Management of Epilepsy in Pregnancy

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We've come a long way…

- Sterilization of people with epilepsy was legal in the early-mid 20th century
- Even today, women with epilepsy (WWE) sometimes receive messages that they should not consider pregnancy
- As a medical community, we should work to eliminate this belief and make pregnancy as safe as possible for WWE

Overview

- Before pregnancy
- During pregnancy
- Postpartum and breastfeeding

Case 1

26 year old female with history of generalized epilepsy with convulsive seizures who presents for preconception counseling. She currently takes divalproex 500 mg daily and is well controlled. Last seizure >2 years ago. She previously failed therapy with levetiracetam, lamotrigine, zonisamide and topiramate.

Should we make any medication changes?

Case 2

21 year old female with focal epilepsy and bipolar disorder on divalproex 1500 mg daily found to be ~5 weeks pregnant. She has never been on any other medications for epilepsy.

Should we make any medication changes?

Contraception

- One third of WWE say that they have never discussed contraception and/or pregnancy with their neurologist
- Seizure medications and OCPs can have significant interactions
- Depending on the patient's AED, IUDs are sometimes the safest option

Seizure medications and OCPs

Lower hormone levels

- **Carbamazepine**
- **Clobazam**
- **Eslicarbazepine**
- Felbamate
- **Oxcarbazepine (>1200 mg)**
- Perampanel
- **Phenytoin**
- Primidone
- Rufinamide
- **Topiramate (>200 mg)**

No significant effects

- **Clonazepam**
- Ethosuximide
- **Gabapentin**
- **Lacosamide**
- **Lamotrigine (estradiol lowers level)**
- **Levetiracetam**
- Pregabalin
- **Valproate**
- Vigabatrin
- **Zonisamide**

Preconception counseling: fertility

- Data have been mixed about fertility
- Women with Epilepsy: Pregnancy Outcomes and Deliveries study
  - Observational cohort study comparing fertility in WWE and control women
  - 197 women included in the study, planned pregnancies
- WWE seeking pregnancy without prior infertility disorders have similar likelihood of achieving pregnancy, time to pregnancy, and live birth rates compared to peers without epilepsy

Pennell et al. JAMA Neurol 2018

Preconception counseling (or lack thereof)

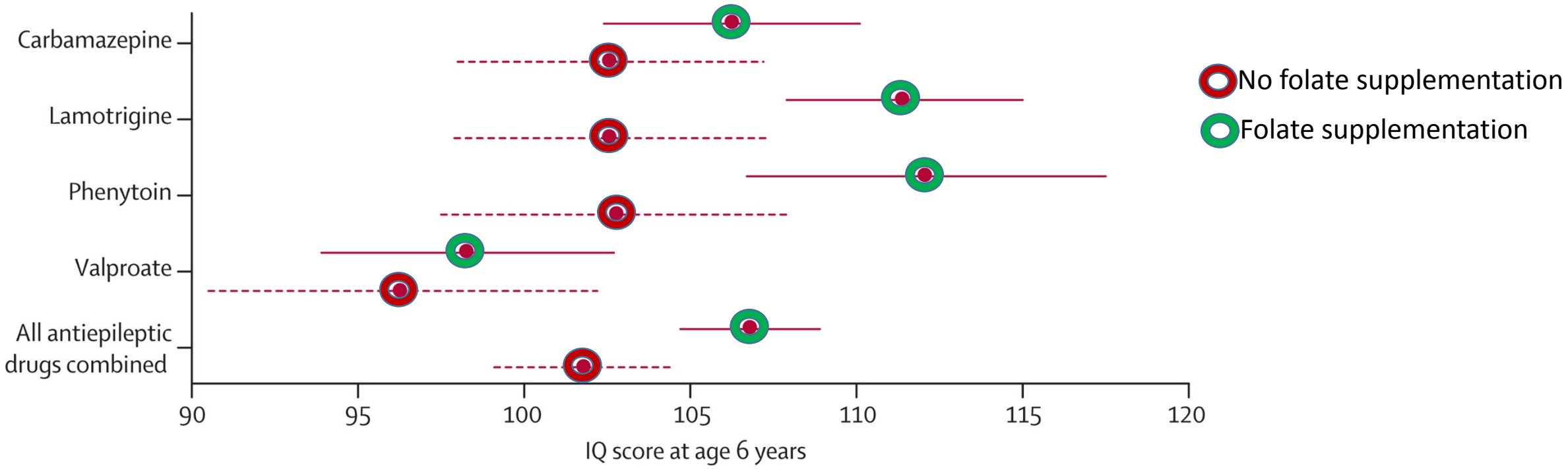
- Up to 50% of pregnancies in WWE are unplanned
- Choice of AED, dose of AED, monotherapy/polytherapy
  - Ideal: monotherapy at lowest possible dose
- Informed consent for AED at initiation
- Most WWE will need to remain on AEDs during pregnancy
- Most children born to WWE are normal

Preconception counseling: FOLATE

- Supplementation provides protection against neural tube defects
- Folate in all women of childbearing age: dose 0.4 mg daily
- Folate in all WWE of childbearing age: dose uncertain = 1 – 4 mg daily

Further benefit of folate supplementation

- NEAD study → Leads to higher IQ (CBZ, LTG, PHT, VPA)



Meador et al. Lancet Neurol 2013

Pregnancy - Prenatal AED exposure

- ~ 4.3 million AED prescriptions written annually for women of childbearing age in the US
- A 2012 study (Bobo et al.) estimated at least 2% of pregnancies are exposed to AEDs and found that AED use during pregnancy increased fivefold from 2001 to 2007
- Use/dose at conception matters because first trimester exposure to some AEDs leads to increased risk for major congenital malformations (MCM)
  - MCM includes heart, skeletal, urologic, neural tube defects, orofacial clefts
- Clinical research is limited → pregnancy registries

AED associated malformation rates

	EURAP	NAAPR
Valproate	9.7% (98/1010)	9.3% (30/323)
Phenobarbital	7.4% (16/217)	5.5% (11/199)
Topiramate	6.8% (5/73)	4.2% (15/359)
Phenytoin	5.8% (6/103)	2.9% (12/416)
Carbamazepine	5.6% (79/1402)	3.0% (31/1033)
Oxcarbazepine	3.3% (6/184)	2.2% (4/182)
Lamotrigine	2.9% (37/1280)	1.9% (31/1562)
Levetiracetam	1.6% (2/126)	2.4% (11/450)

(Malformation rates = 2-3% in the general population)

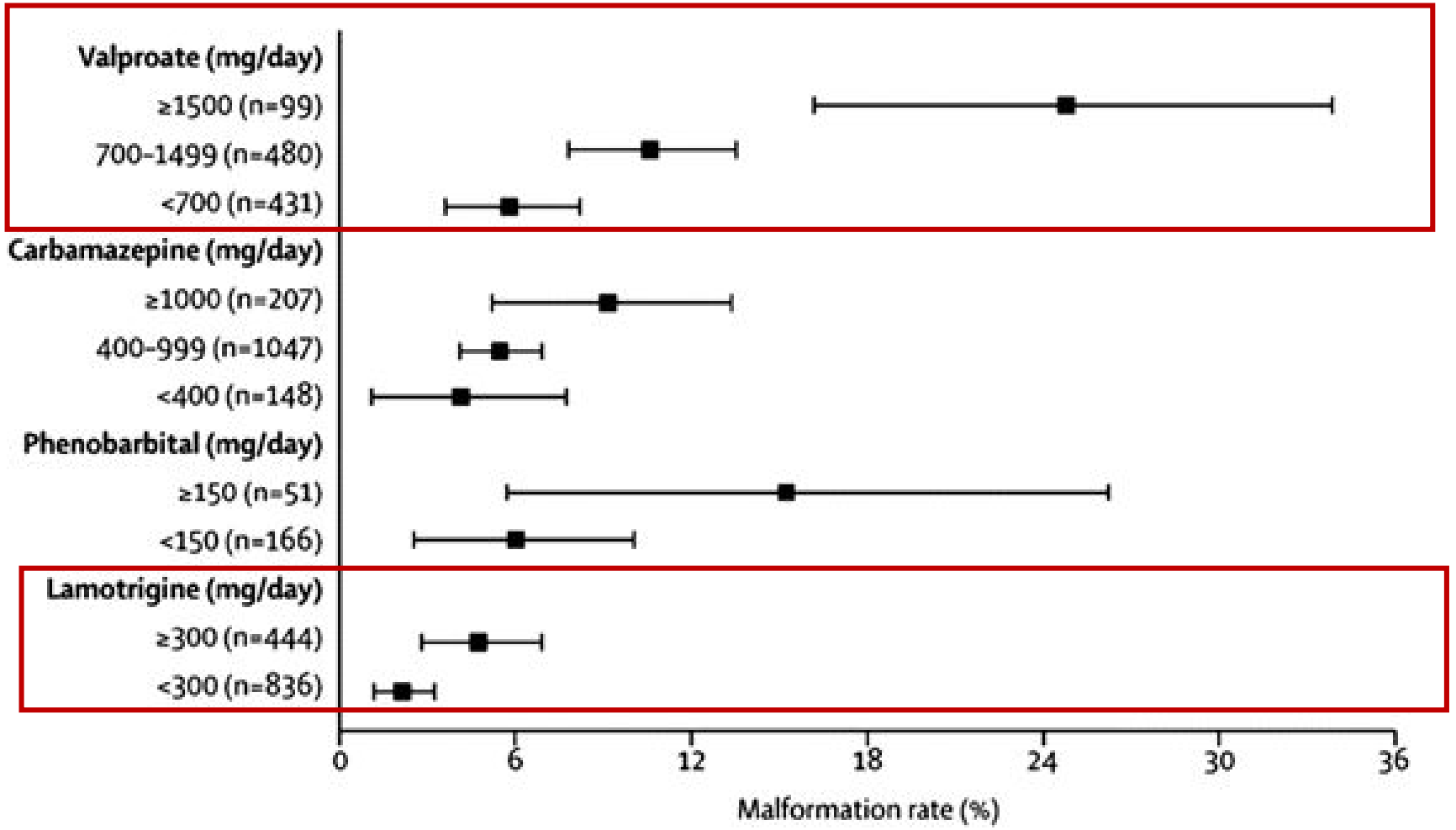
Tomson et al. Seizure 2015

AED associated malformation rates

- 2017 update from North American AED pregnancy registry

	NAAPR
Gabapentin	1.1% (2/179)
Zonisamide	1.3% (2/153)
Clonazepam	2.1% (2/97)

Dose dependent effects



Tomson et al. Lancet Neurol 2011

AED monotherapy vs dual therapy

- Keni et al. (2018) evaluated teratogenicity of antiepileptic dual therapy
  - 1688 completed pregnancies, 368 on dual therapy
  - Risk of MCM was 1.6 times more with dual therapy than with monotherapy
  - Risk of MCM highest with topiramate and valproate dual therapy
  - No MCMs with lamotrigine or levetiracetam dual therapy

AED polytherapy

- Vajda et al. (2018) evaluated seizure control and malformation rates
  - 1810 pregnancies, 508 on polytherapy
  - Polytherapy treated pregnancies were less often seizure free (38.2%) than monotherapy treated pregnancies (60.1%) - focal and generalized epilepsy
  - Drug combinations with dissimilar and similar mechanisms of action achieved similar rates of seizure freedom
  - Increased rate of malformations when topiramate or valproate used
  - Combination of lamotrigine and levetiracetam most frequently associated with birth of normal infant after seizure free pregnancy

Valproate (VPA)

- Structural teratogenesis (broad range)
  - Neural tube, cardiac, cleft lip/palate, hypospadias
- Cognitive teratogenesis
  - With prenatal exposure, IQ 7-10 points lower than with other AEDs (NEAD study)
  - Increased risk for autism spectrum disorder and ADHD

Valproate… more evidence against use

- Elkjaer et al. (2018) evaluated prenatal exposure to valproate and long-term school performance in Danish children
  - 253 children exposed to valproate
  - Substantial decrease in school performance in children exposed to valproate compared with children unexposed to AED and children exposed to lamotrigine
  - Effect maintained even when mothers took <1000 mg valproate daily

Seizures can also be harmful

- Fetal anoxia and maternal injury
- Increase risk of preterm labor and SGA infants
- Developmental delay after 5 or more tonic-clonic convulsive seizures during pregnancy
- Few effective alternatives to valproate for generalized epilepsies
- It may be dangerous to taper or switch during pregnancy

Seizure frequency during pregnancy

- Most WWE do not experience change in seizure frequency
- Seizure stability prior to pregnancy predicts seizure control during pregnancy and immediately post-partum

Seizure frequency during pregnancy

- MONEAD study
  - 351 pregnant WWE compared to 109 non-pregnant WWE
  - Among women who were seizure free at baseline
    - 84.8% pregnant WWE seizure free during pregnancy
    - 85.7% non-pregnant WWE seizure free during 9 months after enrollment
    - 87.8% pregnant WWE seizure free 9 months post-partum
    - 83.7% non-pregnant WWE seizure free subsequent 9 months

AED levels during pregnancy

- Levels of lamotrigine, levetiracetam, oxcarbazepine generally decline during pregnancy
- Other AED levels may also decline
- Widely variable among women and even across repeat pregnancies
- Follow levels closely
  - Baseline level
  - Monthly levels in 2nd and 3rd trimester

Pharmacokinetic changes

AED	Increase in clearance
Levetiracetam	243%
Lamotrigine	65-230%
Oxcarbazepine	56-163%
Phenobarbital	60%
Phenytoin	19-117%

Pennell et al. Int Rev Neurobiol 2008
Harden et al. Neurology 2009

AED levels during pregnancy

- Increase doses as needed to maintain therapeutic baseline level
- Postpartum taper (not an exact science)
  - Renal excretion returns to baseline over 2-3 weeks
  - CyP450 metabolism returns to baseline over 2-3 months
  - Taper of lamotrigine over 10 days reduced postpartum toxicity*
- May need slightly higher than baseline levels to protect during 1-3 months postpartum (sleep deprivation, etc)

*Pennell et al. Neurology 2008

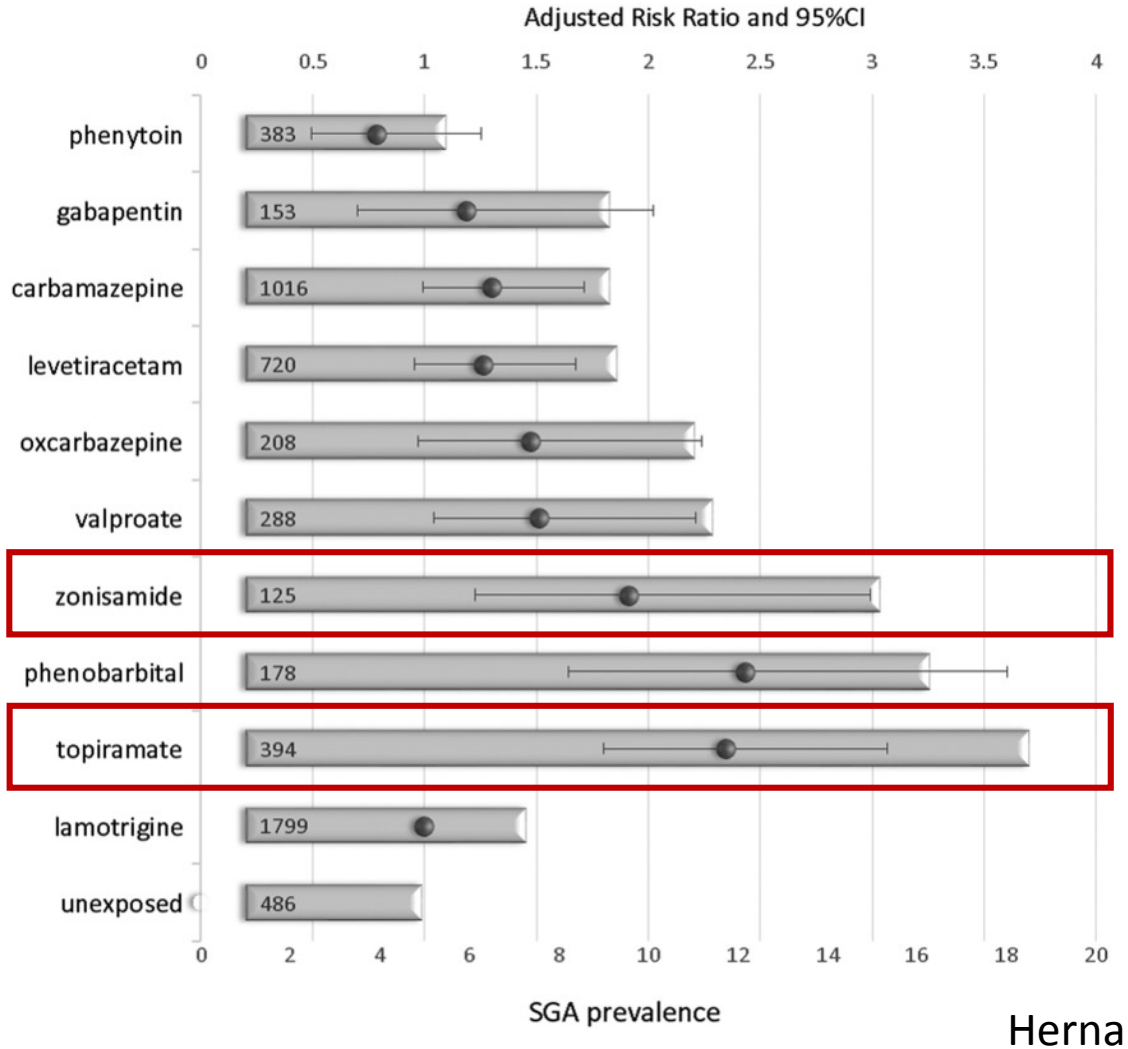
Non-pharmacologic adjunctive treatment options

- Limited data regarding vagal nerve stimulation (VNS) during pregnancy
  - Sabers et al. examined outcomes in 26 pregnancies with VNS (EURAP) and found that the sample size was insufficient to draw conclusions
- One case report of VNS implanted during 3rd trimester without complications (and a reduction in seizure frequency)
- No available data for responsive neurostimulation (RNS) and pregnancy

Obstetrical/perinatal outcomes

- WWE may be at increased risk for gHTN, preE, postpartum hemorrhage
- Preterm birth, IUGR, SGA infants more common in WWE
- Why??
  - Epilepsy
  - Seizures during pregnancy
  - AED effect

Small for gestational age infants



Hernandez-Diaz et al. Ann Neurol 2017

Breastfeeding

- BENEFICIAL
- Transfer of AEDs summarized in 2009 AAN practice parameters
  - Levetiracetam probably penetrates breast milk in “potentially clinically important” amounts
  - Gabapentin, lamotrigine, topiramate possibly penetrate in “potentially clinically important” amounts
  - Valproate, phenobarbital, phenytoin, carbamazepine (highly protein bound) probably do not penetrate in “potentially clinically important” amounts
- Benefits generally outweigh risks
- Ask moms to monitor baby for alertness and skin rashes

Harden et al. Neurology 2009

Breastfeeding

- Children with exposure to carbamazepine, lamotrigine, phenytoin, valproate in breast milk had higher IQs and language scores at 6 yo than children who did not breast feed (NEAD study)

Postpartum safety

- Precautions for bathing and caring for the baby
  - Floor instead of changing table
  - Stroller instead of carrier
  - Avoid stairs
  - Avoid co-sleeping
- Sleep deprivation may increase risk of seizure
- Family support/ need for help
- Screening for postpartum depression

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Should we make any medication changes?

Case 2

21 year old female with focal epilepsy and bipolar disorder on divalproex 1500 mg daily found to be ~4 weeks pregnant. She has never been on any other medications for epilepsy.

Should we make any medication changes?

Summary

- Many anti-seizure medications can reduce the effectiveness of OCPs
- Folate should be supplemented in all WWE of childbearing age
- Levetiracetam and lamotrigine (and probably oxcarbazepine) are NOT associated with increased risk of major congenital malformations
- Valproate should be avoided in women of childbearing age due to high rates of structural and cognitive teratogenesis (if possible)
- Monitor AED levels during pregnancy
- WWE may be at higher risk of complications in the perinatal period
- It is important to address breastfeeding and postpartum safety

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Questions?

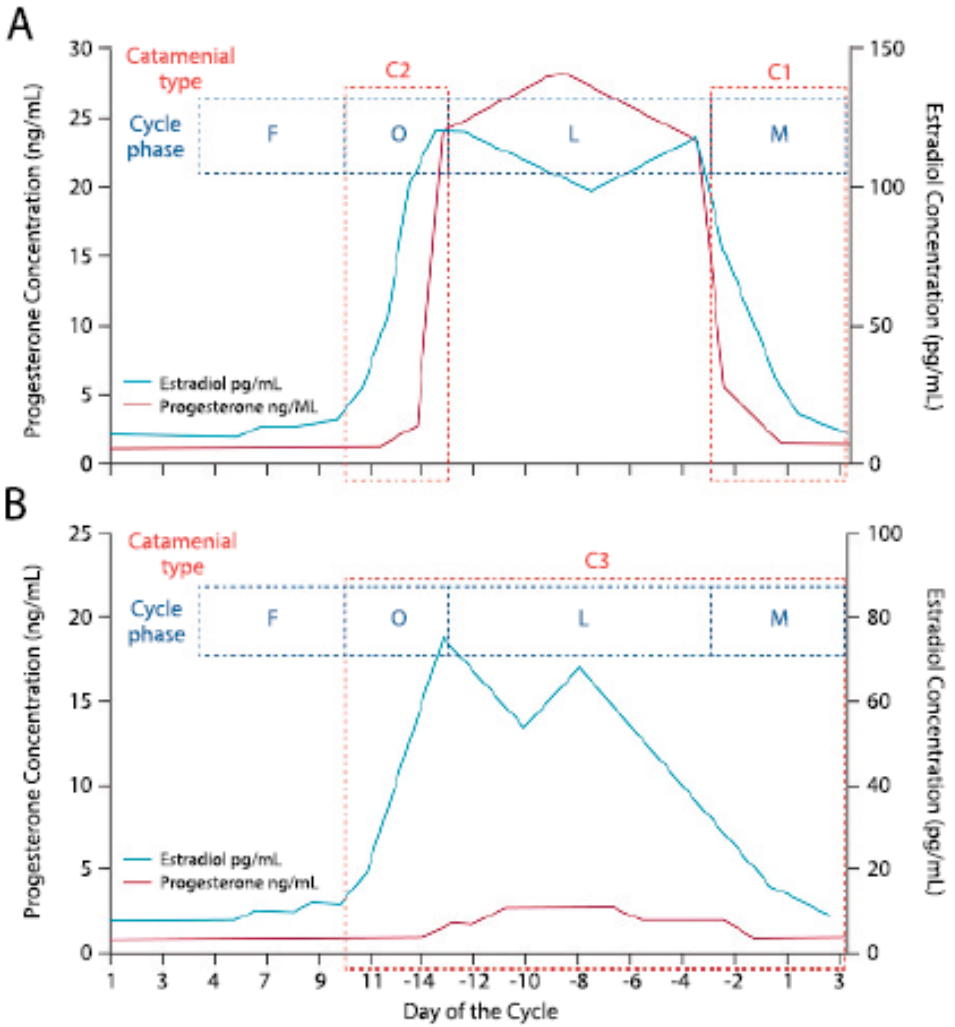
"I'm a very busy woman and I don't have time to be pregnant for 9 months, so I laid an egg."

http://www.glasbergen.com/cartoons-about-pregnancy/

Extra slides

Catamenial epilepsy

- Pattern of increased seizures at specific times in the menstrual cycle (increased estrogen to progesterone ratio)
- Affects up to 42% of women with epilepsy
- 3 patterns
  - C1
  - C2
  - C3
- Decrease in seizures during follicular phase



Treatment of catamenial epilepsy

- Seizure frequency and menstrual cycle must be tracked to understand pattern
- First, treat with standard AED therapies
- Adjunctive therapies are available but unclear if truly effective
  - Acetazolamide
  - Clonazepam
  - Medroxyprogesterone
  - Progesterone lozenges

Vitamin K

- Mothers - vitamin K supplementation did not reduce risk of PPH
- Babies should be given IM vitamin K