ABSTRACT

Epilepsy is a disorder of the brain where there is a persistent predisposition in generate epileptic seizures. It is estimated that one in every 200 pregnant women have epilepsy, 70% of these use antiepileptic drugs. This combination increases by about three times the risk of teratogenicity. The objective of this study was analyse the relationship between the use of antiepileptic drugs in pregnancy and the development of neonatal malformations. It is an integrative review conducted through the bibliographic survey in PubMed and Bireme platforms and in the databases Medline, LILACS and COCHRANE, using combinations of descriptors. From 1,743 articles found only 19 were have been selected for the study. Prospective studies in pregnant women in antiepileptic drug use showed that valproate is the medication most associated with neonatal malformations and cognitive disorders, compared to other antiepileptic drugs. The use of folic acid associated with antiepileptic drugs is related to a lower risk of disorders of neural tube closure. Antiepileptic medicines are potentially teratogenic, so it is necessary to further studies on the subject.

Keywords: epilepsy, pregnancy, teratogenicity.

1. INTRODUCTION

Epilepsy is a brain disorder with predisposition persisted in generate epileptic seizures. Due to your chronic condition, it can lead to neurobiological, cognitive changes, psychological and social influence on the quality of life of the patient. (FISHER et al., 2017)
Currently it is assumed that the global prevalence of epilepsy is at about 0.5 to 1% of the population. Approximately 2% of women are under use of antiepileptic drugs during pregnancy. (JOSE et al., 2014).

The major congenital malformations generated by the use of antiepileptic currently in clinical use are heart defects, cleft lip, hypospadias, neural tube defect, polydactyly, defects in the gastrointestinal tract, kidney defects and other major malformations. In addition, there is a high risk of neuropsychomotor development delay in children exposed to antiepileptic drugs intra uterus. (JOSE et al., 2014)

The use of antiepileptic drugs and risk of congenital malformations are important issues in medical practice. Thus, the study of teratogenic effects is necessary to assist physicians in a safer prescription of drugs antiepileptic, as well as to advice women of childbearing age in use of antiepileptic drugs about the risks they are exposed in the event of pregnancy. This article is a review of the latest data of January 2014 until 2019 for the use of antiepileptic in pregnancy and the risk of teratogenicity.

2. METHOD

The methodological process was characterized by an integrative review, driven from searches on PubMed and Bireme, in the following databases: Medline, LILACS and COCHRANE. We deploy the subsequent descriptors: epilepsy, pregnancy, teratogenic, anticonvulsants, phenobarbital, carbamazepine, valproic acid and phenytoin.

The inclusion criteria used were: original articles; the subjects of the research were pregnant women using drugs antiepileptic (AED), with publication in the languages Portuguese, English or Spanish. Excluded studies that were not original articles and those who have not reported the use of AED and pregnancy in the title of the article.

The survey was conducted by two researchers independently and points of conflict were discussed in meetings with responsible researchers.

With the crossings made were found 1,743 articles. Following the criteria of exclusion and inclusion and subtracting the repeated references, the total number of articles selected for the preparation of this review was 19.
3. RESULTS AND DISCUSSION

Epilepsy is one of the major neurological disorders that require continuous treatment during pregnancy. However, in recent years, studies show that the increased frequency of complications during pregnancy, childbirth, puerperium and malformations in the offspring of women with epilepsy are associated with the use of antiepileptic medicine, including spontaneous abortions, perinatal death, congenital abnormalities and disorders of growth and development of children. The first-generation drugs increase by two to three times the risk of foetal malformations, being even bigger on polytherapy. The risk of epileptic seizures during pregnancy outweighs the teratogenic effect of medicines, and should be the main objective of an effective treatment. However, a study by Guveli et al points out that the regularity of the seizures does not change during pregnancy at 47% to 83% of pregnant women. Despite the disagreement between studies, both claim that pregnancy accompanied with epilepsy is considered high-risk (Guveli et al., 2017; Diaz et al., 2018)

Physiological changes during pregnancy make ideal control of seizures with an AED in your lowest dose effective pre-pregnancy. During pregnancy, there is an increase in total body water and plasma volume by modifying the distribution of the drug and reducing serum concentration. There is an increase in fat deposits, reducing the Elimination of fat-soluble drugs. An increase in cardiac output, hepatic and renal blood flow, and increasing your elimination. There is also a change in cytochrome P450, changing systemic absorption and elimination. In addition, there is a decrease in maternal albumin, which leads to greater availability of drugs. (Moussa et al., 2015)

Meador et al, in research with 932 women of childbearing age with epilepsy, related 53% of them were on monotherapy, 41% in polytherapy and 6% without use of AED. The most common monotherapy were lamotrigine (36%), levetiracetam (18%), carbamazepine (14%), topiramate (9%) and valproate (8%). Only nine AED have reasonable data on the risk of congenital malformations: smaller risk of lamotrigine, levetiracetam, Oxcarbazepine, carbamazepine and Gabapentin possibly; intermediate risk for phenobarbital, topiramate and possibly phenytoin; and greater risk for valproate. With regard to the risks of impairment of neuropsychological development, only six have reasonable data: lower risk of lamotrigine,
levetiracetam and carbamazepine; intermediate risk for phenobarbital and phenytoin possibly; and greater risk for valproate. (Meador et al., 2018; Chittaranjan, 2018)

3.1 ANTIEPILEPTIC DRUGS ASSOCIATED WITH TERATOGENICITY

Given the frequent number of cases with the medications, the studies have intensified, seeking to understand the mechanism of each drug, and teratogenic effects generated by them. Among the AED the first-generation ones are the most studied such as valproate, arguably, with multiple implications in teratogenicity. In addition to this drug include phenobarbital, phenytoin and carbamazepine. Currently, others AED also well documented are lamotrigine, levetiracetam and topiramate; gabapentin and oxcarbazepine should be considered. (Angus-Leppan and Liu, 2018)

3.1.1 VALPROATE

According to the Risk Assessment Committee of the European Medicines Agency Pharmacovigilance of 2018, Valproate (VPA) should not be used during pregnancy. However, it is recognized that some women with epilepsy may have to continue treatment with VPA (taking appropriate expert assistance) during pregnancy. (Angus-Leppan and Liu, 2018)

The VPA is classified by the FDA as 2016 category D. Anvisa (National Health Surveillance Agency of Brazil) directs that the VPA is not intended for use by women of childbearing age unless the other available treatments are ineffective. (Angus-Leppan and Liu, 2018)

The frequency of large defects increased with dose, being greatest at doses greater than or equal to 1,500 mg/day (24%, 19.2% in monotherapies in using VPA associated with another AED and 31% in the use of valproate associated with lamotrigine). The risk of teratogenicity drops considerably with equal doses or less than 700 mg/day (5.9% for monotherapy, 5.4% for valproate another 7.0% for MAE and valproate more lamotrigine). (Thompson et al., 2015)

Recent studies have shown the relationship between the use of VPA in pregnancy and developmental changes, like the neuropsychomotor autism. Children with autism have
changes in cranial nerves and reduce the engine cores, being proven in animals exposed to the VPA during the period of closure of the neural tube. (Thompson et al., 2015)

Guveli et al., have detected greater cognitive impairiment in children exposed to politherapy and VPA. These authors also proved the importance of reducing the dose of antiepileptic drugs for better cognitive development and healthy behaviour of a child. Mothers under VPA treatment who had a baby with malformations are reported as having a higher risk of malformation in her children in following pregnancies. (Guveli et al., 2017).

3.1.2 PHENOBARBITAL

Velez-Ruiz et al. demonstrated in research with mice that phenobarbital produces neural deficits, reduces the weight of the brain and brain catecholamine levels and behavioural development. (Velez-Ruiz and Meador, 2015)

Two double-blind studies conducted with independent samples of human beings, one with 33 individuals and the second with 81 patients. All were exposed, in prenatal care, to phenobarbital. In both, the individuals had verbal intelligence scores significantly lower than found in the population that did not use the drug. (Velez-Ruiz and Meador, 2015)

3.1.3 PHENYTOIN

Phenytoin is a first-generation anti-epileptic, metabolized by the liver through the CYP450 system. Free plasma concentration remains the same level during the first trimester of pregnancy, but vary in the second and third quarters, the monthly monitoring of serum levels is recommended. This drug has a rate of teratogenic effects of 0.7% to 7% and is more commonly associated with foetal hydantoin syndrome, which is characterized by a variable pattern of growth and anatomical changes such as unusual facies and distal phalangeal hypoplasia. In addition, phenytoin can also cause reduced intellectual capacity. Therefore, this medication should be avoided in the first trimester of pregnancy. (Moussa et al., 2015; Velez-Ruiz and Meador, 2015)

In the NEAD study (about the effects of Antiepileptic Drug Neurodevelopment), the average IQ for children exposed to phenytoin was 99 at age three, 105 to four years and six months, and 108 at age six. These scores do not have diverged of children exposed to
carbamazepine or lamotrigine, but were better than those of children exposed to valproate. (Velez-Ruiz and Meador, 2015)

### 3.1.4 CARBAMAZEPINE

Carbamazepine is metabolized in the liver by CYP450, and their plasma concentrations do not increase significantly during pregnancy; thus, monthly monitoring is not mandatory. The teratogenic action is observed in 2-6% of infants and is most commonly associated with cardiac malformations. (Moussa et al., 2015)

In a study conducted in Australia, 2,049 pregnant women were evaluated and observed foetal malformation rate of 2.72 percent in those without AED and 6.25% in those with monotherapy with carbamazepine. With this information it can be concluded that carbamazepine is an anti-epileptic medication potentially teratogenic, requiring further studies to examine the cognitive disorders, malformations, abortion and complications risk during the pregnancy and puerperium. (Vajda et al., 2015)

A study of 35 pre-scholar children born to epileptic women receiving treatment with carbamazepine did not show differences in locomotor function, behaviour, hearing and speech, eye and hand-eye coordination, performance and practical reasoning, when compared with unexposed children. (Velez-Ruiz and Meador, 2015)

Data published by NEAD study showed that IQ scores in children with prenatal exposure to carbamazepine were: 98 to three years, 106 to four years and six months and 105 at age six. These scores did not differ from those of children exposed to lamotrigine or phenytoin. However, children exposed to any of these three-antiepileptic had better results than those who were exposed to the VPA. (Velez-Ruiz and Meador, 2015)

### 3.1.5 LAMOTRIGINA

The lamotrigine (LTG) is the second-generation AED more studied, being metabolized in the liver by glucuronidation, which makes your plasma concentration highly unstable in pregnancy. Has a debug increased in about 65-94%, soon, frequent monitoring is recommended in the second and third quarters. Debugging declines rapidly after birth and
dose adjustments should be made in the first week after delivery. The LTG correlates with a rate of 2 to 3% malformations, cleft lip or palate usually. (Moussa et al., 2015)

Morrow et al. showed that for doses of LTG below 100 mg/day, the risk of malformation was 1.3%; for doses between 100 and 200 mg/day, 1.9%; and for higher doses, 5.4%. Already in the Australian registry data of antiepileptic drugs in pregnant women, the corresponding numbers were 0%, 3.1% and 5.6%, respectively. (Vadja et al., 2014)

In the NEAD study, the IQ average in children exposed to LTG was 101 at age three, 106 to four years and six months, and 108 at age six. These IQ scores don't differentiate of children exposed to CBZ or phenytoin, but were better than those of children with exposure to VPA. Further investigation showed that the LTG proves to be better than the VPA and the CBZ in relation to motor development, and superior to the VPA and phenytoin in relation to adaptive functioning and emotional/behavioural. (Velez-Ruiz and Meador, 2015)

3.1.6 LEVETIRACETAM

Levetiracetam (LEV) is a new AED, superior to others because there is less need to monitor its serum levels; it has no interaction with other AED and has less effect on cognitive functions. Pharmacokinetic studies indicate that he has a linear dose concentration rate. With these properties, the LEV seems to be a proper drug during pregnancy. In studies on the safety of use of LEV, the incidence of malformations in monotherapy was 27 out of a total of 1213 pregnancies. In polytherapy, have been found 34 malformations in 541 pregnancies, so the risk of amendments increases with polytherapy. (Koc et al., 2018)

In a study comparing the cognitive development of children 24 months exposed in uterus to levetiracetam versus sodium valproate and a group of children representative of the general population, children exposed to levetiracetam did not differ from the control group. Another study following these kids between 36 to 54 months showed that children exposed did not differ from the control. In comparison, children exposed to the VPA in utero had lowest score in thick motor skills, comprehension and language skills. (Velez-Ruiz and Meador, 2015)
3.1.7 **TOPIRAMATE**

Topiramate is a second-generation critical AED because, their plasma concentrations vary notably due to renal debugging in pregnancy, reducing its concentration to 30 and 35% in the second and third quarters, respectively. Thus, monthly monitoring is recommended. Topiramate is related to low birth weight, and the appearance of anatomical changes as oral fissure. (Moussa et al., 2015)

3.1.8 **OTHER ANTIEPILEPTIC**

Gabapentin is a drug with few data in the literature, however, it is known that is excreted through the kidneys and your monthly monitoring is recommended. Until now, it has not been proven your risk of congenital malformations, but is associated with premature birth, and has a teratogenic action of 0-6% rate. (Moussa et al., 2015)

It is reported that the Oxcarbazepine (OXC) cause spina bifida, heart defects, and urinary tract of the skeletal system. Guveli et al. observed patent foramen oval with 900 mg/day of OXC and hydronephrosis with 1,200 mg/day of OXC. (Guveli et al., 2017)

3.2 **POSSIBLE MECHANISM OF ANTIEPILEPTIC ACTION IN THERATOGENESIS**

Between the medications, the VPA is the better documented and it has been shown that the target gene of the VPA are histones deacetylases, increases in oxidative stress, foetal antagonism to the folate needed for DNA synthesis, cell cycle arrest in the G1 phase and induction of apoptosis, facilitating neuronal and translocation your malfunction. (Sivathamboo et al., 2018; MacFarlane and Greenhalgh, 2018)

The mechanism involved in phenytoin is on the performance in single electron reduction reactions of cyclic form, producing reactive oxygen species (Ros), which, in large quantities, cause irreversible oxidation of DNA, proteins and lipids, leading to inactivation of many enzymes and cell death. The developing embryo has a weak defence antioxidant, therefore, is particularly susceptible to oxidative stress, particularly in the early stages of organogenesis. (Guveli et al., 2017)
3.2 MAIN ASSOCIATED MALFORMATION

Was discovered an increased risk of congenital malformations in the offspring of women who were exposed in other pregnancies the use of AED, seeming to be a cumulative factor. (Thompson et al., 2018)

In a study conducted by EURAP only 20% of large congenital malformations were detected in prenatal examinations, although 95% of women undergoing the ultrasound. This same study showed that the AED less associated with large birth would be the lamotrigine, levetiracetam and Oxcarbazepine, all with 97% of pregnancies analysed without malformations. Soon after is topiramate with 96% of pregnancies, carbamazepine with 95%, phenobarbital and phenytoin with 94%. Finally, the medicine most closely associated with major malformations is valproate with 90% of pregnancies with no major malformations. (Thompson et al., 2018)

The main defects related to the use of Mothers during pregnancy would be: (Thompson et al., 2018; Thompson et al. .2015)

1. Heart defects: like foramen oval patency, tetralogy of Fallot, coarctation of the aorta, hypoplastic left heart, among others. Present in therapy with phenytoin and phenobarbital, 4% and 3% respectively. Also present in the use of monotherapy of valproate, especially at higher doses (> 700 mg/day), your risk of 2.5%.

2. Cleft lip and palate: your risk revolves around 1% on monotherapy with lamotrigine, levetiracetam, Oxcarbazepine, carbamazepine, valproate and phenobarbital.

3. Hypospadias: Mostly found on monotherapy with valproate (2%) and carbamazepine (1%).

4. Defect of the neural tube closure: More found in monotherapy with phenobarbital and topiramate, 1% of each risk.

5. Polydactyly: Mostly found on monotherapy with phenobarbital 1%

6. Gastrointestinal tract atresia: Medicines safer would be the phenobarbital, phenytoin, and topiramate.
7. Kidney defect: the risk is greater in monotherapy with carbamazepine and valproate, both with 1% incidence.

3.3 USE OF FOLIC ACID AS PREVENTION OF DISORDERS OF THE NEURAL TUBE CLOSURE

Folate supplementation is performed to reduce the risk of congenital malformations, but only 50% of pregnant women use. Inappropriate supplementation is associated with an increase of up to three times the risk of teratogenicity, in addition it was pointed to the association between the use of folic acid and periconceptional a better cognitive performance of children. (Passarelli et al., 2015; Sharma et al., 2015; Thompson et al., 2018)

Supplementation of folic acid is recommended for women of childbearing age that make use of antiepileptic drugs. In Brazil the folic acid is recommended by the Federal Council of Medicine and is present in the guidelines of the Medical Society of obstetrics and Gynecology in dosage of 0.4 mg/day for women three months before conception, and the dosage of 4 mg/day for those that have increased risk of neural tube closure defects, such as those in use of AED and should take folic acid regardless of the desire to become pregnant, because statistics show that 45% of pregnancies in epileptic pregnant women are unplanned. (Passarelli et al., 2015; Sharma et al., 2015)

4 FINAL CONSIDERATIONS

Recent studies have shown that the risk of change in intrauterine development generated by exposure to AED exists and is directly related to medication in use, dose, associated medications and use of folic acid in especially in the first quarter. Thus, our study disassociated among the drugs with lower risk for foetal malformations: lamotrigine, gabapentin, oxcarbazepine and levetiracetam, the latter being considered the best for use in pregnant women, the latter being considered the best for use in pregnant women, since its rate of malformations is similar to that of the general population; carbamazepine, topiramate, phenytoin, and phenobarbital are classified as intermediate risk; and in particular, the VPA is the MAE more associated to foetal malformations as well as to the delay in the
neuropsychomotor development, being appointed as the highest risk medicine. Although the data presented, it is necessary to do more continuous prospective research in humans, mainly in Brazil, to identify the epigenetic mechanisms associated with teratogenesis, as well as to more precisely quantify the risk of the development of teratogenicity.

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