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Review Article

Risks and management of pregnancy in women with epilepsy: a review

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ABSTRACT

Women with epilepsy (WWE) face certain challenges during their pregnancy. In the present article an effort has been made to review the information regarding the frequency of seizure in pregnancy, effects of epileptic seizure on fetus, complications during pregnancy and delivery, incidences of fetal congenital malformations and infant development. The article reviews these concerns with special emphasis on management of pregnancy. Recommendations concerning prenatal counselling, anti-epileptic drug management, breast feeding and contraception are also taken up in the later part of the article.

Keywords: Anti-epileptic drugs (AED), Congenital malformation, Epilepsy, Pregnancy

INTRODUCTION

Handling a chronic medical illness in pregnant women can be a tough task that can test a physician's expertise. The decision to treat the patient is the outcome of concern of several incessant factors. This is mainly evident in case of epilepsy, in which the condition itself poses health hazards for both pregnancy and the patient. Hence, physicians often sensibly take decisions while treating a patient, to make sure that the patient gets suitable care while curtailing the threats. "Epilepsy" is a Greek word meaning "to seize upon". In 1870, Hughlings Jackson, a British neurologist defined epilepsy as "...an intermittent derangement of nervous system due to an excessive and disorderly discharge of cerebral nervous tissue on muscles...".

An estimated 0.2% to 0.7% of pregnant female suffer from epilepsy, the most common major neurological complication during the pregnancy. While approximately over 1.5 million women with epilepsy (WWE) in India

are of child bearing age, to meet their needs, managing maternal epilepsy and monitoring the health of developing fetus remains one of the most perplexing and engaging issues for all healthcare professionals.¹ The modern management of epilepsy which combines the use of improved anticonvulsants with a more sympathetic attitude towards the disability encourages the epileptic to marry. Pregnancy in the epileptic condition has therefore, become a more common therapeutic problem and for better outcome it is important for all healthcare professionals to know what curative measures are necessary to control epileptic attack during the gestation. This article reviews the major risks that epilepsy and Anti-Epileptic Drugs (AED's) have for pregnant women with epileptic problem.

PRE-CONCEPTION COUNSELLING

In developing countries where access to obstetrician and neurologist may not be possible, counseling with subsequent assessment and care can be provided by

general practitioners if aware of impact of different AEDS. Since 50% of the pregnancies are unplanned, reproductive issues should be raised and discussed, by healthcare provider once WWE becomes sexually active, to allow informed and well-considered choices. Healthcare professionals must be sensitive to patient's anxieties and be prepared to manage both their seizures and emotional concerns. Women should be reassured that clear majority of pregnancy ends in safe confinement and healthy babies guidelines and recommendations to be discussed with WWE and their partners can be summarized as follows;

- Optimize treatment before conception;
- If AED is needed, use monotherapy;
- Choose the most effective AED for seizure and syndrome;
- Use lowest effective dose; and
- Avoid high peak levels of drug used by using multiple doses or extended release formulations.

IMPACT OF PREGNANCY ON SEIZURE CONTROL

In general, nearly a third of WWE experience increase in seizure frequency while other third experience a decrease in seizure frequency and others have no change in seizure frequency. In European and International Registry of Antiepileptic Drug in Pregnancy (EURAP) study, with 1718 cases showed that 92.7% WWE remained seizure free, 15.9% had improvement in seizure control in second and third trimesters as compared to the first and 17.3% had worst seizure control.²

In an analysis of seven years outcome data from the Australian register of anti-epileptic drugs in pregnancy it was found that epilepsies that were active in the year before pregnancy tend to increase the risk of intra-partum and post-partum seizures.³ The risk of seizure during the pregnancy was 50% to 70% less if the pre-pregnancy year was seizure free and decreased relatively little more with longer periods of pre pregnancy seizure control.

HORMONAL

Estrogens acts as pro-convulsant while progesterone increases seizure threshold making seizure less likely. Estrogens can increase activity at both N-methyl-D-aspartate (NMDA) and non-NMDA glutamate and the net effect manifests as increased excitability.⁴

METABOLIC FACTORS CAUSING INCREASE IN SEIZURE FREQUENCY

Increased levels of circulating estrogens also increase function of P450 enzyme which leads to more rapid hepatic metabolism of anti-epileptic drugs. Physiological changes during pregnancy which have their implications on drug disposition are summarized in Table 1. The metabolism of nearly every epileptic drug increases,

resulting in lower blood levels, in case the adjustments are not made. Maternal plasma concentration of levetiracetam during third trimester is about 40% of baseline concentration without pregnancy, which suggests that therapeutic monitoring can be of value.⁵

Table 1: Physiologic changes during pregnancy: effects on drug disposition.

Parameters	Consequence
Increased total body water and extracellular fluid	Altered drug distribution
Increased fat stores	Decreased elimination of lipid soluble drugs
Increased cardiac output	Increased hepatic blood flow leading to increased hepatic elimination
Increased renal blood flow and glomerular filtration rate	Increased renal clearance of unchanged drug
Altered cytochrome P-450 activity	Altered systemic absorption and hepatic elimination
Decreased maternal albumin	Altered free drug fraction Increased availability of drug for hepatic extraction.

EFFECTS OF EPILEPSY ON PREGNANCY

Ninety percent of the WWE have uneventful pregnancies, but the incidence of obstetrics complications is higher. Spontaneous abortion is also a common event and may complicate up to 20% of pregnancies in WWE, although the data regarding the risk of abortion in WWE is extremely limited and conflicting.² Several complications of pregnancy have been reported to occur more frequently in WWE than in general population. These include: vaginal hemorrhage, placental abruption, pregnancy induced hypertension and intrauterine growth retardation.⁶ Studies comparing still birth rates, found higher rates in infants of mothers with epilepsy (1.3% to 14%) than in infants of mothers without epilepsy. Studies have demonstrated increased rates of neonatal and perinatal deaths.⁷ Data from Kerala registry of epilepsy and pregnancy indicate WWE have not increased the risk complication of pregnancy or caesarian section.⁸

EFFECTS OF EPILEPSY AND AED ON OFFSPRING

These can be classified as fetal risk, Neo-natal problems and long-term concerns.

Fetal Risks

Anthropometric changes

Low birth weight, reduced length and head circumference have been observed in certain studies in WWE on AED. Hvas CL et al. in their study on 193 pregnant WWE

observed that mean birth weight adjusted for gestational age was reduced by 102 gm in children of WWE as compared to women without epilepsy. The weight reduction was most distinct in the children of women who received carbamazepine and oxcarbazepine monotherapy.⁹

Malformations

The major malformations most commonly associated with AEDs exposure include, congenital heart disease, cleft lip/palate, urogenital defects and neural tube defects. WWE treated with AED have an overall 2-3-fold increased risk of congenital malformation as compared to general population.¹⁰ The chance of a minor anomaly with an infant exposed to AED is roughly 2.5 times the risk in general population.

The first generation of AED Phenobarbital (PB) and phenytoin (PHT) are mainly associated with heart defects and facial clefts. Phenytoin (Fetal hydantoin) syndrome most commonly has hypoplastic phalanges, cleft palate, hair-lip, micro cephal, hypertelorism, mental retardation and other cognitive impairment. The second-generation AEDs, Valproate (VPA) and Carbamazepine (CBZ) are primarily associated with spinabifida aperta (valproate), neural tube defects (CBZ), hypospadias (both), radial aplasia (rare but valproate specific) and probably autism-like disorder (valproate).

Fetal valproate syndrome was recognized by DiLiberti et al. The syndrome includes above anomalies which were reported to be very distinctive with a ridged metopic-suture, short-anteverted nose, broad nasal bridge and small mouth with thin upper lip and averted lower lip. Overlapping toes and joint laxity are also common findings. It comprises of learning and behavioral abnormalities. Developmental milestones are often delayed particularly in speech.¹¹ Ornoy et al. studied the effect of carbamazepine monotherapy on forty-seven children and concluded that in utero exposure to carbamazepine results in carbamazepine syndrome, which is characterized by facial dysmorphic features and mild mental retardation. Facial dysmorphic features include short nose, long philtrum, up-slanting palpebral fissures, hypertelorism, epicanthal folds and nail hypoplasia.¹²

The risk of malformation increases with increased dosage of AED specially CBZ and VPA. In a study by Samren, et al, offspring of mothers on valproate with more than 1000 mg/day were at significantly increased risk of MCM, especially NTDs as compared to offspring of those exposed to less than 600 mg/day of valproate. The incidence of malformations in fetus exposed to AED monotherapy is 10.3%, 5% and 6.7% for sodium valproate, phenytoin and PB respectively.^{13,14}

Third generation of AED's consists of a large number of structurally related or different compounds, some of

which have teratogenic activity in pre-clinical animal experiments, but none have sufficient human pregnancy experience to assess their safety when use by pregnant WWE. Most new drugs are first applied in an add-on regime. This implies polytherapy and increases risk of teratogenicity. The U.K. registry reported major malformation rates of 2.3% (1.4-3.7%) for CBZ (n = 700), 5.9% (4.3-8.2%) for VPA (n=572), and 2.1% (1.0-4.0%) for lamotrigine (LTG; n=390), all in monotherapy.¹⁵ There is a difference in malformation rate when lamotrigine is used as polytherapy with valproic acid (10%) or as polytherapy without valproic acid 4.3%. The malformations attributed to lamotrigine monotherapy in international lamotrigine pregnancy registry were esophageal malformation, cleft palate and club foot.⁸ The preliminary results indicate that LTG may have a less teratogenic potential than VPA but several other factors need to be taken into consideration. LTG has lower efficacy against idiopathic generalized epilepsy when compared with sodium valproate.

Nicholson et al. studied 962 patients with idiopathic generalized epilepsy, one year remission was highest (52.1%) for a person on VPA monotherapy and lower for those using topiramate (34.6%) and LTG (16.7%) monotherapy. Patient on LTG experienced increased seizure frequency during pregnancy because LTG is eliminated much faster than during non-pregnant state. Its clearance increases at least two folds during the pregnancy. The concentration of LTG in breast milk is higher than for other AED's.¹⁶⁻¹⁸ Moore et al undertook a clinical study of 57 children with fetal anticonvulsant syndrome and identified several features previously unrecognized or under reported in these syndromes. These include glue ear, connective tissue problems (including joint laxity), ocular and refractive disorders, laryngeal anomalies and autism or autistic spectrum behavioural problems. Developmental delay, particularly speech delay was common. The recurrence risk after a first affected child was high at 55% which may reflect an underlying genetic predisposition.¹⁹

Neo-Natal problems

Hemorrhage secondary to coagulation defects and sedative effect.

Neo-natal hemorrhage

The hemorrhage appears to result from deficiency of vitamin K dependent clotting factors II, VII, IX and X if WWE on Anti-convulsant (CBZ, PHT, PB and primidone) that induce the cytochrome 450 enzyme system

Sedative effect

PB, primidone and ethosuximide can reach concentrations in breast milk that may sedate the infant who should be monitored for signs of poor feeding, lethargy or hypotonia.

Long term fetal outcome

The background risk of developing idiopathic epilepsy in general population is of the order of 0.5% to 1.0%. But this risk is increased four folds in the offspring of WWE.²⁰

Pennell et al, acquired data from several ongoing pregnancy registries, found that cognitive outcome in children of WWE reported an increased risk of mental deficiency, affecting 1.4% to 6.0% of children of WWE compared with 1% of controls.²¹ Eador et al, in a prospective study from 1999 to 2004 observed the

cognitive function at three years of age after fetal exposure to AED's.²²

The results showed that at three years of age children who had been exposed to valproate in utero had significant lower IQ scores than those who had been exposed to another AED's. After adjustment for maternal IQ, maternal age, AED dose, gestational age at birth and maternal preconception use of foliate the mean IQ with various drugs is shown in Table 2. The finding supports the recommendations that valproate should not be used as a first-choice drug in women of child bearing age

Table 2: IQ scores of children at 3 years of age according to in Utero exposure to antiepileptic drugs.

Variable	Carbamazepine	Lamotrigine	Phenytoin	Valproate
Mean IQ (95% CI)	98 (95-102)	101 (98-104)	99 (99-104)	92 (88-97)
Mean difference in IQ from Valproate group (95% CI)	6 (0.6-12.0)	9 (3.1-14.6)	7 (0.2-14.0)	
P value	0.04	0.009	0.04	

MANAGEMENT OF WOMEN WITH EPILEPSY (WWE) DURING PREGNANCY

Early USG to date the pregnancy: When a pregnant WWE initially presents, the gestational age of the fetus must be established with reasonable accuracy. As WWE usually have irregular cycles one cannot rely on last menstrual period alone.

Monotherapy of AED at lowest effective dose should be advised. Frequent smaller doses or extended release preparations are preferred to decrease the peak plasma levels so that fetal exposure can be minimized.

Monitoring of serum AED levels is mandatory during each trimester of pregnancy. Many neurologists recommend monthly anti-epileptic drug levels during pregnancy as changes in the blood levels can occur rapidly. In case of highly protein bound AED free drug levels to be measured whereas, of minimally protein bound drugs total drug level should be obtained. Drug level should be measured immediately before next dose to confirm that the dosing is adequate.

Selenium supplementation in a dose of 200 µg per day may be important to minimize the free radical mediated damage.

Folic acid supplementation in a dose of 5 mg/day is advised for WWE using AED, which should not exceed an oral dose of 5 mg/day but probably a lower dose (0.5 to 1 mg)/day is sufficient. Side effects of folic acid therapy are few but doses of over 5 mg/day could impair seizure control.

PERINATAL DIAGNOSTIC TECHNIQUES

Perinatal diagnostic techniques recommended as:

- Anatomic USG at 11-13 weeks to identify the neural tube defects
- Maternal serum alpha fetoprotein at 14-16 weeks
- Repeat anatomic USG at 16-20 wks. To identify the abnormalities as orofacial clefts, heart defects and caudal neural tube defects fetal echo can also be done at this time.
- USG at 33-34 weeks to monitor the fetal growth.

VITAMIN K SUPPLEMENTATION

If AED used by the mother is an enzyme inducer, the deficiency of vitamin K dependent coagulation factors can occur. This problem should be treated with 20 mg/day of oral Vitamin K beginning at 36 wks. of gestation until delivery or 2 doses of paraneural vitamin K1 10mg at 34 and 36 wks. of gestation. The infant should receive an intramuscular injection of Vitamin K (1 mg at birth). If two of the Vitamin K dependent coagulation factor in the neonate (II, VII, IX and X) are below 5% of normal then fresh frozen plasma should be given.

MANAGEMENT OF WWE DURING LABOR AND DELIVERY

Serum levels of AEDs must be checked and all healthcare providers in the labor room must be informed that the patient has epilepsy. The obstetricians should plan the type of delivery based on the obstetrical indications.

Vaginal delivery is the route of choice. The indications for caesarean section in WWE are shown in Table 3.

Table 3: Indications for caesarean section in WWE.

Elective caesarean section	Emergency caesarean section
Substantial neurologic or mental retardation	Generalized seizures during labor or near term Fetal asphyxia Other obstetric indications
<ul style="list-style-type: none"> Reduced cooperation of the patient for labor 	
Very poor control of seizures	
<ul style="list-style-type: none"> Daily complex partial seizures Weekly tonic colonic seizures 	
Uterine inertia	Failure of induction of labor Heavy sedation for patient
<ul style="list-style-type: none"> Failure of induction of labor Heavy sedation for patient 	

Labor management should be based on routine standards of care. Epidural analgesia is generally preferred. Pethidine should not be used as it is metabolized to norpethidine which is epileptogenic. Anti-epileptic drug should be administered as per schedule. If oral absorption is erratic, intravenous route is preferred especially in case of PHT and valproic acid. In case of carbamazepine extended release formulation can be used. Benzodiazepines should be avoided as it leads to neonatal cardiac and respiratory depression. Close monitoring of mother and neonate is mandatory. If breakthrough seizure occurs it is treated with IV 1-2 mg of diazepam. If not controlled, then load phenytoin 1 gms is recommended over one hour. Any female having seizure during the labor must be closely observed for next seventy-two hours.

Status epilepticus

Status epilepticus can occur in 1-4% of women in labor. Fetal heart rate must be examined and Eclampsia should always be ruled out. General guidelines for managing SE can be followed in such instances.

Postpartum management

The AED need to be followed using the same third trimester dosage in first three months of post-partum period.

Monitoring of AED levels

AED monitoring should continue 6-12 weeks postpartum as normal metabolism returns 2-3 months after delivery. Any increase in drugs during pregnancy will need to be decreased slowly to pre-pregnancy doses over 3-4 weeks

to avoid toxicity. An exception to this is lamotrigine, its metabolism returns back to normal within a few weeks requiring a more rapid adjustment of the doses.¹⁷

Breast feeding

Breast feeding should be encouraged as the benefits far outweigh the disadvantages. Feeds may be given before women take her AED doses. Most AED's tend to cross into breast milk (Table 4) including the neogeneration AED.^{5,17,18,23}

Table 4: Anti-epileptic drugs in breast milk as a proportion of blood levels.

Drug	Proportion appearing in breast milk
Valproate	<10%
Phenytoin	20%
Carbamazepine	40%
Phenobarbitone	50%
Primidone	80%
Lamotrigine	61%
Topiramate	86%
Oxcarbazepine	80%

Contraception

Enzyme inducing AED (PHT, CBZ, OXB and PB) stimulate activity of cytochrome P450 (CYP) and glucuronyl transferases (GT), hence, OCPs especially low estrogen preparation and progesterone may have reduced efficacy when used along with these drugs. It is recommended that a higher dose of estradiol be considered (>50 µgms). Oxcarbazepine, LTG, felbamate and at dosages ≥200 mg per day of topiramate, stimulate the metabolism of oral contraceptive steroids, possibly by tissue selective stimulation of CYP3A4.²⁴ A spermicidal gel or a barrier method could be used in addition to the pill to increase the level of protection. Anti AED drug effect on hormonal contraceptive agents are shown in Table 5.

Table 5: Anti-epileptic drug effects on hormonal contraceptive agents.

Lowers hormone levels	No significant effect
Phenobarbital	Ethosuximide
Phenytoin	Valproate
Carbamazepine	Gabapantin
Primidone	Pregabalin
Topiramate	Levetiracetam
Oxcarbazepine	Zonisamide
Felbamate	Tiagabine
Lamotrigine	Vigabatrin

Intra-muscular medroxy progesterone (Dipoprovera) are other recommended options, injections be given every 10 rather than 12 weeks to women who are receiving

enzyme inducing AED's.^{23,25} Prolonged use of AED along with medroxyprogesterone can result in bone loss. Sub-dermal levonorgestrel (Norplant) can be used but cases of contraceptive failure are high in women taking enzyme inducing AED.

- Mirena, releases levonorgestrel directly into uterine cavity, is found to be an effective contraceptive.
- Emergency contraceptive pill should contain 3 mg of levonorgestrol as compared to 1.5 mg in case of non-pregnant patient without epilepsy.
- Data on possible interaction between AED's and progesterone only pills, injections, patches and implants are very sparse.
- There is no contraindication for postpartum sterilization.

HORMONAL THERAPIES HAVE BIDIRECTIONAL INTERACTIONS WITH AED'S

Lamotrigine has been shown to have its levels reduced by addition of combined contraceptive steroids. Interestingly interaction follows a cyclic pattern with a marked decrease in LTG level during 21 days of estrogenic pill and a twofold rebound increase in AED concentration during pill free week. Other AEDs eliminated fully or partly by glucuronidation, such as valproate and possibly Oxcarbazepine could also show major changes in clearance following prescription offer combined contraceptive steroids. The drug interactions are unpredictable as they can be influenced by other drugs for example Co-medication with valproate appears to reduce or to prevent the increase in lamotrigine clearance caused by oral contraceptives.¹⁷

While additional exploration is undoubtedly desirable, there is also evidence that existing knowledge is not being effectively incorporated into healthcare.²⁶ National-level guidelines are required for treatment of epilepsy in women, which can handle a range of issues. Epilepsy causes disadvantages for women with epilepsy in pregnancy. While treating the pregnant epileptic woman, the potential harm of epilepsy to both mother and fetus itself must be considered against the potential harm of drug treatments.²⁷

CONCLUSION

Today, the majority of women with epilepsy can conceive and bear normal, healthy children. Some are direct results of seizures, some are due to drug treatment and some are secondary handicaps because of stigmatization. Combined efforts of attending neurologist and obstetricians with appropriate pre-conceptional management, improved diagnostic techniques and host of effective anti-epileptic drugs (AED's) vastly improves epilepsy management and reduce risks to the offspring. Moreover, the women with epilepsy who are pregnant must take part in the pregnancy registry, so that,

particularly with the new anti-seizure medications, information regarding their use can be used to help them.

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