Optimizing Treatment of Adolescents and Women with Epilepsy during Reproductive Years

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Learning Objectives

At the conclusion of this activity, participants should be able to:

1. Deliver effective counseling for women with epilepsy across the reproductive lifespan

2. Understand the effects of cycling sex steroid hormones on seizure patterns and be aware of treatment strategies to women with catamenial epilepsy

3. Anticipate potential effects of the menopausal transition on epilepsy

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How does the expression of Epilepsy differ for adolescent girls / women?

- Common onset of epilepsy during puberty (female>male)
- Estrogen and Progesterone fluctuate, and therefore, have the most obvious influence on seizure frequency (catamenial epilepsy)
- Potential for changes in seizure expression during pregnancy & postpartum, and during menopausal transition
- Safety considerations during pregnancy for mother & child
- Effect of hormone therapies on seizure frequency
- Co-morbidities can differ
  - e.g., bone health, psychiatric, reproductive dysfunction

Better Understanding Leads to Better Patient Care

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Adolescents with Epilepsy and Their Caregivers Want Counseling from Child Neurologists About:

Hormonal Changes

- ❑ If epilepsy affects your period
- ❑ If epilepsy causes hormone problems
- ❑ If your period causes seizures
- ❑ Puberty and epilepsy

Birth Control

- ❑ Does my seizure medicine interact with birth control?
- ❑ Birth control options
- ❑ If birth control affects seizures

Sex & Epilepsy

- ❑ Can seizures occur during sexual intercourse?
- ❑ Can sexual intercourse cause seizures?
- ❑ Consent & how seizures impact consent
- ❑ Seizure first aid training for partners

"I do wish that conversations with my doctors, more often than not, go on with women's health and epilepsy because I really wanna find that out, and, anything happens to me in the future, I want to know beforehand…"

Preparing for Pregnancy

- ❑ Folic acid supplements
- ❑ Importance of planning pregnancy
- ❑ Let doctors know if you're pregnant or trying
- ❑ Safety of pregnancy with epilepsy

Pregnancy with Epilepsy

- ❑ Will my children have birth defects?
- ❑ Will my children have autism or low IQ?
- ❑ Taking seizure medicine during pregnancy

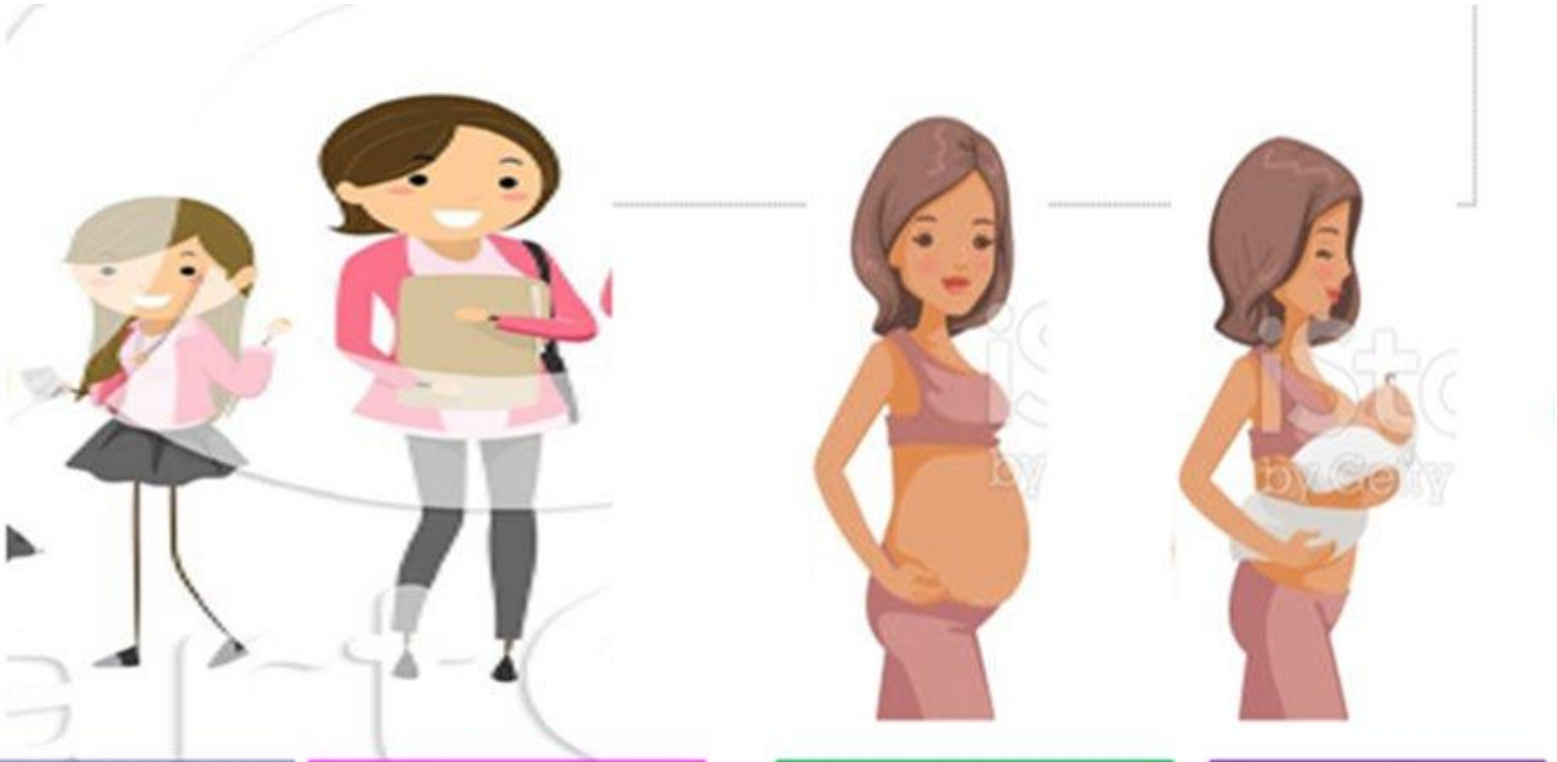
Parenthood & Epilepsy

- ❑ Will my children have epilepsy?
- ❑ Genetic counseling

"I think it's just talking to women starting in eighth [grade or] middle school or high school age so they can be educated so when it does—when they do decide to conceive and have a baby they know what signs to look for and to know if they're having a seizure or not and how to get it taken care of before it's too late."

Kirkpatrick L et al. Pediatric Neurology 2025; PMID: 40884871. Kirkpatrick L, et al. Pediatr Neurol. 2025; PMID: 40884871. Kirkpatrick L et al. Epilepsy & Behavior. 2022. PMID: 35247834.

Counseling



- Counseling needs change across the reproductive lifespan
- Starts in adolescence at menarche
- Continues with more details in pregnancy and postpartum

Contraception counseling

- Importance of planned pregnancy:
  - Optimize antiseizure medication (ASM) regimen, such as avoiding ASMs with adverse teratogenic and neurodevelopmental outcomes
  - Manage tonic-clonic seizures as able to reduce risk of low birth weight,[1] fetal hypoxia,[2] and miscarriage[3]
  - Start folate supplementation for improved neurodevelopmental outcomes and possibly decreased risk of major congenital malformations[4]

1. Fu Y, et al. JNNP 2025;96:621–9; 2. Teramo K, et al. J Perinat Med 1979;7:3–6; 3. EURAP Study Group. Epilepsia 2013; 54:1621–7; 4. Pack AM, et al. Neurology.2024;102(11):e209279.

Folate

- At dose of least 0.4 mg per day:
  - Likely no demonstrated benefit for the prevention of major congenital malformations
  - May be associated with better neurodevelopmental outcomes, such as reduced autistic traits at 3 years and higher global IQ at 6 years

Pack AM, Oskoui M, Williams Roberson S, et al. Neurology. 2024;102(11):e209279.

Contraception considerations

- 53-69% of women with epilepsy at risk of unplanned pregnancy, with 30-53% of those using highly efficacious contraception[6,7]
- Enzyme-inducing ASMs can reduce efficacy of contraception[4]
- Barriers to care, including access to effective contraception[5] and accurate counseling
- Estrogen induces glucuronidation, leading to lower levels of lamotrigine,[1] oxcarbazepine,[2] and valproic acid[3]

1. Sabers A, et al. Neurology 2003; 61(4): 570-1; 2. Mostacci B, et al. Seizure. 2018 Oct;61:200-202; 3. Galimberti CA, et al. Epilepsia. 2006 Sep;47(9):1569-72; 4. Schindlbeck C, et al. Arch Gynecol Obstet. 2006 Jan;273(4):255-6. 5. UN Department of Economic and Social Affairs, Population Division 2022. 6. Davis AR, et al. Contraception. 2008;77(6):405-409. 7. Herzog AG, et al. Epilepsia. 2016;57(4):630-637.

ASMs: Degree of Induction of Metabolism of Systemic Hormonal Contraceptive Agents

Marked Induction	Slight to Moderate Induction	Non-inducers
carbamazepine	clobazam	brivaracetam
cenobamate	lamotrigine	clonazepam
eslicarbazepine acetate	rufinamide	ethosuximide
felbamate	topiramate (doses ≥ 200 mg/day)	gabapentin
oxcarbazepine		lacosamide
perampanel (doses ≥ 12 mg/day)		levetiracetam
phenobarbital		pregabalin
phenytoin		valproic acid
primidone		vigabatrin
		zonisamide

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Long-acting reversible contraception (LARC)

Copper IUD

Levonorgestrel IUD

Contraceptive implant (etonogestrel), **avoid with enzyme-inducing ASMs**

IM medroxyprogesterone[1]

1. Dutton C, Mody SK, Nippita S, et al. Contraception. 2024 Jun;134:110418.

Sex Steroid Hormones:
Influence on Expression of Epilepsy during Reproductive Years

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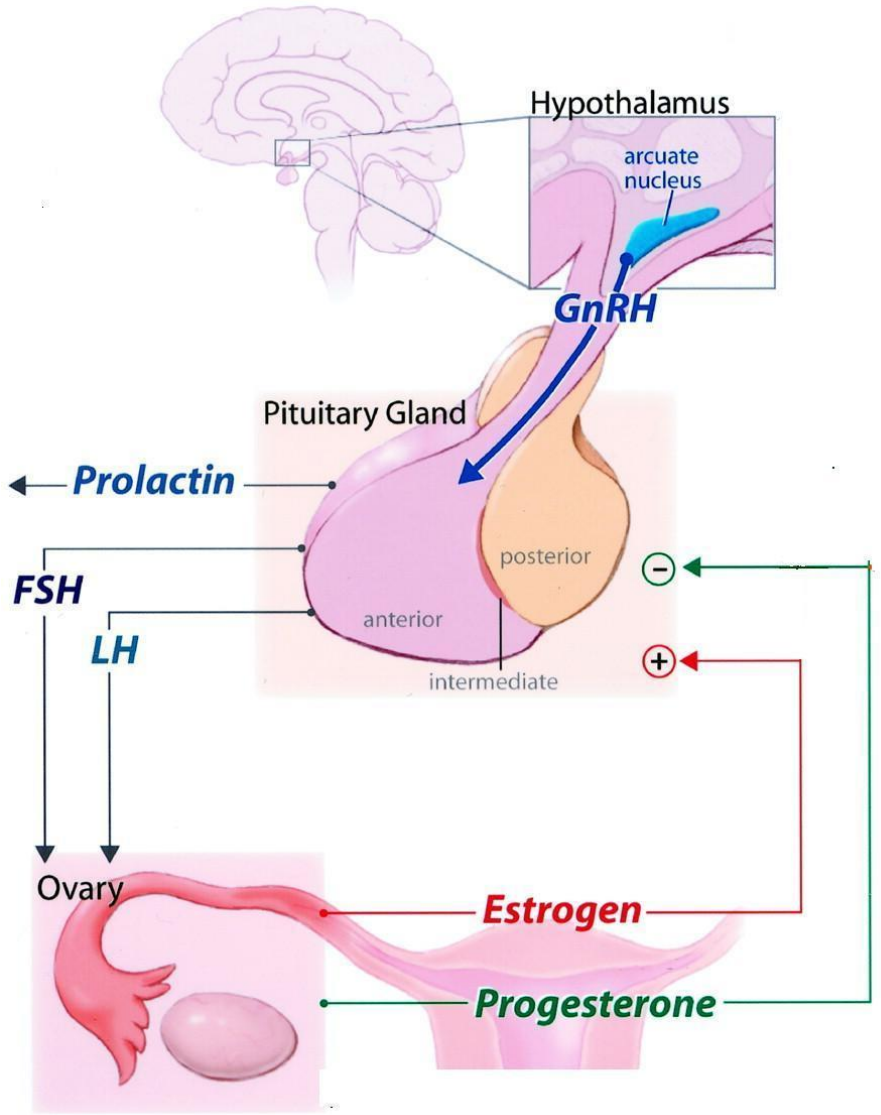
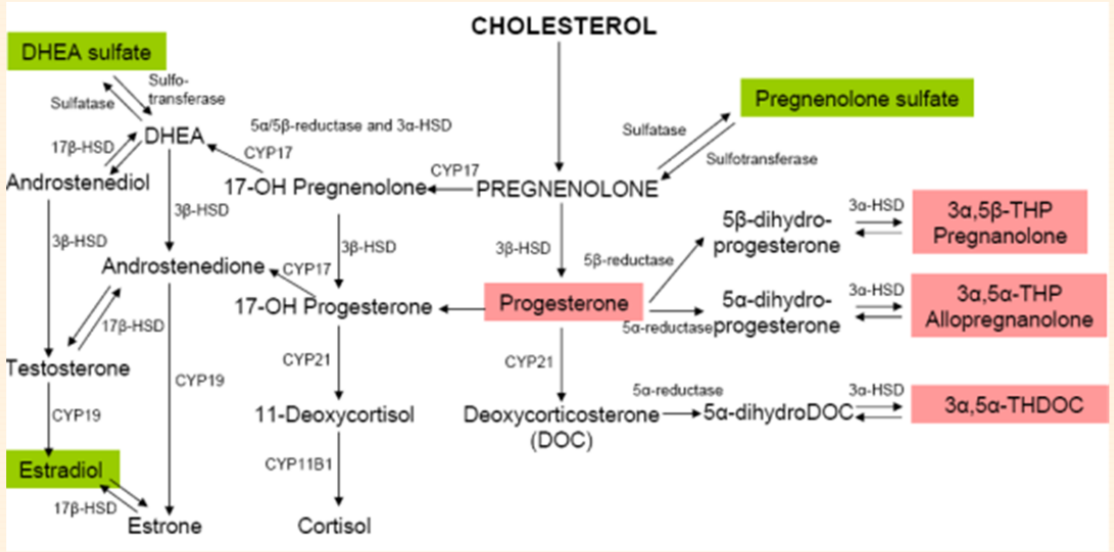
Hypothalamic-Pituitary-Ovarian Axis



Harden CL, Pennell PB. Neuroendocrine considerations in the treatment of men and women with epilepsy. Lancet Neurol. 2013;12(1):72-83. PMID: 23237902; PMCID: PMC4928713.

Sex Steroid Hormones & Neuroactive Steroids (NAS)

Biosynthesis Pathways for Neuroactive Steroids



Green = Proconvulsant
Pink = Anticonvulsant

Pennell PB. Unpublished.

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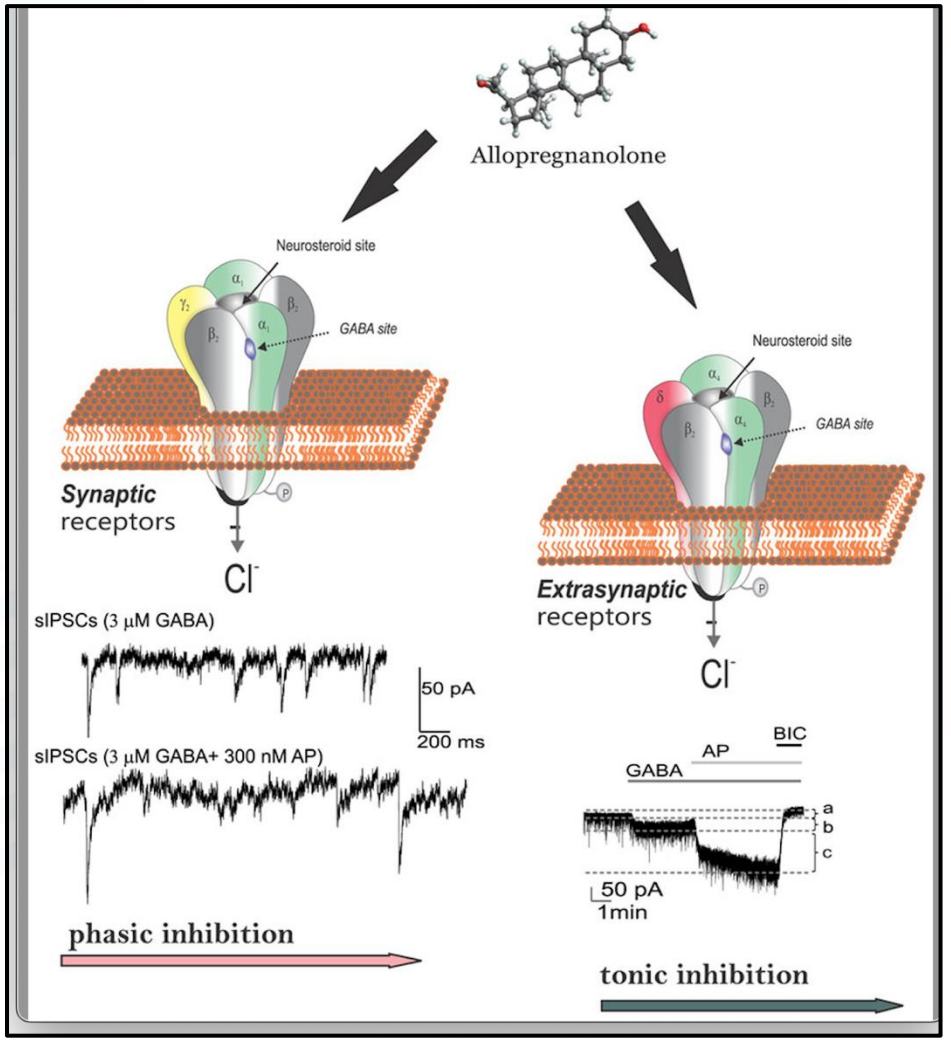
NAS concentrations at the target site derive from peripheral NAS, peripheral precursors, and local synthesis.



Reddy DS. Role of hormones and neurosteroids in epileptogenesis. Front Cell Neurosci. 2013;7:115. PMID: 23914154; PMC3728472.

Catamenial Epilepsy Definition

Catamenial epilepsy refers to patterns of seizure occurrence in females with epilepsy (**FWE**) during the reproductive years which correlate with menstrual cycling

"Herzog criteria" of 3 catamenial patterns are most frequently cited and accepted internationally

Catamenial patterns are difficult or cannot be assessed in:

- In WWE on systemic hormonal contraceptives
- In WWE who are not drug-resistant
- In WWE with irregular menstrual cycles & frequent anovulatory cycles
- During menarchal and menopausal transition, characterized by irregular sex steroid hormone (SSH) patterns

Herzog AG, Klein P, Ransil BJ. Three patterns of catamenial epilepsy. Epilepsia. 1997 Oct;38(10):1082-8. PMID: 9579954.

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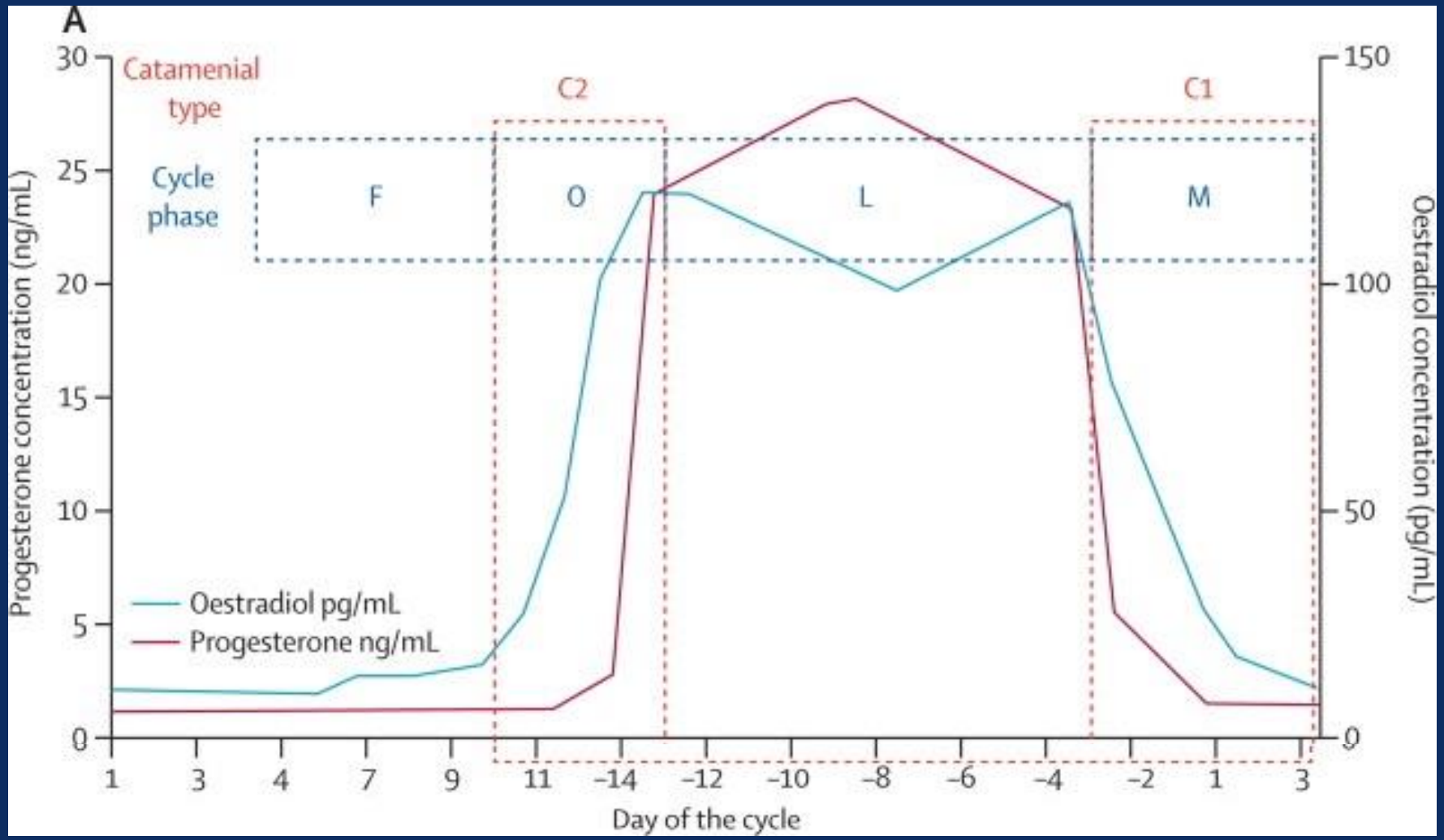
Catamenial Patterns C1 & C2 in Ovulatory Cycles

Cohort: 184 FWE with DRE TLE, FIC and FBTC seizures, aged 18-45 yrs.

Charted seizures for one cycle with midluteal blood sample for Progesterone (>5 ng/mL considered ovulatory)

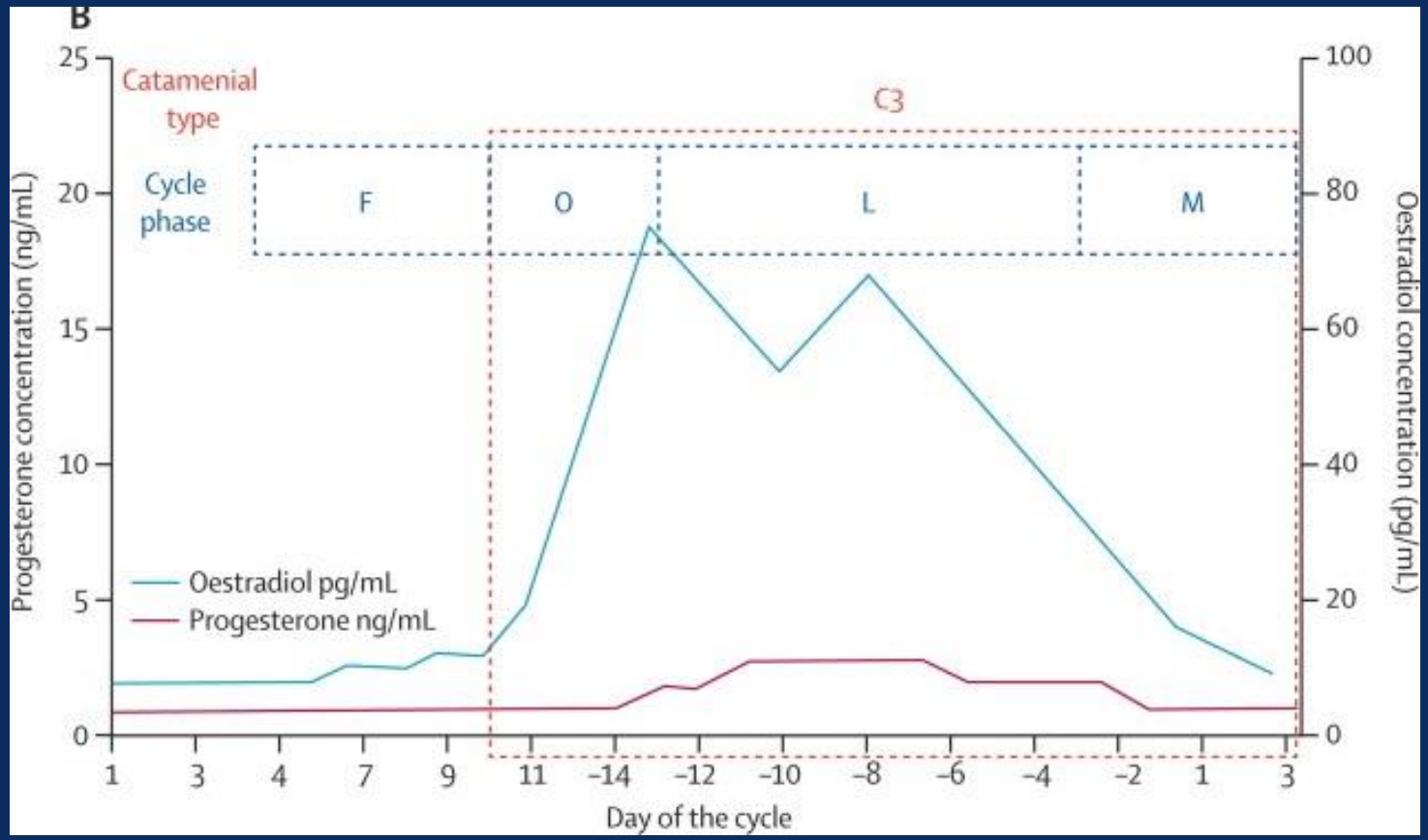
98 normal cycles recorded with 1324 FIC or FBTC seizures

86 inadequate luteal phase cycles, with 1523 seizures



Adapted from Herzog AG, Klein P, Ransil BJ. Three patterns of catamenial epilepsy. Epilepsia. 1997 Oct;38(10):1082-8. PMID: 9579954.
Harden CL, Pennell PB, Lancet Neurology 2013.

Catamenial C3 Pattern in Anovulatory Cycles



Conclusions from Herzog, et al:

- 3 descending S-shaped curves, with points of inflection for optimal distinction between WWE with high vs low susceptibility to hormonal influence on average daily seizure frequency (ADSF).
- Propose a ≥2-fold increase in (ADSF) as a definition of catamenial epilepsy
- Approximately **1/3** of WWE met criteria for a catamenial pattern

Adapted from Herzog AG, Klein P, Ransil BJ. Three patterns of catamenial epilepsy. Epilepsia. 1997 Oct;38(10):1082-8. PMID: 9579954.
Harden CL, Pennell PB, Lancet Neurology 2013.

Catamenial Epilepsy Prevalence and Patterns - *in an unbiased patient sample*

Funded by Milken Family Foundation, & Epilepsy Foundation

Prospective observational cohort study enrolling females with epilepsy (FWE) & healthy controls (HC)

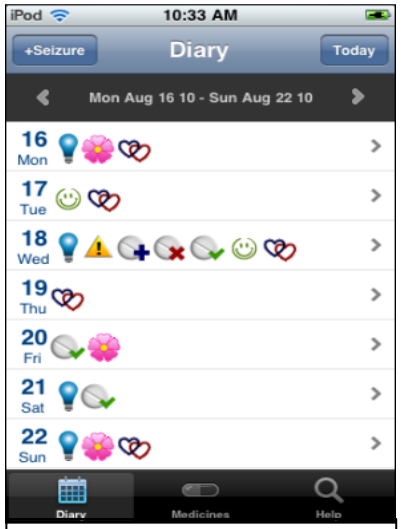
3 Site Study (Multi-PIs): Pennell (BWH), French (NYU), Harden (LIJ)

Enrolled 89 FWE and 108 HC, followed with daily eDiary.

Outcomes Assessed: pregnancy and birth rates (1^0), ovulatory rates (day 21 PROG in ≤2 cycles), seizures, catamenial patterns.

For **Catamenial pattern** analysis:

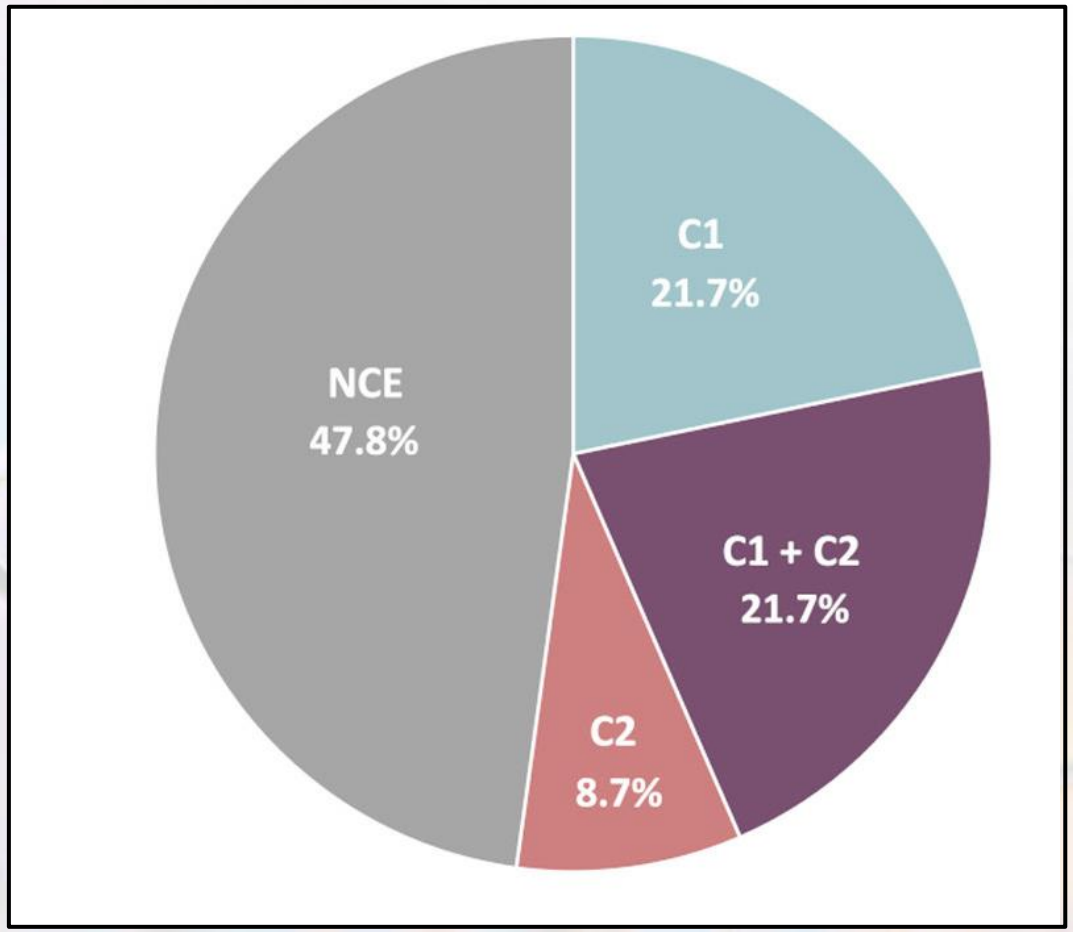
- women with ≥1 seizures and ≥1 menstrual cycle (n=23)
- Cycles were classified as ovulatory and anovulatory



Daily tracking of ASM doses, seizures, mood, sexual activity, menstrual flow

Pennell PB, French JA, Harden CL, et al. JAMA Neurol. 2018;75(8):962-969. PMID: 29710218; PMCID: PMC6142930.

Percentage of WWE with Catamenial Patterns in WEPOD



23 WWE followed prospectively with menstrual and seizure tracking app (6/23 with generalized epilepsy)

12/23 met criteria for catamenial epilepsy

- 5/23 C1 pattern only
- 5/23 combined C1 and C2 patterns
- 2/23 C2 pattern only

(1/23 had anovulatory cycles but did not meet C3 criteria)

No difference in CE between those who reported historical CE than those who did not (Fisher's Exact Test, p=0.855)

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inescu PE, Kelly M, French JA, Harden C, Davis A, Lau C, Ehlert A, Allien S, Osterhaus E, Barnard S, Jain R, Pennell PB. Catamenial lepsy occurrence and patterns in a mixed population of women with epilepsy. Epilepsia. 2023 Sep;64(9):e194-e199. PMID: 37452790.

Treatment Strategies

Progesterone Treatment Trial

Phase III, multicenter RCT (n=294)

- Stratified by catamenial & non-catamenial status

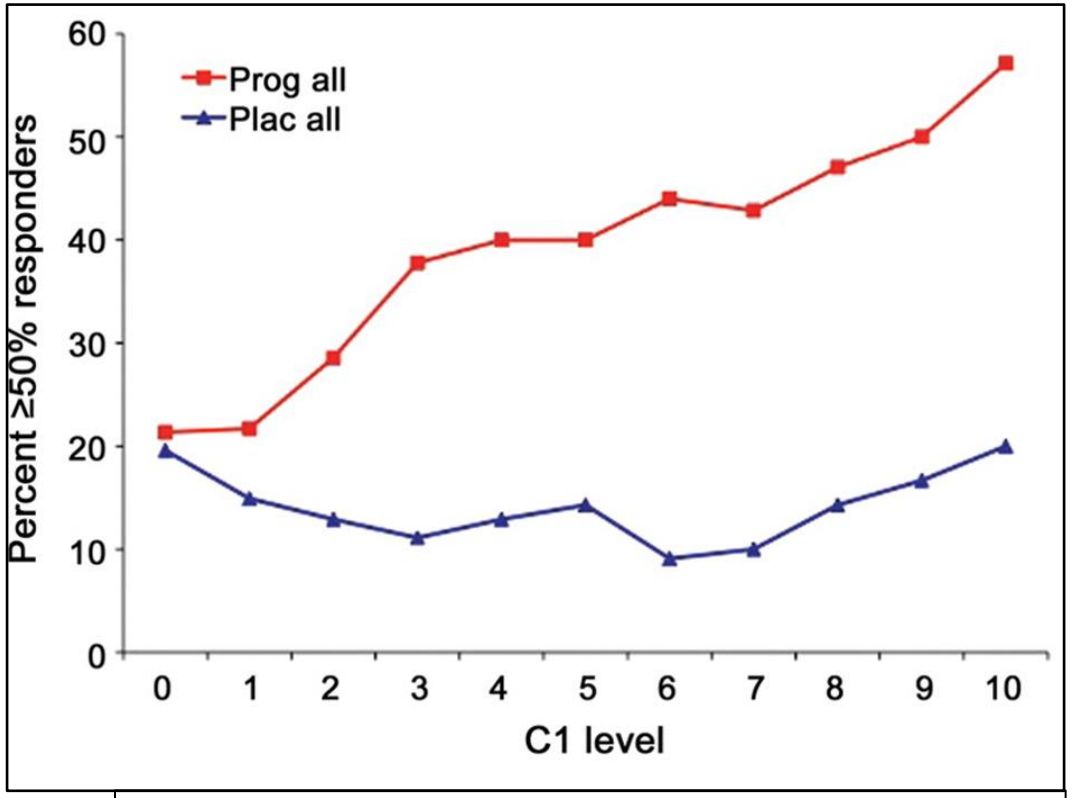
Treatment: progesterone or placebo (2:1)

- 3 baseline mos. and 3 Trx menstrual-cycles
- Progesterone oral lozenges 200 mg TID Days 14-25, 100 mg TID D26-27, 50 mg TID D28, then stop

- **No** difference in Responder Rates (both CE and NCE groups)

Secondary analysis

- C1 exacerbation level was a predictor of response to Progesterone



Responder rates with progesterone and placebo treatment vs perimenstrual (C1) catamenial level of seizure exacerbation

Herzog AG, Fowler KM, Smithson SD, Kalayjian LA, Heck CN, Sperling MR, Liporace JD, Harden CL, Dworetzky BA, Pennell PB, Massaro JM. Progesterone vs placebo therapy for women with epilepsy: A randomized clinical trial. Neurology. 2012;78(24):1959-66. PMID: 22649214; PMCID: PMC3369508.

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Cycle Suppression Therapy for Catamenial Epilepsy
(suppresses ovulation and cycling of Sex Steroid Hormones (SSH))

Cycle suppression therapy can be achieved with:

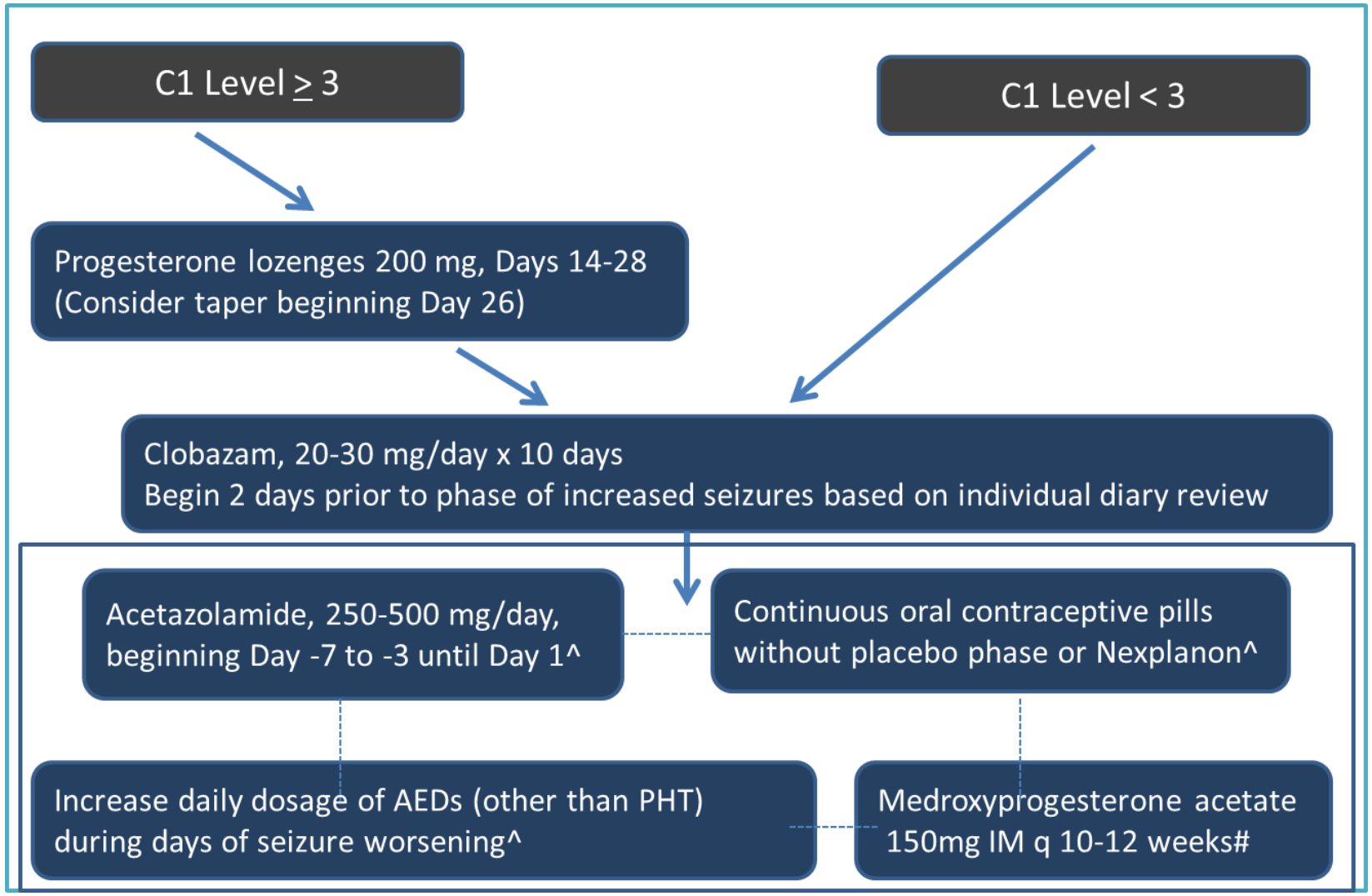
- Combined Oral Contraceptive (COCs)
  - Preferably on a continuous basis
  - Need to consider bidirectional ASM interactions
- Progestin subdermal implants
  - 68 mg etonorgestrel, replaced q3 years
  - Enzyme-inducing ASM (EIASMs) can lower efficacy
- Depo-medroxyprogesterone acetate injections (DMPA)
  - q10-12 weeks (consider q10 weeks for EIASMs)
- GnRH analogue
  - Usually prescribed by gynecologist subspecialist
  - Supplement with balanced HRT to lower risks related to premature menopause, including osteoporosis

Treatment	*DMPA (1984)*	*GnRH agonist depot (1992)*
Regimen	120-150 mg q 6-12 weeks	3.75 mg q 4 weeks
N	14 11developed amenorrhea	10
No. improved	7 (50%)	3 seizure free 4 less seizures 1 less severe
Seizure frequency	-39%*	

Paucity of evidence for these practical approaches

Mattson RH, Cramer JA, Caldwell BV, Siconolfi BC. Treatment of seizures with medroxyprogesterone acetate: preliminary report. Neurology. 1984 Sep;34(9):1255-8. PMID: 6540415; Bauer J, Wildt L, Flügel D, Stefan H. The effect of a synthetic GnRH analogue on catamenial epilepsy: a study in ten patients. J Neurol. 1992 May;239(5):284-6. PMID: 1535100.

Treatment Strategies for Catamenial Epilepsy



^ no randomized trials
# higher risk of osteoporosis and prolonged return to normal fertility

Most treatments are for focal-onset seizures in women with regular menses.

^ no randomized trials
# higher risk of osteoporosis and prolonged return to normal fertility

Nexplanon = etonorgestrol

Harden CL, Pennell PB. Neuroendocrine considerations in the treatment of men and women with epilepsy. Lancet Neurol. 2013;12(1):72-83. PMID: 23237902; PMCID: PMC4928713. Feely M, Calvert R, Gibson J. Clobazam in catamenial epilepsy. A model for evaluating anticonvulsants. Lancet. 1982 Jul 10;2(8289):71-3. PMID: 6123810.

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Do some WWE have more SSH/NAS sensitivity throughout all reproductive stages?

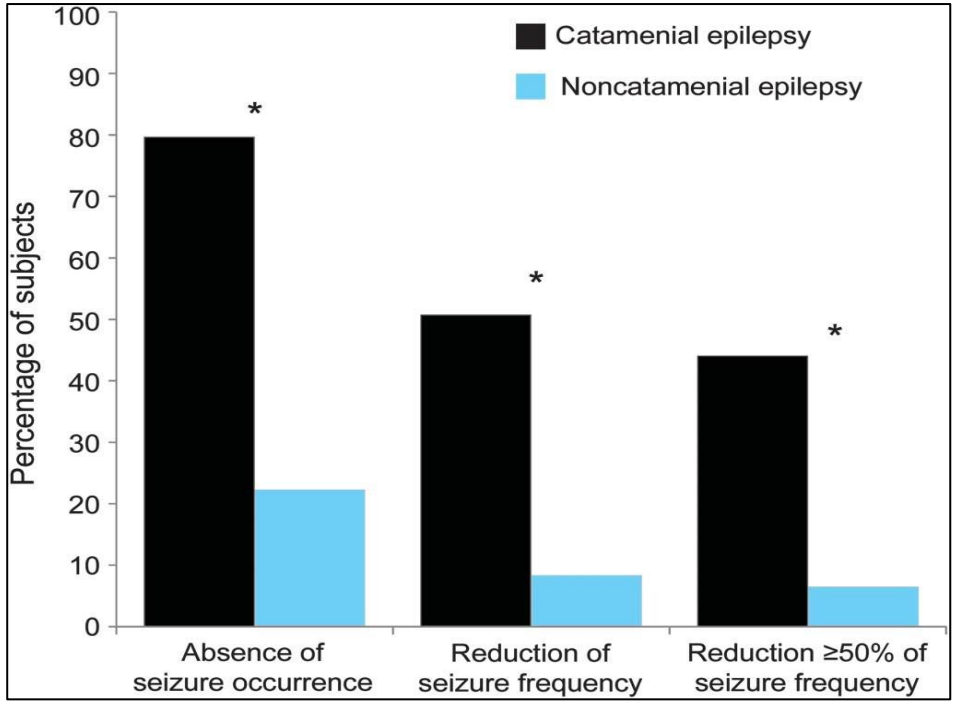
- Reports that Peri-menarchal Seizure Onset is associated with Catamenial patterns, but not well-substantiated in research studies
- Unclear if seizures increase with estrogen-containing contraceptives and if a h/o catamenial epilepsy is a risk factor
- Mixed findings on whether a history of Catamenial Epilepsy is associated with seizure control during pregnancy,
- Small studies suggest that a history of Catamenial epilepsy is associated with seizure worsening during menopausal transition, and hormone replacement therapy

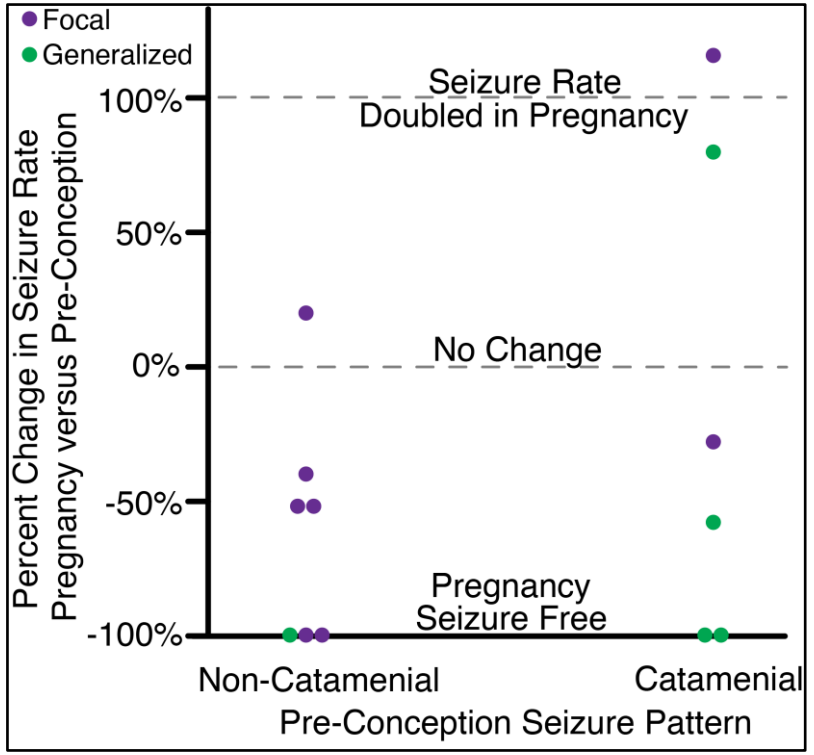
Herzog AG, et al. Seizure. 2019;69:1-6. PMID: 30947081; Herzog AG, et al. Epilepsy Behav. 2021;120:108011.PMID: 33964535.; Harden CL, et al. Epilepsia. 1999 Oct;40(10):1402-7. PMID: 10528936.; Harden CL, et al. Epilepsia. 2006 Sep;47(9):1447-51 PMID: 16981859. Cagnetti C, et al. Neurology. 2014;83(4):339-344. Osterhaus E, et al. ANA annual meeting, 2023. Pennell PB, et. al. NEJM 2020;383(26):2547-2556PMID: 33369356; PMC7919187.

Is CE a Predictor of Seizure Patterns in Pregnancy?

Cagnetti reported that a type 1 CE pattern is a predictor of better outcomes in pregnancy (n=59 with CE, n=215 with NCE)

- Inclusion: pts followed for ≥24 mos pre-conception
- Only C1 pattern considered
- Unclear if ASM dose changes; 27-32% on PB





In WEPOD, the documented CE pattern was not associated with improved seizure frequency (n=13)

In MONEAD, a catamenial pattern history was not associated with seizure improvement in pregnancy

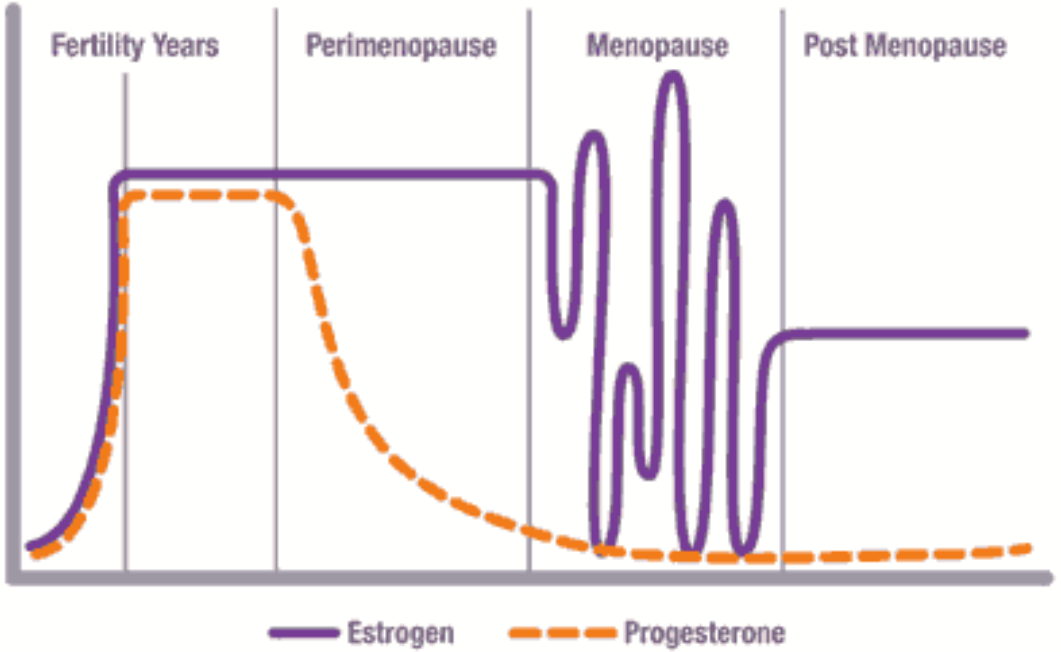
Cagnetti C, Lattanzi S, Foschi N, Provinciali L, Silvestrini M. Neurology. 2014;83(4):339-344. **Osterhaus E,** French JA, Jain R, Khongbantabam N, Pennell PB.Epilepsy and Behavior, in press. Pennell PB, French JA, May RC, Gerard E, Kalayjian L, Penovich P, Gedzelman E, Cavitt J, Hwang S, Pack AM, Sam M, Miller JW, Wilson SH, Brown C, Birnbaum AK, Meador KJ; MONEAD Study Group. NEJM 2020;383(26):2547-2556PMID: 33369356; PMCID: PMC7919187.

Perimenopause and Menopause

- EST levels can be erratic with surges in response to the elevated FSH, until menopause transition is complete
- Increased anovulatory cycles, and less cyclic progesterone
- No prospective, observational data

<u>Cross-sectional evaluation, using questionnaires</u>

- Two-thirds reported an increase in seizures during perimenopause
- H/o catamenial pattern was associated with an increase in seizures
- Decrease in seizures post-menopause more likely with h/o C1 pattern
- HRT was associated with an increase in seizures



Harden CL, Pulver MC, Ravdin L, Jacobs AR. The effect of menopause and perimenopause on the course of epilepsy. Epilepsia. 1999 Oct;40(10):1402-7. PMID: 10528936.

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Menopause and Treatment

- **RCT trial of HRT in postmenopausal females with epilepsy**
- 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate (CEE/MPA)
- single dose and double dose
- study halted early due to findings from Women's Health Initiative study
- Possibly consider a natural progesterone supplement rather than Prempro

Table. Number of subjects with increase in seizure frequency by treatment arm

HRT Group	Simple Partial		**Complex Partial***		2° Gen		**Any Sz Type***		Total # Sz		**Most severe Sz Type***	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Placebo (n=6)	**1**	**16.7**	**0**	**0.0**	**0**	**0.0**	**1**	**16.7**	**0**	**0.0**	**0**	**0.0**
Single CEE/MPA (n=8)	**3**	**37.5**	**1**	**12.5**	**0**	**0.0**	**4**	**50.0**	**3**	**37.5**	**3**	**37.5**
Double CEE/MPA (n=7)	**1**	**14.3**	**3**	**42.9**	**1**	**14.3**	**5**	**71.4**	**3**	**42.9**	**5**	**71.4**

***p≤ 0.05**

Additional Recommendations: Possibly consider a natural progesterone supplement rather than Prempro

Harden CL, Herzog AG, Nikolov BG, Koppel BS, Christos PJ, Fowler K, Labar DR, Hauser WA. Hormone replacement therapy in women with epilepsy: a randomized, double-blind, placebo-controlled study. Epilepsia. 2006 Sep;47(9):1447-51 PMID: 16981859.

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Summary of Treating Adolescents and Women with Epilepsy during the Reproductive Years

- During early adolescence, avoid use of ASMs with elevated teratogenic risk, begin folic acid supplementation, and provide reproductive counseling with an emphasis on effective contraception
- Sex Steroid Hormonal status can affect the expression of epilepsy throughout the different reproductive life stages
- Hormones are unlikely to cause epilepsy directly or be an effective treatment when used alone
- Enzyme-inducing ASMS have additional complexities to consider when prescribed
- Perimenopause may be associated with seizure worsening but seizures can improve after the menopause transition is complete. Effects of HRT on seizure frequency are possible.

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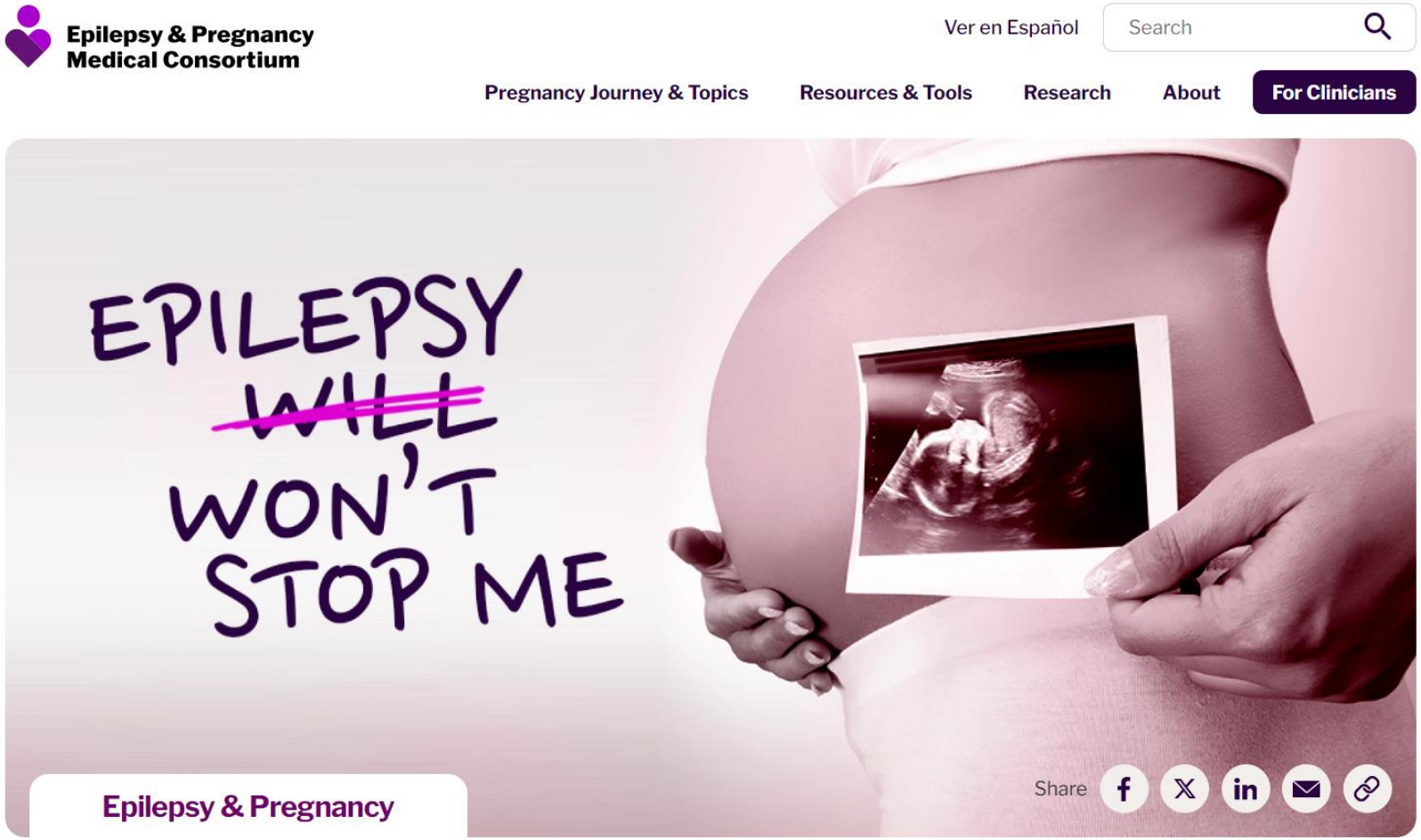

THIS WEBSITE IS NOT INTENDED FOR USE BY INDIVIDUAL PATIENTS SEEKING MEDICAL ADVICE. It is also not intended to be relied on as a replacement for a clinician's independent professional judgment in determining the best course of treatment for each patient on an individualized basis.

With planning, people with epilepsy can have safe, healthy pregnancies and healthy babies.

https://epilepsypregnancy.com/

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Questions