Epilepsy in pregnancy: a challenge for good maternal and fetal outcomes

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ABSTRACT

Epilepsy is a common neurological condition in women of childbearing age. Patients with epilepsy should be carefully advised in pre-pregnancy counseling as well as during pregnancy, with particular emphasis on the level of fetal safety of antiepileptic treatment. During pregnancy, there must be an optimization of the therapeutic strategy so that the teratogenic risks of fetal and maternal convulsions are greatly diminished. The role of this review was to present the approach to this pathology in pregnant women and its management for good neonatal and maternal outcomes.

Keywords: epilepsy, preconception, folic acid, pregnancy outcome, treatment, postpartum care

INTRODUCTION

The association of epilepsy in pregnant women is topical because there is a 1.45-fold increase in the incidence of epilepsy in children of mothers with epilepsy than in the general population compared to paternal epilepsy [1]. The risk of transmitting generalized idiopathic epilepsy to children is 9%-12% [2]. Dominant or recessive genetic epilepsy accounts for 30-40% of epilepsy cases, with first-degree relatives having a 3-4 times higher risk of developing epilepsy. The morphology of the type of convulsions is inherited, being the same as that of the parents, starting at a younger age [3,4]. Epilepsy affects 0.5% of the fertile population and about 2% of the general population [5,6].

Patients with epilepsy of childbearing age are advised to plan their pregnancy, and obstetricians and neurologists must provide all medical information to assist these patients in making the right decision [7,8]. The desire of these patients to have a pregnancy must be fulfilled, and this not be contraindicated. The early approach to this pathology in adolescence ultimately leads to a decrease in the risk of seizures during pregnancy and the teratogenicity effect of antiepileptic drugs, representing a continuing concern of health services regarding the proper management of reproductive desire of these patients [5].

Prenatal counseling for these patients is important because planning a pregnancy in a seizure-free period has reduced fetal side effects and recurrent seizures in pregnancy, and this risk can be managed by the correct administration of antiepileptic therapy [2,5].

In this article, we wanted to present the main concerns of women with epilepsy-related to future pregnancy, such as contraceptive counseling, the risk of seizures during pregnancy, the teratogenic risk of antiepileptics, and monitoring the disease during pregnancy, the mode of delivery, the opportunity to breastfeed, and postnatal care.

PRECONCEPTION THERAPEUTIC CONDUCT

In the case of women with epilepsy, it is recommended to plan the pregnancy, so the risk of fetal abnormalities due to antiepileptic treatment is reduced as well as the appearance of seizures during pregnancy. The optimal concentration of antiepileptic drugs should be established for each patient before conception to maintain the therapeutic goals and avoid fetal risks secondary to drug exposure. In reality, this does not happen, in half of the cases, the patients get pregnant unplanned, which can influence both the safety of the mother and the fetus [9,10]. There may be a lower efficacy of oral contraceptive treatments due to the enzyme-inducing properties of antiepileptic drugs and, in addition, a decrease in seizure control [11,12,13].
An important preconception goal is the administration of folic acid supplements because antiepileptic drugs can interfere with folate metabolism, and thus the serum level of folic acid can decrease. It is well known that folic acid deficiency is an additional risk factor for fetal malformations, miscarriage, and postnatal neurobehavioral development. Thus, it is necessary to supplement with high doses of 4-5 mg/day of folic acid preconceptionally and later throughout the pregnancy [14,15]. Vitamin D supplementation of 400 IU/day should be initiated simultaneously as women on antiepileptic therapy have a low bone mineral density [14].

In the absence of seizures for 2 years, antiepileptic treatment is discontinued by 6-9 months preconceptionally [5]. Control of seizures before pregnancy decreases the chance of seizures in pregnancy [2]. In case of recurrent seizures, it is preferable to administer antiepileptic drugs with low teratogen levels (lamotrigine/levetiracetam) in monotherapy, or the drug that best controls the disease is kept to the minimum required dose [2,5,14]. Prenatal exposure to valproic acid greatly increases the risk of fetal malformations and other developmental disorders. Thus, it is used only in case of lack of control of the disease with other therapeutic alternatives, and its serum level should be kept below 70 mg/ml and administered in divided doses of 3-4 / per day [2,16].

THE EFFECT OF EPILEPSY AND ITS TREATMENT ON PREGNANCY OUTCOME

In pregnant women with epilepsy, the risk of pregnancy complications is higher than in non-epileptic pregnant women, but in over 90% of cases, the pregnancy normally develops with the birth of a healthy baby [17].

Compared to pregnant women without epilepsy, those with epilepsy may experience several complications during pregnancy. Thus, maternal mortality is ten times higher in pregnant women with epilepsy. In addition, there is an increased risk of complications such as preterm labor, preeclampsia, antepartum or postpartum hemorrhage. Seizures during pregnancy are associated with an increased risk of placental abruption or miscarriage due to maternal trauma. Cesarean delivery, induction of labor, and prolonged hospitalization are more common among pregnant women with epilepsy [2,5,18].

Cardiotocography variability may be decreased due to maternal treatment with phenobarbital or diazepam. Seizures cause fetal hypoxia due to decreased placental blood flow, which leads to changes in the cardiotocographic route such as moderate or absent variability, decelerations, or bradycardia that can persist for 30 minutes after a seizure. Although the fetus is resistant to short episodes of hypoxia and adapts, prolonged seizures can lead to sustained fetal hypoxia. The number of seizures or the duration required to affect the fetus is unknown [19,20].

Fetal risks are low birth weight, perinatal mortality, spontaneous preterm birth, low Apgar score, neonatal infections and hypoglycemia, asphyxia-related complications, respiratory distress syndrome, birth defects caused by epilepsy, and maternal medication. The risk of major birth defects due to intrauterine exposure to antiepileptic drugs is 4 - 14%, while the risk is only 1-4% in the general population. Intrauterine exposure to antiepileptic drugs has teratogenic risks and can lead to fetal malformations and dysmorphia [5,20,21,22].

The teratogenic effect is limited to the first trimester and is dose-dependent, so treatment with the lowest effective dose is recommended. Also, the risk of malformation is higher in the case of polytherapy than in monotherapy. Toxic metabolites of antiepileptics, folate deficiency and hypoxia secondary to seizures also contribute to malformations [23,24].

The highest risk of malformations is associated with exposure to valproic acid (9.3%), and the most common are neural tube defects, heart defects (e.g., interventricular septal defect), lip/palate cleft, hypoplasia. There is also an increased risk of congenital malformations for phenobarbital (5.5%), topiramate (4.2%), carbamazepine (3.0%), phenytoin (2.9%), levetiracetam (2.4%) and lamotrigine (2%). As with valproic acid, palate cleft may frequently occur in the administration of phenobarbital and topiramate [16,25].

Fetal hydantoin syndrome may occur with phenytoin and carbamazepine administration and is characterized by facial dysmorphism, skeletal abnormalities (hypoplasia of the fingers), mental retardation, and impairment of state-weight development [26].

Lamotrigine is allowed during pregnancy. Teratogenic risk is dose-dependent, with low teratogenic risk at doses up to 200-400 mg/day, increasing when combined with other antiepileptic drugs, especially valproic acid. Levetiracetam is also allowed during pregnancy, and it is considered a low teratogenic risk medicine when used alone and more effective than lamotrigine [27,28].

Fetal neurodevelopmental and behavioral deficits may occur secondary to neuronal apoptosis, fetal hypoxia during maternal seizures, or physiological and functional changes induced by antiepileptic metabolites. These include a lower intelligence quotient (IQ), increased aggressive symptoms, verbal, comprehensible, expressive, or motor disorders, and autism spectrum disorders [5,24].

Due to these complications, maternal anxiety and depressive disorders may occur more frequently during and after pregnancy [29].
THE EFFECT OF PREGNANCY ON THE COURSE OF THE EPILEPTIC DISEASE

Pregnancy is thought to have an unpredictable effect on the course of the epileptic disease. The absence of seizures during pregnancy is essential for the health of the mother and fetus, so their preconception control is a predictor of their absence in pregnancy.

During pregnancy, estrogen and progesterone alter neuronal excitability, and thus the threshold of seizures may be affected, and an increase in seizure frequency and severity may occur by 15-32%, while 48-60% have no seizures during pregnancy. In addition, there is increased metabolic catabolism of the drug, and it may be necessary to modify the treatment to prevent seizures [2,19].

Other factors that contribute to changes in the pharmacokinetics of antiepileptic drugs in pregnancy are digestive disorders with altered therapy compliance, reduced gastric motility, use of antacids or inhibitors of histamine type-2 receptors, increased plasma volume, altered drug absorption with increased excretion, liver clearance, and decreased serum transport proteins. There is also increased placental absorption of drugs. Insomnia and smoking can also increase the risk of seizures [20,30].

The seizures that occur during pregnancy are especially generalized tonic-clonic seizures and can lead to sudden maternal death, brain damage, impaired quality of life, and damage to the fetus due to trauma. Focal seizures or status epilepticus may occur less frequently [19,31].

THERAPEUTIC CONDUCT DURING PREGNANCY AND BIRTH

Regarding the need for antiepileptic treatment, its change during pregnancy should be avoided, as the teratogenic risk is considered lower than the risk of a new seizure, as well as polytherapy to reduce the risk of fetal exposure to drug combinations. It is also important to monitor the serum level of antiepileptic drugs monthly in the 1st and 2nd trimester of pregnancy and every 2 weeks in the 3rd trimester to adjust the therapeutic dose, especially in case of a convulsive episode or lack of therapeutic compliance, and to minimize fetal drug exposure. Among antiepileptics, lamotrigine is the most susceptible to changes in serum levels. Although this is a common practice method, it is not effective in controlling seizures and maternal or fetal outcomes [24,32,33].

Due to the increased risk of fetal malformations, especially secondary to antiepileptic treatment, fetal ultrasound evaluation is recommended for their diagnosis in the first and second trimesters, focusing on the neural tube, heart, and face defects which are the most common [20,24].

The first convulsive episode requires a differential diagnosis with eclampsia and cerebral venous thrombosis during pregnancy [31]. Most authors recommend initiating anticonvulsant treatment from the first seizure episode and postpartum neurological reassessment with discontinuation of treatment [5,24].

Phenobarbital, carbamazepine, phenytoin, and topiramate are enzyme inducers that cross the placenta and increase the degradation of vitamin K in the fetus. The prevalence of coagulation disorders in newborns is 10%, and the mortality is 30%. Vitamin K supplementation in doses of 10-20 mg/day in the last month of pregnancy is recommended in women treated with antiepileptics or consuming alcohol to prevent hemorrhagic disease in newborns. More recently, the guidelines recommend no antepartum prophylaxis, only vitamin K administration at a dose of 1 mg in newborns >1500 gr, and 0.5 mg in newborns <1500 gr. In cases with poor response to the initial administration of vitamin K, evaluation of the coagulogram is recommended, and the administration of fresh frozen plasma or coagulation factor concentrate may be required (II, VII, IX, X) [20,34].

Delivery must occur in a multidisciplinary hospital to ensure maternal and neonatal resuscitation in case of need. Vaginal delivery increases the risk of seizures in labor by only 3.5%, the elective cesarean section being preferred in the case of recurrent seizures in the 3rd trimester of pregnancy. The incidence of convulsions in labor and the first 24 hours postpartum is 1-2% [20,35,36].

Prophylaxis of seizures is achieved by continuing the administration of maternal treatment and regional anesthesia, as hyperventilation induced by labor pain, maternal exhaustion, and sleep deprivation may precipitate the onset of a seizure. It is recommended to avoid ketamine because anticonvulsant drugs potentiate its central depressant effect [2,20,24].

In case of seizures during labor, it is recommended to administer 1-2 mg of intravenous (IV) diazepam, then 1 g of phenytoin within 1 hour, as magnesium sulfate is not considered an effective treatment. Continuous cardiotocography monitoring is required for at least 1 hour after antiepileptic treatment to evaluate fetal well-being [5,20,37].

If epileptic status occurs, complete laboratory evaluation, determination of serum levels of antiepileptic drugs, toxicological tests, venous line, oxygen administration, and even orotracheal intubation of the patient are recommended. Hydro electrolytic imbalance, hypo/hyperglycemia, and fever are also corrected. Thiamine (vitamin B1) 100 mg IV and pyridoxine (vitamin B6) 5 mg IV are administered. Continuous monitoring of respiratory and heart rate, blood pressure, temperature, oxygen saturation,
and cardiotocography are required. In case of a prolonged crisis, which does not respond to antiepileptic medication, the baby is born by emergency cesarean [36,38].

POSTPARTUM CARE

Although all antiepileptics are excreted in human milk, breastfeeding is permitted because its benefits outweigh the risks of exposure to antiepileptic medication. Their concentrations in breast milk are significantly lower than those in maternal serum and do not cause any harm. The excretion rate in breast milk is 2% for valproic acid, 30-45% for phenytoin, phenobarbital, carbamazepine, and 90% for ethosuximide. Breastfed babies have improved neurological development, IQ, and higher verbal ability than non-breastfed babies [5,24,39,40].

After birth, it is necessary to adjust the dose of antiepileptics because plasma levels may fluctuate in the first 8 weeks due to changes in plasma volume and protein binding. Neurological consultation is recommended to evaluate plasma levels of antiepileptics and dose reduction to avoid overdose. The required dose of lamotrigine decreases to the pre-pregnancy dose in the first 3 weeks postpartum [2,20,33].

Anticonvulsant treatment decreases the effectiveness of oral contraceptives because it has an enzymatic inducing effect and potentiates the hepatic metabolism of contraceptives with decreasing hormone levels. Oral contraceptives also increase the metabolism of some antiepileptics, and it is necessary to increase the dose to avoid seizures. In these patients, the intrauterine device is recommended as a method of contraception [2,5,41].

CONCLUSIONS

Epilepsy in pregnant women is a real challenge for both the obstetrician and the neurologist due to the serious maternal and fetal complications that can occur, as well as the complex therapeutic management. Planning a pregnancy during a stable period of the disease, continuing antiepileptic treatment in the indicated cases using the minimum doses necessary to control the disease and diminishing the teratogenic effects, and carefully monitoring pregnancy and birth lead to successful management with good maternal and fetal results.

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