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Original Article

STUDY ON FACTORS ASSOCIATED WITH POOR SEIZURE CONTROL IN EPILEPTIC PATIENTS DURING PREGNANCY

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Abstract:

The management of epilepsy during pregnancy is always challenging. This study aims to analyze the factors associated with poor seizure control during pregnancy and to describe the most commonly used antiseizure drugs in these patients. We conducted a case-control study of pregnant patients with epilepsy between 2017 and 2022. 50 pregnant women with poorly controlled epilepsy were taken as cases and 50 pregnant women with well-controlled epilepsy were taken as controls. Patients were evaluated in the first and second trimesters of pregnancy and after delivery. Patients' mean age was 32.6 years. 53% had focal epilepsy, 40% had generalized epilepsy and 5 % had undetermined epilepsy. The factors associated with poor control of seizure during pregnancy were duration of epilepsy, poor seizure control in the year prior to pregnancy, treatment with 2 or more antiseizure drugs, untreated epilepsy, missed medication dosages, decline in plasma concentrations of antiepileptic drug, presence of focal activity in EEG and abnormal imaging findings. Anti-seizure medications most widely used in monotherapy were lamotrigine, levetiracetam, carbamazepine, and valproate.

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Background:

Epilepsy is a common neurological disorder requiring treatment during pregnancy, affecting 0.25% of all pregnant women[1]. Most of these patients have a normal pregnancy and delivery, but an increased risk of complications during pregnancy has been reported [2].Seizures during pregnancy have been associated with increased risk of low birth weight, pre-term delivery and small for gestational age [2-4]. Furthermore, antiseizure drugs may have teratogenic effects at both the morphological and the neurocognitive level [5-6]. We gathered data on demographic variables, epilepsy type, aetiology, anti-seizure drugs use and treatment with folic acid. Regarding the factors associated with seizures during pregnancy, the presence of at least one seizure in the year before conception, focal seizures and combination therapy were described to act as predictors of seizures during pregnancy[7-8]. In this study, we analyzed the factors associated with the presence of seizures in pregnancy and describe the most widely used antiseizure drugs.

Methods:

It was a case control study carried out from January 2017 to December 2022. The aim was to find out the factors associated with poor control of seizure in pregnancy. 50 pregnant women with poorly controlled epilepsy were taken as cases and 50 pregnant women with well controlled epilepsy were taken as controls. Patients were evaluated in the first and

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second trimesters of pregnancy and after delivery. We also included untreated patients. Non random sampling was followed for selecting cases and controls.

Patients were evaluated by history, physical examination and related investigations. Inclusion criteria: Pregnant ladies with epilepsy. Exclusion criteria: non-compliant patients.

An epileptic seizure is defined conceptually as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.

We also retrospectively reviewed previous seizure control in the year prior to pregnancy. We defined poorly controlled patients as those presenting at least one seizure in the year prior to conception and well controlled patients as those presenting no seizures in the year prior to conception.

Relevant data were collected by means of a questionnaire and a structured interview with the patients or patients' family members.

Cases as well as controls were evaluated to explore risk factors. Then risk factors between cases and controls were compared. The results were presented as charts. Statistical analysis was done by appropriate methods. Then the results were compared with those of different studies done previously. Analysis of data was done with help of SPSS version 29 software. Appropriate statistical methods were applied for data analysis and comparison (taking p value d"0.05 as significant).

Result:

In this study a total of 50 cases and 50 controls were evaluated for presence of risk factors for poor seizure control. The mean age was found 33.2. ± 5.1 years in cases and 31.1 ± 6.2 years in controls.

The mean age difference was not statistically significant ($p > 0.05$) between cases and controls. The above table shows that longer duration of epilepsy, poor seizure control in the year prior to pregnancy, treatment with 2 or more antiseizure drugs, untreated epilepsy, missed medication dosages, decline in plasma concentrations of antiepileptic drug, presence of focal activity in EEG and abnormal imaging findings were significantly ($p<0.05$) different between cases and controls.

Table I

Factors associated with the presence of seizures during pregnancys=significant, ns=not significant, for age and duration of epilepsy, p value was reached from unpaired T test. For other variables p value was reached from Z test of proportion.

Factors	Cases (with poor control of seizure) (n=50)	Controls (with good control of seizure) (n=50)	P-value
Age(years)(Mean ± SD)	33.2. ± 5.1	31.1 ± 6.2	0.067 ns
Duration of Epilepsy (Mean ± SD) (years)	12.05±7	7.57±4.77	0.001 s
Type of epilepsy			
Focal	28	25	0.548 ns
Generalized	19	23	0.682 ns
Undetermined	3	2	0.645 ns
Family History of Epilepsy	5	3	0.737 ns
Illiteracy	7	5	0.615 ns
Poor control (≥ 1 seizure in the previous year)	24	8	0.001 s
≥ 2 antiseizure drugs	14	5	0.022 s
Untreated epilepsy	10	0	0.0001 s
Sleep deprivation	10	3	0.038 s
Missed medication dosages	12	3	0.012 s
Depression	6	5	0.749 ns
Decline in plasma concentrations of antiepileptic drug	15	6	0.027 s
Presence of focal activity in EEG	18	7	0.011 s
Abnormal imaging findings	8	2	0.045 s

We recorded 90 pregnancies in women (out of 100) receiving anti-seizure drugs (90 %), 71(71%) in monotherapy and 19 (19%) with 2 or more anti-seizure drugs. In the remaining 10 pregnancies, patients were not receiving treatment (10%) at the time of conception.

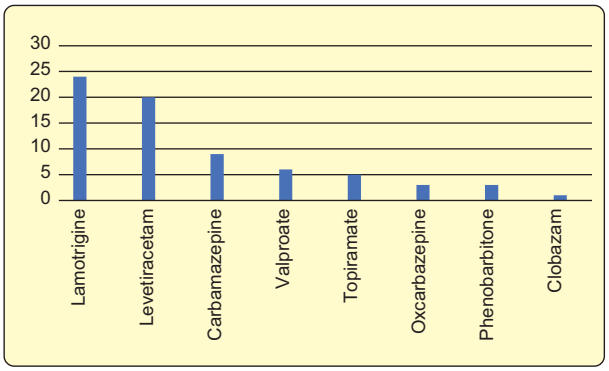

Figure 1: T*he antiseizure drugs most frequently used in monotherapy (n = 71).*

Discussion:

It was a case-control study carried out in the Neurology and Obstetrics & Gynae OPD from January 2017 to December 2022. The aim was to find out the factors associated with poor control of seizure in pregnancy. 50 pregnant women with poorly controlled epilepsy were taken as cases and 50 pregnant women with well-controlled epilepsy were taken as controls. The mean age was found 33.2. ± 5.1 years in cases and 31.1 ± 6.2 years in controls. The mean age difference was not statistically significant. However other studies [9] showed that poor control of seizure in pregnancy was associated with increasing age. However, in our study, older age was not associated with increased seizure frequency.

Duration of epilepsy was significantly associated with increased frequency of seizure in pregnancy(P<0.001). Another author [10] also found the long duration of epilepsy as a risk factor for poor seizure control.

A study conducted [11] on predicting factors of poor seizure control in pregnancy. They established focal seizure activity as a risk factor for increasing seizure frequency. But our study did not find any significant association between seizure types with poor seizure control. Family history of Epilepsy and Illiteracy were not significant risk factors for increased seizure occurrence in pregnancy. Other author[12] had similar finding in their study.

The risk of seizures during pregnancy was greater in patients presenting at least one seizure in the year prior to conception. Treatment with 2 or more ASDs was also associated with a higher risk of seizures during pregnancy; this is probably due to the fact that the patients receiving this treatment regime had presented seizures in the year prior to pregnancy. These results are consistent with those reported in other articles in the literature. In a prospective observational study of 1297 pregnant patients with epilepsy, authors[13] observed that the presence of at least one seizure in the month prior to conception and combination therapy were predictors of seizures during pregnancy. Little information is available about untreated epilepsy in pregnancy. In our study, untreated epileptic patients had frequent seizures in pregnancy compared to treated patients(P<0.0001). Similar findings were reported by other author.[14] in a cohort of 148 untreated patients and 1532 treated patients from the Australian Register of Antiepileptic Drugs in Pregnancy. In that article, 56.1% of untreated patients and 21.9% of treated patients presented seizures during pregnancy.

Studies from Denmark and Norway showed statistically significant association between sleep deprivation and seizure [15], which is similar to our finding. Sleep deprivation has been shown to lower the seizure threshold, so it can easily provoke a seizure attack.

In this study, depression was not found to have a statistically significant positive association with seizure attacks. This is supported by the study conducted in Ethiopia[16]

Lamotrigine is by far the most extensively studied newer-generation AED in conjunction with pregnancy. In patients taking lamotrigine monotherapy serum concentrations usually decline markedly as pregnancy progresses. A decrease in serum concentration can be seen already in the first trimester but is most marked in the mid–third trimester[17]. One author,[18] established that decreased serum level of the drug was associated with increased seizure frequency. Similar fact was also found in our study.

Abnormal imaging finding was identified in 8% of the intractable group compared to 2% of the controlled group. These findings coincide with the results of a systemic review by Sultana and colleagues which found that the most frequently reported correlates and

predictors of drug-resistant epilepsy included symptomatic epilepsy and having an abnormal imaging finding [10]

In a systemic review by Nakken KO et al[19], EEG abnormality (including epileptiform discharge and slow wave) was reported to be a predictor for intractability .In the current study, there was an association between abnormal EEG findings and poor seizure control and this comes in line with the aforementioned risk factors and points toward the idea that a structural/ metabolic etiology of epilepsy especially when it results in electrophysiological abnormities is predictive of a more severe course of epilepsy [10].

In terms of pharmacological treatment, we observed an increase in the percentage of patients receiving monotherapy in recent years, which suggests better planning for pregnancy. Furthermore, as in other articles,[13] we observed a pronounced increase in the use of newer drugs with lower teratogenic risk, such as levetiracetam and, to a lesser extent, oxcarbazepine, as well as a decrease in the use of carbamazepine and valproate. Although lamotrigine continues to be frequently used, alongside levetiracetam, its use has slightly decreased.

The limitations of our study include the small sample size and its single-center design.

Conclusions:

The factors associated with the presence of increased seizures during pregnancy were poor seizure control in the year prior to pregnancy, treatment with 2 or more antiseizure drugs, the absence of treatment, sleep deprivation, missed medication dosages, decline in plasma concentrations of antiepileptic drug, presence of focal activity in EEG and abnormal imaging findings. The most widely used drugs were lamotrigine, levetiracetam, carbamazepine and valproate. We observed a higher proportion of monotherapy in addition to a decrease in the use of carbamazepine and valproate and increased use of levetiracetam and, to a lesser extent, oxcarbazepine. The management of pregnant patients with epilepsy is complex; optimal seizure control is essential and potential teratogenic effects must be avoided. Current recommendations include planning for pregnancy and maintaining monotherapy at the minimum effective dose with an anti-seizure drug presenting low teratogenic risk, such as lamotrigine or levetiracetam. In our experience, it is preferable not to suspend treatment in well-controlled patients due to the high probability of presenting seizures during pregnancy.

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