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MANAGEMENT OF WOMEN WITH EPILEPSY DURING PREGNANCY

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ABSTRACT

Epilepsy is recognized as the commonest serious neurological disorder in the world. Epilepsy itself is associated with a risk of giving birth to a malformed child. Women with epilepsy experienced several gender related physical and social problems. The pre conception management is cornerstone for epilepsy care in women with epilepsy [WWE]. Preconceptional folic acid supplement is possible effective in preventing major congenital malformations in the new born of wwe taking antiepileptic drugs [AADs]. Approximately 1in 200 women is attending attenatal clinics. The evidence for risks and their limitations are reviewed in this article. The aim of treatment is to avoid convulsive seizures that are harmful for both mother and child while minimising risks for treatment of epilepsy.

KEYWORDS: Women with Pregnancy / Antiepileptic Drgs / Management / Epilepsy / Birth Defects.

INTRODUCTION

Epilepsy is common, with up to 0.5–1% of the population having active epilepsy, one third of whom are women of childbearing potential. There is exposure to antiepileptic drugs (AEDs) in approximately 0.3–0.6% of pregnancies. It is estimated that there are over 2.5 million women with epilepsy (WWE) in India, with up to 52% of them being in the reproductive age group. Women with epilepsy in pregnancy should be seen by obstetricians and neurologists in a multidisciplinary team environment. Obstetricians caring for women with epilepsy need to consider the likely impact of pregnancy on seizure frequency, the potential impact of epilepsy on obstetric outcomes, the role of monitoring AEDs levels, surveillance for congenital malformations, continuation of folic acid supplements and the place of vitamin K supplementation. Women with epilepsy should be encouraged to register in the Australian

Pregnancy Registrar (APR) of AEDs. Since the 1960s there have been numerous case series, retrospective studies and prospective cohorts reporting a variety of adverse effects, including intrauterine growth retardation.

Effects of pregnancy on epilepsy

Hormonal effects

Experimental and clinical studies have shown that seizures are influenced by the female sex hormones estrogen and proges- terone. In general, estrogen lowers the seizure threshold and progesterone elevates it.

AEDs effects

The physiological changes that occur in pregnancy influence the distribution, availability and metabolism of AEDs. Prospective studies have consistently shown an overall reduction in total plasma concentration and also the unbound fraction of AEDs during pregnancy, which normalised shortly after delivery. Recent evidence suggests that the particularly marked reduction in lamotrigine levels during pregnancy can result in aggravation of seizures in some women. Effects on fetal and neonatal anthropometric parameters Minor variations in anthropometric features have been observed in infants of mothers with epilepsy. Low birth weight and reduced length and head circumference have been observed in certain studies. A recent study has shown that infants exposed to AEDs may have increased tendency for minor facial anthropometric variations when compared to normal babies.

Maternal risks

Maternal mortality

There were 13 epilepsy related deaths indirectly related to pregnancy reported in the 2004 confidential enquiry into maternal deaths.

Change in seizure frequency

Pregnancy has a variable effect on seizure frequency. Seizure frequency may remain unchanged or decreases in two-third of WWE, whereas it may increase in others. Seizure frequency may also vary between pregnancies in the same. Prospective cohort studies report an increase in seizure frequency in 15–37% of pregnant women, possibly relating to non adherence to medication or sleep deprivation.

Table. 1: Possible causes of increase in seizure frequency during pregnancy.

Mechanism	Examples
Hormonal	Changes in level of estrogen And progesterone
Metabolic	Increased water and sodium Retention
Psychological	Stress, anxiety related to the Pregnancy or other causes
Pharmacokinetics	Decreases in serum levels of AEDs owing to noncompliance delusions
Physiological	Sleep deprivation and physical strain

Complications of pregnancy: It is uncertain whether WWE have more complications of pregnancy. A recent prospective study of 643 pregnancies in WWE showed that the frequencies of several complications of pregnancy in WWE were comparable with those without epilepsy, except for spontaneous abortions, anemia, ovarian cyst, and fibroid uterus. Nevertheless, several other studies have not demonstrated an excess risk of abortion in WWE. There are conflicting reports regarding the increased risk of nonpreteinuric hypertension, pre-eclampsia, eclampsia, and abruptio placenta in WWE.

Induction of labour, instrumental deliveries and caesarean sections may be more common in women with epilepsy compared with controls. It is unclear if this relates to an increase in medical indications or concern on the part of mothers or their obstetricians.

Implications for fetal and child development

Seizures: The absolute risk from convulsive seizures is unknown and may depend on seizure frequency. Although non-convulsive seizures are believed to be of little risk to the fetus, they have psychosocial and socio-economic consequences for the mother.

Fetal loss: Low birth weight and reduced length and head circumference have been observed in certain studies. A recent study has shown that infants exposed to AEDs may have increased tendency for minor facial anthropometric variations when compared to normal babies.

There is consistent evidence of an approximate two-fold increased risk of spontaneous abortion.

Intrauterine growth retardation: The risk of clinically significant low birthweight or small-for-gestational age children was highly variable, representing up to a two-fold risk compared with control groups, but few results were statistically significant. Much of this higher risk may be associated with the use of polytherapy.

Major malformations: Major malformations are structural defects that require medical or surgical intervention. Those most commonly associated with AED exposure include: congenital heart defects, neural tube defects, urogenital defects (glandular hypospadias) and orofacial clefts. Absolute rates reported vary between 1.25–11.5% compared with a rate of 2–3% in the general population. The risk is highest in the first trimester during organogenesis. A teratogenic role for AEDs is suggested by higher rates of malformation among women with treated epilepsy compared with those that are untreated and polytherapy compared with monotherapy exposure. A dose response effect has been suggested for some AEDs. Evidence for the relative risk of individual AEDs and specific patterns of malformation is limited. Data from malformation birth registries suggest that congenital heart defects and facial clefts are associated with phenytoin, phenobarbital and primidone. Valproate has been associated with skeletal defects such as radial aplasia and urogenital defects such as hypospadias. Studies suggest a 1% risk of neutral tube defect with carbamazepine expousure and a 1-2% risk with valproate expousure.

In 1964, Janz first drew attention to the possible teratogenic effects of AEDs. The first systematic study in English lan- guage was by Meadow in 1968. Since then several fetal syn- dromes such as fetal hydantoin syndrome, fetal ethosuximide syndrome and fetal phenobarbitone syndrome have been de- scribed. The commonly observed malformations may affect cardiovascular system, gastrointestinal system, skeletal and connective tissues, and central nervous system. It had been observed that the malformations observed with different AEDs share much in common and are often indistin- guishable. Hence, they are often referred to as fetal AED syndromes.

Table. 2: Relative risk for congential malformations with exposure to various AEDs in mono or polytherapy.

Antiepileptic drug	Number of pregnancies associated with congenital malformations	RR
Non epileptic controls	2/58	1.0
CBZ	4/14	4.9
PB	1/16	2.4
PHT	5/33	2.2
PRM	3/39	1.0
VPA	6/21	4.9
PHT+PB	2/15	1.8
PRM+VPA	1/13	1.0

CBZ:Carbamazepine, PB:Phenobarbitone, PHT:Phenatoyin, VPA:sodium valproate

Minor malformations: Minor anomalies affect 6 to 20% of infants born to women with epilepsy, which is an approximately two- fold increased rate compared with the general popula tion. Minor anomalies include distal digital and nail hypoplasia, and the craniofacial anomalies including ocular hypertelorism, broad nasal bridge, short upturned nose, altered lips, epicanthal folds, abnormal ears, and low hairline. Many of the craniofacial anomalies are outgrown by age 5 years.

Table. 3: Incidence of malformations in women on AEDs.

System	Malformations	n=243[%]
CVS	TOD, ASD, VSD, PDA, Pulm atresia, single ventricle	66{2.0}
Craniofacial	Cleft lip, cleft palate	59{1.8}
Skeletal	Club foot, hip dislocation	29{0.9}
CNS	Neural tube defects	23{0.7}
GIT	Esoph atresia, omphalocele, hernia	10{0.3}
Gut	Renal agnesia, hydronellphrosis, undescended testis	45{1.4}

Folic acid

Recommendation All women with epilepsy should be advised to take folic acid 5mg daily while attempting to conceive and for at least 12 weeks after conception.

Neural tube defects are among the malformations which occur more commonly in women on anti- epileptic medication, particularly with sodium valproate. It is firmly established that peri- conceptual folic acid (in a dose of 4-5mg/day) is effective in reducing the risk of neural tube defect among mothers at high risk due to having had a previous affected child16. Moreover, animal (mouse) studies have shown that high doses of valproate are associated with altered concentrations of specific folate forms in embryonic tissues and increased incidence of neural tube anomalies. However, human studies demonstrating a protective effect of folate supplementation in women with epilepsy are lacking. While there is a range of views about the actual value of folate as a supplement, it seems to be of benefit for healthy women in preventing malformations. The 2009 American Academy of Neurology and American Epilepsy society guidelines state that data are insufficient to determine whether doses higher than 0.4 mg offer greater protective benefits. In contrast, the American college of Obstetricians and Gynecologists recommend 4.0 mg of folic acid daily for women at risk of having offspring with neural tube defects (including women taking AEDs).

Recent data from the Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study group has suggested that periconceptual folic acid may have a positive effect on mean IQ in infants exposed to AEDs in utero. In this study of 225 children, periconceptual folic acid was associated with higher child IQ at age six (mean IQ 108 vs 101, P = 0.0002). This effect was seen across all AEDs studied (carbamazepine, lamotrigine, valproate and phenytoin). Together with results from studies in the general population showing reduced risk of severe language delay with folic acid supplementation in early pregnancy, and improved measures of verbal communication with preconceptual folic acid at high dose (5 mg daily), these data would suggest that it may be of benefit to continue high dose folic acid supplementation throughout pregnancy.

Haemorrhagic disease of the newborn: To be included in the analysis, studies had to compare the risk of neonatal hemorrhagic complications in new- borns of WWE taking AEDs to newborns of women with- out epilepsy. Hemorrhagic complications were defined as any hemorrhage within 24 h of birth. Studies looking solelyatsurrogatemarkersofbleedingrisksuchascoagu- lation factor levelswere excluded.

The choice of AED is determined primarily by the type of epilepsy. Choosing between AEDs is difficult as data for the relative risks of specific monotherapy regimens are limited. However, there is accumulating evidence of a greater risk with valproate exposure in utero for both major malformations and later development. In women with localisationrelated epilepsy there are many alternative drugs available, such as carbamazepine. For women with idiopathic generalised epilepsy the balance of risks needs careful consideration. Neonatal bleeding has been reported in numerous case series in association with maternal use of enzymeinducing AEDs, such as phenytoin, phenobarbital and carbamazepine. Thus, it was advocated that all women on enzymeinducing AEDs receive oral vitamin K (20 mg/day) from 36 weeks of gestation to delivery. A prospective cohort study5 found no significant risk of neonatal haemorrhage despite lack of oral vitamin K supplementation in mothers taking AEDs, provided that neonates received the standard parenteral injection of 1 mg vitamin K at birth.

Risks of developing epilepsy: Human genetic disorders associated with seizures and genetic epilepsies are rare and account for only 1% of cases of epilepsy. The risk of unprovoked seizures is higher in offspring of parents with epilepsy onset before 20 years of age than in offspring of those with later onset epilepsy (9% versus 3%). Risk is also higher in offspring

of parents with a history of absence seizures (9%) than in offspring of those with other generalised (3%) or partial (5%) seizures. Steroid metabolism is potentiated by enzyme-inducing anticonvulsants. Women taking any of these drugs, requiring antenatal steroid therapy because of a perceived risk of preterm delivery, should receive a steroid regimen providing a total of 48mg (rather than the 24mg advocated for other women). This dose may be delivered as two doses of 24mg betamethasone, 12 hours apart.

Breastfeeding

As a general rule, breast feeding should be encouraged for all the usual reasons. In addition breast feeding may help prevent problems in the neonate resulting from sudden withdrawal of the anticonvulsants to which he was exposed in utero. However, it is essential that the new mother is given adequate opportunity for sleep, as sleep deprivation makes seizures more likely. If the father or another relative is able to take over responsibility for the baby at night this may be in the best interests of the family and in some circumstances breast feeding may not be the best option. Each mother should be given support in her choice of the feeding method which best suits her individual family.

Available sources of guidance for patients and their families and for midwives contains sound advice relating to reducing the dangers to the mother with epilepsy and her baby during feeding and child care and are endorsed by the SOGAP group.

The excretion of AEDs in breast milk is variable, depending mainly on the degree of maternal serum protein binding. Phenytoin, carbamazepine and valproate are only found in low concentrations in breast milk as they are all highly protein bound. In contrast, phenobarbital and primidone reach higher levels as they are less protein bound. Preliminary data suggest that lamotrigine and topiramate may be significantly excreted in breast milk, but no adverse effects have been report.

Management and counseling: Women with epilepsy should be referred for high quality ultrasound scanning to screen for structural anomalies between 18–20 weeks. Prenatal screening using serum alphafetoprotein at 15–22 weeks combined with structural ultrasound scan can identify 95% of fetuses with open neural tube defects. More detailed scanning with fetal echocardiography and imaging of the fetal face may be required. Increased surveillance for intrauterine growth retardation in later pregnancy may be required if the mother's weight gain and fundal growth are not appropriate.

Seizures tend to improve or remain unchanged in nearly two- thirds of WWE. The risk of seizures is higher in the first tri- mester of pregnancy and around delivery time. The policy of the IREP is to avoid any change in AEDs once pregnancy had been confirmed in a WWE. Nevertheless, in cases of polytherapy with multiple drugs, it may be possible to elimi- nate the third, and occasionally the second, AED after retain- ing the AED(s) appropriate for the seizure. It is preferable to keep the total daily dose of VPA below 1000 mg as higher doses have been implicated with an increased risk of NTD. Care should be taken to split the daily dose in to three or four di- vided aliquots in order to avoid high peak levels in the blood. It is important to ensure good compliance with AEDs through- out pregnancy in order to avoid relapse of seizures. The dos- age may have to be increased in some patients in the third trimester, especially if the blood levels (preferably free drug levels) are low. The risk of seizure relapse around the time of delivery is three times more than during the rest of the preg- nancy. The increased risk of seizure relapse is probably related to the lack of compliance, dehydration, prolonged fasting, or effect of concomitant medications. Care should be taken to avoid such provoking factors at the time of delivery.

Management of women with epilepsy: 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. Potential parents should understand that there are no 'safe' antiepileptic drugs in pregnancy. The balance of risks, as presently known, should be explained to them. All risk of harm cannot be eliminated. The general schedule of antenatal check-up should be followed in all WWE. Folic acid supplementation should be initiated as soon as pregnancy is confirmed, if it had not been started in the preconception period. Women with epilepsy should always be delivered in a consultant-led obstetric unit equipped with facilities for maternal and neonatal resuscitation. Treatment of seizures during pregnancy and labour should be managed as in any person with epilepsy, and should be in collaboration with an epilepsy team. Recurrent or single prolonged tonic-clonic seizures can be terminated with sub- buccal midazolam, intravenous lorazepam or rectal diazepam. An increase in seizures in the perinatal period can be treated with clobazam 10 mg twice daily if the mother is able to take oral medication.

Counseling the Family when an Abnormality is

Detected: It is very important to offer counseling to the patient and the family prior to and after undergoing screening procedures. The family would require delicate and detailed

counseling if a serious malformation had been detected. The sensitivity and specificity of the findings are also required to be explained to the family. Care should be taken to explain in simple terms The family needs to be counseled about the need for proper spacing of childbirth from the interest of the mother and baby. Oral contraceptives, especially low estrogen preparations and progesterone implants, may have reduced efficacy when used along with enzyme-inducing AEDs (PHT, CBZ, OXB, and PB). TPM may reduce the ethinyl estradiol level by a different mechanism. In presence of such AEDs, it may be necessary to use oral pills with more than 50 µg of estrogen. Non-enzyme- inducing AEDs such as VPA, LTG, and GBT may not interfere with oral contraceptive pills. Medroxyprogesterone depot injections taken once in 3 months or intrauterine devices can be used as alternate methods of contraception

CONCLUSION

WWE have several special problems related with pregnancy, which need careful attention from the attending neurologists and obstetricians. It is comforting to know that majority of WWE can have safe pregnancy and childbirth. Fetal malfor- mations attributable to exposure to AEDs occur in a small proportion of instances only and appropriate preconception management can probably reduce this risk. In women with epilepsy treated with antiepileptic drugs, there is a better than 90% chance that the child will be normal. The most specific therapeutic dilemma and the highest risk is in women who need to take valproate to control their epilepsy. Most infants whose mothers are taking antiepileptic drugs can be successfully breastfed without complications.

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