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Pregnancy and epilepsy

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Summary. In a prospective study, 30 pregnant epileptic patients were followed through their pregnancy to determine the effect of seizures on pregnancy and its outcome and the effect of pregnancy on seizures. An attempt was made to correlate the serum hormone and anticonvulsant drug levels with seizure frequency, complications of pregnancy, occurrence of status epilepticus and teratogenicity. In 14 patients seizure frequency increased, in 15 it remained unchanged and in 1 patient it decreased. There were 2 spontaneous abortions, 2 patients had status epilepticus and 1 offspring of a patient had a ventricular septal defect. This patient was receiving carbamazepine and diphenylhydantoin. Patients with increased seizures frequency had significantly higher oestrogen levels, lower level of progesterone and lower level of anticonvulsant drugs as compared with those with no change in seizures. Patients who had abortions and those who developed status epilepticus had high serum oestrogen levels.

Key words: Progesterone – Oestrogen – Hormones – Teratogenecity – Anticonvulsant drugs

Introduction

There are many gaps in our knowledge regarding the management of epilepsy during pregnancy, the outcome of pregnancy and the effect of anticonvulsant drugs on mother and fetus. Epilepsy complicates 0.3%–0.5% of all pregnancies [7], either occurring in women who had epilepsy before their conception or in women who develop seizures during pregnancy for the first time that are not related to toxaemia of pregnancy.

The effect of seizures on pregnancy and its outcome has been dealt with by various authors [3, 10]. The most comprehensive study available is the Collaborative Perinatal Project of National Institute of Neurological and Communicative Disorders and Stroke [10], in which 54,000 pregnant women were followed up until the children born of these pregnancies reached the age of 7 years. The overall risk of complications of pregnancy, labour and postpartum haemorrhage was doubled in women with seizures, while low birth weight, infant mortality rate and neonatal seizures were increased in the offspring of epileptic women. This study was very extensive but lacked correlative study of serum anticonvulsant drug and hormone levels and their possible relations to various complications of pregnancy and epilepsy.

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Approximately 50% women with epilepsy have no change in their seizure frequency, 37% have increased frequency of seizure and 13% have fewer seizures [6]. Many factors influence the seizure frequency in pregnant patients [6]. Among these, oestrogen was considered to have lowered the seizure threshold in experimental [12] and clinical studies [8]. Progesterone, on the other hand, raises the seizure threshold and decreases seizure frequency [1, 5, 15]. Serum anticonvulsant drug levels which are governed by multiple factors are found to fall during the second and third trimesters of pregnancy and may contribute to increased seizure frequency.

We report the findings of a study of the effect of pregnancy on seizure frequency, outcome of pregnancy in epileptic patients, relationship between serum oestrogen and progesterone level, on the one hand, and serum anticonvulsant drug levels and seizure frequency, on the other.

Patients and methods

Thirty pregnant patients with epilepsy, aged between 20 and 35 years (mean 24 years), were included in the study. Patients were questioned regarding their parity, past obstetrical history, type and frequency of seizures and intake of anticonvulsant and other drugs. Patients with factors known to alter the course of pregnancy and its outcome (toxaemia of pregnancy, hypertension, diabetes mellitus, uraemia and sexually transmitted disease) were excluded from the study. Patients were seen at least once during each trimester of pregnancy and were asked about hyperemesis, fetal loss, prematurity, complications of labour, frequency of seizures and occurrence of seizures in the offspring. All babies born to these patients were examined personally for evidence of any congenital abnormality. Blood was collected once during each trimester for estimation of drug and hormone levels. Drug levels were assayed using a spectrophotometric method [16] and hormonal assay done by radioimmunoassay [4]. Statistical analysis was by paired *t*-test.

Results

Twenty-five patients suffered from generalized tonic clonic epilepsy and 5 had partial epilepsy with secondary generalization. Twenty-four patients were on monotherapy, 20 receiving diphenylhydantoin (DPH) and 4 receiving carbamazepine (CBZ). The other 6 patients were on polytherapy (2 each receiving a combination of DPH and CBZ, phenobarbitone and

Table 1. Comparison of serum anticonvulsant drug levels and hormone levels in patients with increase in seizure frequency and in patients with no change in frequency

	Increased frequency Mean (SD)	No change in frequency Mean (SD)
Serum DPH level (μg/ml)	6.1 (1.1)	16.2 (0.5)*
Serum CBZ level (μg/ml)	6.3 (1.5)	9.7 (0.3)*
Serum oestrogen level (pmol/l)	7786 (514)	1480 (394)*
Serum progesterone level (nmol/l)	2.9 (2.3)	72.0 (19.1)*

* $P < 0.001$

DPH, and CBZ and phenobarbitone). The seizure frequency increased in 14 patients, remained unchanged in 15 patients and in 1 patient seizure frequency decreased during pregnancy. Patients with increased seizure frequency during pregnancy had significantly higher oestrogen levels (7786, SD 514 pmol/l) as compared with those who had no change in seizure frequency (1480, SD 394 pmol/l) ($P < 0.001$). Similarly, the progesterone levels showed a significant difference between the two groups (2.9, SD 2.3 nmol/l and 72, SD 19.1 nmol/l respectively) ($P < 0.001$). The serum anticonvulsant drug levels were also significantly higher in patients with no change in seizure frequency as compared with those with increased seizure frequency (Table 1), though the drug doses in the two groups were similar (mean DPH dose 6.5 mg/kg and 6.4 mg/kg respectively and mean CBZ dose 9.8 mg/kg and 10.0 mg/kg respectively).

Two patients developed status epilepticus, both during the first trimester, one being a known epileptic and the other developing seizures for the first time during pregnancy. Both these patients had high oestrogen levels (6700 and 6800 pmol/l respectively). Two patients had a spontaneous abortion during the first trimester. Both had low anticonvulsant drug levels (DPH 1.2 μg/ml and 6.8 μg/ml) and high oestrogen levels (6480 pmol/l and 2468 pmol/l, respectively). One patient delivered a baby with a ventricular septal defect. This patient was on CBZ and DPH and serum anticonvulsant drug levels were high (DPH 29.05 μg/ml and CBZ 15 μg/ml). Her oestrogen level was also high (3400 pmol/l).

Discussion

In the present study, an increase in seizure frequency occurred in 14 out of 30 patients; it remained unchanged in 15 patients and decreased in 1 patient. These findings are in agreement with those of other authors [6, 13]. What causes increased susceptibility to seizures during pregnancy is unknown. In the present study, patients with an increased seizure frequency had significantly higher oestrogen levels and lower progesterone levels. It was also observed that patients with increased seizure frequency during pregnancy had significantly lower anticonvulsant levels. Proconvulsant action of oestrogen and anticonvulsant action of progesterone, as suggested by clinical studies in which catamenial exacerbation of seizures was associated with high oestrogen levels [9] and in experimental studies [2, 12, 14], may be a contributing factor. It is also known that oestrogen can lower anticonvulsant drug levels by induction of hepatic enzyme activity, thereby increasing seizure frequency. Poor drug compliance is suggested as a cause of low drug levels during pregnancy [13]. Though the drug levels before pregnancy were not available, good drug compliance was likely through repeatedly stressing the need for it at every visit.

Status epilepticus is uncommon during pregnancy [6] but occurred in the present study in 2 of 30 patients. High oestrogen levels in both these patients could be the possible cause of the status. An incidence of 2 cases of abortion, both of which occurred during the first trimester, is similar to another study [6]. It is not possible to state the cause of abortion in these patients. Since the products of conception were not examined microscopically, it is not possible to state if it was due to major congenital or genetic defect. Abortion cannot be attributed to increased seizures, as neither patient experienced seizures during the first trimester. Both had high oestrogen levels, which could explain in part the abortions. Other complications of pregnancy and labour were not encountered at all in this group of patients.

There is a higher incidence of teratogenicity in the offspring of epileptic mothers as compared with non-epileptic mothers and in those receiving anticonvulsants compared with those who do not [11, 16]. Further, those receiving polytherapy have a still higher incidence of congenital malformations than those on monotherapy. One patient receiving DPH and CBZ delivered a baby with ventricular septal defect. It can be said that in utero exposure to multiple drugs, especially during the first trimester, was responsible for this congenital abnormality. Other teratogenetic effects were not seen in any offspring of these patients.

The problems of epileptic women are manifold. In this small study, an attempt was made to correlate the various complications of pregnancy and labour on the one hand and that of epilepsy on the other with serum anticonvulsant drug levels and hormone levels. Certain definite trends are apparent, but a larger study is required to confirm these findings.

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