Epilepsy and Pregnancy

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Scope of the Problem

- In U.S. 1.1 million women with epilepsy are in their active reproductive years
- Epilepsy affects 0.5 to 1% of pregnant women.
- Most frequently encountered neurologic condition in obstetric practice after migraine
- 80% of pregnant women with epilepsy use antiepileptic drugs

Epilepsy and Pregnancy

- Interaction between disease and pregnancy
- Teratogenic risks of Antiepileptic Drugs (AED)
- Management guidelines

Seizure Classification

- Generalized Seizures
  - Absence
  - Tonic
  - Clonic
  - Tonic-Clonic
  - Myoclonic
  - Atonic

- Focal Seizures
  - Simple Partial
  - Complex Partial
  - Secondary Generalized

Antiepileptic Drugs

**Traditional**
- Ethosuximide
- Valproate
- Phenobarbital
- Carbamezapine
- Mysoline
- Phenytoin

**Newer**
- Gabapentin
- Lamotrigine
- Topiramate
- Tiagabine
- Levetiracetam
- Oxcarbazepine
- Zonisamide

LaRoche et al JAMA 2004
Older reports: up to 75% of women experience increased seizure frequency

Recent reports: 15% of experience reduced seizure control

Possible risk factor: High seizure frequency antedating pregnancy

Contributing Factors

- High levels of estrogen
- Increased nausea and vomiting
- Changes in plasma volume
- Altered gastric motility
- Altered protein binding
- Increased metabolic capacity of the maternal liver
- Placental/Fetal Metabolism
- Poor compliance
- Increased life stressors

Seizures in Pregnancy

- Profound alterations in maternal acid-base equilibrium with grand mal seizure
- Maternal serum lactate concentration may rise 10 fold, pH drop as low as 6.9
- Changes in maternal acid-base equilibrium rapidly mediated through placenta to fetus

Tonic-clonic convulsion

- Blood pressure elevated
  - Redistribution of blood flow to brain and muscles, and away from visceral organs
  - Increased intra-abdominal pressure reduces uterine circulation further
Maternal Trauma from Seizure activity
- Term with grand mal seizure
- Fracture of left acetabulum
- Subsequent seizure resulted in right acetabular fracture and fracture of left proximal humerus

Olesen J et al. Ugeskr Laeger 1998

Maternal Mortality
- In U.K. 1985-1999: 1000 deaths from 11 million pregnancies
- 50 of these deaths were to women with epilepsy (WWE)
- Most of these deaths seizure related
- Epilepsy third most common cause of indirect death in pregnancy (behind cardiac deaths and stroke).


Fetal Consequences
- Bradycardia
- Acidosis
- Abruption
- Stillbirth

Single brief tonic-clonic seizure
- Depression of fetal heart rate for more than 20 minutes

Teramo et al. J. Perinat Med 1979

Complex partial seizure during labor
- Prolonged uterine contraction and 3.5 minutes fetal bradycardia

Nei et al. Neurology 1998

Recurrent maternal epileptic seizures
- Fetal intracranial hemorrhage and hydrocephalus

Ohba et al. J Mat-Fet Invest 1998
**Status Epilepticus**
- One seizure that lasts 30 minutes or more OR a series of very closely spaced seizures, without regaining consciousness

- Up to 1.8% incidence in pregnancy
- 30-50% risk of fetal death
- Risk of maternal trauma, aspiration, brain damage and death
- Higher incidence during the third trimester

**Epilepsy: Perinatal Complications**
- Preeclampsia
- Maternal hemorrhage
- Placental abruption
- Cesarean delivery
- Preterm delivery
- Intrauterine growth restriction
- Microcephaly and mental retardation
- Congenital malformations
- Perinatal mortality

**Preeclampsia and hemorrhage double unmatched control group, and increased risk of preterm labor**

- Increased risks of stillbirth, microcephaly and mental retardation
  *Nelson and Ellenberg. Neurology 1982*

- 204 births to epileptic mothers to 612 unmatched controls - 2.8 fold risk low birth weight, 3.7 fold risk low APGAR scores or asphyxia
  *Yerby et al. Epilepsia. 1985*

**Population based cohort study in Norway 1995-2005**
- 2,805 WWE vs. 362,302 without epilepsy

- WWE on AED
  - Mild preeclampsia (1.3-2.4)
  - Gestational Hypertension (1.0-2.2)
  - Bleeding (1.1-3.2)
  - PTD <34 weeks (1.1-2.0)

- No difference for WWE not on AEDs
  *Borhen et al. BJOG. 2009*
180 pregnancies in WWE & 150 matched controls
  - No difference
    - Preeclampsia, Preterm labor, Vaginal bleeding, Perinatal mortality
      

51 WWE and 50 unmatched controls
  - No difference
    - Toxemia, Birth weight, Prematurity
      
      *Watson and Spellacy. Obstet Gyneco 1971*

- **Women with Epilepsy taking AEDs**
  - No substantially increased risk
    - Cesarean delivery or Abruption
  - Possible increased risk
    - Preterm labor and delivery for epileptic women who smoke
    - SGA
    - Apgar <7 at one minute

  *Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society 2009*

- **Largely retrospective literature**
  - With or without matched controls
  - Pregnancy and birth registry data to identify pregnancies complicated by epilepsy
  - Variable study duration and follow-up
  - Variable seizure control
  - Limited information on confounding variables
    - Maternal age
    - Social status
    - Genetic background
    - Other diseases or exposures

**Congenital Malformations**
- Perinatal deaths not significantly different in WWE as compared to background
- 5.3% had congenital malformations compared to 1.5% in controls
  
  *Sabers A et al. Acta Neurol Scand 1998*
- No difference in pregnancy complications except for higher cesarean section rate
- 2.7 fold increased risk of congenital malformations
  
  *Olafsson E et al. Epilepsia 1998*
- Malformations in offspring of women with untreated epilepsy not higher than among nonepileptic controls
  
  Fried et al Drug Safety 2004

- Major malformations in 3.8% of AED exposed fetuses and in 0.8% of unexposed
- Major malformations not associated with seizures in the first trimester
  
  Kaaja et al. Neurology 2003

- AED and malformations: First report 1963
  - Mephenytin
    - microcephaly,
    - Cleft palate
    - Speech defect
    - IQ 60
  
  Mullers-Kuppers, Acta Paedopsychiatr 1963

**Spectrum of Major Malformations**

- Congenital heart disease
- Cleft lip and palate
- Neural tube defects
- Urogenital defects

**Spectrum of Minor Anomalies**

- Fetal Antiepileptic Drug Syndrome
  - Shallow orbits
  - Small nose
  - Distal phalangeal hypoplasia
  - Overlapping fingers
  - Hypertelorism
  - Low set of ears
  - Flat nasal bridge
  - Nail hypoplasia
- 4-9% risk of birth defects with AED use
  - 2-3 times general population risk (2-3%)
  - Valproic Acid 6.2 - 11.1% and OR 2.2-12.7
  - Phenytoin 3.7 - 9.1%
  - Carbamezapine 2.2 - 5.7%
  - Phenobarbital 5.1- 6%
- Polytherapy 6 - 25% (four or more)
- Not clearly associated with seizure frequency

Kaneko et al. Epilepsy Res. 1999
North American AED Pregnancy Registry Holmes et al 2004
UK Epilepsy and Pregnancy Register Morrow et al. 2006
Jentink et al. NEJM June 2010
Third Generation New AEDs:
- Polytherapy, inconsistent pattern malformations
  - Lamotrigine (n=647) 3.2%
  - Levetiracetam (n=22) 0%
  - Gabapentin (n=31) 3.2%
    Morrow et al 2006
  - Oxcarbazepine (n=248) 2.4%
    Montouris 2005

Lamotrigine
- Earlier reports suggested increased risk, but not confirmed:
  - International Registry (n=831) 2.8%
  - UK Registry (n=647) 3.2%
  - North American Registry (564) 2.7%
- No association between dose & anomalies
  Cunnington et al. 2007

AEDs and Congenital Malformations
- If possible avoid valproic acid as part of monotherapy and polytherapy in first trimester
- If possible avoid use of polytherapy in first trimester
- If possible avoid phenytoin, carbamazepine and phenobarbital in first trimester to reduce risk of specific major anomalies


Mechanisms of AED Teratogenesis
- Reactive oxidative metabolites
  - Drug bioactivation and reactive oxygen species formation likely occurs within the embryo
  - Bind to nucleic acids in embryo
  - Result in oxidative chromosomal damage and embryopathies
Folate deficiency

- Folate cofactor for methionine synthetase (crucial for DNA biosynthesis)
- Processes involving closure of neural tube involve folic acid

- AEDs Effect on Folate
  - Displace folate from enzymes
  - Block enzymatic reactions in which folate participates
  - Increase degradation of folic acid
  - Inhibition of folate synthesis
  - Decreased intestinal absorption

Drug induced embryonic arrhythmia

- Blockage of rapid component of delayed rectifying K ion current in the embryonic heart

- Resultant arrhythmia
  - Interrupted oxygen supply
  - Highly toxic reactive oxygen species in embryonic tissues during reoxygenation/reperfusion phase

Intelligence & Psychomotor Development

- Conflicting results - parental intelligence, poor psychosocial environment confounders
- Cognition probably not reduced if not exposed to AED
- Valproic Acid probably associated
  - 6-9 IQ points < compared to lamotrigine, phenytoin, CBZ
- Phenobarbital and Phenytoin possibly associated
- Polytherapy appears to be a risk factor

Management of AEDs in Pregnancy

- Withdrawal of antiepileptic drug therapy
  - No seizure activity during the past 2-5 years
  - A single type of seizure
  - A normal EEG with treatment
  - A normal neurologic exam
  - Completed 6 months prior to planned conception

Monotherapy

- Single most effective drug at minimum effective dose
- Successful control in one third of patients undergoing polytherapy withdrawal

Third generation AED

- Lamotrigine (Pennell 2008)
  - Total and free clearance increased ~90%
  - 39% increase in seizures
  - Predicted by 65% decline in level
  - Toxicity postpartum

- Oxcarbazepine (Tomson 2007)
  - Marked decrease in pregnancy – increased seizures
  - Marked increase postpartum

- Levetiracetam (Tomson 2007)
  - Renal clearance increased in pregnancy
  - 60% reduction in serum levels 3rd trimester

- Gabapentin, Topiramate, Zonisamide
  - Limited data in pregnancy

1st and 2nd Generation AED – Tomson 1994

- Carbamazepine
  - Total fraction decreased by 12% in 3rd trimester
  - No change in free levels

- Phenytoin
  - Total fraction decreased by 61% in 3rd trimester
  - Free fraction decreased by 18% in 3rd trimester

- No relationship AED level change & clinical effect

- Phenobarbitol, Valproic Acid, Primidone, Ethosuximide
  - Sufficient monotherapy data not available
  - Report of the Quality Standards Subcommittee 2009

Antiepileptic Drug Monitoring in Pregnancy

Levels before conception

- Beginning of each trimester
  - Monthly for lamotrigine and oxcarbazepine

- Last month of pregnancy and through 8th postpartum week
  - More closely for lamotrigine and oxcarbazepine

For older generation AED

- Avoid arbitrary increases in drug doses in pregnancy
  - Wide variation, poor clinical correlation
- Increase dose if seizures or marked decline in free fraction
- Avoid high peak levels (3 or 4 divided doses)

- If available follow Free Fraction
Folate Supplementation

- Deficiency strongly associated with increased risk of NTDs
- Supplementation provides risk reduction ranging from 60-100%
- Supplementation studies not conducted on women taking AEDs and efficacy unclear
- Amount of folic acid supplementation extrapolated from general population

- Pre-conception folic acid vs. later or none
  - 1935 WWE vs. 2375 WWE
  - Pre-conception folic acid did not reduce
    - NTDs, clefts, hypospadias, cardiac defects
    - Morrow J, 2008
- Failure of high dose preconception folic acid to prevent NTD in patient on Valproate
  - Craig J 1999

The risk of congenital anomalies is possibly decreased by folic acid supplementation

- Recommend at least 0.4 mg daily prior to and during pregnancy
- Insufficient data to address protective effect of higher doses


Folate: Current Recommendations

- U.S. Public Health Service
  - 0.4mg/day for all women in U.S. capable of becoming pregnant
- 1996 American College of Obstetricians and Gynecologists
  - 4mg/day would “seem appropriate” for patients taking AEDs
- Neonatal administration of 1mg IM Vitamin K
- Antenatal oral supplementation
  - Vitamin K 10mg/day in last month of pregnancy
  - Reduction in PIVKA - decarboxylated forms of Vitamin K dependent coagulation factors
  - No reduction in neonatal hemorrhage
- Insufficient evidence to support or refute antenatal Vitamin K

Obstetrical Management
- Prenatal Diagnosis
  - 18-20 week comprehensive ultrasound
  - Fetal echocardiography
  - Serum alpha-fetoprotein
  - Amniotic fluid alpha-fetoprotein and acetylcholinesterase level

- Antepartum management
  - Fetal growth ultrasounds
  - Nonstress tests
  - Doppler studies
  - AFI
    - No clear consensus
    - Individualize care

- Intrapartum management
  - Team approach - obstetrics, neurology, anesthesia, pediatrics
  - A safe and successful vaginal delivery in majority of women with epilepsy
  - Tonic-clonic seizure in labor in 1-2% of women with epilepsy and in another 1-2% up to 24 hours after delivery
  - Continue administration of AED - consider intravenous or intramuscular administration
**Postpartum Management**
- AED levels may rise in the immediate postpartum period.
- Dose reduction frequently necessary to avoid toxicity – especially lamotrigine.
- Monitor levels at least through the first two months postpartum.

**AEDs and Breast Feeding**
- AED use is not a contradiction to breast feeding.
- Cross into breast milk:
  - Greater for primidone, levetiracetam, gabapentin, lamotrigine.
- Neonatal sedation with phenobarbital, primidone, benzodiazepines?
  - No controlled studies to support effect.
  

**Epilepsy and Pregnancy**
- Cohort study of 414 women with epilepsy compared with 81,759 women without epilepsy.
- Consistent treatment and follow up.

  *Richmond et al. Am J Obstet Gynecol 2004*

**Prepregnancy counseling**
- Preconceptional folic acid 1 mg per day before 1992 and 3.5 mg per day since 1992.
- AED levels monitored monthly.
- Minimum effective AED dose for seizure control.
- Frequent communication between epileptologist and obstetrician.
- Infants examined by a neonatologist after birth and by neurogeneticist/epileptologist in first three months of life.

  *Richmond et al. Am J Obstet Gynecol 2004*
Screening with serum alpha-fetoprotein
Fetal anatomic survey
Echocardiography between 20-22 weeks
Growth scan between 30-34 weeks and if indicated toward end of third trimester

No difference between groups
- Preeclampsia
- Eclampsia
- GDM
- Placental abruption
- Preterm delivery
- Stillbirth
- Neonatal death

Epilepsy and Pregnancy

“...women with a seizure disorder are not at increased risk for obstetric complications, provided appropriate care is available during preconception, pregnancy, labor, delivery, and after delivery. We can reassure women with epilepsy of a good fetomaternal outcome, comparable to that of the general population, except with respect to congenital malformations.”
Main Points
- Partner with a neurologist
- Monotherapy
- If possible avoid Valproic Acid
- Refer for genetic counseling and prenatal diagnosis
- Folic acid supplementation – 4 mg/day

Main Points
- Vitamin K – 10 mg/day in last month?
- Treat patient not plasma drug concentration
  - Exception lamotrigine and oxcarbazepine
- Don’t forget to give medicine in labor
- Breastfeeding is OK