# Neuroendocrine Concerns for Women with Epilepsy

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# Disclosures

- Research-NINDS
- Royalties-Wiley, Up-to-Date

# Learning Objectives:

S.M.A.R.T. (specific, measurable, attainable, realistic, and timely)

1) Learn about the association between antiseizure drugs and polycystic ovary syndrome and learn the signs and symptoms of this syndrome so you can identify them in women with epilepsy
2) Be able to counsel patients about which antiseizure drug exposures are associated with a risk of infertility
3) Understand the emerging information regarding the relationship between seizure occurrence and ovarian failure

# Key Message

- Reproductive functioning for persons with epilepsy has long been a concern and reproductive adverse outcomes are likely associated both with antiseizure medications or epilepsy itself
- Several enzyme-inducing antiseizure medications are associated with infertility.
- Early ovarian failure in women with epilepsy is subtle and may be influenced by seizure occurrence.

# Does epilepsy itself or do AEDs cause endocrine disruption?

## Epilepsy

- More frequent anovulatory cycles?
- Infertility?
- Early menopause
- Caused by chronic abnormal brain physiologic effects on hypothalamus and downstream on ovaries

## AEDs

- PCOS caused or contributed to by VPA use
- Altered reproductive hormone levels with enzyme inducing AEDs (Lossius et al 2007)
- Reversible effects

# Neuroendocrine influences of epilepsy and AEDs : PCOS

- 2006 Androgen Excess Society (AES) Guidelines (Azziz R et al 2006)
  - Patient demonstrates both:
    - Hirsutism and/or hyperandrogenemia
    - Oligo-anovulation and/or polycystic ovaries

*Exclusion of other etiologies of androgen excess and anovulatory infertility is necessary

# A meta-analysis of polycystic ovary syndrome in women taking valproate for epilepsy (Hu x, et al 2011)

- 11 studies
  - 556 women with epilepsy treated with VPA
  - 593 women treated with other AEDs
  - 120 women with untreated epilepsy
  - 329 healthy controls.

- PCOS rates
  - 24%
  - 13%
  - 13%
  - 12%

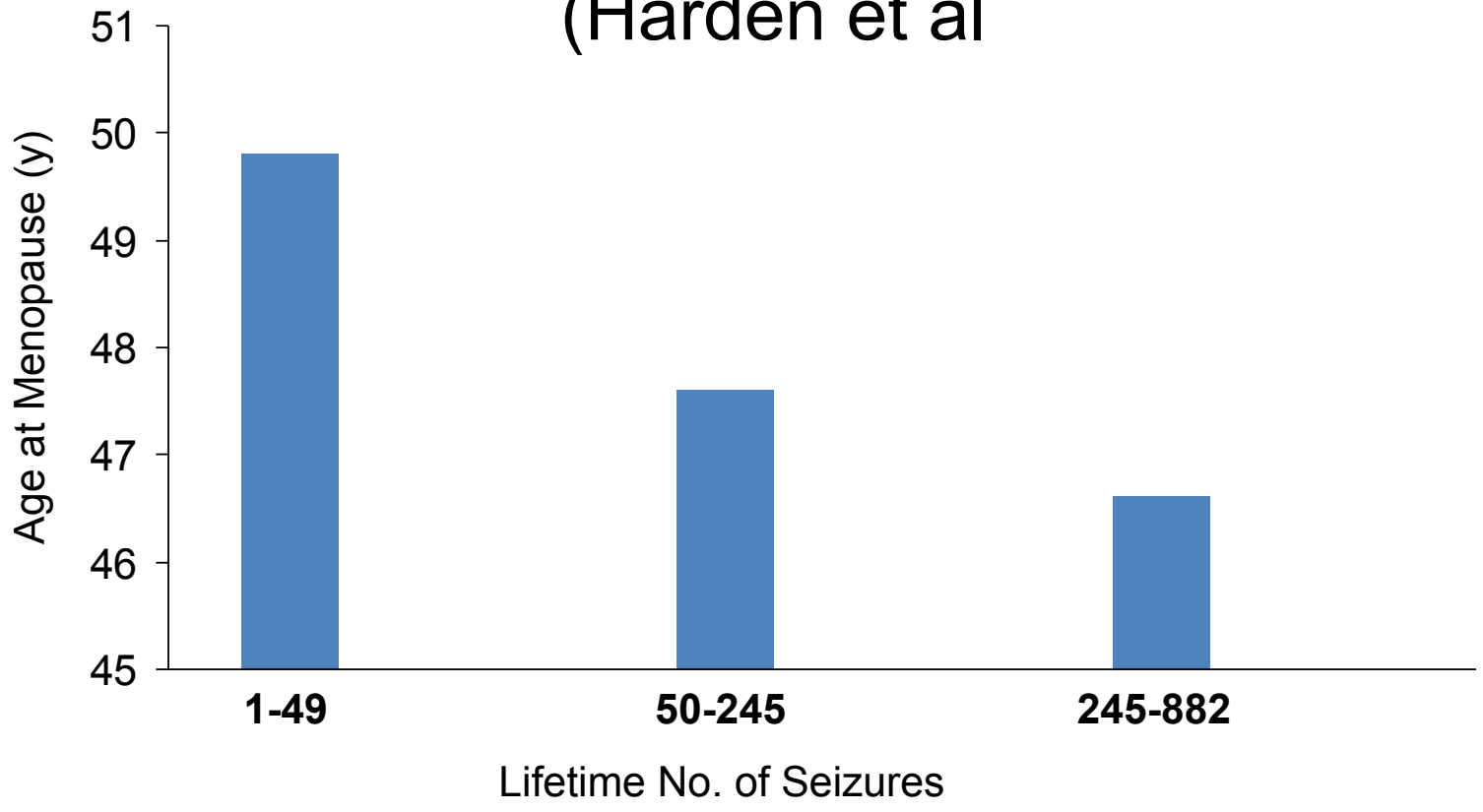
# Premature Ovarian Failure in Women With Epilepsy
## (Klein et al, Epilepsia 2001)

- 50 women with epilepsy onset before age 41 interviewed for symptoms of perimenopause
- 7 of 50 (14%) reported perimenopausal symptoms or were menopausal before age 42 (expected 1%); most had catamenial seizures
- No statistically significant differences between women with premature ovarian failure and those without in:
  - Seizure severity
  - Smoking
  - Age of menarche
  - Age of epilepsy onset, duration of epilepsy, or lateralization of epilepsy
  - Bone mass index

# Menopausal Age in Women With Epilepsy—Study Design
(Harden et al, Neurology 2003)

- Aim: To determine whether epilepsy has an effect on age of menopause using historical factors
- Methods: 68 women with epilepsy who were naturally menopausal (1 year without menses) underwent brief interview and chart review
- Patients from urban epilepsy centers

# Age at menopause in postmenopausal women with epilepsy grouped by estimated lifetime number of seizures (Harden et al




Difference in age at menopause between groups (*P*=.048)

Infertility: “a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse” WHO

- More frequent problem may be unplanned pregnancy!
- Birthrates are lower to men and women with epilepsy; gap is largely accounted for by severe comorbidity (Viinikainen et al, Neurology 2007)
- Actual infertility risk in epilepsy associated with
  - Polytherapy
  - Phenobarbital and phenytoin (polytx) use (Sukumaran et al, Neurology 2010)
  - PCOS features and hyperandrogenemia (Thomas SV et al Neurology 2013)

# Factors associated with infertility; also older age and lower education level

(Sukumaran et al, Neurology 2010)

| # AEDs | Regrs CoEff | P value | OR | 95% CI |
|---|---|---|---|---|
| 0 | | | 1.0 | |
| 1 | 1.664 | 0.116 | 5.3 | 0.6–41.9 |
| 2 | 1.991 | 0.063 | 7.3 | 0.9–59.8 |
| 3 or more | 2.885 | 0.008 | 17.9 | 2.1–149.4 |

| AED | % INF | % FER | P value | OR | 95% CI |
|---|---|---|---|---|---|
| PB | 53 | 57 | 0.028 | 1.5 | 0.94 –2.5 |
| PHT | 11 | 89 | 0.07 | 0.8 | 0.6– 0.9 |
| CBZ | 32 | 68 | 0.65 | | |
| VPA | 33 | 67 | 0.30 | | |
| LTG | 0 | 100 | 0.112 | | |
| OXC | 50 | 50 | 0.514 | | |

# Antimullerian Hormone (AMH) in with epilepsy from WEPOD study


- **WWE and HC aged 18-40 years planning pregnancy were enrolled within 6 months of stopping birth control and were followed until one month post-partum or up to 12 months if they did not conceive.**
- **WEPOD utilizes a customized mobile electronic patient diary application designed by Irody. Daily diary input includes medications, seizures, sexual activity, and menstrual cycling, tracked as bleeding onset and offset.**

# AMH levels are associated with seizure occurrence in women with epilepsy

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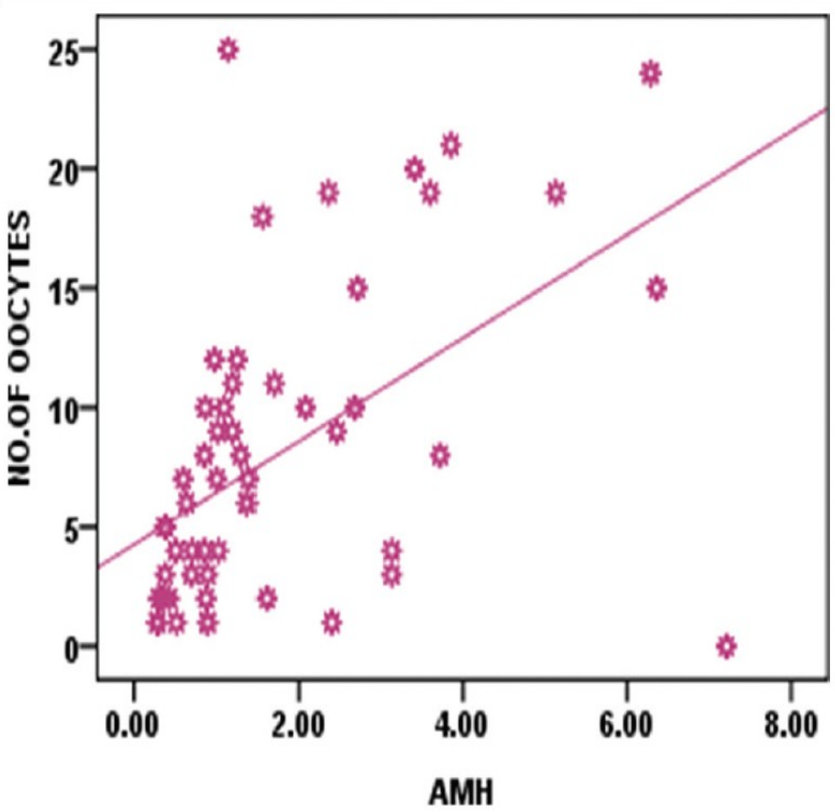
# AMH as biomarker for ovarian reserve

- AMH is exclusively produced by granulosa cells of ovarian follicles during the early stages of follicle development
- AMH levels affected by age, BMI and race
  - reflect the continuous non-cyclic growth of small follicles
  - the best endocrine marker for assessing the age-related decline of the ovarian pool in healthy women

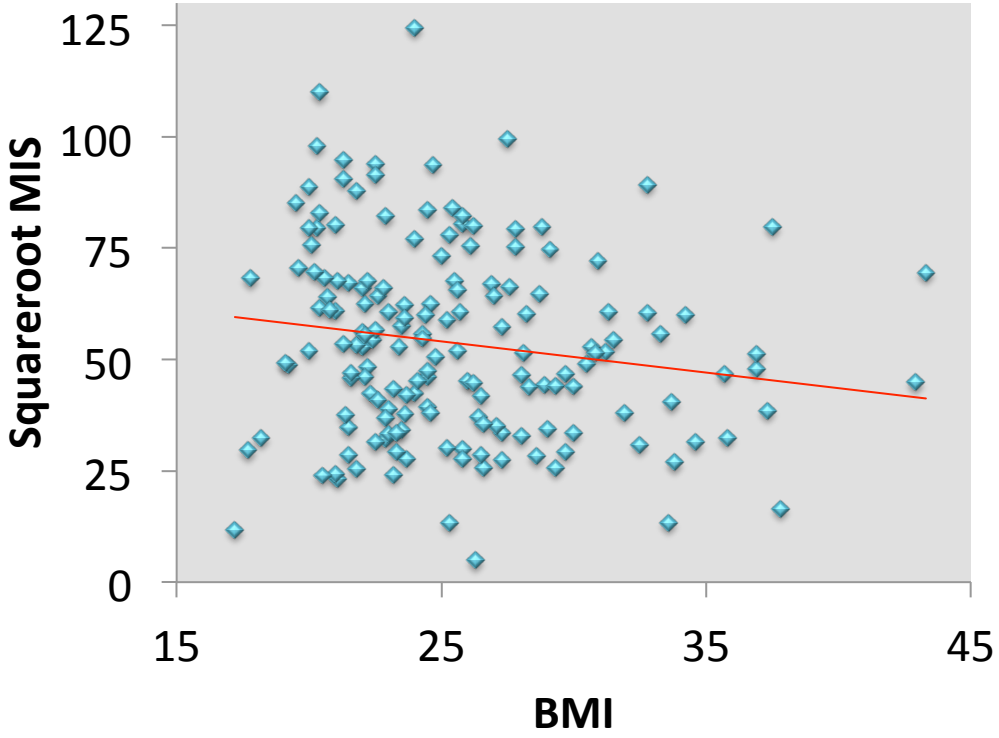



Himabindu et al. J Hum Reprod Sci. 2013 6(1):27–31.

# Background and Methods

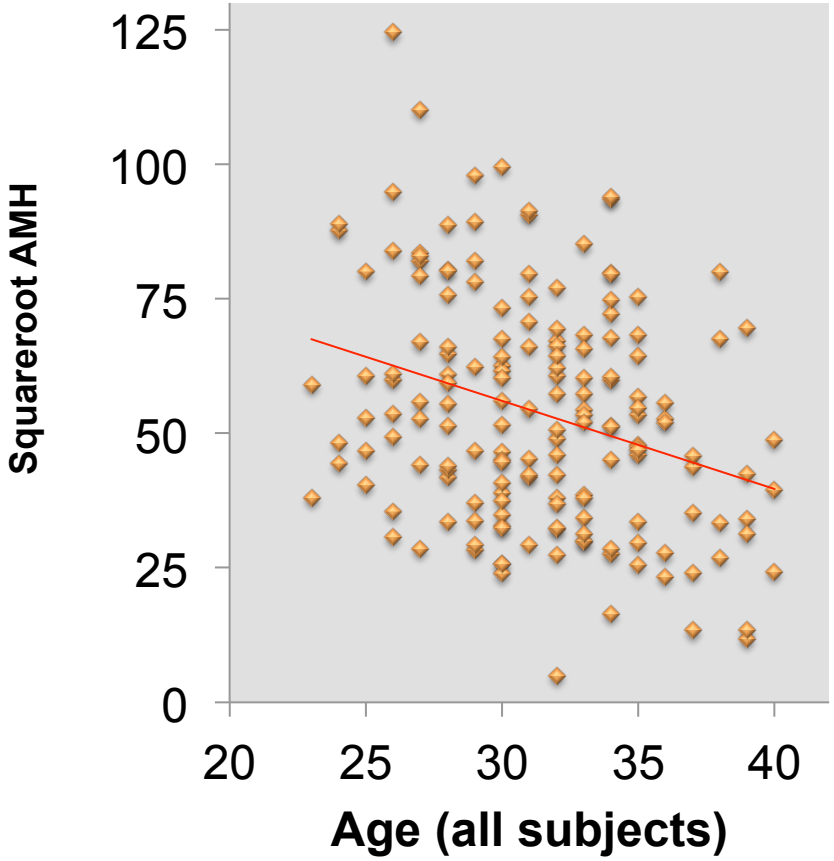
- Clinical features of endocrine disruption in women with epilepsy include early menopause, therefore, the primary hypothesis tested was that ongoing seizure occurrence adversely affects ovarian reserve, assessed by determination of AMH
- A history of infertility or risk factors for such were exclusionary in this study.
- Serum AMH levels were obtained prior to pregnancy, most drawn first day 21 of enrollment.
- Statistics used were t-tests, chi square, correlations and regression.

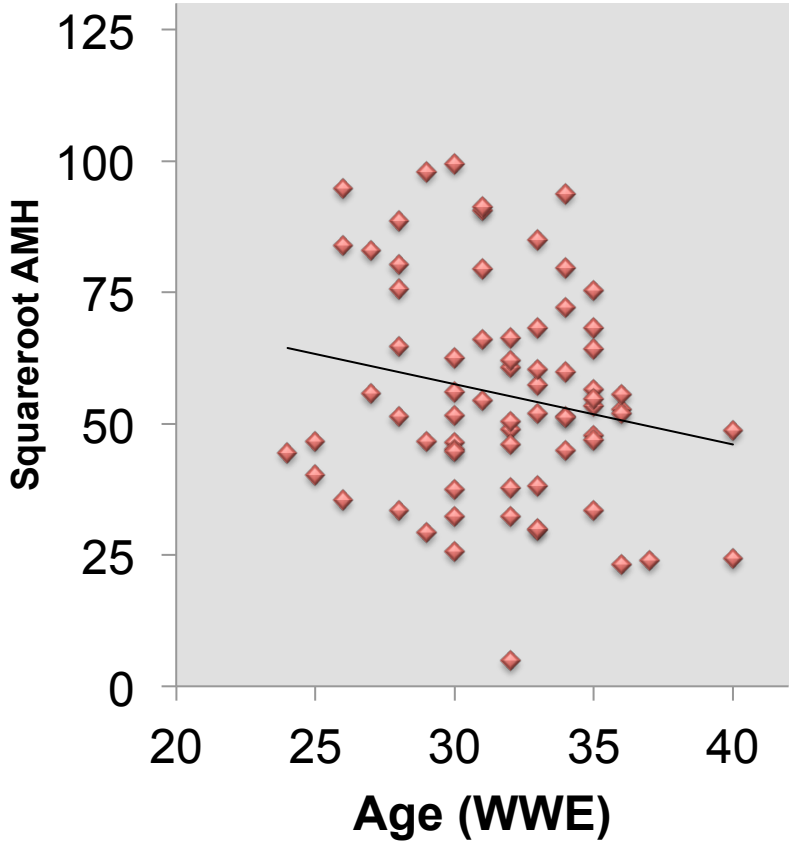
# BMI correlates with AMH in entire study group of epilepsy subjects (n=72 of 90 enrolled) and controls (97 out of 109 enrolled)




BMI and MIS all subjects
correlation -0.160 p=0.039

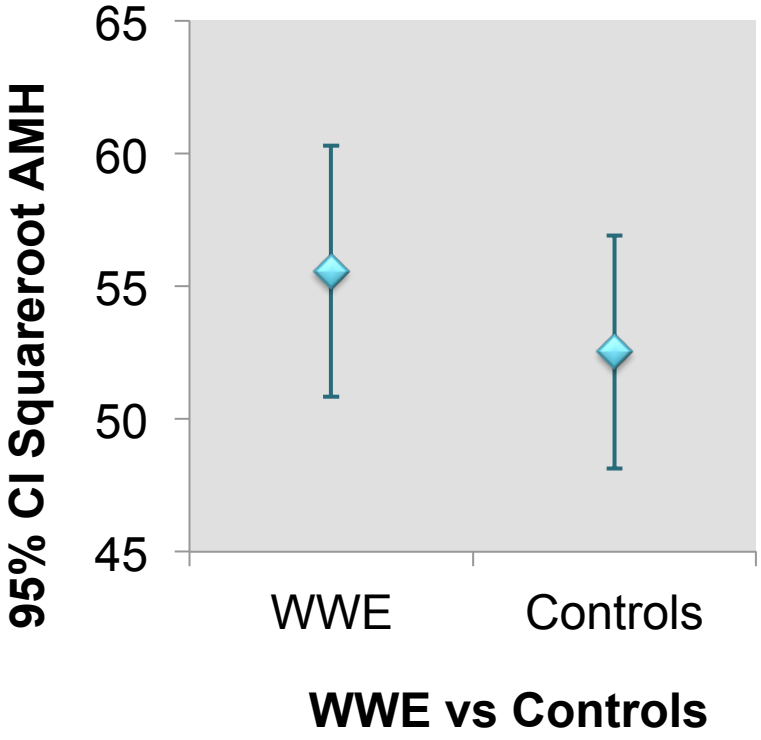
# AMH normally associates wth age, but dissociates with age in the WWE



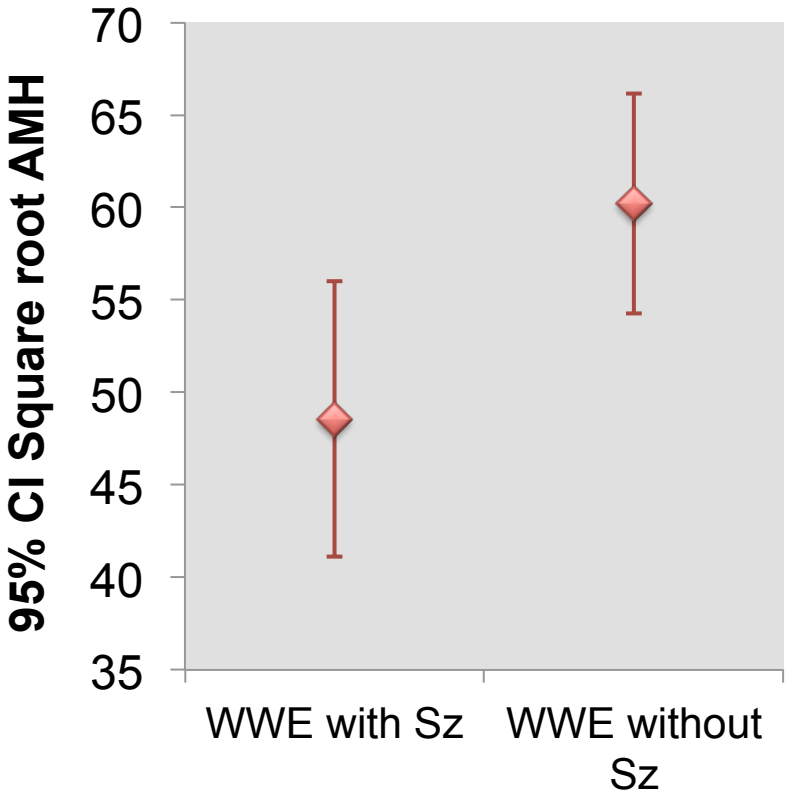
| | Women with Epilepsy n=90 (%) | Healthy Controls n=109 (%) |
|---|---|---|
| Age (years) | | |
| Mean (± SD) | 31.9 (± 3.5) | 31.1 (± 4.2) |
| Median (Range) | 32 (24 – 40) | 31 (23 – 40) |
| Ethnicity | | |
| Hispanic or Latino | 12 (13.3) | 14 (12.8) |
| Not Hispanic or Latino | 78 (86.7) | 95 (87.2) |
| Race | | |
| Asian | 5 (5.6) | 18 (16.5) |
| African American / Black | 1 (1.1) | 17 (15.5) |
| Native Hawaiian or Pacific Islander | 1 (1.1) | 1 (0.9) |
| White | 79 (87.8) | 64 (58.7) |
| Other / Mixed | 4 (4.4) | 9 (8.3) |
| | | |
| AMH Level (pg/mL) | | |
| Mean (± SD) | 3500.75 (± 2438.18) | 3241.13 (± 2647.66) |
| Median (Range) | 2740 (24 – 9900) | 2430 (140 – 15500) |
| First Quartile Q1 | 1978 | 1170 |
| Third Quartile Q3 | 4588 | 4570 |
| | | |
| AED Monotherapy | | |
| LTG | 40 (44.4) | |
| LVT | 25 (27.8) | |
| Strong Enzyme-Inducing AED[a] | 11 (12.2) | |
| Other | 3 (3.3) | |
| AED Polytherapy | | |
| Strong Enzyme-Inducing AED[a] | 5 (5.6) | |
| Other | 4 (4.4) | |
| | | |

Figure 2: Mean and standard deviation of square root AMH in epilepsy and controls; t-test p=0.357.



| | WWE with seizure n=30 (%) | WWE without seizure n=40 (%) |
|---|---|---|
| Age | | |
| Mean (± SD) | 31.4 (± 3.4) | 32.0 (± 3.5) |
| Median (Range) | 32 (24 – 37) | 32 (26 – 40) |
| Hispanic or Latino | 6 (20) | 3 (7.5) |
| Not Hispanic or Latino | 24 (80) | 37 (92.5) |
| Asian | 1 (3.3) | 3 (7.5) |
| African American / Black | 1 (3.3) | 0 (0) |
| Native Hawaiian or Pacific Islander | 1 (3.3) | 0 (0) |
| White | 26 (86.7) | 35 (87.5) |
| Other / Mixed | 1 (3.3) | 2 (5.0) |
| AMH Level (pg/mL) | | |
| Mean (± SD) | 2776.80 (± 2308.07) | 3982.00 (± 2451.93) |
| Median (Range) | 2165 (24 – 9876) | 3025 (590 – 9600) |
| First Quartile Q1 | 1013 | 2220 |
| Third Quartile Q3 | 3603 | 6058 |
| AED Monotherapy | | |
| LTG | 11 (36.7) | 21 (52.5) |
| LVT | 7 (23.3) | 10 (25.0) |
| Strong Enzyme-Inducing AED[a] | 3 (10.0) | 6 (15.0) |
| Other | 2 (6.7) | 1 (2.5) |
| AED Polythereapy | | |
| Strong Enzyme-Inducing AED[a] | 0 (0) | 0 (0) |
| No AED | 0 (0) | 1 (2.5) |
| Seizure Type | | |
| Generalized only | 11 (36.7) | 12 (30) |
| Focal only | 18 (60) | 24 (60) |
| Generalized and Focal | 0 (0) | 1 (2.5) |
| Unspecified | 1 (3.3) | 3 (7.5) |
| | | |
| With Convulsion | 22 (73.3) | 31 (77.5) |
| Without Convulsion | 8 (26.7) | 9 (22.5) |

Mean and standard deviation of square root AMH in epilepsy groups comparing those with and without seizure in the 9 months prior to the study enrollment; t-test p=0.020.



# Key Findings in the epilepsy group

- There was no association of MIS levels with antiepileptic drug factors.
- There was no association of age, BMI, race or parity with seizure occurrence.
- Regression including age and BMI in the analysis, showed a significant effect of seizure occurrence vs no seizure occurrence on MIS levels
  - Seizures in the 9 months prior to enrollment ($p=0.025$).
  - Seizures during the same menstrual cycle and before AMH was drawn ($p=0.012$)
- Seizure occurrence also associated with MIS levels of less than 1000 pg/ml which are associated with incipient ovarian failure by some investigators ($p=0.013$ by logistic regression).

# Conclusions

- These preliminary results suggest that seizures adversely affect ovarian reserve, independent of AED use.
- Refining the association between seizure frequency, type and specific AED use on MIS levels should be performed in a larger study that includes a broad spectrum of women with epilepsy of childbearing potential.

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