

# Ovarian hormones, anticonvulsant drugs, and seizures during the menstrual cycle in women with epilepsy

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**SUMMARY** The excretion of three oestrogen fractions and progesterone metabolites in 64 female epileptic patients was determined during the menstrual cycle, and in 50 women of this sample serum phenytoin and phenobarbitone levels were measured. A significant decrease of both hormones in epileptic patients was found as compared to a control group. The variations in serum phenytoin levels were greater in females with so-called catamenial epilepsy with a marked fall of drug levels between days 27 and 28 corresponding with an increase of seizure frequency. The effect of progesterone deficit on seizure susceptibility before menstrual bleeding is discussed, and the need of serum anticonvulsant level determination during the premenstrual phase in epileptic women is suggested.

The relation between sex hormones and epilepsy has not yet been fully explained. The hormones are known not only to play a role in brain seizure activity but also to interact with antiepileptic drugs. The neuroendocrine system has an influence on seizure incidence mainly in women because of rhythmic hormone activity changes in the hypothalamus-pituitary-gonadal axis. There are considerable discrepancies regarding the incidence of seizures in the premenstrual phase ranging from 10 to 70% of female epileptics.<sup>1-3</sup> In our study analysis of nearly 7000 seizures during 1200 menstrual cycles has shown such a correlation in two-thirds of patients.<sup>4</sup> Numerous experimental investigations have shown a convulsive effect of oestrogens and an inhibitory effect of progesterone on brain seizure activity,<sup>5-7</sup> but the role of ovarian hormones in seizure incidence during the premenstrual stage in women still remains unclear.

Evaluation of the relation between seizures and the menstrual cycle should also include possible

fluctuations of serum anticonvulsant levels. This study was undertaken to investigate whether there is a correlation between ovarian steroid hormones, antiepileptic drug levels and seizure incidence during the menstrual cycle in long-term treated female epileptic patients.

## Material and methods

Sixty-four female patients of the Epileptic Centre at Zabrze, aged 18-38 (mean age  $25.5 \pm 6.1$  years), were studied. The patients had, for several years, been recording seizure and dates of menstruation in standard diaries. In 37 women seizures were found to be correlated with premenstrual phase and menstruation (Group A) whereas no such relation was observed in the other 27 women (Group B). In Group A severe epilepsy was more frequent than in Group B (42% and 26% respectively). Premenstrual tension was present in 78% of Group A and 43% of Group B. All the females were treated with phenytoin in doses of 200-300 mg/day and with phenobarbitone in doses of 30-150 mg/day, except for eight women receiving phenytoin alone. Mean treatment duration was  $8.0 \pm 5.6$  years. None of the patients was taking other drugs or oral contraceptives.

Twenty-four urinary excretions of oestrone ( $E_1$ ), oestradiol ( $E_2$ ) and oestriol ( $E_3$ ) were estimated by column chromatography.<sup>8</sup> Progesterone metabolites ( $\alpha$  and  $\beta$  pregnanediol) were measured by thin layer chromatography.<sup>9</sup> The urinary excretion was determined for observation of metabolism of these hormones lasting 24 hours. Examinations were performed during hospitalisation at the Department of Neurology on cycle days 5, 6, 13, 14, 15,

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22, 27 and 28. Results were compared with control values obtained from nine healthy females in the same age range who had examinations performed in our laboratory during normal menstrual cycles. In 50 patients (29 from Group A and 21 from Group B) serum levels of phenytoin and phenobarbitone were determined on the same days of cycle. Blood samples were collected 3 hours after the morning drug administration and serum level was measured by spectrophotometry.<sup>10</sup> The coefficients of variation (V) for this method were 3% (n = 35) for phenytoin and 4% (n = 35) for phenobarbitone. In addition, function of the liver and kidneys as well as total protein and protein fractions were evaluated in all the patients by routine methods. The data were analysed statistically using Student's *t* test ( $p < 0.02$ ).

## Results

### Ovarian hormone excretion in female epileptics

Mean values of total oestrogen fractions and progesterone metabolites are given in table 1. The percentage ratio between particular oestrogen fractions and  $\alpha$  and  $\beta$  pregnanediol was not changed, therefore total oestrogens and pregnanediol values are given. No significant differences were found between oestrogen excretion in Group A and Group B, although in patients with seizures related to premenstrual phase (Group A) the values were slightly higher. Significant differences ( $p < 0.01$ ) were noted between the results in epileptic and control women except for the 5th and 6th days. No correlation between oestrogens and seizure incidence could be observed (figs 1, 2). The hormone levels were found to be similarly low on days with the greatest (27 and 28) and a smaller number of seizures (days 5 and 6).

A comparison between the urinary levels of progesterone metabolites in epileptic and healthy women

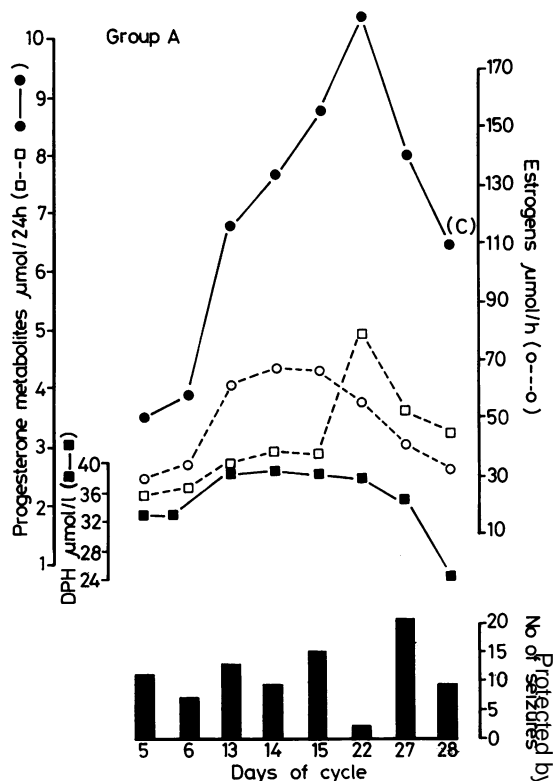


Fig 1 Total oestrogens (E), progesterone metabolites (P) excretion, serum phenytoin levels (DPH), and seizure frequency during menstrual cycle in women with seizures related to premenstrual phase (Group A). Progesterone metabolites in control group P(C). Oestrogens in control group are shown in fig 2.

Table 1 Mean values of total oestrogen and progesterone metabolites ( $\alpha$  and  $\beta$  pregnanediol) excretion during menstrual cycle in 64 female epileptics (Group A and B) and control groups

Days of cycle	Group	Total oestrogens nmol/24 h				$\alpha$ and $\beta$ pregnanediol umol/24 h			
		Epileptic females		Control group		Epileptic females		Control group	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
5	A	31.06	13.00	29.98	10.84	2.16*	1.01	3.59	1.93
	B	28.17	10.47			2.20*	0.70		
6	A	35.03	14.09	29.98	10.84	2.30*	0.90	3.93	1.93
	B	31.42	11.92			2.34*	0.62		
13	A	62.13*	22.75	124.25	36.48	2.59*	1.03	6.86	2.93
	B	54.90*	18.78			2.32*	0.88		
14	A	67.90*	27.09	141.23	39.37	2.91*	1.01	7.80	3.43
	B	50.93*	20.23			2.74*	1.22		
15	A	68.27*	27.49	128.59	37.20	2.93*	1.16	8.84	3.74
	B	56.35*	21.31			3.21*	1.31		
22	A	57.43*	21.31	92.11	33.59	4.95*	1.53	11.54	2.93
	B	52.01*	21.31			6.49*	2.18		
27	A	31.42*	10.47	81.27	29.26	3.69*	0.94	8.08	2.90
	B	26.37*	9.75			4.32*	1.50		
28	A	33.95*	14.45	75.49	28.11	3.37*	1.25	6.48	2.80
	B	28.53*	11.20			3.95*	1.25		

\* $p < 0.01$  compared with control group.

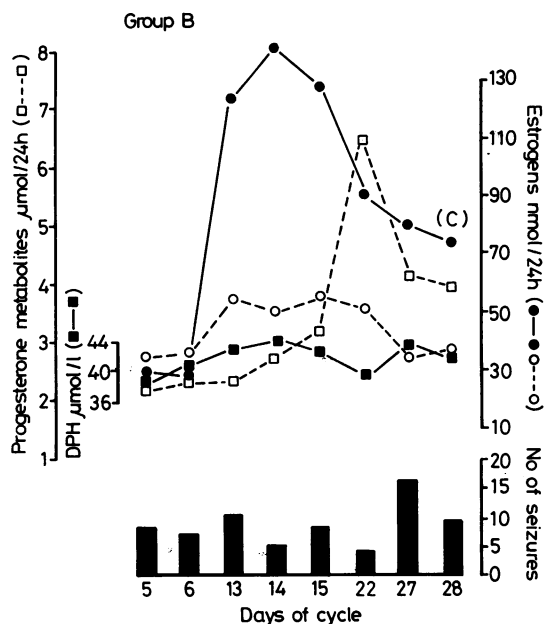


Fig 2 Total oestrogens (E), progesterone metabolites (P) excretion, serum phenytoin levels (DPH), and seizure frequency during menstrual cycle in women with seizures unrelated to premenstrual phase (Group B). Oestrogens in control group E(C). Progesterone metabolites in control group are shown in fig 1.

showed significant differences in total pregnanediol values on each day examined ( $p < 0.01$ ). During the luteal stage the mean levels of pregnanediol were lower in Group A than in Group B, although the difference was not significant (table 1). As shown in figs 1, 2 some correlation may be noted between progesterone metabolites and seizures: namely, at the peak of pregnanediol excretion (day 22) the seizure number was smallest in both groups. It can also be observed that in premenstrual phase (days 27 and 28) when pregnanediol, as compared to con-

trol values, fell more than in follicular stage (days 5 and 6), the seizure incidence increased in both groups.

*Serum phenytoin and phenobarbitone levels during the menstrual cycle*

Mean doses of phenytoin and phenobarbitone with serum drug levels are shown in table 2. The serum drug levels were lower in Group A than in Group B; however, the dosages in the former group were slightly higher. The difference in phenytoin levels between these groups was significant on the cycle day 28 ( $p < 0.02$ ). Moreover, the variations were more evident in women with seizures related to premenstrual phase (Group A) with the lowest level on 28th day. The decrease by more than 30% of the highest serum phenytoin concentration was found on day 28 in 16 females (55%) from Group A, and only in three patients (14%) from Group B (table 2). Mean coefficients of variation including the fluctuations of phenytoin levels during eight cycle days examined in Group A were 21% with a range of 5–44%, and in Group B 15% with a range of 3–34%. Coefficients of variation above 15% were found in 15 females (52%) from Group A and in 10 women (47%) from Group B (table 3).

Serum phenobarbitone levels were more stable during the menstrual cycle (table 2). Mean coefficients of variation were 10% with a range of 2–18% in Group A, and 8% with a range of 2–16% in Group B. Coefficients of variation higher than 15% were noted only in four patients (14%) of Group A and in two women (10%) of Group B (table 3). The comparison between serum drug levels, hormones and seizures is shown in figs 1, 2. A correlation between phenytoin and hormone levels could be seen in Group A only. A decrease of phenytoin levels between days 27 and 28, corresponding with a rise of seizure incidence, was found in Group A but the correlation was not significant (fig 1).

Table 2 Mean phenytoin and phenobarbitone doses (in mg/day), and mean serum phenytoin and phenobarbitone levels (in μmol/l) with standard deviation (SD) during menstrual cycle in females with seizures related (Group A, n = 29) and not related (Group B, n = 21) to premenstrual phase

Drug	Group	Mean dose mg/day	Drug serum levels (μmol/l) days of menstrual cycle							
			5	6	13	14	15	22	27	28
Phenytoin	A	293.1	33.3	33.3	38.4	38.92	38.0	38.0	34.4	24.5*
		±53.0	±24.5	±26.9	±28.9	±28.5	±27.7	±28.1	±29.7	±17.8
	B	288.1	38.8	39.9	43.1	43.9	42.3	39.6	43.5	42.2*
		±49.7	±20.9	±22.9	±22.1	±22.5	±23.7	±21.7	±22.9	±24.1
Phenobarbitone	A	85.7	53.8	54.3	56.8	57.7	59.9	57.3	56.4	58.6
		±42.2	±24.1	±24.5	±28.0	±27.1	±27.5	±27.5	±28.4	±29.7
	B	76.6	59.0	60.3	61.2	62.0	61.6	59.9	56.8	58.1
		±33.0	±32.7	±32.7	±30.6	±31.0	±30.1	±28.8	±28.4	±29.3

\*p < 0.02.

Table 3 Fluctuations in serum phenytoin and phenobarbitone levels during menstrual cycle in women with seizures related (Group A) and unrelated (Group B) to premenstrual phase

Drug	Group	Mean level in whole cycle $\mu\text{mol/l}$	Difference between lowest and highest level in $\mu\text{mol/l}$ * mean SD	Patients with *decrease of level on day 29		Coefficient of variation (v) % mean range	Patients with v > 15%	
				n	%		n	%
Phenytoin	A (n = 29)	36.07	15.0 $\pm$ 11.4	16	55	21 (5-44)	15	52
	B (n = 21)	41.62	12.0 $\pm$ 6.2	3	14	15 (3-34)	10	47
Phenobarbitone	A (n = 29)	57.49	13.0 $\pm$ 6.8	4	13	10 (2-18)	4	14
	B (n = 21)	60.38	11.6 $\pm$ 4.5	1	5	8 (2-16)	2	10

\*Expressed as percentage of the highest level. The decrease was admitted when drug level fell on day 28 more than 30%.

## Discussion

The results obtained in this study do not confirm the opinion<sup>11-13</sup> that a possible catamenial increase of seizure frequency is due to greater oestrogen activity during the premenstrual period<sup>13</sup> or at the time of the oestrogen peak during ovulation.<sup>5,11</sup> We found that the values of this hormone were nearly the same on days of both high and low seizure incidence. There was a decrease in oestrogens on preovulatory and premenstrual days as compared to control values. The analysis of progesterone metabolite measurements suggests that seizure incidence during the menstrual cycle is connected with a deficit of this hormone rather than with elevated oestrogen levels. Our hypothesis is based on the anticonvulsant properties of progesterone and the negative correlation between seizure incidence and amounts of pregnanediol in female epileptics. It should be mentioned that the lowest number of seizures was noted when progesterone reached its highest level (day 22). Although pregnanediol values were higher on days 27 and 28 than on days 5 and 6, the difference between the results in patients and controls was greater on two premenstrual days than on days of follicular stage. This was also accompanied by difference in seizure incidence between the two cycle phases (33 seizures on days 5 and 6, and 60 seizures on days 27 and 28). This result was in agreement with our preliminary study in which ovarian hormones were determined two days before menstrual bleeding.<sup>14</sup> The "protective effect" of progesterone on brain seizure activity in women can be confirmed by the use of synthetic progesterone in the therapy for catamenial epilepsy. Recently, Mattson *et al*<sup>15</sup> have observed a reduction of seizure frequency in 7 of 10 women treated with medroxyprogesterone.

The results of serum LH determinations by RIA during the menstrual cycle in the same population studied confirmed the presence of changes in progesterone activity.<sup>16</sup> We suppose that the luteal deficit and, in consequence, a decrease in progesterone secretion together with a greater number of unovulatory

cycles, as shown by cytochemical smears,<sup>17</sup> may be one of the factors responsible for a lower fertility index in female epileptics than in the general population.<sup>18</sup> Furthermore, there is a possibility that a reduced antiepileptogenic effect of progesterone may be among the causes of increased seizure reactivity before menstrual bleeding. It is also possible that the convulsive susceptibility increases before menstruation in the vast majority of women with epilepsy because progesterone deficit was found in females with fits both related and unrelated to premenstrual phase. However the risk of seizure incidence is greater in women with so-called catamenial epilepsy. It should be recognised, however, that in individual cases the seizure occurrence at the time of increased premenstrual convulsive predisposition may also depend on other than hormonal factors.

Variations in drug levels during the menstrual cycle and their influence on seizure incidence should also be taken into consideration. Bäckstrom and Jorpes<sup>19</sup> found slight fluctuation in phenytoin, phenobarbitone and carbamazepine levels during two out of nine menstrual cycles in seven women. In our study the phenytoin levels were not constant during the menstrual cycle but showed a tendency to fluctuate. In the whole sample half of the females had a coefficient of variation in the range of 15-44%. Variability of phenytoin serum levels in particular phases of cycle suggest the influence of the changes in ovarian hormone activity on drug metabolism. According to Cereghino,<sup>20</sup> and Kutt and MacDowell<sup>21</sup> oestrogens cause an elevation of serum phenytoin level by prolonging its metabolism.<sup>22</sup> This may account for simultaneous increase or decrease in both oestrogens and phenytoin levels (except day 28) in Group A in which drug level variations were more marked than in group B. No data concerning interaction between progesterone and anticonvulsants have been found in the literature available.

From the practical point of view the fall in phenytoin levels between days 27 and 28, corresponding with an increase of seizure frequency in women with

so-called catamenial epilepsy (Group A), is an important observation. In this group 55% of patients had decreased serum phenytoin levels on day 28 as compared to 14% in group of women without relation between seizures and cycle (Group B). The reason for the fall of drug serum level on the day preceding menstruation is not clear. Although the ovarian hormone excretion in both groups did not show significant differences, females with so-called catamenial epilepsy had premenstrual tension more frequently, which is connected with greater endocrine disturbances and changes in water-electrolyte balance. Thus, the effect of this syndrome on serum concentration of anticonvulsants during premenstrual phase can not be neglected.

The problem of interaction between ovarian hormones and antiepileptic drugs requires further investigations. At present we suspect that a decrease in serum phenytoin level on days of higher convulsive activity may be an additional factor provoking seizure incidence before menstrual bleeding. This would also indicate that serum anticonvulsant level should be determined on premenstrual days in order to increase the drug dose when its level is found to be diminished.

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