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MANAGING ANTI-EPILEPTIC DRUGS DURING PREGNANCY ; EVOLVING CONCEPT

Medicine

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ABSTRACT

Epilepsy is one of the few neurological disorders that require a constant treatment during pregnancy.Besides epilepsy Anti-epileptic drugs (AEDs) are also commonly used for psychiatric disorders,pain disorders,and migraines. No Anti-epileptic drugs is safe during pregnancy . Anti-epiletic drugs exposure during pregnancy causing intra- uterine growth retardation,cognitive dysfunction,low IQ,microcephaly,major conjenital anomalies and infant mortality. Use of anti-epileptic drugs (AEDs) in pregnant women with epilepsy requires monitorning and maintaining a balance between limiting seizures and decreasing fetal exposure to the potential teratogenic effects. In this review we analysed the data on the pharmacokinetics of various AEDs in pregnancy, neurological teratogenic effects and providing a basis for management of safety of AEDs during pregnancy

KEYWORDS

Anti-epileptic drugs[AED],Pregnancy,

INTRODUCTION

Anti-epileptic drugs (AED)s are class of drugs that are used to treat epilepsy as well as neuropathic pain, migraines,and psychiatric disorders. Approximately 1.5 million women with epilepsy are of child bearing age in USA and give birth to approximately 3-5 babies per 1000 born.[1] Epilepsy in pregnancy could be more serious complication. Research studies suggested that child bearing women suffering from epilepsy have two to three folds more chances to find deformities in their offspring then normal pregnant women.[2] Anti-epileptic drugs are also administered to pregnant epileptic patients; however, they have negative consequences to foetus.[3] As, Anti-epileptic drugs are very important for the treatment of epilepsy, most of the women with epilepsy require Anti-epileptic drugs to control seizures to entire period of pregnancy. The most concerning issue in pregnant with epilepsy is the development of the tonic-clonic seizures, which may lead to the adverse effects to the fetus such as: intracranial hemorrhage, transient hemorrhage and heart beat abnormalities.[4]

There may be multiple mechanisms through which AEDs affect fetal neurodevelopment. While scientists have still not properly characterized the pathways through which this may occur, a number of studies have investigated the mechanism through which this may occur. Cognitive defects can still occur in fetuses that are exposed to AED dosages that are lower than those that produce structural abnormalities. There are various hypothesis that have been set forward that may explain the ability of AEDs to produce functional defects; these may include suppression of neurons, ischemic condition in utero, formation of free radicals, apoptosis in neurons and decreased folate metabolism (Fig. 1) [5]

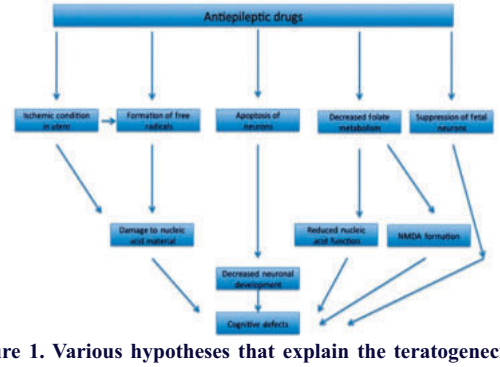

Figure 1. Various hypotheses that explain the teratogenecity of AEDs. There may be multiple mechanisms that lead to the formation of cognitive defects in fetuses, including ischemic condition, neural suppression, decreased folate absorption, neural apoptosis and an increase in free radical formation (5). AEDs, antiepileptic drugs.

Planing During Pregnancy.

Childbearing-aged women with epilepsy should be informed that epilepsy is not a contraindication to giving birth. Over 90% of women with epilepsy deliver healthy children. Before conception, a comprehensive management plan is desirable. The diagnosis of epilepsy needs to be validated, the epilepsy syndrome elucidated, 'optimal' antiepileptic drug treatment established and folate supplements given.

Clinical studies have shown that folic acid supplementation can prevent malformations in children of women taking AEDs, hence the recommendation of a dose of 5 mg/day of folic acid for women considering pregnancy and during the first months of pregnancy [6,7]. High doses of folic acid (above 5 mg/day) are not recommended as they may lower the seizure threshold

Women with epilepsy who are considering pregnancy should be treated with the least teratogenic but most efficacious antiepileptic drug for their particular type of epilepsy at the lowest effective dose.Monotherapies generally bear a lower risk than poly therapy. The risk of congenital malformations in children of mothers with epilepsy depends on the type of administered drug, the number of drugs, and the dosage—it is higher than in the general population and reaches 3% in those using carbamazepine (CBZ) or lamotrigine (LTG); 7% for valproate (VPA); 15% in those receiving two or more AEDs [8]. Since VPA is a frequently used AED, it is important to assess the benefits and risks of its application on a case-by-case basis [9]. Epilepsy is not a contraindication to natural childbirth, epidural anesthesia during labor, or breastfeeding. Women with epilepsy who decide not to have children may receive effective contraception [9].

Pregnancy counselling and planning are strongly advised. When an unexpected pregnancy happens and embryogenesis has already occurred, there is usually little to gain and there may be substantial risk in stopping or changing Antie-pileptic drugs. Early monitoring for an adverse fetal outcome and appropriate counselling are advisable. It is important to explain the issue to the patient and her relatives and to emphasize that a potential teratogenic factor, such as the use of AEDs, is already present in the first days after conception. To reduce the risk of birth defects, it is recommended to administer the lowest effective dose of the most appropriate AED until at least the end of the first trimester of pregnancy [8.9].

Discontinuation of medication may be considered in women after a three-year seizure-free period [9]. Pregnant women who have had seizures a year before conception require increased monitoring of their epilepsy treatment. Most women (67%) do not experience seizures during pregnancy. Between 74% and 92% of women who have been

seizurefree for at least 9 months to 1 year before pregnancy will remain free of seizures during pregnancy [9,11,12]. The data from EURAP (European Registry of Antiepileptic Drugs and Pregnancy) have shown that pregnant women with idiopathic generalized epilepsy are more likely to be free of seizures (74%) than those with focal epilepsy (60%) [10]. Women with epilepsy should be informed that implementing a few safety guidelines can significantly reduce the risk of seizures and minimize anxiety about the effects of AEDs on the child [13–15].

Preconception Period Recommendations Follow

- Every woman with epilepsy during preconception should be provided with comprehensive information on the course of epilepsy during pregnancy.
- If treatment with AEDs is necessary, monotherapy should be used if possible.
- If a change of an AED is necessary, it should be done before pregnancy.
- A woman planning pregnancy should take folic acid (5 mg/day) before and during the early stages of pregnancy.
- Women using AEDs that induce liver enzymes may receive vitamin K during the last period of pregnancy.
- All pregnancies of women with epilepsy should be reported to an appropriate epilepsy and pregnancy registry [16]

Pharmacokinetic Alterations Of Anti-epileptic Drugs In Pregnancy

Serum concentrations of most AEDs may fluctuate in pregnancy due to changes in pharmacokinetics during absorption, metabolism, or excretion.The most marked declines in serum concentrations during pregnancy are seen with Lamotrigine,Levetiracetam or Oxcarbazepine, up to 30–50% but also occur with Phenobarbital, phenytoin,topiramate and zonisamide.[8,9].The extent to which pregnancy affects AEDs blood levels varies between individual women. Lower drug concentrations may lead to intensified seizures. It is therefore recommended to monitor the serum levels of these drugs before pregnancy and at least once during each trimester of pregnancy and additionally in special situations such as lack of seizure control or the occurrence of adverse symptoms [17]. Considering Lamotrigine, this AED penetrated into amniotic fluid with a ratio of 0.68, umbilical cord (penetration ratio—0.92), and breast milk (0.77) [18]. Again, these data may recommend therapeutic drug monitoring [18].In settings where therapeutic drug monitorning is unavailable,it might sometimes be advisable to double the dose of lamotrigine and increase the dose of oxcarbazepine/levetiracetam gradually from the second trimester.

Safety of AEDs during pregnancy

If women with epilepsy must receive AEDs during pregnancy, it is safer for the mother and her child to use the AED with low teratogenicity and at the lowest effective doses possible. The risk of congenital malformations in children of women with epilepsy not using AEDs is found in the range of 1.1–3.3% and is similar to the risk of malformations in the general population (2.1–2.9%) [19]. The risk of congenital defects in children of women with epilepsy and using AEDs is 4–9% and increases with VPA and polytherapy [20–24]. It has been reported that monotherapy with newer AEDs such as Levetiracetam [22,25], Lamotrigine [22], Oxcarbazepine, and Zonisamide[26,27] is relatively safe for pregnant women. Levetiracetam and Lamotrigine are considered safe for pregnancy and their use has not been associated with an increased risk of birth defects, compared with the control group [22,28]. Currently, there are not yet sufficient data (small number of pregnant women surveyed) to assess the risk of birth defects for other AEDs used in monotherapy, such as gabapentin (GBP), lacosamide (LCM), Oxcarbazepine, pregabalin (PGB), or Topiramate [8]. However, the current data on the use of new-generation AEDs, while still limited, indicate a more favorable safety profile and lower teratogenic risk than older drugs [29]. The incidence of defects in children of mothers treated with AEDs depends not only on the type of AED but also on its dose. The risk of a defect increases with higher doses of a drug [30]. The EURAP registry assessed the incidence of congenital malformations manifesting up to 1 month of age and then those diagnosed later up to 1 year of age [10,31].

Teratogenic Risk Profiles of Antiepileptic Drugs

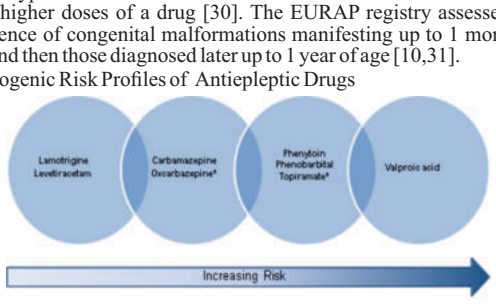

Fig. 2 Summary of relative teratogenic risk profiles of antiepileptic drugs, based on available data at the time of writing. The risk profiles include data about major congenital malformations, fetal growth, and neurodevelopmental outcomes when available, with consideration of the range of relative risks reported from multiple studies, number of patients studied, and confidence intervals. * Neurodevelopmental outcomes are not yet known.

CONCLUSION

It is clear that AEDs differ in their teratogenic potential. Valproate is associated with the greatest risks for malformations as well as for adverse cognitive and behavioral outcomes and should, whenever possible, be avoided in the treatment of patients who can become pregnant. Lamotrigine and levetiracetam are associated with the lowest risks for malformations, but data on neurodevelopment for levetiracetam are based on a small sample and evidence on the effects of prenatal exposure on the neurodevelopment is lacking or insufficient for other AEDs. Teratogenic risks should be considered early at the time of initiation of treatment in young female patients. Pre-pregnancy counseling is essential to ensure that the woman conceives while on folate supplementation and the most appropriate AED treatment with the least risk to the woman and her baby. Once pregnancy is established, close monitoring is warranted and ideally in collaboration between epilepsy care and obstetric care. It should finally be emphasized that the most women with epilepsy will have uneventful pregnancies and give birth to normal children. The aim of the recommendations in this review is to further facilitate such positive pregnancy outcomes.

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Conflict of interest
None

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