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Analysis of maternal and fetal complications resulting from epilepsy and its management during pregnancy

Análise das complicações maternas e fetais decorrentes da epilepsia e seu manejo durante a gravidez

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ABSTRACT

Epilepsy is a brain disorder that occurs due to excessive electrical discharges and manifests itself from epileptic seizures. During pregnancy, seizure control may become more difficult due to organic changes that occur during this period. The regimen of Antiepileptic Drugs (AED) used in pregnancy will influence fetal development, resulting in both congenital abnormalities and changes in child development. The objective of this study is to analyze the potential maternal and fetal complications resulting from epilepsy itself and/or its clinical management during pregnancy. We analyzed 35 medical records and interviewed women with ICD G40.0 to G40.9 who became pregnant during the period from 2005 to 2017. After data collection, statistical analysis was performed using Fisher's exact test and simple statistical analysis with the data obtained. It was concluded that the type of AED, as well as its regimen with greater teratogenic potential, has still been widely used by pregnant women with epilepsy, demonstrating the need for awareness for better therapeutic management for these patients.

Keywords: Epilepsy, Pregnancy, Congenital abnormalities, Child development.

1 INTRODUCTION

Epilepsy is a brain disorder that occurs due to excessive electrical discharges in a group of cells, characterized by a persistent predisposition to generate epileptic seizures and their neurobiological, cognitive and psychosocial consequences [1,2]. Epileptic seizures vary in frequency, ranging from less than one per year to several during the day [1].

Several challenges permeate the clinician when faced with epilepsy in women. This is because it is a disease that can affect different phases of the reproductive cycle: sexual development, pregnancy, breastfeeding and menopause [3].

Pregnancy produces physiological, hormonal and psychological changes, some or all of which may contribute to the reduction of the seizure threshold. These physiological changes modify the pharmacokinetics of AFE, leading to a decrease in the plasma levels of medications and to the worsening of seizures in epileptic pregnant women [4].

Epilepsy is one of the most common neurological diseases in the world, affecting approximately 50 million people [1]. Its lifetime prevalence ranges from 0.6% for developed countries to 1.5% for developing countries [5]. According to data obtained by DATASUS, epilepsy affects around 14,000 people aged 0 to 14 years and just over 186,000 people over 15 years of age [6]. During the gestational period, its prevalence ranges from 0.3 to 0.7% [7,8,9].

Exposure to AFE during pregnancy increases the risk of congenital malformations, such as craniofacial defects, orofacial clefts, and heart defects [3]. Its incidence in the general population is 1-2%, while in pregnant women using AFE monotherapy it is 4-9% [10, 11].

The use of AFE during pregnancy is also related to alterations in Neuropsychomotor Development (NPMD), with valproate (VPA) being the one that causes the most important deficits and lamotrigine (LTG) and levotiracetam being the ones that are related to fewer events. It is also important to consider that polytherapy increases the risk of alterations [12].

The choice of appropriate and less teratogenic medications for the control of maternal epilepsy, in monotherapy and with the lowest effective dose, is essential to reduce the risk of congenital abnormalities and alterations in child development. Considering the lack of planning in most pregnancies and considering that the critical stage of fetal development occurs up to the first trimester, a preconception therapeutic adjustment is essential for all epileptic women of reproductive age, in addition to folic acid supplementation before and during the gestational period [12,13].

The objective of this study is to analyze the potential maternal and fetal complications resulting from epilepsy itself and/or its clinical management during pregnancy.

2 LITERATURE REVIEW

The prevalence of epilepsy varies from 0.3 to 0.7% during the gestational period[7,8,9].

Pregnancy is not contraindicated in cases of epilepsy, and 95% of women treated with antiepileptic drugs during this period go through it safely. It is extremely necessary to discuss with

the patient the possibilities of teratogenicity of the drugs and also the expected risks in pregnancy [16].

The pharmacological treatment of epilepsy aims to prevent seizures, since generalized tonic-clonic seizures can cause adverse effects to the fetus. They can lead to hypoxia, causing irreversible damage to the central nervous system, and in cases of prolonged hypoxia, fetal death can occur [17]. In addition, there are cases in which trauma resulting from seizures can lead to intracranial hemorrhage in the fetus [18].

The rates for malformations associated with the use of antiepileptic drugs during pregnancy for the first, second, and third trimesters were, respectively, 6.7%, 6.8%, and 5.3% [19]. In addition to fetal outcomes, maternal changes may also occur, such as postpartum hemorrhage, spontaneous abortion, hypertensive disorders, labor induction, and cesarean section[20].

The choice of the best medication for the treatment of women of childbearing age should be based on the lowest teratogenic potential and the use of the drug, whenever possible, as monotherapy. VPA is the drug with the greatest evidence of inducing malformations and should be avoided during pregnancy. LTG is the drug with the greatest evidence of safety, but even so, its use carries greater risks of malformations when compared to the general population. Folic acid supplementation is indicated before and during pregnancy to reduce neural tube defects [13].

In many studies, AEDs have been linked to changes in the neuropsychomotor development of children exposed to them during pregnancy. VPA is the most severe affect of this development, followed by phenobarbital (PBT) and phenytoin (PHT). While LTG and levetiracetam (LEV) are considered the safest for cognitive development. In relation to monotherapy or polytherapy, the second option is more risky for the development of these deficits, especially if VPA is used [12]).

During the gestational period, plasma concentrations of antiepileptic drugs may vary as a consequence of changes in their absorption, hepatic and renal clearance, increased plasma volume and enzymatic induction caused by steroid hormones [13]. Serum levels of the drugs should be kept close to those found in preconception, and sometimes it is necessary to adjust the dose to avoid epileptic seizures[4].

3 METHODOLOGY

The study was quantitative and cross-sectional. Quantitative research analyzes hypotheses from objective data, basically using statistics [21]. Cross-sectional studies analyze a sample of a given population, verifying, concomitantly, exposure to risk factors and the development or absence of morbidities [22].

Data were collected from the medical records of patients at the neurology outpatient clinic of a large hospital in western São Paulo, where high and medium complexity care are treated. An average of 100 patients are seen monthly in this outpatient clinic, including men and women, over 18 years of age, referred by the primary care of the Unified Health System (SUS). The diseases treated in this service refer to neurological problems such as: epilepsy, headache, neuropathies, Alzheimer's, Parkinson's, Multiple Sclerosis, among others, and this list of diseases is merely illustrative.

We analyzed 35 medical records of women with ICD G40.0 to G40.9, who became pregnant during the period from 2005 to 2017. As an inclusion criterion, the medical records of female patients under previous treatment and/or during pregnancy, with current age between 18 and 45 years, were selected. The exclusion criteria were: patients diagnosed with epilepsy after pregnancy and epileptic patients under 18 years of age.

These medical records were searched by the hospital's Information Technology (IT) team and then located and separated by the Patient Record Service (PPS) team to be analyzed. The analysis of the medical records was performed by verifying the following items: current age of the patient, age at which she became pregnant, comorbidities – diabetes mellitus, systemic arterial hypertension, smoking, alcoholism, infectious diseases, psychiatric disorders -, number of pregnancies, abortions (if any, the gestational age at the time of the abortion will be investigated) and previous deliveries, complications in pregnancy, classification of the type of epilepsy according to the ILAE of 2016, what was the AEF regimen before and during pregnancy, frequency of epileptic seizures during pregnancy, whether prenatal care was performed and from what gestational age, whether folic acid was supplemented in the 1st trimester of pregnancy, whether there were gestational complications/complications, information about delivery – type, gestational age, birth weight, Apgar score at 1 and 5 minutes, head circumference, if the newborn had congenital malformations (at birth or later) and if the child died (if so, what was the date and cause of death). In addition, from the medical records, the telephone contact of the patients was obtained.

After this phase, the pregnant women were located and an objective questionnaire was applied at the patient's home or at the outpatient clinic of the hospital in question, with the objective of collecting information about the patient and the pregnancy that was sought in the medical records, but was not present, such as: current age of the patient, age at which she became pregnant, comorbidities – diabetes mellitus, systemic arterial hypertension, smoking, alcoholism, infectious diseases, psychiatric disorders -, number of pregnancies, abortions (if any, the gestational age at

the time of abortion will be investigated) and previous deliveries, classification of the type of epilepsy according to the 2016 ILAE, what was the AEF regimen before and during pregnancy, frequency of epileptic seizures in pregnancy, whether prenatal care was performed and from what gestational age, if folic acid was supplemented in the 1st trimester of pregnancy, if there were gestational complications/complications, information about delivery – type, gestational age, birth weight, Apgar score at 1st and 5th minute, head circumference, if the newborn had congenital malformations, at birth or later, and if the child died, if so, what was the date and cause of death. The patient's prenatal booklet can be used to obtain this information.

The data obtained were transferred to Microsoft Excel spreadsheets and stored for statistical analysis. Fisher's test and statistical analysis were used.

The results were shown by means of tables and were interpreted based on a literature review in order to establish the relevance of such data.

The study was initiated after the approval of the Research Ethics Committee of UNOESTE. The ethical norms in force in resolution 466/2012 were also followed, safeguarding the confidentiality of the information, as well as the anonymity of the subject who participated in the research, so that the medical records of pregnant epileptic women who were selected, but who did not have a contact telephone number or who did, but who refused to participate in the study or who did not answer will be discarded. The data from the medical records and those collected in the interview about the pregnancy were only used after the participant had signed the Free and Informed Consent Form (ICF).

4 RESULTS

A total of 35 patients were evaluated, totaling 51 pregnancies that occurred between 2005 and 2017. The use of polytherapy was 56%, of those who used polytherapy, 81% did not have their epilepsy controlled. The remaining patients used monotherapy, and 56% of them did not control their seizures.

The use of AFE was present in the following percentages: Carbamazepine 52%, Phenobarbital 49%, Phenytoin 16%, Valproate 11% and Lamotrigine 8%.

No cases of congenital malformations were found in the **n** studied, regardless of epilepsy control, AFE used, and drug regimen used.

Table 1 - Relationship of each medication with abortion and p-values of Fisher's exact test.

Abortion[1]			
Therapy	**YesN (%)**	**No N (%)**	**P-value**
Monotherapy	6 (22%)	21 (78%)	0,7119
Polytherapy	3 (14%)	18 (86%)	

Percentages given in relation to total patients per therapy

As shown in Table 3, only 14% of pregnant women who use polytherapy have had an abortion, compared to 22% of those who use monotherapy. According to the p-value of the test, there was no significant relationship between boarding and mono/polytherapy.

Table 2 - Relationship of each medication with epilepsy control and p-values of Fisher's exact test.

Controlled Epilepsy[1]			
Road	**SimN (%)**	**No N (%)**	**P-value**
Phenobarbital	7 (14%)	18 (37%)	0,5376
Diazepam	0 (0%)	4 (8%)	0,2876
Phenytoin	3 (6%)	5 (10%)	1
Carbamazepina	6 (12%)	21 (43%)	0,1113
Lamotrigine	1 (2%)	3 (6%)	1
Clonazepam	0 (0%)	2 (4%)	1
Topiramate	0 (0%)	2 (4%)	1
Valproic Acid	4 (8%)	2 (4%)	0,0782
Oxcarbamazepina	0 (0%)	2 (4%)	1

[1] Percentages given in relation to total patients

As shown in Table 4, no statistically significant relationship was found between the control of epilepsy and the use of drugs. However, it is noteworthy that 37% of the pregnant women in the study use phenobarbital, and do not have their epilepsy controlled.

Table 3 - Relationship of each medication with preterm and term medication.

Droga	Pré-termo	Termo
Fenobarbital	2 (20%)	17 (30%)
Diazepam	1 (10%)	3 (5%)
Fenitoina	0 (0%)	6 (11%)
Carbamazepina	6 (60%)	17 (30%)
Lamotrigina	1 (10%)	2 (3%)
Clonazepam	0 (0%)	2 (3%)
Topiramato	0 (0%)	2 (3%)
Depakene	0 (0%)	5 (9%)
Oxcarbamazepina	0 (0%)	2 (3%)

[1] Percentages given in relation to the total number of patients at term.

For the data in Table 5, no significant relationship was found between any medication and preterm or term infants, at a confidence level of 5%. In addition, Spearman's correction coefficient between preterm and term was 0.57, indicating that there was no high linear relationship between them.

Regarding the association between preterm and term with epilepsy control, it was identified that 5 (10% of all) pregnant women in preterm were not under control, as well as 23 (47%) during term. However, the p-value of Fisher's exact test was equal to 1, indicating that there was no significant relationship between preterm or term with epilepsy control.

Of the 49 pregnancies for which data on prenatal care were collected, only 5 (10%) did not receive prenatal care, compared to 44 (90%) who sought the service.

Of the 45 pregnant women for whom information on folic acid supplementation was obtained in the first 12 weeks, 35 (78%) supplemented and 10 (22%) did not.

4 DISCUSSION

CBZ, PHT, LMT and levotiracetam are considered relatively safer to use during pregnancy compared to other AEDs [12]. PBT, on the other hand, has a higher risk of causing malformations, along with VPT and Topiramate. Despite the proven teratogenic risk of VPT, it is still used in clinical practice[13]. Difficult-to-control epilepsy is conceptualized as the failure to achieve seizure control after using an AEP with maximum levels and doses. When there is no control with the use of monotherapy, more drugs are introduced[23].

Polytherapy offers a higher risk of delay in NPMD due to exposure to drugs during the three gestational trimesters, in addition to being a marker of the frequency and severity of seizures, as it reveals an epilepsy that is difficult to control. Monotherapy is the preference of prescriptions to reduce malformations. Studies show that polytherapy and treatment with VPT are more associated with adverse effects in the children of epileptic mothers in the long term[12,13].

VPA is the one that most severely affects the child's development, followed by PBT and PHT[12]. This study showed that 37% of the pregnant women in the study use PBT, a drug with high teratogenic potential and do not have epilepsy controlled. No evidence was found in the literature that the use of PBT has reduced efficacy for maintaining control of epileptic seizures.

It was found that seizure control and the type of AED used during pregnancy were not related to the gestational age of the newborn at the time of delivery. Studies indicate that seizures during pregnancy are not related to fetal complications, except in cases of maternal hypoxia, with consequent fetal bradycardia, reversible with the end of the seizure[24,25]). However, some studies

have reported a risk of preterm birth in women with untreated epilepsy compared to women without epilepsy[26,27]. In a previous cohort, it was evidenced that pregnant epileptics and smokers had an increased risk of premature birth[28].

It was found that most women had prenatal care and folic acid supplementation. It is considered a protective factor against the risk of neural tube malformations[29].

5 CONCLUSION

It was concluded that many pregnant women still use drugs such as VPT and PBT, and polytherapy, without being successful in treatment. Polytherapy and unsafe medications for pregnancy can lead to malformations and delay in NPMD, even though this was not evidenced in the present study. Thus, the importance of an evaluation with a neurologist was verified for a better adequacy of the AED, preferably preconception, and thus to obtain control of epilepsy in a less harmful way to the fetus.

Treatment with AED in women on menacme requires special care in the choice of less teratogenic drugs and at the lowest possible dose to achieve seizure control, taking into account the possibility of the patient becoming pregnant due to lack or failure of contraceptive method, especially if there are concomitant mental disorders. It is important to advise not to interrupt therapy with AFE when the pregnancy is discovered.

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