Epilepsy, Special Concerns in Women

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Disclosure

None
Objective

The participants will be able to:

- Recognize the interaction between female hormonal-reproductive factors and epilepsy.

- Develop safer treatment strategies in the setting of pregnancy and epilepsy.

- Identify and manage concomitant conditions with epilepsy.
Seizure

An abnormal hypersynchronous electrical discharge of a large pool of cortical neurons resulting in some alteration in awareness, sensory or motor function.

ANYTHING CAN BE A SEIZURE!

Epilepsy

A disorder characterized by 2 or more recurrent unprovoked seizures

Causes of Provoked Seizures

Toxic/metabolic, drug ingestion, febrile
Epilepsy, Definition

A condition of recurrent seizures
Affects ~4% of US population
Whereas; 10% lifetime incidence of seizures
Numerous causes
Proper treatment depends on diagnosis of seizure type and epilepsy syndrome
Review of current diagnostic tests, treatment options, and current research
Special Concerns in Women with Epilepsy

Why?

1.5% of the population is diagnosed with epilepsy, also known as seizure disorder. This translates into ½ million female patients in child bearing age!

Neuroactive hormones (Cross BBB): Estradiol, Progestrone, Testosterone
Neuosteriods hormones (produced in CNS): possibly all, but definitely Allopregnanalone

Historically: 1959: infusion of estrogen in female patients with epilepsy increased EEG interictal discharges!
Special Concerns in Women with Epilepsy

Hormones and Epilepsy
Catamanial Seizures
Hormones and AEDs
Sexuality & Reproduction
Contraception & AEDs
Pregnancy, complications due to Epilepsy and AEDs
Eclampsia
Fetal AED side effects
Breast Feeding and AEDs
Menopause, Hormone replacement
Osteoporosis
Concomitant Conditions, eg Migraine, PCOS
The ovarian hormones are neuroactive steroids and neuromodulators

<table>
<thead>
<tr>
<th></th>
<th>Estrogen</th>
<th>Progesterone &amp; its metabolites</th>
<th>Androgen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proconvulsant</td>
<td>Anticonvulsant</td>
<td>Anticonvulsant</td>
</tr>
<tr>
<td>Effect on neuronal excitability</td>
<td>Decreases neuronal electric threshold by increasing the number of excitatory neuronal synapses.</td>
<td>Increases neuronal electric threshold</td>
<td>Increases neuronal electric threshold</td>
</tr>
<tr>
<td>Effect on GABA-$\alpha$</td>
<td>reduces inhibition at the receptors</td>
<td>Increases inhibition</td>
<td>Increases inhibition</td>
</tr>
<tr>
<td>Effect on Glutamate</td>
<td>enhances excitation at the glutamate (NMDA) receptor</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Effect on BNDF</td>
<td>Increases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect on NPY</td>
<td>Increases</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Catamenial Epilepsy

Seizure Exacerbation, not a specific localization or epilepsy syndrome

30-50% of women with epilepsy have a catamanial pattern. The frequency and severity of their seizures increases at certain times during their menstrual cycle.

Seizure frequency, severity and type varies as a factor of ratio of estrogen to progesterone.

Other Possible causes:
- Role of LH/FSH
- Antiepileptic medications effects on hormones
- Water retention
- Changes in other hormone modifying organs: adrenal, liver, and fat
Menstrual Cycling

Estrogen rises at ovulation first

Progesterone withdraws premenstrually

For inadequate luteal phase cycles (anovulatory), Estrogen-to-progesterone ratio is elevated throughout luteal phase

3 Types of Catamanial Seizures
Increase in seizure frequency during:

<table>
<thead>
<tr>
<th>Perimenstrual (C1)</th>
<th>during the menstrual phase ((\text{days } -3 \text{ to } +3)) compared with the midfollicular and midluteal phases in normal ovulatory cycles.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periovulatory (C2)</td>
<td>ovulatory phase ((\text{days } +10 \text{ to } -13)) compared with the midfollicular and midluteal phases in normal ovulatory cycles.</td>
</tr>
</tbody>
</table>
| Inadequate Luteal (C3) | during the ovulatory, luteal, and menstrual phases than during the midfollicular phase in women with inadequate luteal-phase cycles.  
This seizure exacerbation may extend from day 9 of one cycle to day 2 of the following cycle. |

71% of women with normal ovulatory cycles had perimenstrual or periovulatory type. 78% of women with inadequate luteal-phase cycle showed the luteal type.

Seizure Frequency in Normal Cycles

Number of seizures=1324
Number of cycles=98

Seizure Frequency in Luteal Phase Cycles

Number of seizures=1523
Number of cycles=86

Difficult to control with AEDs, but increasing doses of AEDs premenstrually may be beneficial. Needs monitoring of levels.

**Acetozolamide**: 40% may be responders (Lim LL; Foldvary N; Mascha E; Lee J, Epilepsia, 2001)

Intermittent use of **benzodiazepines** during periods of vulnerability.

**OCP possibly with limited withdrawal weeks** (every 3 months) such as with Seasonale-stable hormone levels.

**Depo-medroxyprogesterone acetate** improved seizures in small series.

**Natural progesterone** during luteal phase reportedly effective in small series.

Future trends: **Neuroactive Steroids** (Ganaxolone, synthetic allopregnanolone)
Treatment Approach to Catamanial Seizures

First document several menstrual cycles to establish cycle length and seizure pattern, then:

<table>
<thead>
<tr>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Irregular menses:</strong></td>
</tr>
<tr>
<td>Medroxy-Progesterone Oral contraceptives with withdrawal weeks</td>
</tr>
<tr>
<td><strong>Regular Menses:</strong></td>
</tr>
<tr>
<td>C1 Type Natural Progesterone If no success, follow C2, C3 pattern:</td>
</tr>
<tr>
<td>C2, C3 Type Acetazolamide Benzos: eg Clobazam Increase baseline Antiepileptics</td>
</tr>
</tbody>
</table>

Navis, Harden: 2017
Effects of Epilepsy on Hormones

Multifactorial effect of epilepsy on hormones:

“A” seizure can disturb the hypothalamic-pituitary axis:
- abnormal pituitary response to GnRH
- Prolactin secreted with gtc, cps, sps
- increase in ACTH and Growth hormone
- increase in GABA, serotonin, endogenous opioids

More commonly in temporal lobe epilepsy, esp arising from the LEFT TEMPORAL AREA.
Reproductive and sexual dysfunctions

Consequence:
- Late Menarche
- Early Menopause
- Irregular menses (30%), later ovulation during a cycle
- Sexual dysfunctions (arousal, vaginismus, dyspareunia)
- Lower fertility (compared to general population and to their siblings)
- Lower birth weight

Causes:
- Effects of Seizures on hormones
- Effects of antiepileptic medications on hormones
- But also psychosocial factors, fear of pregnancy, later and fewer marriages
Effects of Epilepsy on Hormones

-Women with epilepsy may develop menstrual disturbances, weight gain, hyperandrogenism, ovulatory failure, and polycystic ovaries.

-20% to 30% have some degree of sexual dysfunction, including problems with libido, arousal, and orgasm.

The amygdala is emerging as a brain structure with significant involvement in sexuality in patients with epilepsy, as shown by alterations in sexual functioning after temporal lobectomy.

Patients with temporal lobe epilepsy have reduced genital blood flow in response to erotic stimulation; the etiology of this phenomenon is not well understood.

Psychosocial factors, including sexual anxiety and stigma associated with epilepsy, can also affect the sexual life of patients with epilepsy.
Effects of AEDs on Hormones

The majority of antiepileptic drugs block voltage dependent sodium and calcium channels, enhance GABAergic transmission and/or antagonize glutamate receptors.

Potentially, neurochemical mechanisms are engaged in the interaction of these drugs with synthesis of hypothalamic neurohormones such as gonadotropin-releasing hormone (GnRH), thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH) and growth hormone releasing hormone (GHRH).
Effects of AEDs on Hormones

-CYP450 inducers (PHT, PHB, CBZ, OXC)
  -increase metabolism of all sex hormones and contraceptives
  -decrease the level of free and bound thyroxine.

-CYP450 inhibitors (VPA)
  -decrease metabolism of all sex hormones

- Carbamazepine decreased testosterone level but enhanced SHBG concentration.
- Carbamazepine, oxcarbazepine or joined administration of carbamazepine and valproate decrease thyroxine (T4).
- Valproate decreases FSH-stimulated estradiol release and enhanced testosterone level.

- New antiepileptics such as levetiracetam, tiagabine, vigabatrine or lamotrigine had no effect on thyroid hormones.

To this end, no effect of antiepileptic drugs on adrenocorticotropic hormone (ACTH)/cortisol circadian rhythmicity was found.
Oral contraception (OC) when used impeccably, has an annual failure rate of <1% (PDR 2005)

With AEDs: Usual OC annual failure rate is 2-7% (Trussel J, Contraception, 2004)

OC metabolism is induced by increasing activity of the Cytochrome P450 isoenzyme system 3A4 by many AEDs. (PHT, PHB, MSO, CBZ, OXC)

27% of neurologists and 21% of gynecologists report failing OC in their patients who are on AEDs.

Only 4% of neurologists and none of the gynecologists knew enzyme inducing antiepileptic medications can lower CO levels.
# Interaction With Hormonal Contraception

<table>
<thead>
<tr>
<th>Potential Interaction</th>
<th>No Reported Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine*</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>Felbamate*</td>
<td>Levetiracetam</td>
</tr>
<tr>
<td>Oxcarbazepine*†</td>
<td>Tiagabine</td>
</tr>
<tr>
<td>Phenobarbital*</td>
<td>Zonisamide</td>
</tr>
<tr>
<td>Topiramate*†</td>
<td>Valproate</td>
</tr>
<tr>
<td>Phenytoin*</td>
<td>Pregabalin</td>
</tr>
<tr>
<td><strong>Lamotrigine‡</strong></td>
<td><strong>Vigabatrin</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Vagus Nerve Stimulator</strong></td>
</tr>
</tbody>
</table>

*P450 inducers, may decrease efficacy of oral contraceptives.
†At higher dosage.
‡Oral contraceptives may reduce lamotrigine plasma levels.

Hormonal oral contraception can be used in women with epilepsy taking AEDs. Higher, not low dose OCs should be used (at least 35-50 mcg estrogen, not 15-25 mcg). Then, it provides pregnancy prevention comparable to other women. Consider other methods such as IUD or Depo-Provera.
Special Concerns in Women with Epilepsy

Pregnancy

- Complications of pregnancy due to epilepsy
- Optimal Seizure control
- AEDs indication and dosage
- Eclampsia
- Teratogenicity of AEDs
Maternal Epilepsy and Congenital Malformations

No Evidence that maternal epilepsy is associated with any major malformations

- 0.8% in offspring of 237 women with epilepsy not on AEDs (Kaaja, et al 2003)
- None in 98 infants of women with epilepsy not on AEDs; some minor malformations (Holmes et al, 2001)
- 57 children born to mothers with epilepsy not on AEDs compared to 57 controls; Major malformations in 8.7% of study group and 5.3% of controls (p=0.358) (Holmes et al, 2000)
- 2/42 offspring of women with epilepsy not on AEDs; not different from general population (Olafsson et al 1999)
- 0/25 malformations of any type in offspring of women with epilepsy not on AEDs (Canger et al, 1999)
Seizures During Pregnancy

Prevention of seizures during pregnancy is considered optimal care

35% of patients can have worsening of their epilepsy.
- Hormonal changes (estrogen/progesterone ratios)
- Dropping antiepileptic medications levels
- Stress
- GI absorption
- Sleep deprivation
- Water retention

55% of patients remain stable.

10% of patients can have improvement of their epilepsy.

Eclampsia
- Mg remains gold standard (1-4 gm/hr during the first few hrs, superior to Benzos and phenytoin)

Seizures during labor
Other reasons to prevent seizures with AEDs during pregnancy

Seizures are a risk to the pregnancy

- **Trauma during pregnancy** can result in abruptio placentae (20-50% of blunt injuries), premature labor and fetal death

- **Generalized convulsions** have caused fetal heart rate depression, fetal hypoxia and acidosis, intracranial hemorrhage (Minkoff et al 1985, Teramo, et al, 1979, Hiilesmaa et al 1985)

- One case of decreased fetal heart rate after complex partial seizures (Nei et al 1998)

- **Status epilepticus** during pregnancy is associated with high maternal and fetal mortality rate (Teramo et al 1982)
More reasons to prevent seizures during pregnancy

Seizures during pregnancy may be associated with

- Intrauterine growth retardation
- Miscarriage
- Fetal loss after 20 weeks (fetal wastage)
- Neurocognitive deficits: 5 or more seizures during pregnancy associated with lower verbal IQ (Vinten et al, Neurology 2005)
## Alterations During Pregnancy

<table>
<thead>
<tr>
<th>AED</th>
<th>Increases in Clearance</th>
<th>Decreases in Total Concentrations</th>
<th>Decreases in Free Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHT</td>
<td>20%–100%</td>
<td>55%–61%</td>
<td>18%–31%</td>
</tr>
<tr>
<td>CBZ</td>
<td>0%–20%</td>
<td>0%–42%</td>
<td>0%–28%</td>
</tr>
<tr>
<td>PB</td>
<td>—</td>
<td>55%</td>
<td>50%</td>
</tr>
<tr>
<td>PRM</td>
<td>—</td>
<td>55%</td>
<td>—</td>
</tr>
<tr>
<td>Derived PB</td>
<td>—</td>
<td>70%</td>
<td>—</td>
</tr>
<tr>
<td>VPA</td>
<td>35%–183%</td>
<td>50%</td>
<td>Inconsistent</td>
</tr>
<tr>
<td>ETX</td>
<td>—</td>
<td>Inconsistent decreases</td>
<td>—</td>
</tr>
</tbody>
</table>

### Pharmacokinetic of AEDs during pregnancy and lactation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Decrease in total plasma concentration (%)</th>
<th>Ratio of infant/ maternal plasma concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>25–50</td>
<td>0.1–0.6</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>25–50</td>
<td>0.3–0.5</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td></td>
<td>0.8–1.0</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>&lt;25</td>
<td>0.1–0.3</td>
</tr>
<tr>
<td>Valproate</td>
<td>25–50</td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>MHD &gt;50</td>
<td>0.5</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>&gt;50</td>
<td>0.4–0.8</td>
</tr>
<tr>
<td>Gabapentin</td>
<td></td>
<td>0.7–1.3</td>
</tr>
<tr>
<td>Topiramate</td>
<td></td>
<td>0.7–1.1</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>&gt;50</td>
<td>0.8–1.3</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>25–50</td>
<td>0.5–0.9</td>
</tr>
</tbody>
</table>
Guidelines for the Use of Antiepileptic Drugs During Pregnancy (AAN)

- Use the **most effective antiepileptic drug** in monotherapy, at the lowest possible dose.
- With a family history of neural tube defects, try to **avoid valproate and carbamazepine**.
- Monitor the **free (nonprotein-bound) fraction of the antiepileptic** drug at each trimester, before delivery, and four to eight weeks after delivery.
- Adjust the antiepileptic drug dosage according to the nonprotein-bound (free) level.
- **Provide folate supplementation** at a dosage of 0.4 to 4 mg per day before conception and throughout gestation.
- Offer prenatal testing with anatomic ultrasound and maternal serum **alpha-fetoprotein** at 15 to 20 weeks of gestation.
- Provide the pregnant woman with vitamin K, 10 mg/day during the last month.
Management of AEDs during pregnancy

Gold standard is to keep patients seizure–free at lowest dose of AEDs, preferably monotherapy.

- Generally, AEDs are not changed during pregnancy.
- Majority of women who are seizure-free on AEDs will remain so if levels are maintained during pregnancy
- Valproate and phenobarbital are not recommended as first-choice therapy for women of child-bearing potential
- In general, total levels decline but free, unbound levels increase
- Levels should be monitored every 4-12 weeks
- CBZ levels are among the most stable
- Lamotrigine levels can rapidly and drastically decline, up to 300%, and quickly reverse after delivery
- Check levels after delivery an adjust dose
Pregnancy and Antiepileptic Drugs (AEDs)

Approximately 3 to 5 births per 1000 will be to women with epilepsy

FDA, Category C AEDs: gabapentin, felbamate, lacosamide, lamotrigine, levetiracetem, oxcarbazepine, pregabalin, topiramate, tiagabine, Parampanel and zonisamide

Category D (adverse human fetal risk) AEDs: valproate, carbamazepine, and phenytoin
Current AED Registries

North American antiepileptic medications Pregnancy Registry
Clinicians should ask their pregnant patients to register by calling 1-888-233-2334 or online

United Kingdom Epilepsy and Pregnancy Register
EURAP-European Pregnancy Register
Kerala, India Pregnancy Registry
Australian Registry of Antiepileptic Drugs in Pregnancy
GlaxoSmithKline Lamotrigine Pregnancy Registry (Closed)
UBC (Levetracitam & Vimpat)

Also, EpilepsyBirthControlRegistry.com by Columbia
## Summary of study design in five AED and pregnancy registries

<table>
<thead>
<tr>
<th>Registry</th>
<th>North America</th>
<th>United Kingdom</th>
<th>Australia</th>
<th>EURAP</th>
<th>Kerala, India</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enrolled #</strong></td>
<td>7,175</td>
<td>7,312</td>
<td>1,150</td>
<td>13,999</td>
<td>1,306</td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
<td>Prospective/Retrospective</td>
<td>Prospective</td>
<td>Prospective/Retrospective</td>
<td>Prospective/Retrospective</td>
<td>Prospective</td>
</tr>
<tr>
<td><strong>Patients with:</strong></td>
<td>AED dose, regime, brand</td>
<td>AED dose, regime</td>
<td>AED dose, regime</td>
<td>AED dose, regime</td>
<td>AED dose, regime</td>
</tr>
<tr>
<td><strong>Diagnosis by</strong></td>
<td>Patient and MD reports</td>
<td>MD</td>
<td>MD</td>
<td>MD</td>
<td>MD</td>
</tr>
<tr>
<td><strong>Patient population</strong></td>
<td>On AED for any reason</td>
<td>Epilepsy and AED</td>
<td>Both groups</td>
<td>Any AED exposure at conception</td>
<td>Both groups</td>
</tr>
<tr>
<td><strong>Evaluated by</strong></td>
<td>Teratologist</td>
<td>Geneticist</td>
<td>Medical record</td>
<td>MD, echo, ultrasound</td>
<td></td>
</tr>
<tr>
<td><strong>Time Window of assessment</strong></td>
<td>2 occasions, first 3 months</td>
<td>first 3 months</td>
<td>first 3 months</td>
<td>first 3 months</td>
<td></td>
</tr>
</tbody>
</table>

**NewYork-Presbyterian**
Brooklyn Methodist Hospital
The North American antiepileptic medications Pregnancy Registry

<table>
<thead>
<tr>
<th>7,242 as of Nov 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pregnancy</strong></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;: 39%</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt;: 30%</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt;: 16%</td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt; +: 15%</td>
</tr>
<tr>
<td><strong>Education</strong></td>
</tr>
<tr>
<td>Some High school 20%</td>
</tr>
<tr>
<td>Some College 30%</td>
</tr>
<tr>
<td>College 35%</td>
</tr>
<tr>
<td>Postgraduate 21%</td>
</tr>
<tr>
<td><strong>Race</strong></td>
</tr>
<tr>
<td>White 96%</td>
</tr>
<tr>
<td>Black 4%</td>
</tr>
<tr>
<td>Hispanic 6%</td>
</tr>
<tr>
<td>Other 4%</td>
</tr>
<tr>
<td><strong>Monotherapies:</strong></td>
</tr>
<tr>
<td>25 types</td>
</tr>
<tr>
<td><strong>Polytherapies</strong></td>
</tr>
<tr>
<td>197 types</td>
</tr>
</tbody>
</table>
For major malformations
Polytherapy increases teratogenicity:

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Polytherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.3% - valproate (Depakote)</td>
<td>LMC+VPA: 10.2%</td>
</tr>
<tr>
<td>5.5% - phenobarbital</td>
<td>CBZ+VPA: 6.9%</td>
</tr>
<tr>
<td>4.2% - topiramate (Topamax)</td>
<td>LMC+CBZ: 3.2%</td>
</tr>
<tr>
<td>3.0% - carbamazepine (Tegretol)</td>
<td></td>
</tr>
<tr>
<td>2.9% - for phenytoin (Dilantin)</td>
<td></td>
</tr>
<tr>
<td>2.4% - levetiracetam (Keppra)</td>
<td></td>
</tr>
<tr>
<td>2.2% - for oxcarbazepine (Trileptal)</td>
<td></td>
</tr>
<tr>
<td>2.0% - for lamotrigine (Lamictal)</td>
<td></td>
</tr>
</tbody>
</table>
Congenital Malformations due to AEDs
Teratogenicity
Conclusion

Risk is roughly 2 times that in general population

4-6% in women with epilepsy vs 2% in the general population.

- AEDs are associated with major malformations
- Valproate and phenobarbital clearly increase rate (10 and 6.5%)
- Other standard AEDs including lamotrigine have risk around 2.9%; slightly increased over expected; little info for newer AEDs
- Monotherapy poses less risk than polytherapy
- Valproate associated with lower verbal IQ (cognitive, psychomotor, Autism)
- Seizures may be associated with major malformations, but are associated with lower verbal IQ

Indications for Folic Acid supplement (1-4 mg/day)
Congenital Malformations due to AEDs Teratogenicity

<table>
<thead>
<tr>
<th></th>
<th>Major Malformations</th>
<th>Minor Malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Neural Tube Defects, Microcephaly, Growth retardation</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Ventricular septal defect, coarctation of the aorta, tetralogy of Fallot, aortic valve stenosis, hypoplasia of mitral valve</td>
<td></td>
</tr>
<tr>
<td>Genitourinary</td>
<td>mild hydronephrosis, absence of one kidney</td>
<td>undescended testicle, Penile hypospadias</td>
</tr>
<tr>
<td>Head/face</td>
<td>Cleft lip and cleft palate, Hypoplasia of midface/fingers</td>
<td></td>
</tr>
<tr>
<td>Extremities</td>
<td>Club foot, Flexible flat foot, Hip dysplasia</td>
<td></td>
</tr>
</tbody>
</table>
Potential Mechanisms of AED Teratogenesis

- Suppression of **neuronal physiology** by AEDs
- Decreased **folic acid** by AED interference with metabolism or absorption
- Altered **NMDA/GABA** related mechanisms caused by AEDs (similar to fetal alcohol syndrome)
- **Apoptosis of fetal cells** by valproate and other AEDS; not levetiracetam
- **Ischemia/hypoxia** due to AED effects on cardiac function

Reactive intermediates

- Epoxides-but not formed in fetal tissues
- Free radicals of bioactivated AEDs
## Effect of Antiepileptic medications on Neuro-cognitive functions

A Meta Analysis evaluated 29 studies, including 5100 infants and children with exposure to antiepileptic medications during pregnancy and breast feeding. Veroniki et al; 2017

<table>
<thead>
<tr>
<th>Neuro-cognitive functions</th>
<th># of Children</th>
<th>Antiepileptics contributing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Developmental Delay</td>
<td>933</td>
<td>-Valproic Acid</td>
</tr>
<tr>
<td>Psychomotor Developmental Delay</td>
<td>1145</td>
<td>-Valproic Acid&lt;br&gt;-Valproic Acid+Carbamazepine +Phenobarb</td>
</tr>
<tr>
<td>Autism / Dyspraxia</td>
<td>2551</td>
<td>-Valproic Acid&lt;br&gt;-Crabamazepine&lt;br&gt;-Lamotrigene&lt;br&gt;-Valproic Acid +Lamotrigene</td>
</tr>
<tr>
<td>ADHD</td>
<td>816</td>
<td>None</td>
</tr>
<tr>
<td>Social Impairement</td>
<td>422</td>
<td>None</td>
</tr>
</tbody>
</table>
Breastfeeding on AEDs

- Antiepileptic medications are present in breast milk.
- Transmission via breast milk depends on protein binding; The higher protein bound the AEDs are, the less they pass into milk.
- Anticonvulsant exposure from breast milk is lower than in utero

<table>
<thead>
<tr>
<th>AED</th>
<th>Breast Milk/Plasma Concentration</th>
<th>Adult $t_{1/2}$</th>
<th>Neonate $t_{1/2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>0.4–0.6</td>
<td>8–25</td>
<td>8–28</td>
</tr>
<tr>
<td>PHT</td>
<td>0.2–0.4</td>
<td>12–50</td>
<td>15–105</td>
</tr>
<tr>
<td>PB</td>
<td>0.4–0.6</td>
<td>75–126</td>
<td>45–500</td>
</tr>
<tr>
<td>ETX</td>
<td>0.9</td>
<td>40–60</td>
<td>40</td>
</tr>
<tr>
<td>PRM</td>
<td>0.7–0.9</td>
<td>4–12</td>
<td>7–60</td>
</tr>
<tr>
<td>VPA</td>
<td>0.01</td>
<td>6–18</td>
<td>30–60</td>
</tr>
<tr>
<td>LTG</td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Yerby, Collins. 1997.
Breastfeeding on AEDs

- It is very difficult to have good studies in breastfeeding and side effects of AEDs on newborn.

- Only measurements of AEDs concentrations in milk, and anecdotal AEDs side effects are documented.

- Generally, if mother is interested in breastfeeding, it is recommended to do so, and monitor newborns for side effects. Lamictal might be an exception!
Women with catamenial seizure patterns may experience hormonal sensitivity at perimenopause and menopause.

At perimenopause, estrogen levels initially increase slightly as progesterone declines, therefore E/P ratio may be higher in general, permitting seizure occurrence.

After menopause, lack of hormonal cycling may have a beneficial effect on seizure occurrence.
Epilepsy influences the age of menopause

Possibly 3-year difference in age of menopause between intractable and non-intractable epilepsy

Number of lifetime seizures is associated with lower age of menopause

No statistically significant association between early menopause and any specific older AED use

Results suggest an effect of epilepsy on hypothalamic functioning; promotes early failure of HPA

Peri-menopausal women—epilepsy pattern

*Significantly associated with an increase in seizures ($P=0.02$)
** Significantly associated with a decrease in seizures ($P=0.02$)

HRT and Epilepsy: Conclusions

Hormone replacement therapy with Prompera (CEE/MPA) may increase seizure frequency in postmenopausal women with epilepsy (dose-related).

When short term hormone replacement therapy is needed:
- natural progesterone eg: progestin +
- an estrogenic compound eg: 17β-estradiol

Lamotrigine levels may decline with HRT use

No other changes in AED levels associated with HRT
Polycystic Ovary Syndrome and Epilepsy

- New Consensus Definition of PCOS (Best Practice Res Clin Ob/Gyn, Oct 2004)
- Two of the following three features
  - Polycystic ovaries
  - Abnormal elevation of testosterone or clinical evidence of hyperandrogenemia
  - Anovulation or oligo-ovulation
- NIH consensus definition does not include polycystic ovaries

PCOS occurs in 5-8% of the general population; Other characteristics are
  - insulin resistance in 30-35% of women with PCOS with or without obesity
  - Elevated LH to FSH ratio which is important link to epilepsy since LH pulsatility is abnormal in women and men with epilepsy

PCOs occur in 20-30% of premenopausal women
  - PCOs are not sensitive for predicting ovulatory dysfunction, but when present with any other sign or symptom of PCOS are associated with subfertility (Hassan, et al., 2003)
PCOS in epilepsy

Of 93 women with focal epilepsy of long duration, PCOS (NIH criteria) occurred in 10.6% (Bauer et al., 1997)
No difference was found between women taking
- carbamazepine (n=20; 10%)
- valproate (n=18; 11.1%)
- No AEDs (n=19; 10.5%)

-Epilepsy is likely a cause of PCOS or a cause of a PCOS variant possibly from central LH dysregulation
-Many women seem to have PCOS features at onset of diagnosis
-Valproate has effects that look like PCOS

Valproate causes weight gain; does it cause insulin resistance when weight gain does not occur?
Valproate is associated with
- Polycystic ovaries, Elevation in androgens in men and women, Blocks conversion of testosterone to estradiol, anovulation
Preconception counseling

Patients should be aware of a number of issues relating to future pregnancy, including methods and consequences of prenatal screening, genetics of their seizure disorder, teratogenicity of AEDs, folic acid and vitamin K supplements, labor, breast feeding, and childcare.
Bone Health

Older AEDs produce accelerated bone loss: phenobarbital, primidone, phenytoin, carbamazepine, and valproate.

Newer AEDs are probably safer; however, data is limited.

Mechanisms:
- Hepatic enzyme induction, producing vitamin D catabolism
- Direct effects on bone cells
- Impaired calcium absorption

Management:
- DEXA for everyone, taking older AEDs for more than 5 years.
- Supplemental vitamin D and Ca for patients taking the older AEDs
- If osteoporosis, treat and consider changing AED
Supplementing women with epilepsy with at least 0.4 mg of folic acid before they become pregnant may be considered (Level C) Monitoring of lamotrigine, carbamazepine, and phenytoin levels during pregnancy should be considered (Level B) Monitoring of levetiracetam and oxcarbazepine (as monohydroxy derivative) levels may be considered (Level C).

insufficient data for the following hypothesis! Risk of hemorrhage in neonates born to WWE taking antiepileptic medications? Does prenatal vitamin K supplementation reduce the risk of hemorrhage?

American Academy of Neurology and American Epilepsy Society 2009
Take Home Message

- Estrogen is proconvulsant/ Progesterone is anticonvulsant.
- Strategies to manage catamenial seizures
- Encourage patients to register in Pregnancy Registry.
- Guidelines for pregnancy AEDs
- Older AEDs cause more frequently:
  interaction with OCP, teratogenicity, osteoporosis
- Supplement and screening for osteoporosis
- HRT with high Estrogen can precipitate seizures
1. A Treatment Approach to Catamanial Epilepsy
Navis A, Harden C.


3. Pregnancy and epilepsy: meeting the challenges over the last 25 years: The rise of the pregnancy registries.
Kinney MO, Craig JJ.: Seizure. 2017 Jan;44:162-168