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ANTIEPILEPTICS IN PREGNANCY: A REVIEW

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ABSTRACT

Exposure to Anticonvulsant drugs by pregnant women to prevent seizures are among the most common causes of potential harm to the foetus. Even though prenatal exposure to antiepileptic drugs (AEDs) is known to cause relatively higher risks of major congenital malformations, prospective studies have provided refined data that allow us to differentiate the risks of different types and doses of AEDs. Women with epilepsy (WWE) are recommended to continue antiepileptic drugs (AEDs) during pregnancy to reduce maternal and foetal trauma associated with seizures. Substantial pharmacokinetic changes occur with most of the medications during pregnancy and postpartum, and inter individual variability supports the use of therapeutic drug monitoring for most AEDs. During pregnancy, vigilance and close monitoring should also include intrauterine foetal growth, obstetric complications, and neonatal complications.

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INDRODUCTION

Epilepsy is one of the most common neurological conditions in pregnancy which affects approximately 0.5 to 1% of pregnant women. About 80% of women with epilepsy use antiepileptic drugs (AED), which need to be continued throughout pregnancy to prevent seizures regardless of their adverse effects on the foetus. [1] The management of epilepsy in women during pregnancy carries a special challenge as both seizures and antiepileptic drugs (AEDs) can have harmful effects on mother and foetus [2].There is a wide concern with the possible teratogenic effects of antiepileptic drugs and the risks imposed by the drugs must be weighed against the risks associated with the disorder being treated.[3] Major malformations such as congenital heart disease , neural tube defects , urogenital defects and cleft lips or palates ,occur in about 3-7% of women with epilepsy who take antiepileptic drugs.[4] In spite of these risks, physicians need to prescribe AEDs to women with epilepsy who are planning to become pregnant because seizures can harm the mother as well as her foetus.[5] Foetal death has been reported in conjunction with prolonged seizures, such as status epilepticus, and frequent tonic–clonic seizures during pregnancy. And these are associated with poorer cognitive development of the child. On the other hand, AEDs can be teratogenic; they can increase the risk of congenital malformations as well as adverse cognitive outcomes. Recent publications from epilepsy and pregnancy registries have suggested that AEDs differ in their teratogenic potential, but also that these adverse effects of AEDs on the foetus are dose-dependent.[6]

SEIZURE DURING PREGNANCY

The reason for increased frequency of seizure in pregnancy is not clearly understood and is likely to be multifactorial. A variety of physiological, endocrine and psychological changes are associated with pregnancy, any or all of which might contribute to lowering the seizure threshold. The pharmacokinetics of the AEDs is altered by physiological changes during pregnancy, which may result in lower levels and seizure deterioration in WWE. Numerous factors are attributed to seizure deterioration, including reduction in plasma AED concentration and changes in AED metabolism, hormonal changes, sleep deprivation and psychosocial stress.[7] Two hypothesis regarding the cause of eclampsia have received the most consideration, both of which focus on the cerebral vasculature and autoregulation of cerebral blood flow (CBF) during hypertensive episodes. During preeclampsia the cerebral circulation is in a state of "over autoregulation" which elevates cerebral perfusion pressure causing ischaemia. This hypothesis is based on brain imaging in women with eclampsia that shown areas of vasospasm.[8] since cytotoxic and vasogenic oedema have been demonstrated in eclampsia ischaemic brain injury may be a cause of seizures. Clinical and neuroimaging findings are more consistent with vasogenic oedema.

The second hypothesis on the underlying mechanism for the neurological symptoms and oedema formation during eclampsia is that it is a form of hypertensive encephalopathy during which a rapid rise in blood pressure overcomes the myogenic vasoconstriction of cerebral arteries and arterioles causing the loss of auto regulatory capacity and blood-brain barrier (BBB) disruption with subsequent vasogenic oedema. This process has more recently been termed the posterior reversible encephalopathy syndrome (PRES) in order to highlight the propensity for oedema formation to occur in the posterior cerebral cortex. The propensity for hyper perfusion and oedema to form posteriorly is unexplained, but many suggest decreased sympathetic innervation of the posterior cerebral arteries for lack of a better explanation. [9]

PREGNANCY AND PERINATAL COUNSELING

Approximately 24,000 women with epilepsy become pregnant each year. In the majority of women with epilepsy, pregnancy has no effect on their seizure frequency; therefore, if seizures are well controlled, they are likely to remain so during pregnancy. However, in approximately 20% to 35% of pregnancies in women with epilepsy, an increased seizure frequency occurs during pregnancy. In an analysis of data from the European Registry of Antiepileptic Drugs and Pregnancy (EURAP), an international AED and pregnancy registry, 33.4% of pregnant women experienced seizures during pregnancy. Seizure frequency was unchanged in 70.5%, reduced in 12.0%, and increased in 15.8% of women with epilepsy. The Australian Pregnancy Registry for women with epilepsy found that, between 1998 and late 2016, seizures had occurred during pregnancy in approximately 43%. Seizures of any type occurred in 78.4% of pregnancies when seizures had occurred in the previous year (active epilepsy) and in 22.3% of those associated with inactive epilepsy. From these data, having a seizure disorder that was active in the year before pregnancy and in early pregnancy appears to be the best predictor of seizure recurrence during pregnancy. The reasons for seizure recurrence during pregnancy are multifactorial, including lowering or stopping anti seizure medications because of fear of harming the baby, hormonal fluctuations, and a higher estrogen-to-progesterone ratio especially in weeks 8to16 of pregnancy, sleep deprivation, and psychosocial stress. The most common cause of seizure recurrence in pregnancy, however, is likely reduced plasma concentration of AEDs and changes in AED metabolism. The plasma AED concentration fluctuates during pregnancy because of several physiologic reasons, including increased renal clearance, altered hepatic absorption, increased plasma volume of distribution, and hepatic enzyme induction by steroid hormones.

In counseling women with epilepsy who plan to become pregnant, practitioners should discuss the need for staying on antiseizure medication, simplifying the medication regimen, attempting monotherapy, and selecting medications with more favourable side effect profiles. Base line pre pregnancy AED levels should be obtained to guide adjustment of the dose during pregnancy. Monthly levels during pregnancy will help in detecting a significant decrease in levels. In case of any seizure recurrence or fall, the patient should be evaluated at the obstetrics clinic to ensure maternal and fetus well-being. The patient with active epilepsy should be managed by a team of high-risk obstetricians and epileptologists working together to manage her throughout her pregnancy, delivery, and immediate postpartum period. [9]

TREATMENT OF WOMEN WITH EPILEPSY

Pregnancy by 35% or more compared with baseline levels may be the cause of an increase in seizures. During pregnancy, the dose of antiseizure medications should be adjusted based on the patient's seizure history and pre pregnancy levels. Lamotrigine metabolism through hepatic glucuronidation is enhanced during pregnancy by elevated concentrations of sex hormones. Declining plasma concentrations of lamotrigine during pregnancy, therefore, may be associated with increased seizure frequency in more than 40% of patients. Worsening seizure control in the second and third trimester is more common in women taking lamotrigine than those taking carbamazepine or valproic acid. Lamotrigine clearance during pregnancy is 2 to 3 times higher than before pregnancy. The levels after delivery reach pre pregnancy levels within 1 to 3 weeks. zonisamide serum concentration may fall by more than 40% during pregnancy. The lowest zonisamide serum concentration occurred in gestational months 6 to 9, with significant inter individual variability, and 4 of 10 patients who were previously seizure free developed breakthrough seizures during pregnancy. The plasma concentration of the active metabolite of oxcarbazepine declines by 36% to 50% in the late stages of pregnancy and is associated with increased seizure frequency in 50% of women. Therefore, an adjustment in the dose of oxcarbazepine is necessary during pregnancy. The elimination rate of levetiracetam is significantly increased during pregnancy because of increased renal glomerular filtration in late pregnancy. Therefore therapeutic drug monitoring and dose adjustment is needed. The American Academy of Neurology (AAN) practice guidelines recommend that checking AED levels at baseline before conception and monthly thereafter. Dose adjustments should be considered to maintain an effective and stable level throughout pregnancy, at least for women with epilepsy who are taking lamotrigine, oxcarbazepine, levetiracetam, carbamazepine, and phenytoin. Despite limited evidence for changes in levels of other AEDs during pregnancy, AED levels should be regularly monitored during each trimester of pregnancy because of the potential for altered AED bioavailability, metabolism, and clearance.[7]

NEURODEVELOPMENTAL EFFECTS OF ANTIEPILEPTIC DRUG

Exposure of the fetus to AEDs through the placenta may have adverse cognitive and behavioral effects, such as lower IQ, language deficits, autism, and attention deficit hyperactivity disorder. Several factors contribute to IQ scores, such as maternal IQ, maternal age, gestational age at birth, prenatal folic acid supplementation, socioeconomic status, and maternal use of tobacco or alcohol. Meador and colleagues in the NEAD (Neurodevelopmental Effects of Antiepileptic Drugs) study reported that fetal valproic acid exposure was associated with a lower IQ and reduced cognitive abilities across a range of domains at 6 years of age in a dose-dependent manner. The adjusted mean IQ score of children exposed to high-dose (more than 800 mg/d) valproic acid was significantly lower than that of controls by 9.7 points. Exposure to other AEDs, including carbamazepine, lamotrigine, and phenytoin, was not associated with a lower IQ in children.[7]

MGSO4 FOR PREVENTION OF SEIZURE

MgSO4 is the drug of choice for preventing convulsions during pregnancy. MgSO4 is a calcium antagonist and as such could inhibit vascular smooth muscle contraction. MgSO4 is a potent vasodilator, however, its effects in the cerebral circulation are considerably less effective than systemic vasculature. MgSO4 has been shown to protect the BBB, likely through its calcium antagonistic effects in the cerebral endothelium. MgSO4 could prevent recurrent seizure by protecting the BBB. MgSO4 is an NMDA receptor antagonist and thus would act as an anti-convulsant if it were present at a high enough concentration in the brain.[9]

CONCLUSION

AEDs have been associated with MCMs in human pregnancy. The evidence base is variable for each individual agent reflecting a combination of factors including clinical effectiveness, frequency of use in certain types of epilepsy, length of availability and other safety concerns. If antiepileptic drug dosages in pregnant women with epilepsy are adjusted carefully and at frequent enough intervals during pregnancy and the postnatal weeks, the adjustments being guided whenever feasible by plasma antiepileptic drug concentration monitoring, the risk of maternal harm from loss of seizure control or from drug over dosage should be reduced, so long as the pregnant woman complies with the dosage recommendations. Such management is likely to prove more satisfactory if full, or best achievable, seizure control is obtained before pregnancy commences.

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CONFLICT OF INTEREST

Nil

ABBREVIATIONS

AEDs: Antiepileptic Drugs
WWE: Women With Epilepsy
BBB: Blood Brain Barrier
CBF: Cerebral Blood Flow
PRES: Posterior Reversible Encephalopathy Syndrome
EURAP: European Registry of Antiepileptic Drugs and Pregnancy
AAN: American Academy of Neurology
NEAD: Neurodevelopmental Effects of Antiepileptic Drugs)
MCMS: Major Congenital Malformation

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