Women and Epilepsy

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Overview

- Catamenial Epilepsy
- Menstrual and Reproductive Disorders
- Birth Control
- Pregnancy
- Menopause and Bone Health
- Genetics
Catamenial Epilepsy

Epilepsy can be influenced by female hormones and the menstrual cycle

- Female Hormones
  - Estradiol (PRO-convulsant)
    - INCREASES seizure likelihood
  - Progesterone (ANTI-convulsant)
    - DECREASES seizure likelihood

- May occur in up to 75% of all WWE

Klein P, Herzog AG. Hormonal effects on epilepsy in women
Epilepsia 1998;Supp 8S9-16
Normal Menstrual Cycle

![Graph showing the levels of estrogen and progesterone during a 28-day menstrual cycle.]
Common Patterns of Catamenial Epilepsy: # C1 and C2

Common Patterns of Catamenial Epilepsy: #C3

Do I have Catamenial Epilepsy?

- **Menstrual and seizure diaries**
  - Chart ovulation
    - Temperature changes
    - Over-the-counter ovulation kits
  - 3-6 menstrual cycles to establish diagnosis

- More common with focal than generalized epilepsies

- Initial seizure onset around menarche
Special Treatment for Catamenial Epilepsy

- Acetazolamide (Diamox)
- Progesterone
  - Birth control pill with high progestin
  - Depo-Provera (injection)
- Benzodiazepines
- No value for use of AED around menses
Menstrual and Reproductive Disorders
Menstrual Disorders

- Anovulatory and irregular cycles
- WWE have a 32% higher chance of menstrual irregularities than the general population
  - More common in patients on > 1 AED
  - More common in patients with a higher seizure frequency (> 5 / year)
  - More common in patients with focal vs. generalized epilepsy

Reproductive Disorders

- Polycystic Ovarian Syndrome (PCOS)
  - Chronic anovulatory menstrual cycles
  - High levels of androgens
  - Insulin resistance
  - Multiple ovarian cysts

Herzog AG and Schachter SC. Valproate and the polycystic ovarian syndrome: Final thoughts. Epilepsia 2001;42(3):311-315
PCOS and Epilepsy

- 10-20% in WWE vs. 5-6% in general population
- Adolescence and PCOS
  - Girls who stop taking AEDs before adulthood are not at an increased risk
  - Girls that continue AEDs into adulthood are at an increased risk
- WWE on valproate (Depakote) are more likely to have PCOS than those on other AEDs

Herzog AG and Schachter SC. Valproate and the polycystic ovarian syndrome: Final thoughts. Epilepsia 2001;42(3):311-315
What are the Symptoms of Menstrual and Reproductive Disorders?

- Abnormal menstrual cycle (< 23 or > 35 days, no cycle)
- Mid-cycle bleeding
- Painful or excessive bleeding
- Weight gain
- Hirsutism (excessive body and facial hair, scalp hair loss)
- acne
- Infertility and miscarriage
- Disorders of sexual desire/arousal

Penovich PE. The effects of epilepsy and its treatment on sexual and reproductive function. Epilepsia 2000;41 Suppl 2:53-61
How are these disorders diagnosed?

- See your OB/GYN
- Blood tests
  - Testosterone
  - DHEAS (dehydroepiandrosterone)
  - SHBG (sex hormone binding globulin)
  - FAI (free androgen index)
  - Fasting insulin levels
Birth Control and Epilepsy

- All female methods: 73%
- Withdrawal: 8%
- Male condom: 13%
- Vasectomy: 6%
Is there an Interaction between Birth Control Pills and AEDs?

- Certain AEDs REDUCE the effectiveness of birth control pills:
  - Carbamazepine (Tegretol)
  - Felbamat (Felbatol)
  - Oxcarbazepine (Trileptal)
  - Phenytoin (Dilantin)
  - Phenobarbital
  - Primidone (Mysoline)
  - Topiramate (Topamax) > 200 mg/day

Crawford P. Interactions between antiepileptic drugs and hormonal contraception CNS Drugs 2002;16(4):263-272
Birth Control Pills and AEDs

- It is safe to take the pill and an enzyme-inducing AED, but:
  - Birth control pill with at least 50 ug of estrogen is recommended
    - Less common formulation
    - No increase in seizure frequency
  - Folic acid supplementation
  - Backup contraceptive method
  - Overall failure rate <5%
    - Breakthrough bleeding

Crawford P. Interactions between antiepileptic drugs and hormonal contraception CNS Drugs 2002;16(4):263-272
Birth Control Pills and AEDs

- Birth control pills REDUCE the effectiveness of lamotrigine (Lamictal) up to 50%
  - The dosage of Lamictal may need to be adjusted if birth control pills are started or stopped during treatment
  - Important to keep both your Neurologist and OB/GYN informed of your medication changes

Other Contraceptive Methods

- **Depo-Provera (medroxyprogesterone)**
  - Increase frequency of injection if on enzyme-inducing AED
  - <1% failure rate
  - Long-term use not recommended
  - Consider in adolescents

- **Intrauterine Device (IUD)**
  - Releases progesterone
  - No interaction with enzyme-inducing AEDs
  - 3% failure rate

- **Barrier method**
  - No interaction with any medications
  - 12-18% failure rate
Pregnancy and Epilepsy
The Facts...

- Over 90% of WWE will have a normal pregnancy, delivery, and a normal healthy baby

- WWE are at an increased risk for adverse outcomes
  - Congenital malformations due to AEDs are the most widely reported adverse outcome
    - General population 2-3%
    - WWE on AEDs 4-6%

What are the Fetal Risks of AED Use?

- Congenital heart disease
- Cleft lip/palate
- Urogenital defects
- Cognitive dysfunction
- Low birth weight
- Neural tube defects

Neural Tube Defects

- Uncommon
- 6/10,000 pregnancies
- Myelomeningocele and anencephaly most common type associated with AED use
  - Result of abnormal neural tube closure during 3rd and 4th week of gestation

General Risks for Neural Tube Defects

- Increased risk if:
  - Previous pregnancy associated with a neural tube defect
  - Insulin-dependent diabetes mellitus
  - Hispanic descent
  - Pre-pregnancy obesity
  - Folic acid deficiency
Should I Stop Taking my AED Before or when I Become Pregnant?

- No!
- You and your doctor can consider stopping AEDs only if:
  - Seizure-free for at least 2 years
  - Normal exam
  - Normal MRI of the brain
  - No history of status epilepticus (prolonged seizures)
  - There is one exception!!!
How do I Protect Against Possible Birth Defects?

- Planned pregnancy
- Folic acid supplementation 1-4 mg per day, at least 3 months before conception
- Single AED at the lowest effective dose
  - Extended-release formulations
  - More frequent, smaller doses

Yerby M. Clinical Care of pregnant women with epilepsy: Neural tube defects and folic acid supplementation. Epilepsia 2003;44 (Suppl 3):33-40
Prenatal Diagnostic Testing

- Maternal serum a-Fetoprotein (14-16 weeks’ gestation)
- First trimester ultrasound (11-13 weeks)
  - Neural tube defects
- Second trimester ultrasound (18-22 weeks’ gestation)
  - Cardiac development
  - Head spine anatomy
  - Cleft lip and palate
Pregnancy Registries

- The North American Pregnancy Registry
  - 1-888-233-2334
  - www.massgeneral.org/aed
- European Registry of Antiepileptic Drugs in Pregnancy (EURAP)
  - www.eurapinternational.org
- United Kingdom Epilepsy and Pregnancy Registry
- Australian Pregnancy Registry
Do all AEDs Have the Same Risk of Birth Defects?

- New AEDs are classified as category C:
  - Evidence of birth defects in animals, but no studies in humans
- Old AEDs are classified as category D:
  - Evidence of birth defects in animals and humans

Pregnancy Outcomes on Depakote

- Old AED

- Meador et al. 2006 study:
  - 343 mother and child pairs
  - Over 20% of pregnancies exposed to Depakote had serious adverse outcomes (fetal death or congenital malformation)
  - Seven other studies have had similar results

“The epilepsy drug Valproate poses a higher risk for fetal and birth defects than other commonly used AEDs”
Depakote and childbearing age: Recommendations

- Depakote should not be the medication of choice for any woman of child-bearing age
  - If on Depakote, and can switch to another medicine, do so before thoughts of pregnancy
- If not possible to be on another AED:
  - Reduce dose if possible
  - Spread doses out during day
  - Folate supplementation
  - Reduce other risk factors (smoking, alcohol)
Pregnancy Outcomes on Tegretol

- Old AED
- Meador et al. Study
  - 110 pregnancies
    - 3.9% fetal deaths
    - 4.5% congenital malformations
Pregnancy Outcomes on Dilantin

- Old AED
- Meador et al. study:
  - 56 pregnancies
    - 3.6% fetal death
    - 7.1% congenital malformations
Pregnancy Outcomes on Lamictal

Lamotrigine Monotherapy
35 major defects/1558 outcomes (2.2%)

Polytherapy including Valproate
16 major defects/150 outcomes (10.7%)

Polytherapy not including Valproate
12 major birth defects/430 total outcomes (2.8%)

Holmes et al., LAMOTRIGINE PREGNANCY REGISTRY FINAL REPORT PAGE 3 1 SEPTEMBER 1992 THROUGH 31 MARCH 2010
What Happens if I Have a Seizure During Pregnancy?

- **Convulsive seizure (“grand mal”)**
  - Can cause lack of oxygen to mother and fetus
  - Decrease fetal heart rate
  - Trauma
  - Prematurity
  - Miscarriage

- **Non-convulsive seizure (“petit mal”)**
  - unclear
How will Pregnancy Affect my Seizures?

- 24% may have increase in seizure frequency due to:
  - Non-compliance of medication
  - Sleep deprivation
  - Weight gain and change in drug metabolism
    - Drug levels monitored before conception, during each trimester, weekly during 9th month, and 8 weeks post-partum
    - May need to increase dosage during pregnancy
    - After delivery, return to pre-pregnancy dosage

- 53% no change, 23% improve
Delivery Concerns

- Epidurals are safe
- 1-2% risk of having generalized seizures during or after delivery
  – Seizures during labor is an indication for a C-section
Is it Safe to Breastfeed?

- Yes, and is encouraged
- Monitor babies for sedation, irritability and weight gain
Menopause and Bone Health
How will Menopause Affect my Epilepsy?

- **Catamenial Epilepsy**
  - More likely to see a change
  - Possible increase in seizure frequency during premenopause
  - Possible decrease during menopause

- **HRT (hormone replacement therapy)**
  - Possible increase in seizure frequency

- **WWE at increased risk for early menopause**

AEDs can Decrease Bone Density

- WWE at risk for osteoporosis and osteopenia
- Monitor vitamin D, calcium, PTH levels
- Monitor bone mineral density with a DEXA scan
  - If normal, calcium 600 mg twice a day + vitamin D 400 IU per day
  - If osteopenia, calcium 600 mg three times a day + vitamin D 800-1200 IU/day
  - If osteoporosis, refer to endocrinologist

Genetics and Epilepsy
Will my Children Inherit my Epilepsy?

- Generalized epilepsies are more often inherited than focal epilepsies
  - Childhood absence epilepsy
  - Juvenile myoclonic epilepsy
  - Autosomal dominant nocturnal frontal lobe epilepsy
Conclusion

- WWE have unique needs
- WWE should become active participants in their care
- Education of women and health care providers is the first important step in WWE care
Resources

- The Epilepsy Foundation
  - www.epilepsyfoundation.org
  - 1-800-332-1000
- The Keppra Pregnancy Registry
  - 1-888-537-7734
- Gabapentin Pregnancy Registry
  - 617-638-7751
- International Lamotrigine Pregnancy Registry
  - 1-800-336-2176