REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Treatment of Women With Epilepsy

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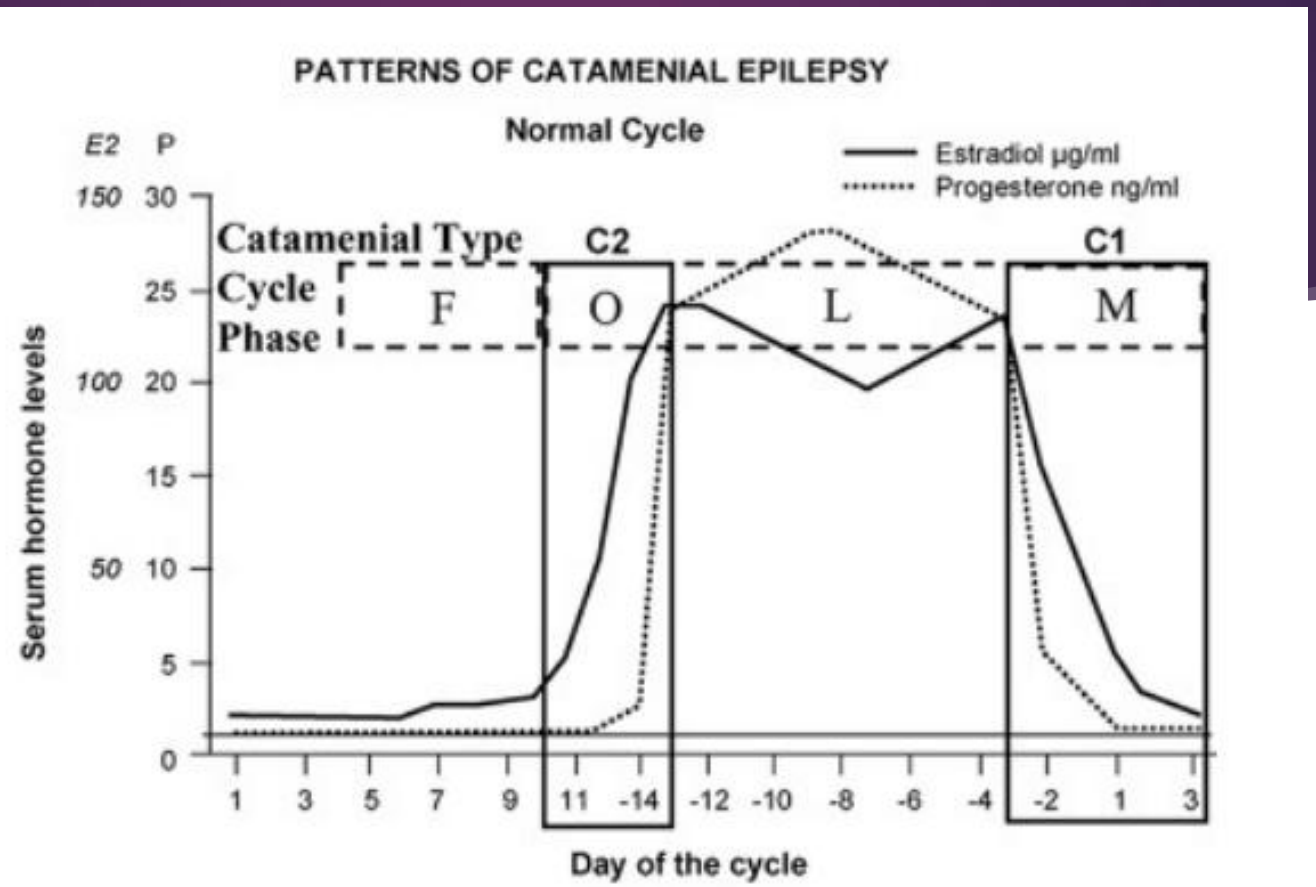
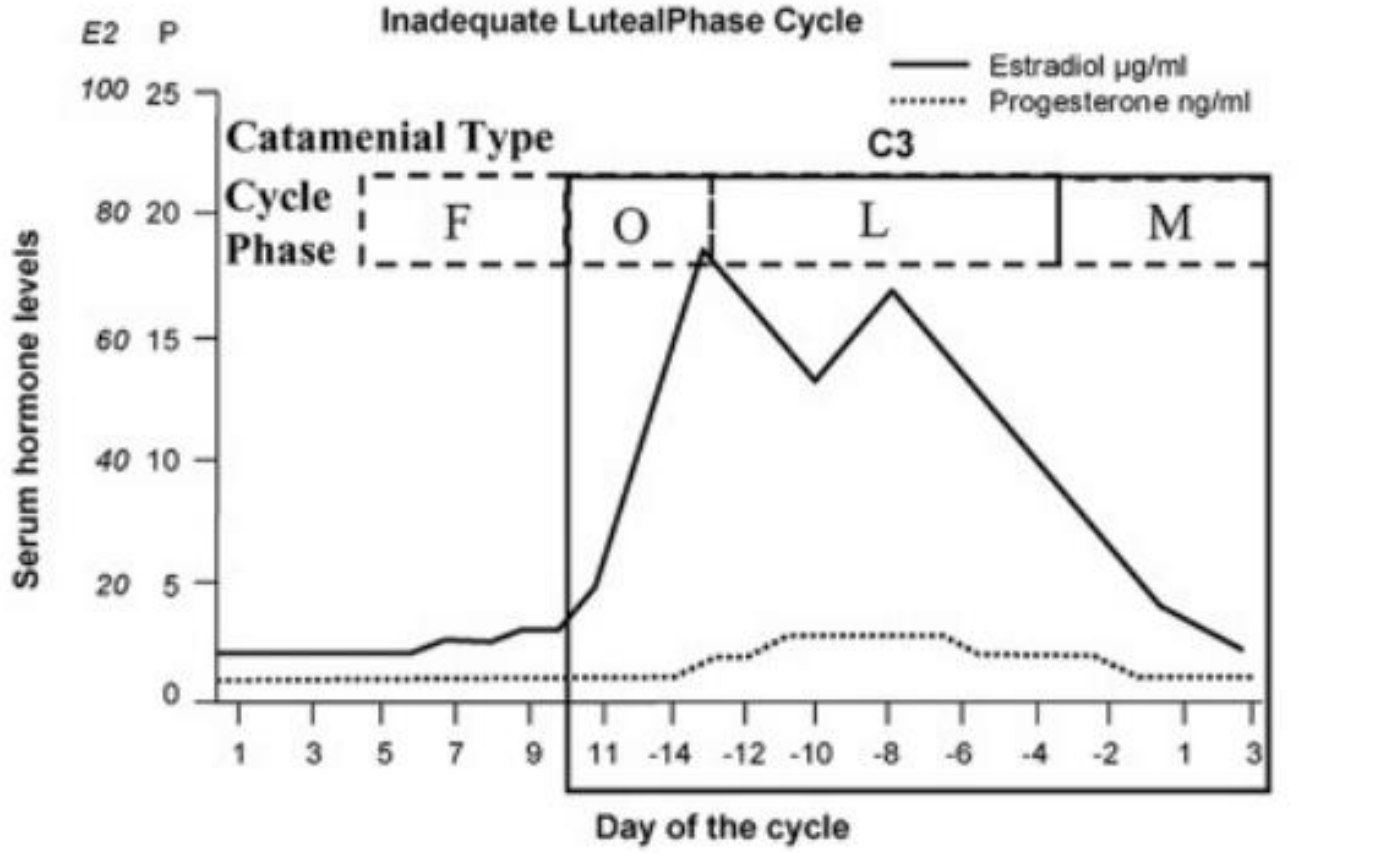
Important considerations in the care of women with epilepsy

- whether antiepileptic drugs (AEDs) interact with Contraceptives
- how AEDs impact fertility, teratogenic risk, and libido
- Whether seizures and AED concentrations change during pregnancy, postpartum, and
- Lactation
- the risk of osteoporosis associated with AEDs and epilepsy.

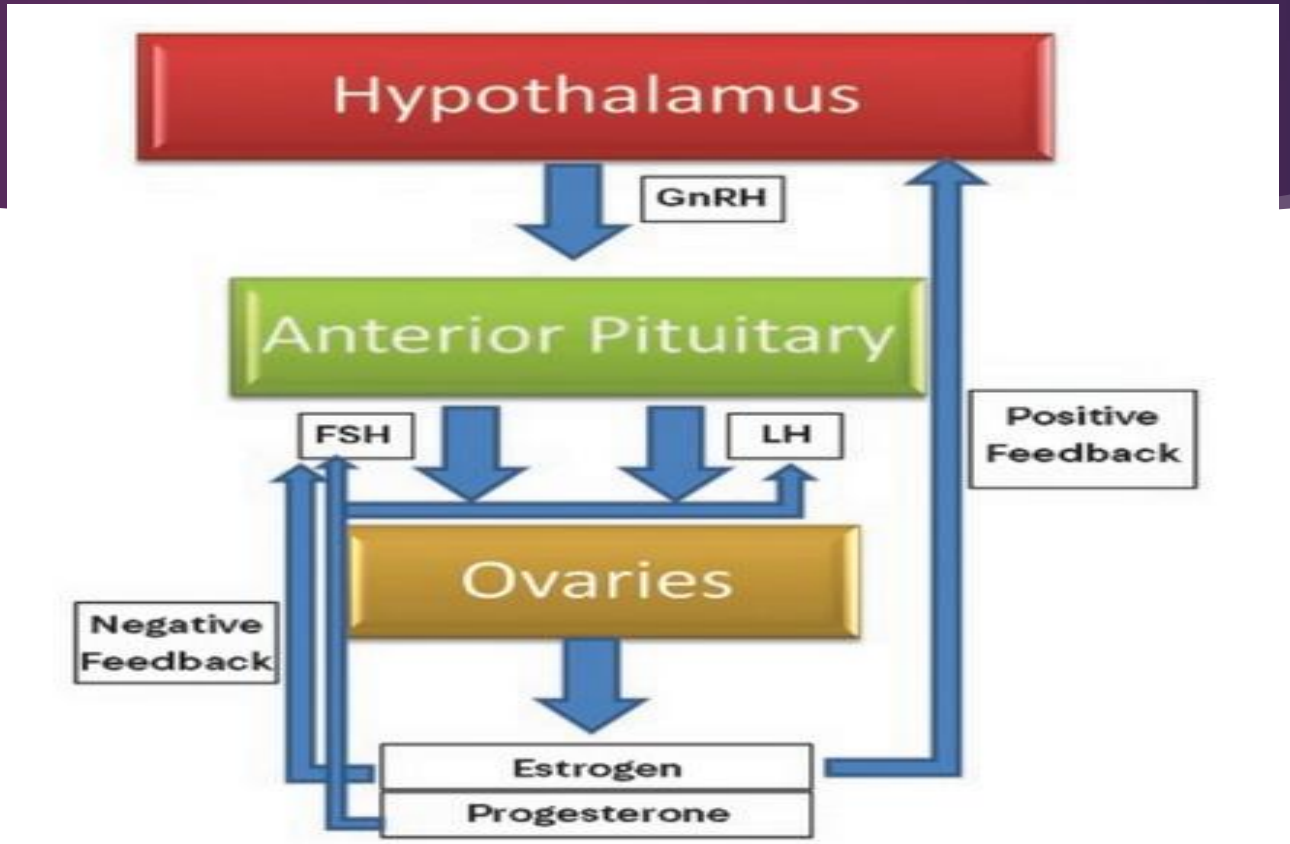
CATAMENIAL EPILEPSY

- Nearly 1.5 million women of childbearing age in the United States live with epilepsy.
- Catamenial epilepsy is reported in at least one-third of women with epilepsy.
- Women with catamenial epilepsy have a cyclic exacerbation of their seizures with the fluctuation of their hormones.
- As a rule, estrogens are proconvulsant (OCP) and progesterone is anticonvulsant.


PATTERNS OF CATAMENIAL EPILEPSY
Normal Cycle
E2
P
150
30
25
100
20
15
50
10
5
0
Serum hormone levels
Estradiol µg/ml
Progesterone ng/ml
Catamenial Type
Cycle
Phase
C2
C1
F
O
L
M
1
3
5
7
9
11
-14
-12
-10
-8
-6
-4
-2
1
3
Day of the cycle


Inadequate LutealPhase Cycle
E2
P
Estradiol µg/ml
Progesterone ng/ml
Catamenial Type
C3
Cycle
Phase
F
O
L
M
Serum hormone levels
100
80
60
40
20
0
25
20
15
10
5
1
3
5
7
9
11
-14
-12
-10
-8
-6
-4
-2
1
3
Day of the cycle

THE HYPOTHALAMIC-PITUITARY-OVARIAN AXIS AND EPILEPSY



Suggested Treatment Options in Women With Catamenial Epilepsy

1 Determine True Catamenial Epilepsy

A Establish whether the seizures are, in fact, catamenial in nature by using seizure diaries. Ask the patient to chart daily the seizure type and frequency with simultaneous recording of ovulation and menstruation status using an ovulation kit or basal body temperature recording for three menses.

B Determine whether there is an increase in the number and severity of seizures by twofold or greater during the specific days of the patient's menstrual cycle and establish C1, C2, or C3 type of catamenial epilepsy.

2 Choose One of the Options Below

A Progesterone lozenges/natural progesterone for C1 pattern

For the C1 type, consider using progesterone lozenges 200 mg 3 times daily around the days of seizure exacerbation or days 14 to 28 of the cycle.

B Synthetic progestin

Consider oral daily synthetic progestin or intrauterine devices with progestin versus depot- medroxyprogesterone acetate.

C Acetazolamide

Consider using at 250 mg twice daily or 500 mg twice daily to be taken around the 7-10 days of seizure exacerbation as determined by the seizure diary.

D Clobazam

20 milligrams to 30 mg divided twice a day or one dose at night for 10 days, starting 2 days before and throughout the identified seizure exacerbation dates.

E Small increase in baseline antiepileptic drugs

These can be taken approximately 2 days before the identified period of seizure exacerbation for up to 10 days. Be cautious about phenytoin, carbamazepine, or other medications with a higher risk of toxicity.

REPRODUCTIVE DISORDERS

1- direct effects of Seizures

2- secondary to use of certain antiepileptic drugs

Direct Effects of Seizures

- polycystic ovary syndrome
- Infertility
- decreased libido
- Menstrual disorders
- Reproductive endocrine disorder

Antiepileptic Drug Effects

- resulting in abnormalities in fertility, thyroid hormones, sexual function, and bone health.
- Microsomal hepatic enzyme–inducing AEDs, such as phenytoin, carbamazepine, and phenobarbital, can increase sex hormone–binding globulin concentrations.
- Valproic acid is also known to cause endocrine side effects. Approximately 45% of these women had menstrual disorders, and of those, 90% had polycystic ovary syndrome or hyperandrogenism, or both.

- Sexual dysfunction and decreased libido and satisfaction with sex lives are also reported in women taking enzyme-inducing AEDs, such as carbamazepine and phenytoin.
- The full endocrine side effect profile of newer AEDs is unknown. Lamotrigine is not found to cause endocrine side effects.

The oral contraceptive failure rate is 1% in healthy women but 3% to 6% in the population of women with epilepsy.

Antiepileptic Drugs and Contraceptive Failure

Antiepileptic Drugs Causing Contraceptive Failure

- Carbamazepine
- Clobazam
- Eslicarbazepine acetate
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Primidone
- Rufinamide

Antiepileptic Drugs Causing Contraceptive Failure at Higher Doses

- Felbamate
- Perampanel
- Topiramate

Antiepileptic Drugs With No Known Effect on Contraceptive Failure

- Clonazepam
- Ethosuximide
- Gabapentin
- Lacosamide
- Lamotrigine
- Levetiracetam[a]
- Retigabine/ezogabine
- Tiagabine
- Valproate[b]
- Vigabatrin
- Zonisamide

PREGNANCY AND PERINATAL COUNSELING

- Intrauterine devices are a safe and effective method of contraception in women with epilepsy
- In most women with epilepsy, pregnancy has no effect or a protective effect on their seizure frequency
- Having a seizure disorder that was active in the year before pregnancy appears to be the best predictor of seizure recurrence during pregnancy
- There is evidence for better seizure control during pregnancy in women with catamenial epilepsy

compared with women with epilepsy in general

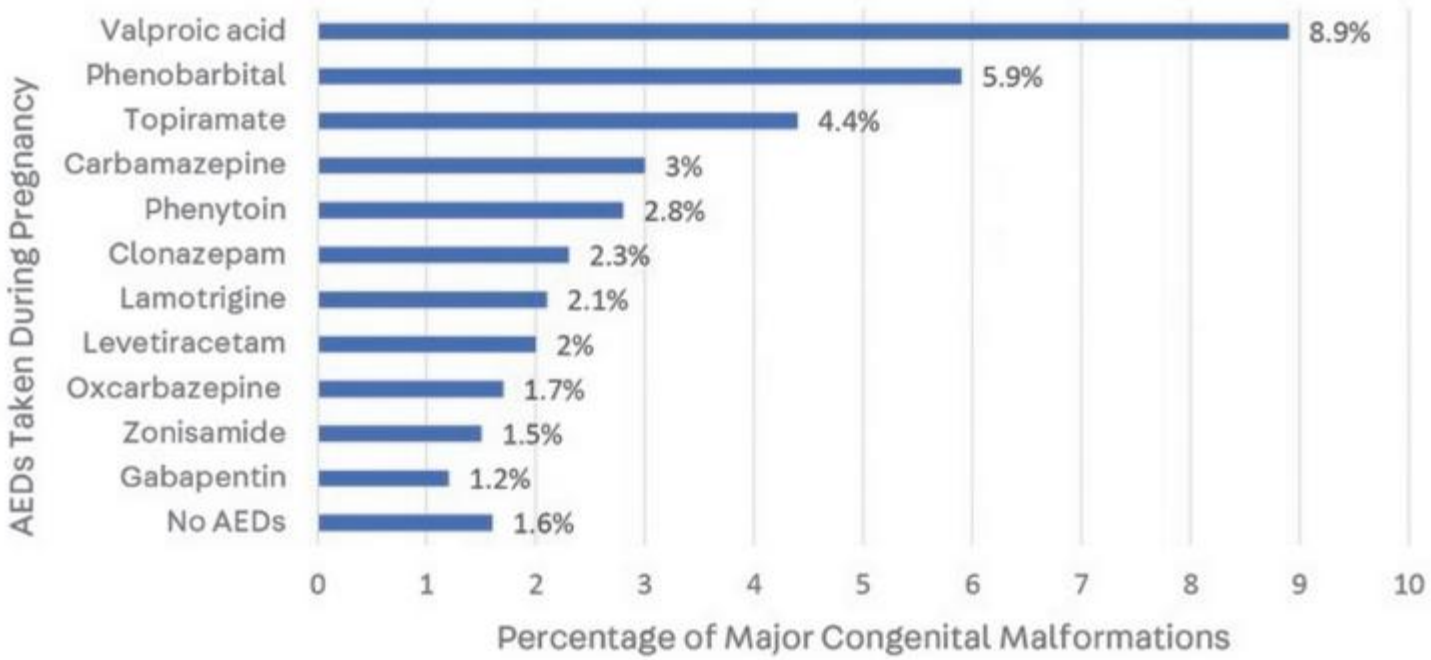
- The most common cause of seizure recurrence in pregnancy is likely a reduced plasma concentration of antiepileptic drugs and changes in antiepileptic drug metabolism
- American Academy of Neurology guidelines recommend checking antiepileptic drug levels at

baseline before conception and monthly thereafter.

Risks to the Fetus Because of Maternal Seizure Recurrence

- Women with epilepsy who experience seizures during their pregnancy are at increased risk of delivering preterm, low-birth-weight, and small-for-gestational-age newborns.
- This seizure-related risk may be related to fetal hypoxia, acidosis, decreased blood flow to the placenta, deceleration of fetal heart rate, and trauma as a result of a maternal fall.
- frequent maternal tonic-clonic seizures during pregnancy were associated with a lower verbal IQ in their offspring.

Risk of Birth Defects or Fetal Death Because of Antiepileptic Drugs



In counseling women with epilepsy who plan to become pregnant, the practitioners should discuss the need for staying on antiseizure medication, simplifying the medication regimen, attempting monotherapy, and selecting medications with a more favorable side effect profile.

Neurodevelopment and Fetal Antiepileptic Drug Exposure

Exposure of the fetus to AEDs through the placenta may have adverse cognitive and behavioral effects, such as lower IQ, language deficits, autism, and attention deficit hyperactivity disorder.

FOLIC ACID SUPPLEMENTATION

Folic acid is essential during gestation. Some AEDs, such as valproic acid, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, and primidone, alter folic acid metabolism and may decrease folic acid levels in the blood.

Other studies recently found that periconceptional folate supplementation has a positive association with a better neurodevelopmental outcome, a lower rate of autism spectrum disorder in the general population,91 and a higher IQ in children exposed to AEDs in utero.

- recommended dose of 0.4 mg/d of folate for all women of childbearing age to prevent neural tube defects.
- systematic review concluded that folic acid 5 mg/d in women without epilepsy may provide 85% protection against neural tube defects.

- Some experts have recommended the use of a higher folic acid dose of 4 mg/d to 5 mg/d in women taking valproic acid, carbamazepine, phenobarbital, phenytoin, and primidone;

BREAST-FEEDING

- All AEDs can be transmitted into the breast milk to some degree, but this amount is much less than that previously transmitted through the placenta to the fetus.
- The AED level transmitted to an infant via breast milk depends on multiple factors, including the amount of AED excreted into breast milk and AED absorption and clearance by the infant.
- The actual infant AED exposure from breast milk is usually low, and the benefits of breast-feeding are ultimately felt to outweigh the potential risks for most women with epilepsy and their newborns.

- For barbiturates and benzodiazepines, the risk-benefit ratio should be evaluated more carefully
- Except for barbiturates and benzodiazepines, the reported side effects in infants who are breast-fed on other AEDs have been rare or infrequent, and the benefit may outweigh the risks.

PERIMENOPAUSE AND MENOPAUSE

- A history of catamenial epilepsy and the use of hormonal replacement therapy were associated with an increase in seizure frequency. Menopausal women generally report a decrease in seizure frequency.
- seizure frequency significantly increased in a dose-related manner with the use of hormone replacement therapy.

- For women with catamenial epilepsy who are at risk of seizure exacerbation during the perimenopause state, antiseizure medications may need to be adjusted to higher therapeutic levels.
- Once menopause is reached, AED doses may be reduced back to their baseline.

BONE HEALTH

- Some AEDs are identified as an independent risk factor for low bone density and secondary osteoporosis.
- The duration of epilepsy and cumulative drug load both correlate with a progressive reduction in bone mineral density, predisposing patients to fractures.
- Many AEDs are known to alter bone metabolism, especially the enzyme-inducing AEDs.

- Levels of vitamin D metabolites, such as 25-hydroxyvitamin D, may be low in people with epilepsy who are taking enzyme-inducing AEDs.

Antiepileptic Drug	Lowering Bone Mineral Density/ Affecting Bone Metabolism
Benzodiazepines	Yes
Carbamazepine	Yes
Gabapentin	Yes
Lamotrigine	No
Levetiracetam	Maybe
Oxcarbazepine	Yes
Phenobarbital	Yes
Phenytoin	Yes
Primidone	Yes
Topiramate	Maybe
Valproic acid	Yes
Zonisamide	Yes

Recommendations for Women With Epilepsy at Risk of Osteoporosis

If Osteopenia or Osteoporosis Is Not Detected

- Monitor calcium and vitamin D levels 1 to 2 times per year
- Follow bone density (dual energy x-ray absorptiometry [DEXA] scan), every 2 years, especially if postmenopausal
- Consider calcium (at least 1200 mg/d) and vitamin D (at least 600 IU/d) supplements or greater amounts to achieve a level of >30 ng/mL
- Encourage weight-bearing exercises
- Encourage cessation of smoking
- Suggest limiting alcohol consumption
- Recommend avoiding excessive caffeine

If Osteopenia or Osteoporosis Is Detected

- Increase vitamin D supplement to 1500–2000 IU/d to achieve a level of >30 ng/mL
- Lifestyle modifications to decrease the risk of falls and fractures
- Discuss advantages and disadvantages of switching to another non-enzyme-inducing antiseizure medication
- Consider bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid)
- Consider estrogens and hormone therapy, parathyroid hormone (teriparatide), and estrogen agonist/antagonist (raloxifene)