REVIEW ARTICLE

Pregnancy with Epilepsy

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There are special problems in the management of women with epilepsy related to their role in reproduction, which starts at menarche and continue until after menopause.

Epilepsy is one of the most frequently encountered neurological disorders in pregnancy.(1) Approximately, 0.5-2.0 percent of the population is affected; complicating 1 in 200 pregnancies.(2-3)

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. The word epilepsy is derived from Greek word meaning 'to seize upon'. The preferred terminology suggested in 1981 by the International League Against Epilepsy(4) is shown below :

The International Classification of Epileptic Seizures

I. Partial Seizures

A. Simple partial seizures (consciousness not impaired)

1. With motor signs.
2. With sensory symptoms.
3. With autonomic symptoms.
4. With psychic symptoms.

B. Complex partial seizures (impaired consciousness)

C. Partial seizures evolving to secondary generalized seizures

II. Generalized Seizures

A. 1. Absence seizures

2. Atypical absence seizures

B. Myoclonic seizures

C. Tonic seizures

D. Tonic clonic seizures

III. Unclassified Seizures

The treatment of epilepsy with modern antiepileptic drugs (AED) is very effective, with as many as 50% of the patients being seizure free. Unfortunately, evidence suggests that optional standards of care are frequently not achieved in pregnant women, both preconceptually and antenatally.(5) To compound these problems, approximtely 50% of all pregnancies are unplanned.(6-7) Thus, reproductive issues should be raised and discussed, once the woman with epilepsy (WWE) becomes sexually active.

Effect of Pregnancy on Epilepsy

Seizure frequency : Hollingsworth and Resnik(8) reviewed studies including 2385 pregnancies and found 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 increase 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 begining of the second trimester(9). Increased seizure frequency is often associated with subtherapeutic anticonvulsant levels or a lower seizure threshold or both. The apparently higher risk of seizures among women treated with oxcarbazepine prompts further studies on pharmacokinetic changes of the drugs.(10)

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

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increases drug metabolism.

(e) Increased glomerular filtration hastens drug clearance.(11)

(f) Non-compliance.

Seizure threshold is lowered by

(a) Exhaustion from sleep deprivation.

b) Hyperventilation during labour.

Gestational Epilepsy: 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 spotaneous recurrent seizures(12).

Effect of Epilepsy on Pregnancy : Over 90% of pregnant women with epilepsy have uneventful pregnancies(13). 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 and vigorous treatment should be undertaken as seizures cause fetal asphyxia and bradycardia.

Nelson and Ellenberg(14) 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 (WWE)

The conventional drugs i.e. phenytoin, carbamezapine, phenobarbitol, valproate are all appropriate in pregnancy. The main practical issue is the teratogenecity of these drugs. 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 (15). Recent pregnancy databases have suggested that valproate is significantly more teratogenic than carbamezapine, and the combination of valproate and lamotrigine is particularly teratogenic.(16)

Teratogenecity of main anticonvulsants:

1. **Phenobarbitone:** Probably no rise in malformation rate.
2. **Phenytoin:** Orofacial clefts, congenital heart defects, dysmorphic facial features, fetal hydantoin syndrome.
3. **Carbamazepine :** Craniofacial defects, finger nail hypoplasia, developmental delay.
4. **Valproic acid:** Neural tube defects.

The cause of this teratogenecity could be due to direct drug toxicity, drug-induced folate deficiency (16) or genetically determined lack of epoxide hydrolase or free radicals (17). The role of the hepatic mixed function oxidase system may be specially important in conferring teratogenic risk.However, system such as epoxide hydrolase, glutathione reductase, hyperoxide dismutase and other toxin scavenging systems may be imporant modifiers that lower the risk. Knowledge is also accumulating on the interactions of AEDs(Anti Epileptic Drugs) with molecular targets such as histone deacetylase and peroxisomes proliferator activator receptors that may play important roles in teratogenesis (17).

General Management : First and foremost, it should be determined whether a woman of childbearing age requires antiepileptic drugs, as far as possible monotherapy should be the aim.

- Diet before conception should contain adequate amounts of folate.(18)
- Supplementation of vitamin-K in pregnant women receiving AEDs prevent haemorrhagic disease in the newborn.(19)
- Free or plasma levels of AEDs should be regularly checked.
- Ultrasonography at 18-22 weeks to rule out major congenital malformations and at 22-24 weeks to detect oral clefts and heart anomalies.

Breast Feeding : 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.

Postpartum Contraception: should be discussed. Co-administration of oral contraceptives and AEDs may cause breakthrough bleeding and contraceptive failure because these induce hepatic P450 microsomal enzymes and increase in estrogen metabolism. American College of Obstetricians and Gynecologists recommends that oral contraceptives containing 50

microgram of estrogen should be used (20). Barrier method and intrauterine contraceptive device are preferable methods.

Newer Anticonvulstants: Gabapentin, lamotrigine, triagabine, topiramate and vigabatrin. These can be used as add-on therapy for patients with intractable seizures (21). The newest generation of AEDs have demonstrated teratogenic effects in preclinical animal experiments with the possible exception of lomotrigine. None of the agents has been sufficiently tested during human pregnancy to assess safety or teratogenicity (22).

To conclude, WWE who become pregnant should be cared for by a multidisciplinary team of general practitioners, neurologists, obstetrician and neonatologist. Hence, efforts can be made to optimise pregnancy outcomes.

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