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Pregnancy with Epilepsy

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Abstract **Review Article**

Epilepsy (Seizure disorder) is one of the most common neurological conditions encountered in pregnancy. The management of epilepsy during pregnancy is quite challenging. The goal of treatment is optimal seizure control with minimal or no in-utero fetal exposure to AEDs in order to minimize the risk of teratogenicity.

Keywords: Epilepsy, pregnancy, seizure, teratogenicity.

INTRODUCTION

Epilepsy is one of the most common neurological conditions encountered in pregnancy, with a prevalence of 0.5 - 1% [1]. About 30% of women with epilepsy are in the reproductive age group [1]. Effect of pregnancy on seizure frequency is a matter of controversy; almost one-third pregnant patients with epilepsy may show an increase in frequency, while the remaining patients show a decrease or no change. However, if epilepsy is under control prior to pregnancy, there is reduced risk of worsening during pregnancy [2]. The risk of death is increased manifold in pregnant women with epilepsy as compared to those without it, especially those among poorly controlled seizures [3]. The risk of major congenital malformation in the fetus is increased in patients taking antiepileptic drugs (AEDs) during pregnancy. Exposure to sodium valproate and certain other AEDs may also adversely affect the neurodevelopment of the newborn in the long term. Maternal concerns regarding the effects of AEDs on the baby may lead to discontinuation or reduction in the dose of the AEDs, thereby increasing the woman's risk of seizures and SUDEP (sudden unexpected death in epilepsy) [4]. Also, the concentrations of most AEDs reduce during pregnancy and this may increase seizure frequency [5-7]. Seizure deterioration and AED exposure in pregnancy have an enormous impact on the life of the mother.

DEFINITION

Epilepsy is clinically defined as a heterogeneous disorder characterized by recurrent (two or more) unprovoked seizures. A seizure is a brief and paroxysmal disorder of cerebral function due to sudden, abnormal and hyper-synchronous neuronal activity in the brain with or without loss of consciousness [8].

Etiologies of epilepsy include:

- Intracranial diseases like head trauma, cerebral infections, cerebral tumors and cerebrovascular accidents
- Biochemical abnormalities like hypoglycemia, hyperglycemia, hyponatremia, hypocalcemia, uremia etc.
- Alcohol- and other drug withdrawals
- Connective tissue disorders
- Idiopathic

If no underlying cause is found after detailed evaluation, the epilepsy is termed as idiopathic and its diagnosis should be one of exclusion [8].

Classification (Table 1) [9]

Broadly, seizures can have focal-onset, generalized-onset or unknown-onset. In focal-onset seizure (previously known as partial seizure), the seizure activity starts focally in the cerebral cortex and affects a correspondingly localized area of neurological function. In focal-onset aware seizure (simple partial), cognitive function is preserved and recovery is rapid. The seizure starts in one region of the body, producing tonic/clonic/myoclonic movements. The seizure activity may also manifest as sensory/autonomic/psychological dysfunction. Whereas, a focal-onset impaired awareness seizure (complex partial) is often preceded by an aura

and followed by impaired cognition manifested by sudden behavioral arrest or motionless stare. Involuntary movements such as picking motions or lip smacking are common.

In generalized-onset seizure, the seizure activity appears abruptly and rapidly involves neuronal networks in both the cerebral hemispheres. It is always associated with cognitive impairment. In a generalized tonic-clonic seizure, loss of consciousness is followed by tonic contractions of the muscles and rigid posturing, and then by clonic contractions of all extremities while the muscles gradually relax. Return to consciousness is gradual, and the patient may remain confused and disoriented for several hours. Absence seizure is a type of generalized-onset seizure that manifests as a brief loss of consciousness without muscle activity followed by immediate recovery of consciousness and orientation.

Table 1: International League against Epilepsy 2017 Classification of Seizure Type

Focal Onset (Aware/Impaired Awareness)	Generalized Onset	Unknown Onset
Motor Automatisms Tonic Clonic Myoclonic Atonic Hyperkinetic Epileptic spasms	Motor Tonic-clonic Tonic Clonic Myoclonic Atonic Epileptic spasms	Motor Tonic-clonic Epileptic spasms
Non-motor Autonomic Behavior arrest Cognitive Emotional Sensory	Non-motor (absence) Typical Atypical	Non-motor Behavior arrest

Source: Epilepsia, 58(4): 512-521, 2017, Wiley Periodicals, Inc

Preconception

Women on AEDs should be informed regarding increased risk for fetal malformations as the commonly used AEDs (carbamazepine, phenobarbitone, phenytoin and valproic acid) cross the placenta and hence can affect the fetus. Valproic acid carries the greatest risk; especially for neural tube defects and poor cognitive development [10]. Higher malformation rates are reported among children exposed to phenytoin, carbamazepine, phenobarbitone and topiramate in-utero in first trimester as compared to those who are unexposed to AEDs (Table 2) [11]. The risk for fetal malformation increases manifold if multiple agents are required. The risk is comparatively lower with newer AEDs like levetiracetam, oxcarbazepine, gabapentin and lamotrigine. These drugs are considered relatively safe in pregnancy [11]. Folic acid supplementation with 0.4 mg is started at least 1 month before conception. The dose is increased to 4 mg when the woman taking antiepileptic medication becomes pregnant. These medications are adjusted with a goal of monotherapy using the least teratogenic medication. If this is not feasible, then attempts are made to reduce the number of medications used and to use them at the lowest effective dose. Medication withdrawal should be considered if a woman satisfies the following criteria: (1) seizure free for 2 years or more, (2) displays a single seizure type, (3) has a normal neurological examination and normal intelligence, and (4) shows electroencephalogram (EEG) results that have normalized with treatment [12].

Table 2: First trimester antiepileptic monotherapy and associated major malformation risk

Antiepileptic Drug	Malformation rate (%)
Unexposed	1.1
Lamotrigine	2.0
Carbamazepine	3.0
Phenytoin	2.9
Levetiracetam	2.4
Topiramate	4.2
Valproate	9.3 (contraindicated)
Phenobarbitone	5.5
Oxcarbazepine	2.2
Gabapentin	0.7
Clonazepam	3.1

Source: Hernandez-Diaz S, Smith C, Shen A, Mittendorf R, Hauser W, Yerby M, *et al,* Comparative safety of antiepileptic drugs during pregnancy. Neurology 2012; 78: 1692

Epilepsy during Pregnancy

Epilepsy should be well controlled before conception by making necessary dose adjustments and selecting the optimal therapy for patients. Seizure control is the main priority during pregnancy as higher frequency of seizures has been reported in 20-30 percent of pregnant women. Greater seizure frequency is associated with decreased and thus sub-therapeutic

serum levels of AEDs, a lower seizure threshold, or both [4].

Numerous pregnancy-associated alterations can result in sub-therapeutic serum levels of AEDs which include [5-7].

- Vomiting
- Slower gastrointestinal motility
- Antacid use that reduces drug absorption
- Pregnancy associated increase in plasma volume
- Induction of hepatic enzymes such as cytochrome oxidases
- Presence of placental enzymes that metabolize drugs
- Increased glomerular filtration that accelerates drug clearance
- Fall in Albumin levels in pregnancy leading to lower total drug levels

These changes reverse back in the post-partum period. Some women discontinue AEDs due to teratogenicity concerns. The seizure threshold can also be affected by pregnancy-related sleep deprivation and by hyperventilation and pain during labor.

Complications during Pregnancy

Women with epilepsy have an increased risk of pregnancy complications including [13, 14]

- Spontaneous abortion
- Placental abruption
- Preeclampsia
- Oligohydramnios
- Fetal-growth restriction
- Preterm birth
- Still birth
- Cesarean delivery
- Post-partum hemorrhage

Some studies have reported a significantly higher maternal mortality in women with epilepsy. Post-partum depression rates are also higher in epileptic women. Exposure to AEDs increases the risk of osteopenia and osteoporosis due to alteration in bone metabolism. Increase in the fracture risk is due to seizures and osteoporosis. It is important to prescribe prophylactic calcium and vitamin D to patients on AED and to counsel them on good bone health practices [14].

Embryofetal Malformations

Fetus of an epileptic mother on anticonvulsant therapy has a greater risk for congenital malformations. Monotherapy is associated with a lower risk of congenital malformation as compared to treatment with multiple agents. Thus, if necessary, increasing monotherapy dose is initially preferable to adding another agent. AEDs that are folic acid antagonists such as phenytoin, phenobarbitone, carbamazepine, and primidone, increase the risk of neural tube, orofacial, cardiovascular, and urinary tract defects, which can be minimized by optimal use of folic acid [15]. Teratogenic effects of common AEDs are summarized in Table 3 [16-19].

Table 3: Teratogenic effects of common AEDs

Antiepileptic Drug	Abnormalities described
Valproate	Neural tube defects, cleft lip/palate/both, cardiac anomalies, neuro-developmental delay
Phenytoin	Fetal hydantoin syndrome – craniofacial anomalies, fingernail hypoplasia, growth deficiency, developmental delay, cardiac anomalies, cleft lip/palate/both, coagulopathy
Carbamazepine, Oxcarbazepine	Spina bifida, mild mental retardation, typical facial dysmorphic features - upslanting palpebral fissures, epicanthic folds, micrognathia, broad nasal bridge, high arched palate/cleft palate (Carbamazepine syndrome)
Phenobarbitone	Cleft lip/palate/both, cardiac anomalies, uro-genital defects, neural tube defects
Lamotrigine	Increased risk for clefts (cleft lip/palate/both)
Topiramate	Cleft lip/palate/both
Levetiracetam	Theoretical – skeletal abnormalities, impaired growth in animals

Management

Guiding Principles: The major goal is seizure prevention. For this, treatment for nausea and vomiting is provided, seizure-provoking stimuli are avoided, and medication compliance is emphasized. AEDs with the lowest malformations rates should be used for treatment during pregnancy. The fewest necessary anticonvulsants are given at the lowest effective dosage for seizure control. Monitoring serum concentration of AEDs may be unreliable in pregnancy because of altered protein binding. Drug levels may be most informative if measured following seizures or if non-compliance is suspected [5, 6].

It is mandatory to supplement with 0.4 mg of folic acid in women with epilepsy before conception to reduce the risk of major congenital malformation [15]. Levetiracetam is generally considered a safe option for women of childbearing age. Oxcarbazepine is also considered safe in these patients [10, 11]. Lamotrigine, carbamazepine, and phenytoin levels change significantly during pregnancy due to their increased clearance and can lead to an increase in the seizure frequency. Monitoring of serum concentrations of these drugs should be considered. Valproate must be avoided for seizure control in women of childbearing age to

avoid malformations in fetus and to prevent learning disabilities. Carbamazepine and lamotrigine seem comparatively safer options, but lamotrigine is associated with the pharmacokinetics changes in drug levels during pregnancy and can lead to breakthrough seizures. Carbamazepine is the first choice of drug in focal seizures [10-12]. Despite the small increase in the risk of fetal malformations associated with AEDs, women should be encouraged to strictly adhere to treatment during pregnancy because the potential harm of uncontrolled seizures on the mother and fetus is considered greater than the teratogenic effects of AEDs. Dosage of commonly used AEDs is shown in Table 4 [8].

Table 4: Dosage of commonly used AEDs

Antiepileptic Drug	Typical Dosage; Dose Interval
Carbamazepine	600-1800 mg/d; bid
Clonazepam	1-12 mg/d; od-tid
Gabapentin	900-2400 mg/d; tid-qid
Lamotrigine	150-500 mg/d; bid
Levetiracetam	1000-3000 mg/d; bid
Oxcarbazepine	900-2400 mg/d; bid
Phenobarbitone	60-180 mg/day; od-tid
Phenytoin	300-400 mg/day; od-tid
Topiramate	200-400 mg/day; bid

Source: Harrison's Principles of Internal Medicine. 19th Edition. McGraw-Hill Education

For women taking AEDs, a targeted ultrasound between 18 and 20 weeks is recommended to search for fetal anomalies. If seizures recur, a short acting benzodiazepine should be given. AEDs should be continued during labour. Seizures during labour can cause fetal hypoxia. Most of the patients with epilepsy can have a vaginal delivery, and the mode of delivery can be decided according to obstetric indications. Cesarean section may be needed in refractory status epilepticus [15].

The newborn should be thoroughly examined for any abnormality. Enzyme inducing drugs like phenytoin, carbamazepine, oxcarbazepine, topiramate, phenobarbitone and primidone cause a transient and reversible deficiency of Vitamin K dependent clotting factors in almost 50% of newborn infants. Although neonatal hemorrhage is uncommon, the mother should be treated with oral vitamin K (20 mg/day, phylloquinone) in the last 2 weeks of pregnancy and the neonate should receive injection Vitamin K intramuscular (1 mg) at birth to prevent coagulopathy [20, 21]. Breast feeding is not contraindicated. Almost all AEDs cross into breast milk; and data regarding the safety of various AEDs are limited [22]. The amount of AEDs transferred through breast milk is in smaller quantities as compared to the levels exposed in utero. But newborns do not have a fully developed drug-eliminating mechanism; hence, there can be an accumulation of AEDs. However, no obvious deleterious effects have been reported [23, 24].

Contraception

Combined oral contraceptive pills (OCPs) should be avoided as they have interaction with AEDs such as carbamazepine, phenytoin, phenobarbitone and topiramate which can significantly reduce the efficacy of OCPs via enzyme induction and other mechanisms. IUCDs or DMPA can be used in women on AEDs [7].

Status Epilepticus

Status epilepticus is defined as seizure activity that is ongoing for more than 30 minutes or recurrent seizures without full recovery of consciousness between episodes. Initial measures directed at avoiding injury, maintaining airway, breathing and circulation should be initiated immediately. AEDs like IV benzodiazepine (Lorazepam 0.1 mg/kg or Midazolam 0.2 mg/kg) followed by IV Phenytoin (20 mg/kg at a rate of not more than 50 mg/min) or IV Levetiracetam (20-30 mg/kg) should be administered. Ventilation and Pentothal sodium may be necessary if anticonvulsants fail to control seizures [6, 8]. Complications of status epilepticus in pregnancy include preterm labour, premature rupture of membranes (PROM), abruption placenta, fetal distress and fetal death [13, 14].

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