabolite that can potentiate γ-aminobutyric acid (GABA)-induced chloride currents,[32] and would appear to be a potentially interesting agent to be assessed in future trials.

Reproductive dysfunction and endocrine disorders are unusually common among women with partial epilepsy.[30] Amenorrhoea occurs in 14 to 20% of women with epilepsy and menorrhagia and metrorrhagia in 43%.[33] Married women who have epilepsy have only 69% of their expected number of liveborn children (probably at least partly due to reproductive dysfunction). Herzog et al.[34] found a 20% occurrence of polycystic ovarian disease (PCOD) and a 12% occurrence of hypogonadal hypogonadism in a group of 50 women with temporal lobe epilepsy. A high number of abnormal cycles, characterised by failure of ovulation or an inadequate luteal phase, occurs in women with epilepsy (unpublished personal observation).[12,21]

Clomifene (clomiphene), an agent with both estrogenic and anti-estrogenic effects, was reported to reduce seizure frequency when administered in addition to pre-existing antiepileptic therapy to 2 men and 1 woman.[35,36] Herzog[37] administered clomifene (in addition to pre-existing antiepileptic drug therapy) to 12 women who had complex partial seizures and reproductive endocrine abnormalities, specifically the polycystic ovarian syndrome in 9 and an inadequate luteal phase in 3. Treatment resulted in fewer seizures and normal menstrual

patterns in 10 women; the overall seizure frequency was reduced by 87%. Significant adverse effects, including an unwanted pregnancy and severe abdominal pain secondary to ovarian cysts, were seen in 6 patients. Clomifene must be used with great care, and only in highly selected patients.[38]

2.4 Drug Interactions

The interaction between sex hormones and antiepileptic drugs is complex, with evidence for significant interactions coming from several sources. These include *in vitro* metabolic studies, clinical studies of both female patients with catamenial seizures and women with epilepsy who were taking the oral contraceptive pill, and observed changes in sex hormone–binding globulin.

2.4.1 In Vitro *Metabolic Studies*

The metabolism of phenytoin, phenobarbital (phenobarbitone) and many endogenous steroids depends on the same metabolic enzymes.[39] Drug therapy can alter the rate of hydroxylation of steroid hormones, and hormone treatment can alter the metabolism of various drugs.[40] Phenytoin and phenobarbital are potent inducers of hepatic microsomal enzyme activity in animals.[40] Carbamazepine induces its own metabolism as well as that of other drugs.[41]

Other recent animal and experimental evidence has helped shed some light on hormone-drug interactions. In rats and rabbits, phenobarbital pretreatment increased the metabolism of norethisterone both in the gut wall and liver.[42] Phenobarbital, phenytoin and carbamazepine induce cytochrome P450 enzymes. The specific isoenzyme [CYP3A4 ($P450_{NF}$)] induced by these drugs is responsible for the 2-hydroxylation of ethinylestradiol.[43] This has particular implications for oral contraceptive use in women with epilepsy. The effect of hormones on seizure activity may also be influenced by other factors, such as gender and dosage. In male and female rats with kainic acid–induced seizures, the effects of estradiol benzoate, clomifene and medroxyprogesterone are gender dependent,[44] a finding not yet replicated human studies.

Sex hormone–binding globulin is involved in the binding of sex steroids in plasma. Only 2% of sex steroids circulate in the free, pharmacologically active form.[45] Phenytoin, carbamazepine and phenobarbital increase the concentration of sex hormone–binding globulin,[46,47] with a subsequent decrease in the free fraction of circulating hormones.

2.4.2 Clinical Studies

Several clinical observations also support a possible interaction between antiepileptic drugs and sex hormones. Kutt and MacDowell[48] reported on a patient who experienced phenytoin intoxication after estrogen treatment, and proposed that this was due to reduced phenytoin metabolism.

Studies specifically examining the concentrations of antiepileptic drugs over the menstrual cycle in women with epilepsy have suggested that there may be an interaction between hormones and antiepileptic drugs. Shavit et al.[49] examined total phenytoin concentrations over the menstrual cycle in 17 women with epilepsy and demonstrated that the concentrations were significantly lower in the perimenstrual phase than at midcycle. More detailed studies of the apparent phenytoin clearance were performed in 5 of their patients with catamenial exacerbations of seizure activity, and an increase in apparent phenytoin clearance was demonstrated.

Kumar et al.[50] measured the changes of total phenytoin concentrations over the menstrual cycle in 8 patients with catamenial epilepsy and in 8 age-matched controls. They demonstrated that phenytoin concentrations decreased significantly in the menstrual phase in the catamenial group of patients and that there was a small, but statistically non-significant, increase in the clearance of phenytoin during the menses as compared with midcycle.

Backstrom and Jorpes[51] examined the changes in total phenytoin, carbamazepine and phenobarbital concentrations in 7 women with epilepsy and found slight fluctuations in the concentrations of the drugs in 2 of 9 cycles. There was generally a poor correlation between the drug concentrations and the estradiol and progesterone levels in these

patients. The authors suggested that the correlation between hormone levels and seizures they had previously described[21] was not due to changes in the concentrations of antiepileptic drugs.

Rosciszewska et al.[52] examined the changes in antiepileptic drug concentrations in 50 women with epilepsy. They found that the fluctuations in total phenytoin concentrations were greatest in women with catamenial epilepsy, with a marked decrease in concentrations between days 27 and 28 of the cycle, corresponding to the days of greater seizure frequency.

We have measured daily concentrations of antiepileptic drugs and sex hormones in saliva, which reflects free drug concentrations,[13] and found that the concentrations of phenytoin, carbamazepine and phenobarbital decrease in the 4 days preceding the onset of menses, with no change in the concentration of these drugs at the midcycle.

Few studies of the concentration changes of valproic acid (sodium valproate) over the menstrual cycle have been reported.

The use of intermittent, or an increased dosage of, anticonvulsant therapy around the time of menstruation has been based on these findings. A beneficial effect of clobazam 20mg compared with placebo (given over a 10 day period in each menstrual cycle) in 78% of treated women was found in a double-blind, crossover study.[53] Other approaches include an increase in the dosage of drug taken in the perimenstrual phase of the cycle. While attractive on theoretical grounds, this approach has not been studied in a proper clinical trial.

3. Practical Treatment Guidelines

The treatment of menstrually related seizures is hindered by a paucity of appropriate clinical trial data. However, based on the data presented in sections 1 and 2, my personal approach is to consider:

(i) The use of acetazolamide 250 to 500 mg/day beginning 10 days prior to the expected onset of menses and continuing until the cessation of menstrual flow. Adverse effects include drowsiness and parathesiae.

(ii) An increase in the daily dose of antiepileptic drugs for 5 or so days prior to the expected onset of menses, and continuing until the cessation of menstrual flow.

(iii) In highly selected groups of women, the use of hormonal manipulation, e.g medroxyprogesterone or clomifene, under the close supervision of a gynaecologist, in order to quickly detect adverse effects.

The treatments are added to pre-existing antiepileptic drug therapy and should be continued for several menstrual cycles in order to try and gauge efficacy. Seizure diaries may be useful in this regard.

4. Conclusions

The treatment of menstrually related seizures has not been studied in a controlled fashion. Evidence would suggest that hormonal therapies may be of value in patients with moderately severe endocrine disturbances or for those with a midcycle peak in seizure frequency, and that increasing antiepileptic drug concentrations may be useful for the perimenstrual increase in seizures. Acetazolamide may also have a role. Prospective clinical studies, carefully correlating seizure frequency, hormone levels and drug concentrations, will be of value in assessing these therapies.

References

1. Herkes GK, Eadie MJ, Sharbrough F, et al. Patterns of seizure occurrence in catamenial epilepsy. Epilep Res 1993; 15: 47-51
2. Newmark ME, Penry JK. Catamenial epilepsy: a review. Epilepsia 1980; 21: 281-300
3. Locock C. Discussion of Sieveking EH. Analysis of 53 cases of epilepsy observed by the author. Lancet 1857; 1: 527-8
4. Gowers WR. Epilepsy and other chronic convulsive diseases: their causes, symptoms, and treatment. 2nd ed. New York: William Wood, 1901: 204-8
5. Spratling W. Epilepsy and its treatment. Philadelphia: Saunders, 1904
6. Turner WA. Epilepsy: a study of the idiopathic disease. New York: Raven Press, 1907: 43-6
7. Church A, Peterson F. Nervous and mental diseases. 8th ed. Philadelphia: Saunders, 1914
8. Healey FH. Menstruation in relation to mental disorders. J Ment Sci 1928; 74: 488-92
9. Lennox WG, Lennox MA. Epilepsy and related disorders. Boston: Little, Brown, 1960; 2: 645-50
10. Laidlaw J. Catamenial epilepsy. Lancet 1956; 271: 1235-7
11. Ansell B, Clarke E. Epilepsy and menstruation. The role of water retention. Lancet 1956; 2: 1232-5

12. Rosciszewska D. Analysis of seizure dispersion during menstrual cycle in women with epilepsy. Monograms in neurological science. Basel: Karger, 1980; 5: 280-4
13. Herkes GK, Eadie MJ. Possible role of frequent salivary antiepileptic drug monitoring in the management of epilepsy. Epilep Res 1990; 6: 146-54
14. Blyth W. The pitressin diagnosis of idiopathic epilepsy. BMJ 1943; 1: 100-2
15. McQuarrie I. Some recent observations regarding the nature of epilepsy. Ann Intern Med 1932; 6: 497-505
16. Logothetis J, Harner R, Morrell F, et al. The role of estrogens in catamenial exacerbation of epilepsy. Neurology 1959; 9: 352-60
17. Engel J. Seizures and epilepsy. Contemporary neurology series, no. 31. Philadelphia: FA Davis Company, 1989
18. Bandler B, Kaufman IC, Dykens JW, et al. Seizures and the menstrual cycle. Am J Psychiatry 1957; 113: 704-8
19. MacKinnon PCB, MacKinnon IL. Hazards of menstrual cycle [letter]. BMJ 1956; 1: 555
20. Crawford P. Catamenial seizures. In: Trimble MR, editor. Women and epilepsy. London: John Wiley and Sons, 1991: 159-64
21. Backstrom T. Epileptic seizures in women related to plasma estrogen and progesterone during the menstrual cycle. Acta Neurol Scand 1976; 54: 321-47
22. Mattson RH, Kamer JA, Caldwell BV, et al. Seizure frequency and the menstrual cycle: a clinical study [abstract]. Epilepsia 1981; 22: 242
23. Timiras PS, Hill HF. Hormones and epilepsy. In: Glaser RH, Penry JK, Woodbury DM, editors. Antiepileptic drugs: mechanisms of action. New York: Raven Press, 1980: 655-66
24. Woolley DE, Timiras PS. The gonad-brain relationship: effects of female sex hormones on electroshock convulsions in the rat. Endocrinology 1962; 70: 196-209
25. Logothetis J, Harner R. Electrocortical activation by estrogens. Arch Neurol 1960; 3: 290-7
26. Zimmerman AW, Holden KR, Reiter EO, et al. Medroxyprogesterone acetate in the treatment of seizures associated with menstruation. J Pediatr 1973; 83: 961-3
27. Hall SM. Treatment of menstrual epilepsy with a progesterone only oral contraceptive. Epilepsia 1977; 18: 235-6
28. Dana-Haeri J, Richens A. Effects of norethisterone on seizures associated with menstruation. Epilepsia 1983; 24: 377-81
29. Mattson RH, Cramer JA, Caldwell BV, et al. Treatment of seizures with medroxyprogesterone acetate: preliminary report. Neurology 1984; 34: 1255-8
30. Herzog AG. Intermittent progesterone therapy and frequency of complex partial seizures in women with menstrual disorders. Neurology 1986; 36: 1607-10
31. Holmes GL, Kloczko N, Weber DA, et al. Anticonvulsant effect of hormones on seizures in animals. In: Porter RJ, Ward AA, Mattson RH, et al., editors. Advances in epileptology. Fifteenth Epilepsy International Symposium. 1984: New York: Raven Press, 1984: 265-8
32. Mienville JM, Vincine S. Pregnenolone sulphate antagonises GABA A receptor mediated currents via a reduction of channel opening frequency. Brain Res 1989; 49: 190-4
33. Jensen I, Vearnet K. Temporal lobe epilepsy: follow up investigation of 74 temporal lobe resected patients. Acta Neurochir (Wein) 1977; 37: 173-200
34. Herzog AG, Seibel MM, Schomer DL, et al. Reproductive endocrine disorders in women with partial seizures of temporal lobe origin. Arch Neurol 1986; 43: 341-6
35. Login IS, Dreifuss FE. Anticonvulsant activity of clomiphene [letter]. Arch Neurol 1983; 40: 525
36. Herzog AG. Seizure control with clomiphene therapy: a case report. Arch Neurol 1988; 45: 209-10
37. Herzog AG. Clomiphene therapy in epileptic women with menstrual disorders. Neurology 1988: 38; 432-4
38. Herzog AG. Endocrine aspects of treating seizures in patients with reproductive endocrine disorders. In: Sperling MR, editor. Endocrine and reproductive dysfunction in epilepsy. American Epilepsy Society Annual Course; 1990 Nov 11: San Diego, 1990: I1-I22
39. Conney AH. Pharmacological implications of microsomal enzyme induction. Pharmacol Rev 1967; 19: 317-66
40. Conney AH, Jacobson W, Levine W, et al. Decreased central depressant effect of progesterone and other steroids in rats pretreated with drugs and insecticides. J Pharmacol Exp Ther 1966; 154: 310-8
41. Eadie MJ, Tyrer JH. Anticonvulsant therapy, pharmacological basis and practice. 2nd ed. London: Churchill Livingstone, 1980
42. Back DJ, Brenkenridge AM, Crawford FE, et al. Phenobarbitone interaction with oral contraceptive steroids in the rabbit and rat. Br J Pharmacol 1980; 69: 441-52
43. Guengerich FR. Oxidation of 17-α-ethynylestradiol by human liver cytochrome P-450. Mol Pharmacol 1988; 33: 500-8
44. Nicoletti F, Speciale C, Sortino MA, et al. Comparative effects of estradiol benzoate, the antiestrogen clomiphene citrate, and the progestin medroxyprogesterone acetate on kainic acid induced seizures in male and female rats. Epilepsia 1985; 26: 252-7
45. Sodergrad R, Backstrom T, Shanbhag V, et al. Calculation of free and bound fractions of testosterone and estradiol-17β to human plasma proteins at body temperature. J Steroid Biochem 1982; 16: 801-10
46. Back DJ, Breckenridge AM, Crawford FE, et al. The effect of oral contraceptive steroids and enzymic inducing drugs on sex hormone binding globulin capacity in women. Br J Clin Pharmacol 1980; 9: 115
47. Isojarvi JIT, Parkarinen AJ, Ylipalosaari P, et al. Serum hormones in male epileptic patients receiving anticonvulsant medications. Arch Neurol 1990; 47: 670-6
48. Kutt H, MacDowell F. Management of epilepsy with diphenylhydantoin. JAMA 1968; 203: 145-9
49. Shavit G, Lerman P, Korczyn AD, et al. Phenytoin pharmacokinetics in catamenial epilepsy. Neurology 1984; 34: 959-61
50. Kumar N, Behari M, Ahuja GK, et al. Phenytoin levels in catamenial epilepsy. Epilepsia 1988; 29: 155-8
51. Backstrom T, Jorpes P. Serum phenytoin, phenobarbital, carbamazepine, albumin and plasma estradiol, progesterone concentrations during the menstrual cycle in women with epilepsy. Acta Neurol Scand 1979; 59: 63-71
52. Rosciszewska D, Buntner B, Guz I, et al. Ovarian hormones, anticonvulsant drugs, and seizures during the menstrual cycle in women with epilepsy. J Neurol Neurosurg Psychiatry 1986; 49: 47-51
53. Feeley M, Calvert R, Gibson J. Clobazam in catamenial epilepsy: a model for evaluating anticonvulsants. Lancet 1982; 2: 71-3

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