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ANTIEPILEPTICS AND PREGNANCY: A REVIEW

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ABSTRACT

Epilepsy in a pregnant woman is a serious and potentially life-threatening condition for both mother and child. Most pregnant women with epilepsy will need to take at least one antiepileptic drug. The goal for all concerned is a healthy, seizure-free mother and an undamaged child. However, epilepsy as well as antiepileptic drugs cause some serious effect on the fetus. So, for epileptic women it is important to obtain appropriate information about possibility to have children and about risks connected with their pregnancy. Every physician should be informed about risk to the fetus that is associated with seizures and drugs used for treatment during pregnancy. Drugs used in girls and young women should be chosen with the respect to the future reproduction, because the use of antiepileptic drugs (AED) in women with epilepsy is in fact a balance between seizure control and adverse effects of drugs. The purpose of this review is to provide an update on management of Women with Epilepsy (WWE) prior to and during epilepsy.

Keywords: Epilepsy, antiepileptic drugs, pregnancy, women with epilepsy (WWE)

INTRODUCTION

Epilepsy is the tendency to have recurrent unprovoked seizures. It is universal, with no age, sex, geographical, social class or racial boundaries. Epilepsy imposes a large economic burden on health care systems of countries. There is also a hidden burden associated with stigma and discrimination against the patient and even his/her family in the community, workplace, school and home. Many patients with epilepsy suffer severe emotional distress, behavioral disorders and extreme social isolation.

Epilepsy is one of the most common chronic illnesses encountered by obstetricians, affecting around 1 in 200 women attending antenatal clinics. Epilepsy itself is associated with a risk of giving birth to a malformed child around 25% higher than for pregnant women generally (in whom the risk is 2-3%) and, for women with epilepsy who are taking anti-epileptic drugs, the increased risk is around three-fold. The babies of women with epilepsy (WWE) are also at increased risk of neonatal problems, including hemorrhagic disease of the newborn and 'abstinence syndrome' In addition to these effects of epilepsy and anti-epileptic medication on the progress of pregnancy, the pregnancy may also influence the progress of epilepsy, with an increase in seizure frequency in around a third of women and altered metabolism of anti-epileptic drugs. During pregnancy, the clinician faces the dual challenge of maintaining seizure control, yet minimizing teratogenic risk.

What is epilepsy?

Epilepsy can be defined as "the occurrence of transient paroxysms of excessive or uncontrolled discharges of neurons, which may be due to a number of different causes leading to epileptic seizures". The actual presentation or manifestation differs among individuals,

depending upon the location of the origin of the epileptic discharges in the brain and their spread. A person should only be diagnosed as having "epilepsy" if there are recurrent manifestations i.e. there should be at least two or more unprovoked similar episodes in 24 hours. Hence, the first episode of a seizure is called "single seizure" and not epilepsy.

Prevalence of epilepsy

Approximately 50 million people are affected by epilepsy globally. About 40 million or 80% are assumed to live in developing countries. Multiple studies worldwide indicate that the prevalence of epilepsy globally is in the range of 5 to 8 per one thousand populations.

Risk factors for epilepsy

There are well recognized risk factors for the development of epilepsy. Febrile seizure occur in 2% to 4% of otherwise healthy children younger than age 5 years; however a history of a complex febrile seizure or a neurodevelopmental abnormality or a family history of epilepsy may increase the risk of developing epilepsy by 2% to 4% [(1)]. A history of significant head trauma also is a risk factor. Studies of Vietnam War veterans showed a risk of 50% after a penetrating head trauma [(2)]. Head trauma with loss of consciousness, amnesia or a skull fracture increases the 5 year risk to approximately 2%; however the risk is increased with severe head injuries, with 12% of survivors developing epilepsy [(3)]. Vascular lesions are a significant cause of epilepsy.

Epilepsy develops in 6% to 44% of individuals with arteriovenous malformations [(4)]. Cavernous malformations commonly present as seizures [(5)] and cerebrovascular disease is the major cause of epilepsy in elderly [(6)]. Brain tumours account for approximately 4% of cases of epilepsy [(1)] and seizures is often the presenting feature of brain tumours. CNS infections can also increase the risk of developing epilepsy, particularly in children and in elderly. The risk is further increased with certain types of infection and if there are symptomatic seizures early in the course of infection. For example, in patients with viral encephalitis and early seizures, the risk of epilepsy is 10% by 5 years and 20% by 10 years [(7)]. Degenerative CNS diseases are associated with an increased risk of epilepsy. Alzheimer's disease increases the risk by 10 fold and 10% of long term Alzheimer's disease survivors eventually develop epilepsy [(6)]. Up to 5% of patients with multiple sclerosis develop epilepsy [(8)]. Mental retardation (MR) and cerebral palsy (CP) are important risk factors for the development of epilepsy in children and young adults. Prematurity and birth complications are risk factors for both CP and MR, but pre or perinatal events themselves are not independent risk factors for epilepsy when children with CP or MR are excluded [(9)]. Finally, patients with a first degree relative with epilepsy have a twofold to four fold risk of developing epilepsy [(10)].

Reproductive function and fertility in WWE

Increased rates of sexual dysfunction are reported among both men and WWE. This may arise from both neuroendocrine disturbances related to seizure activity, as well as the alteration of endogenous sex steroid metabolism in the presence of enzyme-inducing AEDs[(11)]. Hypothalamic amenorrhoaea, hyperprolactinemia and premature menopause are over-represented among WWE, thought partly because of interference with normal hypothalamic and pituitary function by tempero-limbic discharges commonly involved in epilepsy [(12)]. An increase in anovulatory cycles and polycystic ovarian syndrome (PCOS) has also been observed in WWE [(12, 13)]. While this may partly relate to disturbance of the Hypothalamic-pituitary-adrenal (HPA) axis, AEDs may also play a role in this [(13)]. Enzyme-inducing (EI) AEDs increase serum sex hormone binding globulin (SHBG) levels, resulting in decreased levels of biologically active estradiol and testosterone. In addition, valproic acid (VPA) is associated with an increased rate of hyperandrogenism, ovulatory dysfunction and

PCOS, particularly among young (<26 years) women [14]. The birth rate was lower in WWE than the population without epilepsy, (hazard ratio 0.83, 95% CI 0.83–0.93) [15]. Differences between treated and untreated women [16] suggesting that while women may have a mild reduction in fertility associated with epilepsy, the use of AEDs does not significantly impact further. Pregnancy has a variable effect on the frequency of seizures. In some women there is no change; up to a quarter of women may experience a reduction in the number of seizures, whilst in up to one third of women their seizure frequency will increase. A study by Hollingsworth and Resnik [17] which included 2385 pregnancies showed increased seizure frequency in 35%, decreased frequency in 15% and no change in 50%. The more frequent the seizures, before conception, the more likely do these increases in frequency during pregnancy. Seizure exacerbation may occur at any time, but is most frequently encountered at the end of the first and at the beginning of the second trimester [18]. The apparently higher risk of seizures among women treated with oxcarbazepine prompts further studies on pharmacokinetic changes of the drugs [19]. Subtherapeutic levels are caused by: (a) Nausea and vomiting leading to skipped doses. (b) Decreased gastrointestinal motility and use of antacids decrease drug absorption. (c) Expanded intravascular volume lowers serum drug levels. (d) Induction of hepatic, plasma and placental enzymes increases drug metabolism. (e) Increased glomerular filtration hastens drug clearance [20]. (f) Non-compliance.

Seizure threshold is lowered by Exhaustion from sleep deprivation and Hyperventilation during labour. Some WWE may experience seizure only during pregnancy which is termed gestational epilepsy; such women would be seizure free between pregnancies. Another subgroup (Gestational onset Epilepsy) may have their first seizure during pregnancy and thereafter may continue to get spontaneous recurrent seizures [21].

Effect of epilepsy on pregnancy

Over 90% of pregnant women with epilepsy have uneventful pregnancies [22]. During labour, there is a three-fold rise of seizure breakthrough due to drug default; lack of sleep, fasting, dehydration and concomitant medication, 1% may have status epilepticus. Nelson and Ellenberg [23] reported an increase in the incidence of pre-eclampsia, perinatal mortality, cesarean delivery and preterm birth among epileptic women, as well as increased incidence of low birth weight, congenital malformations, seizures, mental retardation in Women with Epilepsy. Maternal epilepsy is associated with a two-fold increase in the incidence of congenital anomalies in children born to women with epilepsy. Some of this increase in the incidence of congenital anomalies appears to occur even in the absence of anticonvulsant medication. The conventional drugs i.e. phenytoin, carbamezapine, phenobarbitol, valproate are all appropriate in pregnancy. The main practical issue is the teratogenecity of these drugs. Anticonvulsant therapy does appear to further increase the incidence of congenital abnormalities in children of epileptics, particularly with polypharmacy. In general, the risk of congenital defects is low (2-3%) in overall population of pregnant women which increases to 4-5% in women taking anticonvulsants [24]. Recent pregnancy databases have suggested that valproate is significantly more teratogenic than Carbamazepine and the combination of valproate and lamotrigine is particularly teratogenic [25].

Obstetric complications associated with epilepsy

There is an increased risk of vaginal bleeding, anemia, hyperemesis gravidarum, abruption placentae, eclampsia, premature labour, spontaneous abortions and fetal congenital malformations.

Effect of antiepileptics on pregnancy

The first report of a malformation associated with AEDs was described in a child exposed to

mephenytoin in utero who had microcephaly, cleft palate, a speech defect and an IQ of 60 [(26)]. Infants of mothers with epilepsy after exposure to AEDs in utero are twice as likely to have birth defects as infants not exposed to these drugs. Meador et al reported that the rate of total congenital malformations was significantly higher for polytherapy (9.84%; 95% CI = 7.82, 11.87) than for monotherapy (5.3%; 95% CI = 3.51, 7.09) [(27)]. In addition to the direct effect of AEDs, there may be contribution from toxic AED metabolites, reduced folate availability, hypoxic injury associated with seizures and genetic predisposition [(28)]. Malformation rates in the general population range from 2-3 %. Reports of malformation rates in various population of exposed infants range from 1.25% to 11.5% [(29- 36)]. The precision of risk estimation with any individual AED is imperfect as there is a paucity of controlled data, and an uncertain impact of potential confounders, such as type of epilepsy, seizure frequency, and family history of birth defects, socio-economic factors, nutrition and exposure to additional teratogens [(37)].

Valproic Acid (VPA) – Valproate has been associated with a distinctive pattern of anomalies called "Fetal Valproate Syndrome". This involves poor growth, small head circumference, characteristic facial features, heart defects, cleft lip/palate, and limb anomalies (particularly absent radius). A variety of developmental issues have also been reported, including developmental delay, decreased IQ scores, hyperexcitability, behavior problems, autism spectrum disorders and neurological dysfunction. Numerous small studies have suggested cognitive and language impairment and an increase in autistic spectrum disorder in children who have been exposed to antiepileptic drugs in utero [(38)]. Recent reports suggest that these problems may be highest in children who have been exposed to valproate. Valproate should therefore be avoided in reproductive women wherever possible. When it is unavoidable, the lowest effective dose should be used. It should not exceed 1000 mg/day in divided doses. Breastfeeding is considered compatible with valproate therapy. Valproate concentrations in breastfed babies are low.

Phenytoin -- The primary site of action appears to be the motor cortex where spread of seizure activity is inhibited. It promotes sodium efflux from neurons and tends to stabilize the threshold against hyperexcitability caused by excessive stimulation or environmental changes capable of reducing membrane sodium gradient. This includes the reduction of post tetanic potentiation at synapses. Loss of post tetanic potentiation prevents cortical seizure foci from detonating adjacent cortical areas. Phenytoin reduces the maximal activity of brain stem centers responsible for the tonic phase of tonic-clonic (grand-mal) seizures. The use of phenytoin during pregnancy has been associated with a 2-3 fold increased risk (6-15%) for malformations, including heart defects, microcephaly and cleft lip and palate. A characteristic pattern of abnormalities, called "Fetal Hydantoin Syndrome", has been reported in about 10% of infants born to women who took phenytoin during pregnancy. Features of this syndrome include a unique facial appearance, abnormalities of fingers, toes and nails, growth delay and developmental delay/disability. Also it produces cardiac anomalies such as atrial septal defects and ventricular septal defects.

Diazepam -- Diazepam is prescribed as a tranquilizer, muscle relaxant, preoperative medication, and as an adjunct to anticonvulsant therapy. There is a no consistent pattern of malformations observed in infants exposed to diazepam. Some neonatal behavior problems have been noted in exposed infants.

Phenobarbital -- Chronic use of phenobarbital late in pregnancy has been associated with transient neonatal sedation or withdrawal symptoms in infants. Features seen in these infants include hyperactivity, irritability and tremors. Perinatal or neonatal hemorrhage has been observed occasionally in infants of women

who took phenobarbital late in pregnancy. This has been attributed to drug-induced suppression of the synthesis of vitamin K-dependent clotting factors.

Carbamazepine (CBZ) -- The use of carbamazepine during pregnancy has been associated with an increased risk for spina bifida of up to 1% (1/100), as compared to the general population risk of 1/1000. It is also associated with a unique facial appearance and the underdevelopment of the fingers, toes, and nails. Similarly, malformations have been reported in 6/248 (2.4%) of patients receiving oxcarbazepine in pregnancy [(39)] and 2/44 (4.5%) of patients receiving gabapentin [(40)]. Vigabatrin is associated with acquired visual field defects and its safety is not established in pregnancy [(41)]. The cause of this teratogenecity could be due to direct drug toxicity, drug-induced folate deficiency or genetically determined lack of epoxide hydrolase or free radicals [(42)]. The role of the hepatic mixed function oxidase system may be especially important in conferring teratogenic risk. However, systems such as epoxide hydrolase, glutathione reductase, hyperoxide dismutase and other toxin scavenging systems may be important modifiers that lower the risk. Knowledge is also accumulating on the interactions of AEDs with molecular targets such as histone deacetylase and peroxisomes proliferator activator receptors that may play important roles in teratogenesis [(43)].

Lamotrigine

It remains uncertain whether lamotrigine is associated with an increased risk of facial clefting [(44, 45, and 46)]. However, The North American Pregnancy Register has reported that exposure to lamotrigine in the first trimester may cause an increased risk of oral clefts (a rate of 8.9 per 1000, as compared to 0.37 per 1000 in the reference population) [(47)]. Significant dose related teratogenesis with lamotrigine exceeding 200 mg/day has been reported [(48)]. Lamotrigine clearance increases steadily through to 32 weeks of pregnancy. Plasma concentrations of lamotrigine fall early in pregnancy, so dose increase may be necessary to control seizures. A trough plasma lamotrigine concentration before pregnancy, at the onset of the second trimester of pregnancy and every two months during pregnancy may help to guide any necessary increase in lamotrigine dose. Postpartum, the lamotrigine concentration rises within a few days and prompt dose reduction may be required to prevent toxicity [(49)].

Levetiracetam

There have been small case series suggesting an increase in low birth weight among infants of WWE receiving Levetiracetam [(50)]. There appears to be a substantial increase in clearance during pregnancy and an associated fall of blood concentrations [(51)]. Although Levetiracetam is secreted into breast milk, recent data suggest that the neonatal concentrations are low.

Neurocognitive defects

In addition to structural malformations associated with AEDs, there has been increasing concern regarding the potential adverse effect of AEDs on fetal cognitive development. While structural malformation risk is essentially confined to the first trimester, cognitive effects of AEDs have the potential to impact throughout gestation. Animal studies suggest that these cognitive effects may be mediated by AED-induced neuronal apoptosis [(52)]. Several investigators have reported an increase in educational requirements [(53, 54)], poorer neuropsychological performance and reduced verbal IQ among children exposed prenatally to VPA [(55)].

AEDS and neural tube defect

Valproate and carbamazepine have been independently associated with the development of neural tube defects (NTDs). NTDs are anomalies of central nervous system and its membranes resulting from abnormal development of neural tube. They are classified as either open defects lacking a covering of overlying skin, or closed defects that are covered with skin. Robert and Guibaud [(56)] were the first to make the association

between VPA and CBZ and the development of NTDs. More recent studies have revealed an association between CBZ exposure in utero and NTDs [57, 58, and 59]. Other investigators have identified spinabifida aperta as the specific NTD associated with VPA & CBZ exposure [60].

Pathophysiology of NTDs

NTDs are uncommon malformations occurring in 6/10,000 pregnancies. Spina bifida and anencephaly are the most commonly reported NTD and affect nearly 2500 to 3000 births in the United States each year [61, 62]. The types of NTD associated with AED exposure are primarily myelomeningocele and anencephaly, which are the result of abnormal neural tube closure between the third and fourth week of gestational age. In previous thinking about NTDs, the fusion of the neural tube was visualized as a process in which the lateral edge met in the middle and fused both rostrally and caudally. Recent studies have suggested that there are multiple sites for neural tube closure [63, 64] and that different etiologies may result in different types of abnormality. There are four different sites along the neural tube where neurulation develops. The first is midcervical. The second is at the cranial junction of the prosencephalon and mesencephalon. The third is at the site of the stomodeum. This region fuses in caudal direction only. VPA appears to have species differential effects, being associated with spina bifida in humans and exencephaly in mice [65].

Management of anticonvulsant therapy in pregnancy

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. If a pregnant woman is maintained on the same dose of an anticonvulsant throughout pregnancy, total blood levels of the anticonvulsant will tend to go down during the pregnancy due to a pregnancy related increase in hepatic and renal clearance of the drug and a pregnancy related increase in the volume of distribution of the drug (this effect is least for carbamazepine) [66]. This drop in total blood levels is partially counteracted by the fact that free (and, therefore, active) drug levels may increase due to a normal decrease in the concentration of serum protein that occurs in pregnancy. Some of this reduction is related to the reduction in serum protein in pregnancy, meaning that the total drug concentration is lower, but the unbound (active) concentration is stable. This is particularly relevant for highly protein bound drugs, such as VPA and phenytoin [67, 68]. As noted above, a clinically significant reduction in plasma concentrations of both lamotrigine and oxcarbazepine occurs in pregnancy [69, 70] as well as Levetiracetam [66, 67, and 68]. There is a paucity of data on the pharmacokinetics of the newer AEDs, such as gabapentin, topiramate and zonisamide [67]. Therefore, for any given total drug level there is likely to be freer drug available during pregnancy than there would be in a nonpregnant individual. Because of the difficulty in interpreting serum drug levels of anticonvulsants during pregnancy, it is advisable to check total serum drug levels if available monthly in pregnant women and adjust their dose accordingly. It is best to use the least number of drugs at the lowest dose possible to prevent seizures.

In WWE, the goal of therapy is to maintain seizure control using the lowest effective AED dose. The International League against Epilepsy position paper recommends that drug concentrations be determined during pregnancy [68]. It is recommended that – prior to pregnancy – an individual 'therapeutic level' during a period of optimal seizure control should be determined, which can then serve as a 'target level' for pregnancy [66, 68]. Among patients with good control, serum concentration should be performed each trimester, but more frequent (for example, monthly) levels may be required in patients with complicated epilepsy, breakthrough seizures, significant side effects and those WWE requiring lamotrigine and oxcarbazepine where highly

variable and more clinically significant fluctuations in drug concentration have been observed [66, 68].

Can a woman breastfeed her baby if she is taking AEDs?

All anticonvulsants are excreted in breast milk but levels are exceedingly low and not a cause for concern. Women are encouraged to feed in a secure position. Possible effects of anti-epileptic drugs in breast milk include drowsiness and feeding difficulties with the baby. These are more common with barbiturate anti-epileptic drugs. Other side-effects are rare.

How a WWE be looked after in pregnancy?

The risk of malformation in the baby caused by anti-epileptic drugs is highest during early pregnancy, so counseling before pregnancy is essential. If anti-epileptic drugs are needed, normally the most effective single drug should be given at the lowest possible dose that controls the seizures. To further minimize this risk, high dose (5 mg) folic acid is generally recommended for at least 1 month preconceptually and throughout the first trimester [71]. Enzyme inducing AEDs and valproate are known to interfere with folic acid metabolism [72] and Kjaer et al. reported fewer congenital malformations in women taking AEDs with folic acid, compared to those not given additional supplementation [73]. Dansky et al [74] found significantly lower blood folate concentration in WWE with abnormal pregnancy outcomes. Treatment of mice with folic acid, with or without vitamins and amino acids, reduced malformation rates and increased fetal weight and length in mouse pups exposed to phenytoin in utero [75]. In the general population the utility of folate supplementation in reducing the risk for NTDs is clearly established. Whether risk will be reduced for WWE taking AEDs is unclear. The recommended daily allowances of folate have been increased to 0.4mg/day for non-pregnant women, 0.6 mg/day for pregnant women and 0.5 mg/day for lactating women. The increased folate catabolism during pregnancy, coupled with variation of requirements by individual women has led some to call for higher folate supplementation on the order of 0.5-0.6 mg/day [76]. Women with epilepsy, like all women of child bearing age should take folate supplementation the dosage recommended by Center for Disease Control and Prevention (CDC) but 0.4 mg/day may not be high enough for many women who do not metabolize folate effectively [77]. Stopping anti-epileptic treatment may be appropriate if the epilepsy produces a single type of seizure and the woman has been free from seizures for the previous 2 years and EEG and neurological examination are normal. This must always be discussed with the doctors who look after her epilepsy. Stopping anti-epileptic medications in pregnancy without medical advice can be very harmful to the woman and her baby in the womb if severe seizures occur. All pregnant women with epilepsy should be offered detailed ultrasound scanning for fetal abnormality. The use of enzyme inducing AEDs may induce fetal hepatic enzyme activity culminating in vitamin K deficiency and increased risk of neonatal bleeding and that vitamin K should be administered to such women in late pregnancy to minimize this risk [25]. During the last month of pregnancy vitamin K 10 mg/day by mouth is recommended for pregnant woman on certain anti-epileptic therapies and in such circumstances it is usually recommended that the baby should be given 1 mg vitamin K intramuscularly or intravenously. Maternal oral vitamin K_1, for example 10 mg/day for one month prepartum, has been recommended when enzyme-inducing antiepileptic drugs are prescribed because the drugs may potentially predispose the baby to haemorrhagic disease of the newborn [78].

CONCLUSION

Labour and delivery is a relatively high risk time for seizure recurrence. The reasons for this are multifactorial including poor bioavailability and compliance with AEDs, sleep deprivation, anxiety and hyperventilation in labour. All centers

delivering obstetric care should therefore be mindful of the increased risk of seizure in labour, and manage WWE accordingly [25, 79, and 80].

Most AEDs are compatible with breast feeding. The optimal method of estimating drug exposure is to measure the milk drug concentration and multiply it by the estimated daily intake. Typically, a value 10% of the weight-based therapeutic drug dose is considered safe. The estimated levels for carbamazepine, phenytoin and VPA are 3–5% of therapeutic dose and are considered safe. Estimates for lamotrigine and Levetiracetam are approximately 10% and Gabapentin approximately 12% [81, 82]. During their postnatal stay, WWE and all their maternity care providers should be aware of the risk of postpartum seizures, particularly in the setting of sleep deprivation. Ensuring such women get adequate sleep and attention to medication compliance is of the utmost importance. Although the risk to the infant from maternal seizures is generally low, women with juvenile myoclonic epilepsy are a particular concern, since myoclonic jerks tend to be more frequent in the early morning, often around the time of infant waking [83]. To minimise the risk of harm if a seizure occurs, changing or feeding the baby on the floor is recommended, the use of baby slings should be avoided, stair climbing should be minimised where possible and bathing the baby should be avoided when alone [25,83]. The chances of perinatal problems such as difficult labour, prematurity and low birth weight are a little higher in the case of pregnancies of women with epilepsy than in normal pregnancies. The risk of jaundice during the neonatal period could also be higher in these children. Congenital malformations in newborns are sometimes associated with pregnant women who have been treated for epilepsy with anti epileptic drugs such as phenobarbitol, valproic acid, phenytoin and carbamazepine.

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