Women’s Issues in Epilepsy

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How are women different?

- Different habitus
- Different metabolism
- Different co-morbidities
- Different psychosocial stigma
- Different hormonal status
  - Catamenial seizures
  - Pregnancy
  - Menopause
Hormones and Epilepsy

- Estradiol
  - exerts direct excitatory effects at the neuronal membrane by augments N methyl-D-aspartate (NMDA) mediated glutamate receptor activity
  - decreases inhibition by decreasing GABA synthesis
  - Logothetis et al. showed that intravenously administered conjugated estrogen activated epileptiform activity in 11/16 women, and associated with seizures in 4
Hormones and Epilepsy

• **Progesterone**

  • progesterone, especially its neuroactive metabolite (allopregnanolone) exert direct membrane-mediated inhibitory effects by potentiating GABA A-mediated chloride conductance

  • also potentiates the action of the powerful endogenous inhibitory substance adenosine

  • Backstrom et al. found that iv progesterone at sufficient doses was associated with decrease interictal spikes in 4/7 women with partial epilepsy
Estrogen – Proconvulsant

Progesterone – Anticonvulsant
Epilepsy and Fertility

- Decreased fertility among women with epilepsy (II)
  - Polycystic Ovarian Disease
  - Sexual Dysfunction
  - Psychosocial effect of epilepsy
  - AED effect to the fetus
  - Effect of seizures for the fetus

- AED and OCP interactions
Polycystic Ovarian Disease (PCOS)

• Failure of the ovarian follicle to complete normal maturation during the menstrual cycle

• Syndrome of
  – hyperandrogenism (raised testosterone levels)
  – multiple ovarian cysts
  – anovulatory cycles
  – hirsutism
  – obesity

• Prevalence of PCOS
  – in women without epilepsy is between 4% -6%
  – in women with epilepsy unknown (~ 2 x that of women without epilepsy), even in those not taking AED medication*
  – more common in women taking valproate, especially if started < age 20
AEDs and OCPs

• Increased breakthrough bleeding noticed when dosing of OCP decreased from 50-100ug to < 50 ug (due to risk of thrombosis)

• Modern available combined OCPs contain 20–35 ug of ethinylestradiol and < 1 mg of progestogen
Lamotrigine*
- cOCP can decrease lamotrigine trough levels by 25–70% AND...
- 20% to 100% of progestogen-only oral contraceptive

Benzodiazepines
- no effect on OCP

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### Effect of antiepileptic drugs (AEDs) on hormonal contraceptive agents

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<th>Enzyme-inhibiting AEDs</th>
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<td></td>
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<td>Zonisamide</td>
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For women on enzyme-inducing AEDs wishing to take OCPs

• cOCP
  • Start with 50 μg/day ethinyl oestradiol dosage (C)
  • If breakthrough bleeding occurs, increase the dose of ethinyl oestradiol to 75 or 100 μg/day (C)

• Other contraceptive methods
  • Medroxyprogesterone injections effective (III) but take q10 weeks rather than 12 weeks if using enzyme-inducing AEDs
  • IUDs also effective (acts locally)
  • Emergency contraceptive pill can be used in women with epilepsy after unprotected sexual intercourse (C)

• Ineffective
  • Progesterone only pill (III)
  • Levonorgestrel implants - high failure rate (III)

• Should always recommend second contraceptive methods
Catamenial Seizures
Catamenial Seizures

- Doubling of seizures around menses
- Occurs in about 12% of women with epilepsy (II)
- Can affect ~ 1/3 of women with localization-related epilepsy

- 3 catamenial seizure patterns have been identified
  - Ovulatory cycles
    » During perimenstrual days (pattern C1)
    » Periovulation (pattern C2)
  - Anovulatory cycles
    » Post-ovulation, when luteal phase inadequate (pattern C3)
Ovulatory Cycles

• Seizure frequency shows positive correlation with serum estradiol/progesterone ratio

• Ratio is highest during days prior to ovulation and menstruation and is lowest during the early and midluteal phase (post-ovulatory)

• Premenstrual exacerbation of seizures has been attributed to the rapid withdrawal of the antiseizure effects of progesterone
Ovulatory Cycle

Normal Cycle

Serum hormone levels

Estradiol µg/ml
Progesterone ng/ml

Catamenial Type Cycle Phase

F
O
L
M

Day of the cycle

1 3 5 7 9 11 14 -12 -10 -8 -6 -4 -2 1 3
Anovulatory Cycle

Inadequate Luteal Phase Cycle

Catamenial Type

Cycle Phase

E2  P

0 25 50 75 100

Day of the cycle

F  O  L  M

Estradiol µg/ml
Progesterone ng/ml

Serum hormone levels

University Health Network
Catamenial Seizures

- Catamenial seizure exacerbations primarily related to changing sex hormone concentrations during the menstrual cycle.

- But also alterations in AED concentrations, as seen with phenytoin and lamotrigine, throughout the menstrual cycle.
Catamenial Seizures – Treatment Strategies

- ↑ AED dose around time of ↑ seizures
- Avoid cyclic variation by a continuous OCP
- Supplemental progesterone during luteal phase
- Double-blind, randomized, placebo-controlled trial of cyclic supplemental progesterone currently underway
Catamenial Seizures – Treatment Strategies

• For women already on AEDs
  • intermittent clobazam on days when ↑ seizures (B)
  • acetazolamide perimenstrually (C)
  • progestogens perimenstrually (C)

• For women not already taking AEDs
  • intermittent perimenstrual clobazam (5 to 30 mg/day)
  • COCP; depot progestogen therapy; or perimenstrual progestogen (III)
Pregnancy and Epilepsy
Pregnancy and Epilepsy

• > 90% of women with epilepsy have a normal pregnancy

• Obstetrical risks of pregnancy inconclusive
  - low birth weight
  - preeclampsia
  - bleeding
  - placental abruption
  - prematurity
  - neonatal or perinatal death reported 2-3x higher, though wide variability in studies, including one study with no increased risk of death*

• No increased risk of major fetal malformation
Pregnancy and Epilepsy

• Most women will have no change of their seizure pattern during pregnancy (~50%), 25% will have improved seizure frequency

• Factors that may exacerbate seizures
  • noncompliance
  • nausea and vomiting
  • inappropriate decrease in AED
  • changes in blood volumes
  • sleep deprivation

• If a patient has been seizure free for at least 2–3 years with no risk factors for seizure recurrence, consider withdrawing AEDs 6 months prior to planned conception
Pregnancy and Anticonvulsants

- Increased risk of fetal malformations with intrauterine exposure to 4 major anticonvulsants
  - Phenytoin
  - Carbemazepine
  - Valproic acid
  - Phenobarbital

- Major fetal malformations is 4-6% vs 2-3%

- Most studies identify valproate (~7-10%) or polytherapy (15%) exposure as the highest risk, especially in first trimester*
Pregnancy and Anticonvulsants

- **Valproic Acid**
  - 1-2% of babies with neural tube defects (10-20x)
  - Major birth defects in VPA monotherapy 10.7% vs 2.9% for other AEDs
  - Dose related
    - \( \leq 1000 \text{ mg/day} \) OR \( \sim 1 \)
    - \( \leq 1500 \text{ mg/day} \) OR \( = 3.7 \)
    - \( >1500 \text{ mg/day} \) OR \( = 10.9^{*} \)

- **Lamotrigine**
  - Best studied newer AED
  - \( \sim 3\% \) incidence of major malformations with 1st trimester exposure
  - North American AED Pregnancy Registry noted a higher than expected prevalence of cleft palate and/or cleft lip (not reproduced)
Longterm effects of AED exposure

• Intrauterine exposure to valproate resulted in children with IQ scores ~ 6-9 points lower than those exposed to other AED (lamotrigine, phenytoin, or carbamazepine)

• No specific dose response established
Post-partum

- 1-2% of women with active epilepsy will have a tonic–clonic seizure during labor

- Further 1–2% will have a seizure within 24 h*

- If AED dose increased during pregnancy, gradually reduce it to preconception dose over the few weeks following delivery, to reduce the risk of maternal drug toxicity
Breastfeeding and AEDs

• Any theoretical risks need to be balanced against the known benefits of breastfeeding,
  • psychological benefits for mother and child
  • reduced infant mortality
  • fewer infectious disease
  • decreased risk of immunologically mediated disorders (type 1 DM)*

• Current recommendations all support breastfeeding
  • Watch for lethargy (especially with benzodiazepines, barbituates)
  • Lamotrigine
    – Increased risk of toxicity
    – Suggest lamotrigine levels should be monitored in breastfed children whose mothers are taking high-dose lamotrigine
Recommendations

• AED therapy should be optimized prior to conception (monotherapy preferred)
  • No agreement to which AED is most or least teratogenic
  • AED that stops seizures in a given patient is the one that should be used (VPA*)
  • Plasma drug level should be monitored regularly during pregnancy (free drug levels more reliable)
  • Screen for neural tube defects, specialized OB centre

• Folic acid daily prior to conception

• Vitamin K (20 mg/day po) in last month, infants should receive 1mg IM at birth

• Breast feeding recommending even while on AED
Epilepsy and Menopause
Epilepsy and Menopause

• Epilepsy can alter timing of menopause*
  – Association between partial epilepsy and premature menopause
  – Relationship between seizure frequency and age at menopause
  – Increased frequency of premature ovarian failure in women with epilepsy
Epilepsy and Menopause

• Small survey studies report ↑ seizures during the perimenopausal transition, but improved seizure frequency once menopause complete*

• Catamenial epilepsy pattern a hallmark for the observed increase at perimenopause but decrease at menopause

• Multicenter, randomized, placebo-controlled trial in postmenopausal women with epilepsy demonstrated ↑ seizure frequency in a dose-dependent fashion with HRT (Prempro, conjugated equine estrogens plus medroxyprogesterone acetate)*
Epilepsy and Menopause

- During menopause seizure frequency
  - Worsens in ~ 40%
  - Improves in ~30%
  - No change in ~ 30%*

- HRT significantly ↑ seizure frequency during menopause, more likely in women with history of catamenial epilepsy
Epilepsy and Bone Health

• Women with epilepsy at ↑ risk of fractures, osteoporosis, and osteomalacia

• ~10% of women with epilepsy have premature bone demineralization, especially if using AEDs that induce the hepatic cytochrome P450 enzyme system

• Multifactorial
  – Adverse effects of AEDs on bone metabolism, vitamin D, bone turnover
  – Trauma of seizures
  – Subtle effects of AEDs on coordination

• Most effective therapy for AED-induced osteoporosis has not been established
## Risk factors for early osteopenia and secondary osteoporosis

- Inadequate nutrition, especially deficient calcium intake
- Weight < 127 lb
- Inadequate weight-bearing exercise
- Neuromuscular impairment
- Institutionalized or wheelchair/bed-bound status
- Treatment with phenobarbital, primidone, phenytoin, carbamazepine*, or valproate*
- Smoking
- Excessive alcohol intake
- Prolonged steroid therapy
- Menopause
- Fair complexion, or Asian or northern European ancestry

* Studies are being completed.
Recommendations

• Screening with bone scans of the spine or hip should be obtained in at-risk women and be repeated every 2 years or if a fracture occurs.

• Women should be counseled about adequate calcium intake, and a dietary history should be obtained.

• Supplementation with calcium and vitamin D.
Conclusions

• Women with epilepsy have unique issues
  • Fertility
  • Catamenial seizures
  • Pregnancy
  • Menopause
  • Bone Health
Thank you!