Epilepsy and Women: treatment consideration

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Financial disclosure

- I have no financial disclosure.
Women with epilepsy in USA

- 1% population has epilepsy: ~3 million
- Half are women: ~1.5 million

A focus on health: women & girls with epilepsy

- How hormonal changes affects girls and women with epilepsy
- How ASMs (anti-seizure medications) may impact birth control (contraception)
- Special consideration before, during and after the pregnancy
- Special consideration for breast feeding
- Mature women with epilepsy- menopause and bone health
- Q and A
Patient case

- Sania is a 22-year-old female with focal epilepsy plus migraines
- Was started on valproate
- Sania wants to become a nurse and would like to have kids in 1-2 years.
- She is hesitant to change her valproate
- Felt best after a year of seizures
- She wants to know about different options and their benefits and side effects.

“Old” ASMs and women

Valproate

- Hyperandrogenism
- PCOS
- Weight gain: 50 – 60% of women
- Valproate induces a metabolic syndrome: centripetal obesity, hyperinsulinemia, lipid abnormalities and polycystic ovaries/hyperandrogenism in women with epilepsy.
**Phenytoin:**
- Problem: coarse facial features, a combination of hirsutism, gingival and facial connective tissue hyperplasia and acne
- Incidence: about 50% of women taking phenytoin.

**Contraceptive failure in women receiving seizure medication**

- The most common cause of contraceptive failure is steroid (estrogen or progesterone) levels insufficient to block ovulation.
- Enzyme-inducing seizure medication metabolized by liver enzymes can be responsible for more rapid clearance of steroid hormones.
How hormones can affect seizures?

**Estrogens**
- reduce seizure threshold → increase seizure
- parenteral estrogens increase epileptiform discharges in women with seizures

**Progesterone**
- has the opposite effect of estrogen: No seizures
- Oral contraceptives containing high dose progestin combinations have no effect on seizure frequency.

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**ESTROGEN**
- This hormone can “excite” the brain – making seizures more likely when levels are high.

**PROGESTERONE**
- This hormone can “inhibit” the brain – making seizures less likely when levels are high.

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Catamenial epilepsy

- Keep a track of your seizures and menstrual cycle to determine if you have seizures or increased seizures around certain times during your menstrual cycle.
- Treatment may be tailored to your cycle.
Patient case

- Sania meets her epileptologist at her next visit
- Valproate is switched to Lamotrigine 100mg twice a day
- 1 mg folic acid
- Pre-pregnancy Lamotrigine level = 8
- She wants to know about the effect of ASM and epilepsy during the pregnancy.

Planned pregnancy

- Extremely important to avoid unplanned pregnancy
- Because of the documented teratogenicity (birth defects) of many of the ASMs, as well as increased maternal and fetal risks.
- Communication between the patient’s neurologist/Epileptologist and OB-GYN is important.
Altering ASMs before pregnancy.

1. Are ASMs really necessary (does the patient have epilepsy)?
2. If the patient is seizure free for at least 2 years, consider withdrawing ASM.
3. If ASM therapy required:
   a. avoid valproate and carbamazepine. In the case of carbamazepine, consider switch to oxcarbazepine (Trileptal™).
   b. monotherapy when possible
   c. folate supplementation 1mg q.d.

New ASMs and women’s issues

- Lamotrigine: Teratogenicity appears to be low to nonexistent.
- Levetiracetam and brivaracetam probably low.
- Oxcarbazepine also has good data
- Once you are pregnant and cross 12 weeks then your epileptologist might not change your ASM based on seizure risk.
- Having seizures is riskier than changing your medication.
Critical Periods of Development

Red denotes highly-sensitive periods

Congenital malformations

a. Incidence:
   ▶ 4–7% of births to epileptic women (about 2-3X higher)
   ▶ 2–3% in general population
Factors That Increase Risk of Malformations

- ASM selection
- Polytherapy
- High treatment dose
- Folic acid deficiency
- Family history of birth defects
- Previous pregnancy with malformation: 35% if + malformation vs 3% incidence if no malformation in first pregnancy especially if VPA

Teratogenic effects of Anti-seizure medication

1. Two types of abnormalities.
   - Congenital (minor) anomalies: deviations from normal morphology that do not constitute a threat to health, do not require interventions, and do not impair function.
   - Congenital malformations: physical defects that warrant medical or surgical intervention and cause major functional problems
Principles of management of epilepsy in women during reproductive years.

- Folic acid supplements:
  - Four-fold reduction in risk of neural tube defects in offspring of women receiving folic acid in general
  - All women of reproductive age group must take 1-4 mg of folic acid per day.
- Full and detailed discussion of all the risks of ASM, the risk of a slight increase in seizure frequency in some women during pregnancy, and the importance of avoiding alcohol and tobacco during pregnancy.

Sania conceives after 6 months.
- Frequent visits and lamotrigine levels are monitored
- Makes sure that OBGYN and epilepsy physician is aware
- Breakthrough seizure in first trimester
- Lamotrigine 150mg twice a day
- Last trimesters, Lamotrigine level= 4,
- Lamotrigine 200mg twice a day
Management during pregnancy

- ASM level monitoring during pregnancy.
- Most studies have demonstrated reduction in plasma ASM levels
- AAN recommendations for ASM monitoring
  - baseline preconception level
  - at the beginning of each trimester, sometimes monthly.
  - in the last month of pregnancy
  - monthly postpartum for 3-4 month
  - more frequent monitoring if clinically indicated (increased seizure frequency, non-compliance)

Prenatal detection of malformation

Indication
- women with epilepsy in general
- women taking valproate or carbamazepine in particular
When: 18 – 20 weeks
What:
- Ultrasound: many malformations, neural tube defects/spina bifida (90% sensitivity)
- Blood test: Maternal alpha fetoprotein
- amniocentesis for alpha fetoprotein and acetylcholinesterase levels.
- Since amniocentesis has a 1% risk of miscarriage, it is generally recommended if ultrasound inconclusive.
Peripartum management

- Woman with epilepsy, slight increased risk of seizures during and immediately after labor (2 – 4%)

1. Eclampsia
Definition. Occurrence of convulsions not caused by a pre-existing epileptic disorder in women who meet the criteria for pre-eclampsia (hypertension, proteinuria, edema)

Case

- Lamotrigine 200mg twice a day
- Sania delivers healthy baby girl via normal vaginal delivery
- Immediately after delivery Lamotrigine level 12
- Calls her epileptologist
- Lamotrigine 150mg
- At 6-8 weeks—Lamotrigine 100mg twice a day
Safety in Postpartum Period

➢ Risk of seizures:
  - Physiological ASM level changes
  - Sleep deprivation/interruption
  - Stress and lack of routine and possible decreased adherence
➢ Transport of infant
  - Additional nighttime caregiver—dads are a part of the family too!
  - Low-to-ground diaper changing
  - Supervised bathing of infant

Postpartum management

➢ Follow mother’s ASM levels and alter oral dose of ASM as indicated
➢ Breast-feeding: yes, very much encouraged due to advantage of breast milk to baby.
➢ Important motherhood experience!
➢ All ASMs cross into breast milk. Case to case basis.
➢ General consensus is that breast feeding permissible in women on ASMs with careful monitoring of the infant for sedation, etc.
CASE

- Sania decides to breast feed her baby
- Baby and mommy do very well
- She follows with epileptologist and OBGYN regularly.
- She is part of women in epilepsy group on social media
- She asks all her concerns to her doctors

After 3 years…

- Sania is on 2 ASM with her seizures well controlled
- Discusses with her OB and Epileptologist about wishes to have one more baby
- Physicians and Sania with her family work as a team
- Safe pregnancy and delivers a healthy baby boy
- Doing well and she is a nurse now.
Sexuality and ASMs

- One day Sania hesitantly discusses with her OB/GYN about decreased sexual drive.
- Her OB/GYN encourages her to discuss with her epileptologist about the potential effect of ASMs.
- Epileptologist provides her resources and things she can do.

Women experienced significantly more sexual difficulties than men.

Higher dysfunction in Temporal lobe epilepsy than extratemporal focal epilepsy.

Valproate, Dilantin, carbamazepine, phenobarbital, Topiramate, pregabalin and gabapentin may cause sexual dysfunction, whereas oxcarbazepine, lamotrigine, levetiracetam and brivaracetam may improve sexual function.

Please talk to your epilepsy physician and OB/GYN about this.
After 10 years....

- Sania is an epilepsy advocate now
- She is educating patients about epilepsy and effects of ASMs at her job
- She wants to know about long term effects

Bone Health Issues

- Phenytoin (Dilantin)
- Carbamazepine (Tegretol, Carbatrol)
- Valproic acid (Depakote)
Bone Health Issues: what should you do?

<table>
<thead>
<tr>
<th>Guidelines for Maintenance and Monitoring</th>
<th>If Abnormal</th>
<th>Treatments</th>
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<tr>
<td>Ca++ 600–1,500 mg/day</td>
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<tr>
<td>Vit D up to 2,000 IU/day</td>
<td>2,000–5,000 IU/day</td>
<td>5,000–15,000 IU/day or 50,000 per week x 8 weeks, then 2,000–5,000/day</td>
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<tr>
<td>Baseline Ca++, Ph, vitamin D, PTH, alk ptase</td>
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<tr>
<td>Baseline DEXA, every 2–5 years, T score &lt; -1 and &gt; -2.5</td>
<td>T &lt; -2.5 or fracture</td>
<td>Referral for treatment</td>
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<tr>
<td>Post-menopausal</td>
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Perimenopause

- Premature ovarian failure (before age 40): 5% of women with epilepsy
- Menopause occurs earlier by 3–6 years
Epilepsy During and After Menopause

- Perimenopause
  - Seizures may worsen with significant fluctuation in ovarian steroids
  - Hormone replacement increases seizures in perimenopause
- Menopause
  - Seizures may improve, most often if prior catamenial pattern
  - HRT with unopposed estrogen may worsen seizures
  - Risk of symptomatic bone disease

Questions??

WOMEN AND EPILEPSY