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REVIEW ARTICLE

Current approach to the treatment of epileptic pregnant women: a literature review

Abordagem atual do tratamento da gestante epiléptica: uma revisão de literatura

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ABSTRACT

Epilepsy is a neurological disorder that affects approximately 15 million women of reproductive age. During pregnancy, epilepsy can pose risks to the mother and fetus due to the occurrence of seizures and the potential deleterious effects of antiepileptic medications (AEDs).Seizures during pregnancy are associated with complications such as premature birth, intracranial hemorrhage and fetal death. In addition, antiepileptic medications can have teratogenic effects due to their effect on reducing blood folate levels and the metabolism of vitamin K, affecting the development of the fetus. Adequate prenatal care is essential to control seizures during pregnancy.

Some antiepileptic medications are considered teratogenic during pregnancy and pass through breast milk. Despite this, breastfeeding should certainly be encouraged due to its benefits already well documented in the literature. For better control, the child exposed to these medications should be followed up and monitored to anticipate possible adverse effects of antiepileptic drugs. A multidisciplinary approach, with proper clinical care and medications, is essential to ensure a healthy pregnancy. This information is based on an updated review of the literature, with emphasis on the main information about epilepsy in pregnancy.

Keywords: Epilepsy; Pregnancy; Anticonvulsants.

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RESUMO

A epilepsia é uma doença neurológica que afeta aproximadamente 15 milhões de mulheres em idade reprodutiva. Durante a gravidez, a epilepsia pode representar riscos para a mãe e o feto devido à ocorrência de convulsões e aos efeitos potenciais deletérios das drogas antiepiléticas (DAEs). Convulsões durante a gestação estão associadas a complicações como parto prematuro, hemorragia intracraniana e morte fetal. Além disso, as drogas antiepiléticas podem ter efeitos teratogênicos devido ao seu efeito na redução dos níveis de folato no sangue e no metabolismo da vitamina K, afetando o desenvolvimento do feto. Conclui-se, portanto, que é fundamental um acompanhamento pré-natal adequado para controlar as convulsões durante a gravidez.
Alguns Medicamentos antiepiléticos são considerados teratogênicos durante a gestação e possuem passagem através do leite materno. Apesar disso, a amamentação deve ser seguramente incentivada pelos seus benefícios já bem documentados na literatura. Visando melhor controle, a crianças expostas à essas medicações devem ser posteriormente acompanhandas e monitoradas para antever possíveis efeitos adversos dos medicamentos antiepilépticos. Uma abordagem multidisciplinar, com cuidados clínicos e medicamentosos adequados é essencial para garantir uma gravidez saudável. Estas informações são baseadas em uma revisão atualizada da literatura, com ênfase nas principais informações sobre a epilepsia na gravidez.

Palavras-chave: Epilepsia; Gravidez; Anticonvulsivantes.

Introduction

Epilepsy is a chronic and severe neurological disease characterized by the occurrence of two or more spontaneous and unprovoked seizures, requiring a clinical diagnosis based on the history of their occurrence[1-22]. There are approximately 15 million women worldwide with epilepsy who are of reproductive age[2,12,22].

According to the meta-analysis by Cabral ACV, 2017, approximately 5 out of every 1000 adults have epilepsy, occurring in 0.2% of pregnant women. It is important to emphasize that the deaths of pregnant women with epilepsy can be avoided and are related to the ineffective control of seizures[22].

It is known that intrauterine exposure to antiepileptic drugs is associated with adverse outcomes in the fetus. The risk of fetal malformations is 4-8% and may include more severe congenital defects, impaired fetal growth, as well as behavioral and neurocognitive impacts, especially in the first trimester, since these drugs cross the placental barrier[6,8,2,15]. However, most women with epilepsy require continuous treatment with these medications throughout pregnancy[10,2].

Thus, during prenatal care classified as high risk, it is essential to emphasize the importance of adherence to anticonvulsant medication. However, it is crucial that the woman is also properly guided on the use of folic acid, since these drugs are folate despoilers. The recommended dosage of folic acid supplementation is 4-5 mg/day for at least three months before conception, since folic acid deficiency is clearly associated with defects in neural tube closure[6,19,17,22].

It is important to highlight that the lack of treatment of epilepsy before, during and after pregnancy can result in uncontrolled seizures, which impact the health capacity of both the mother and the baby, and can even lead to death[1,2]. This highlights the need to find a balance between the teratogenic potential of antiepileptic drugs and the benefits of their use[2,12,22].

This bibliographic review aims to present the importance of care for epileptic women during pregnancy, as well as attention to prenatal, perinatal and postpartum control. In addition, it explains the potential risks of using antiepileptic drugs for the woman and the fetus.

Methodology

To carry out this literature review, only content published between the years 2016-2023, no more than 7 years since publication, from the Medical Literature Analysis and Retrieval System on Line (MEDLINE)/Public MEDLINE (PubMed) was used as inclusion criteria. Clinical studies, meta-analyses, randomized controlled studies, review studies and systematic reviews in Portuguese, English and Spanish were used, using the keywords “epilepsy”, “pregnancy” and “anticonvulsants”. The initial selection was made by

reading works that allowed the choice of those related to the points to be addressed by the review, resulting in a total of 25 journals. After reading the articles and selecting the information, 23 articles were used in the final construction of this paper, based on the levels of evidence and relevance of the information.

Discussion

Effects of epilepsy in pregnancy

During pregnancy, there are physiological, psychological and endocrinological changes that alter the seizure threshold. Epilepsy that begins during pregnancy is not uncommon. Approximately 20 to 30 out of every 1000 pregnant women suffer from this condition, which can be explained by the exacerbation of latent circumstances, hormonal changes and physiologies typical of the period. This diagnosis must be differentiated from eclampsia, which begins predominantly after the 20th week of pregnancy[22,11].

At the beginning of pregnancy, women may have reduced concentration of drugs in their bodies due to vomiting and nausea in the first trimester. Thus, one should try to adjust the dose of the antiepileptic drug, since changes occur throughout pregnancy that influence the course of the disease and the pharmacokinetics of the drugs due to the increase in urinary flow, plasma expansion, renal clearance and changes in metabolism, with the induction of liver enzymes and a decrease in albumin[3,22]. The decrease in drug concentration represents 10% for carbamazepine and phenobarbital and 50% for lamotrigine, levetiracetam and valproic acid. This change in drugs may predispose to seizures by reducing the minimum therapeutic serum concentration[7,22].

Teratogenesis and epilepsy

It is known that in focal seizures with intact consciousness, there is no fetal damage. However, generalized tonic-clonic crises, which involve greater hemodynamic stress and present a greater possibility of trauma, are more worrisome. It is important to note that epilepsy is not an indication for a cesarean section unless it provokes a seizure during the second stage of labor and the patient is unable to cooperate with a vaginal delivery due to sedation[1,2,11,15,22].

Data show that the control of seizures in the pre-gestational period is the most relevant factor for complications during pregnancy. Women who had seizure episodes in the month before conception had a significantly increased risk of seizures during childbirth[2,15,22].

Although most women with epilepsy can have an uneventful pregnancy and give birth to healthy children, there are fetal risks associated with treating the disease. These risks include deleterious effects on fetal growth, increased risks of important birth defects, as well as adverse effects on neurocognitive and behavioral development[1].

According to the meta-analysis by Cabral ACV, 2017, the most common anomalies found in the fetuses of mothers treated for epilepsy are cleft palate, cleft lip, hypospadias, atrial septal defects and skeletal anomalies[22]. The teratogenicity of anticonvulsant drugs is one of the main factors that require attention in the monitoring of an epileptic pregnant woman, and it is worth highlighting valproate for its high contribution to this factor[18,22].

Anticonvulsants have control teratogenic effects on folate, since these drugs use the vitamin to act upon the brain. Folate plays a key role in the biological process of formation of embryonic and fetal structures, allowing methylation of the embryo's DNA and reducing homocysteine levels, while increasing methionine levels. This interaction is essential to protect embryonic development[22].

In order to reduce the risk for the fetus, it is recommended that treatment be performed with monotherapy whenever possible, avoiding the use of multiple drugs together (polytherapy). This approach aims to minimize the potential effects of anticonvulsants and increase safety during pregnancy, prioritizing the health and well-being of the fetus[22].

Medication

Medications cannot be stopped abruptly, and drugs with lower teratogenicity potential should always be chosen. In addition, the peak concentration of the medication should be reduced, and a more stable level should be planned during the day, always aiming at the use of monotherapy[16,22,9]. In addition to medication adherence, for better control of seizures, women should avoid factors that trigger seizures such as fear, anxiety, sleep restriction and tiredness. The doctor must be aware of the need to request dosages of anticonvulsants in serum as well. Due to the intimate relationship with specific malformations and the use of certain AEDs, a morphological ultrasound should be directed to the fetal segments with the highest teratogenic risk[22].

There is also an increased risk of low birth weight for gestational age (SGA), and there are studies that confirm greater chances of small head circumference among children exposed to polytherapy with AEDs or monotherapy with primidone or valproate. In addition, there are increased rates of microcephaly with carbamazepine and valproate, though normalization occurs at the age of two. The effect on growth varies between different AEDs and seems to be more pronounced with topiramate[2,18].

Studies have shown that lamotrigine demonstrated excellent efficacy and safety in relation to risks to the fetus, being considered a preferred option in the treatment of epilepsy during pregnancy, as well as in the therapy of epilepsy in women of reproductive age. Studies on carbamazepine are relatively reassuring, although its use is associated with an increased risk of fetal malformations and reduced verbal skills. The most commonly observed abnormalities in patients

receiving carbamazepine monotherapy were cardiovascular in nature. Regarding the rates of malformations associated with the use of phenytoin, variable results are seen, with a higher risk of malformations compared to pregnant women without epilepsy or who do not receive treatment with this antiepileptic drug. Topiramate appears to be linked to an increased risk of malformations such as oral fissures and hypospadias compared to the general population. As for the use of levetiracetam, no specific associations were found with malformations[7,11].

The teratogenicity of valproate is the most known and documented in the literature. The drug is related to neural tube defects such as midline defects, spina bifida, hypospadias and brain malformations, in addition to the occurrence of cardiac, orofacial/craniofacial and skeletal defects. Thus, folate supplementation in synthetic form (folic acid) is recommended three months before pregnancy at 4mg per day.[23] The risk of the appearance of main congenital malformations (MCMs) with the use of valproate is 10%, being associated with the administered dose. Furthermore, exposure to valproate is associated with an increased risk of autism spectrum disorder, as well as a reduced intelligence quotient (IQ) and other cognitive functions in preschool years. These developmental neuropsychomotor problems occur along with repetitive behaviors, impaired communication and social isolation[1,2,4,5,10,11,13,17,18].

The risk of malformations with polytherapy is 6.0% as opposed to 3.7% with monotherapy; however, more recent studies indicate that the type of AED included in polytherapy is more important than their number, with the inclusion of valproate being the main cause of prevalence of MCMs. It is also known that there is an additional risk associated with polytherapy with levetiracetam[1,2,11,18].

Over the years, there has been a reduction in the use of valproate and carbamazepine, while there has been an increase in the prescription of lamotrigine and levetiracetam during pregnancy. These changes in clinical practice have resulted in a 27% decrease in the prevalence of major congenital malformations (MCMs) over this period. Studies have indicated that lamotrigine, levetiracetam, carbamazepine, oxcarbazepine, gabapentin, and phenytoin have a teratogenic risk similar to that of the general population. However, both levetiracetam and lamotrigine have been associated with a lower teratogenic risk[1,2,7,9,18,20].

According to the American Academy of Neurology (AAN) guidelines, it is recommended that levels of anti-epileptic drugs (AEDs) be regularly monitored throughout pregnancy. In general, AED levels should be checked quarterly. However, it is important to be aware that lamotrigine and oxcarbazepine presented the most frequent monitoring, with stable intervals, due to the increased clearance of these drugs in case of increased estrogen levels. Furthermore, it is crucial to closely monitor levetiracetam and zonisamide concentrations, since these drugs are sharply decreased during pregnancy due to increased renal clearance[1,2,7,9,20].

During pregnancy, there is an increase in clearance and consequent decrease in concentrations of lamotrigine, levetiracetam, active metabolite of oxcarbazepine (licarbazepine), topiramate and zonisamide. However, debugging from carbamazepine and clobazam did not present changes in pregnancy. It is important to note that when the concentration of antiepileptic drugs (ADs) drops to 65% or less of the target value, the risk of worsening seizures significantly increases[1,2,3,7,20].

Table 1. Table of drugs used during pregnancy - dose and risk of MF.

Drug (Commercial Name)	Daily Dose	Teratogenicity	Observation
Phenobarbital (Gardenal)	150 to 200 mg	Low	It promotes sedation in the neonate of lactating women in use
Valproate (Depakene)	250 to 500 mg	High	Contraindicated in pregnancy and lactation
Carbamazepine (Tegretol)	400 to 800 mg	Low	Marked drop in serum levels during pregnancy. Make dose adjustments
Phenytoin (Hydantal)	200 to 500 mg	High	Fetal Hydantoin Syndrome. Contraindicated
Topiramate (Amato, Topimax)	200 to 400 mg	High	Risk of fetal abnormalities. Avoid use
Lamotrigine (Neural)	200 to 400 mg	Low	Controlling seizures during pregnancy is more difficult
Levetiracetam (Keppra)	1000 to 3000 mg	Low	Dose adjustment necessary in pregnancy

(Cabral ACV. Treatment of Epilepsy in Pregnancy. In: CIP-BRASIL, editor. Obstetrics Pocket Guide. 2nd ed. Rio de Janeiro: Atheneu; 2017. p. 241-8).

Below, we present a table 1 with the anticonvulsant drugs used during pregnancy and the risk of fetal malformation associated with each of them.

Prenatal control

During the prenatal period, it is critical that professionals provide accurate information and empower patients to properly manage their condition. In this sense, it is crucial that prenatal control be performed carefully in patients with epilepsy, with the aim of controlling the disease and avoiding seizures. Adherence to treatment is one of the most important factors to be considered in this follow-up[22].

In addition to adequate treatment, risk factors for seizures such as tiredness, poor sleep quality or sleep deprivation, anxiety and fear should be avoided[22]. Early pregnancy symptoms, such as vomiting, which decrease the concentration of anticonvulsant drugs, should be treated appropriately to prevent exacerbation of epilepsy[12]. In addition, the importance and indication of carrying out tests that help in the prevention and early identification of fetal anomalies is worth mentioning, such as a morphological ultrasound and a serum dosage of anticonvulsant concentrations, which should be performed when necessary[10].

Studies indicate that adequate supplementation during pregnancy can reduce the risk of defects in the neural tube closure by a designed range of between 60% and 86%. Among the essential nutrients in this context, folic acid and methylfolate have been associated with a reduced risk of miscarriage in women using AEDs. In addition, the supplementation of these vitamins is also related to a decrease in the risk of hematological abnormalities and an increase in IQ in children exposed to these nutrients[11].

Vitamin K

The use of anticonvulsant drugs can have a negative impact on fetal vitamin K metabolism, thus increasing the risk of bleeding after birth. For this reason, pregnant women who use antiepileptic drugs should undergo prophylaxis against hemorrhagic disease of the newborn, a condition associated with high rates of neonatal complications. It is recommended that K be administered orally, at a dose of 10-20 mg per day, by the mother, during the last month of pregnancy. In addition, newborns should receive a dose of 1 mg of vitamin K intramuscularly soon after birth and another dose at 28 days of life.[22]

Care during delivery

To prevent hypoxia in the newborn and ensure a safe and active delivery, it is recommended that the delivery be referred to safe health institutions, which have all the necessary resources to deal with obstetric urgencies and emergencies. During the peripartum period, approximately 1% to 2% of pregnant women with epilepsy may experience seizure episodes, which can be harmful to both the fetus and the mother, increasing the risk of hypoxia with a poor prognosis[2,21].

To deal with these situations, fast-acting benzodiazepines can be administered in low doses, either nasogastrically or parenterally. However, it is important to exercise caution with the administration of meperidine and morphine during the peripartum period, as these drugs can cause seizures. With the aim of mitigating seizure episodes, epidural anesthesia may be a suitable option, since it reduces the stimuli that trigger seizures, such as angiogenic peaks and pain[2,21].

During a seizure episode in the peripartum period, the uterus can increase the duration of contractions, which can lead to a decrease in the fetal heart rate. A study conducted in Sweden, involving 1,429,652 births, revealed a higher prevalence of labor induction, elective cesarean section, placental abruption and peripartum infection in patients with epilepsy. In addition, a survey in the United States of 20,449,532 deliveries, including 69,385 patients with epilepsy, showed a higher incidence of preterm delivery, pre-eclampsia, caesarean section, increased length of hospitalization (greater than 6 days) and an increased risk of mortality (OR=11.46).[1]

When it comes to the mode of delivery, having epilepsy is not, by itself, an indication for cesarean section. However, a cesarean section may be considered if there is an increase in the frequency of seizures in the weeks before the baby is born. In general, most pregnancies in women with epilepsy can allow a vaginal delivery.[21] It is important to emphasize that home births are not encouraged in these conditions.[2]

Breast-feeding

Concerns about the presence of anticonvulsants in breast milk and their possible adverse effects on children have been felt by both mothers and physicians. It is relevant to note that certain drugs, such as lamotrigine, may have higher concentrations in breast milk compared to other AEDs.[22, 15]

This fraction of anticonvulsants present in breast milk can cause sedation in newborns, with phenobarbital being the drug most associated with this effect. However, the absence of neurocognitive effects in children exposed to anticonvulsants through the ingestion of breast milk from mothers treated with these drugs has been demonstrated[22,15].

In addition, continuous breastfeeding in the first 6 months of life promotes the development of fine, gross and psychosocial skills as well as reducing the risk of developing epilepsy in the child. It is important that mothers who are on anticonvulsant therapy discuss the benefits and risks of breastfeeding with their physicians to make an individualized decision[1,7].

The benefits of breastfeeding are well described, hence there is strong evidence to support its safety in mothers with

epilepsy. General breastfeeding should be encouraged among epileptic pregnant women, but it is important that there be a balance according to the need for adequate sleep.[16,11] In addition, babies should be monitored for adverse effects when the mother is using AEDs with potential cumulative effects. This measurement can be performed by measuring the baby's serum levels if side effects are suspected[16,11].

The American Academy of Neurology (AAN), 2009, did not give a definitive opinion in this regard, though it has discussed the penetration of certain AEDs into breast milk. Thus, it was postulated that primidone and levetiracetam probably penetrate milk in potentially important amounts. Gabapentin, topiramate and lamotrigine possibly penetrate breast milk in relevant amounts, whereas phenytoin, phenobarbitone, carbamazepine and valproate probably do not penetrate milk in significant amounts[11,1]. It should be noted that children already exposed in utero to antiepileptic drugs are less likely to develop drug withdrawal syndromes, since they continue to be in contact with micro-doses even after the intrauterine period[22].

Care in the puerperum

Epilepsy is one of the main causes associated with an increased risk of maternal death during and after pregnancy. Sleep deprivation, lifestyle changes and risk behaviors interfere with correct adherence to medication and, consequently, reduce seizure thresholds, increasing the frequency and severity of seizures[12].

In the postpartum period, it is recommended that women with epilepsy make an appointment with the gynecologist 6 weeks after delivery and with the neurologist 12 weeks after delivery. During pregnancy, the doses of antiepileptic drugs can be increased, while after delivery, it is usually necessary to reduce them. However, there is no clear evidence about the exact moment to start dose reduction, since the postpartum period is associated with emotional and physiological changes that may predispose to seizures.[22]

In this sense, it is recommended that the dose of medication be maintained so that the woman's emotional state is stable and even sleep is adequate. It is important to discuss the best time to start reducing the dose with a neurologist, taking into account each woman's individual context, for emotional stabilization and sleep quality. Regular medical follow-up is essential to monitor the woman's condition and make the necessary adjustments in antiepileptic therapy during the postpartum period.[22]

Conclusion

In conclusion, a pregnant woman with epilepsy faces additional challenges due to the teratogenic potential of seizures and antiepileptic medications. Adequate control of epilepsy during pregnancy is essential to avoid complications such as fetal malformations, impaired growth and development, and cognitive deficits. It is important to adjust the drug dose, taking into account the physiological and pharmacokinetic changes that occur during pregnancy.

Lack of proper epilepsy treatment can lead to uncontrolled seizures, resulting in fetal loss and cognitive impairment. It is necessary to strike a balance between the teratogenic risks of drugs and the benefits of their use. Some antiepileptics have been linked to a higher risk of malformations, while others seem to have a better safety profile.

During prenatal care, it is essential that pregnant women understand the importance of adherence to antiepileptic medication and the use of folic acid before conception. Abrupt discontinuation of medications should be avoided and preference should be given to medications with lower teratogenic potential, seeking monotherapy whenever possible.

In addition to medication adherence, it is recommended that women avoid seizure triggers such as stress, anxiety, sleep deprivation and fatigue. Monitoring blood levels of anticonvulsants and specialized fetal monitoring during prenatal care are important to assess the teratogenic risk.

Regarding delivery, most pregnant women with epilepsy can have a vaginal delivery, while an elective cesarean section can be considered as seizures become more frequent in the weeks leading up to delivery.

Regarding the postpartum, it is reassuring to know that the presence of anticonvulsants in breast milk does not have a significant influence on the health of the newborn. Therefore, breastfeeding should be encouraged even while using these drugs.

Specialized and multidisciplinary care is crucial to ensure the best control of epilepsy during pregnancy, minimizing the risks for the fetus and the mother. The balance between the benefits and risks of antiepileptic drugs, combined with a comprehensive approach that involves medication adherence, a healthy lifestyle and adequate monitoring, will contribute to a safer and healthier pregnancy for women with epilepsy.

Authors' Contributions

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