Pregnancy and Epilepsy

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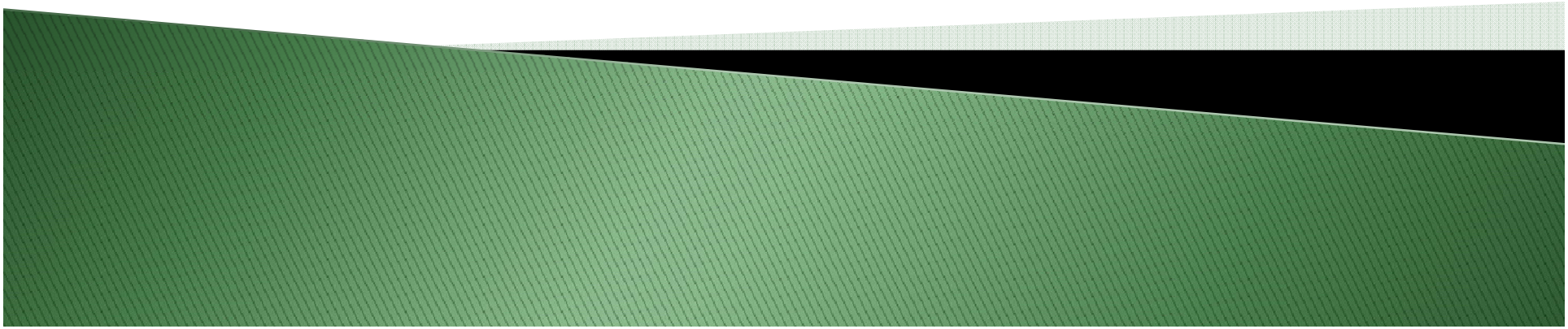
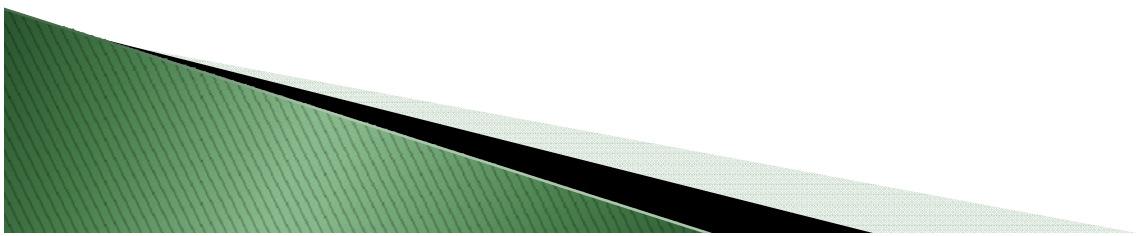


OBJECTIVES

- Learn to provide prenatal counseling to women with epilepsy of child bearing age.
- Define antenatal care for pregnant women with epilepsy.
- Describe postpartum care for mom and child.



Incidence and Prevelance

- Incidence of Epilepsy: 48/100,000
- Female/Male ratio: 1:1
- Estimate of ½ to one million women with childbearing potential
- 50% of pregnancies in US are unplanned

- 3-5 births per thousand will be to WWE

•Hirtz et al, 2007; Harden el al. 2009; Yerby, 2000

Prenatal counseling in WWE

- Contraceptives
- Folic acid
- Potential complications
- Seizure frequency

Prenatal Counseling in WWE

- Avoidance of unplanned pregnancy is important
  - Discussion of contraception at every visit
  - Place all women with child bearing potential on Folic Acid
    - 0.4mg/day (at least)
    - Typically we use 1mg/day
    - No evidence that higher dosage leads to better outcome, but dosage up to 4mg/day have been used

- Czeizel AE, et al. Hunagarian cohort-controlled trial of periconceptional multivitamin supplementation shows a reduction in certain congenital abnormalities. Birth Defects Res A Clin Mol Teratol 2004; 70: 853-861

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Prenatal Counseling in WWE

- "Appropriate" AED serum free level must be established *prior* to conception
- GOALS:
  - good seizure control
  - no debilitating side effects

Hormonal effect on epileptogenesis

- Lower progesterone:estrogen ratio → decreases seizure threshold
  - Manifests as *catamenial seizure clustering* in some patients.
- Estrogen has excitatory neuronal effects
- Progesterone appears to have an anticonvulsant effect.
  - Effect largely mediated by its natural progesterone metabolite (allopregnanolone).
  - Synthetic (Depo-provera) versus natural progesterone (prometrium)

AED effect on hormonal contraception:

	Steroid Hormone Binding Globulin	Hormone Level
Inducers **Carbamazepine** **Phenytoin** **Phenobarbital/Primidone** **Felbamate** **Topiramate (≥400mg/d)** **Oxcarb (≥1200mg/d)**	↑	↓ (reduction up to 50%)
Inhibitor **Valproate**	↓	↑
No effect **Ethosuximide** **Gabapentin** **Lamotrigine** **Levetiracetam** **Tiagabine** **Zonisamide**	no significant effect	no significant effect

Contraceptives in WWE: pt on enzyme inducers

- Use Combination OCP with higher dose of estrogen:
  - minimum of 50-100ug of estrodial – adjusted based on breakthough bleeding.
  - Avoid progesterone only pill
  - Higher failure rate with levonorgestrel implants, i.e. hormonal IUD *Mirena*.
- Depo Medroxyprogesterone:
  - interval should be shorten from 12 to 8 weeks.
- Consider addition of barrier method until stable pattern of menstration is established.

Effect of OCP on AEDs:

- Obtain levels at baseline and then repeat after 3 months after OCP initiation.

- Special attention to LTG as OCP can markedly reduce serum concentrations!
  - Also decreased during pregnancy.
  - LTG eliminated by glucuronic acid conjugation and by UGT1A4.
    - Glucoronic acid conjuagtion known to be induced by OCP.

- Saber A. et al. Oral contraceptives reduce lamotrigine plasma levels. Neurology 2003.

Prenatal Counseling

- No substantial increase risk of c-section
- No increase in pregnancy bleeding
- No increase risk of premature contractions or premature labor and delivery.
  - Except for those who smoke as compared with smokers who are non-epileptics.

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Seizures and Pregnancy

- No Sufficient evidence to determine the change in seizure frequency during pregnancy.
  - No non-pregnant control group
  - Unclear if variation is due to nature of the disease versus the pregnancy.

- 84-92% of WWE who are seizure free for at least 9 months prior to pregnancy will likely remain seizure free during pregnancy(Gjerde et al, 1988; Tomson et al., 1994)

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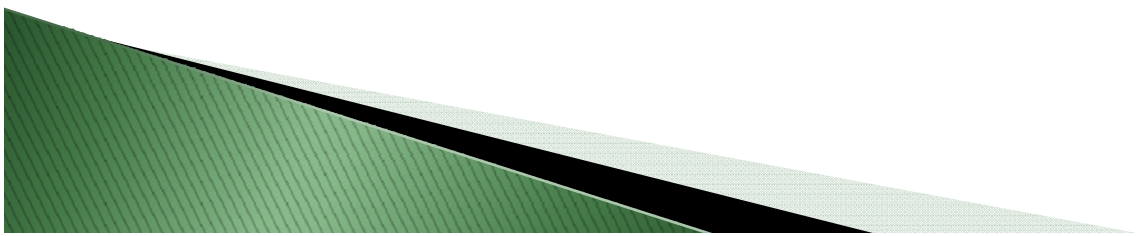
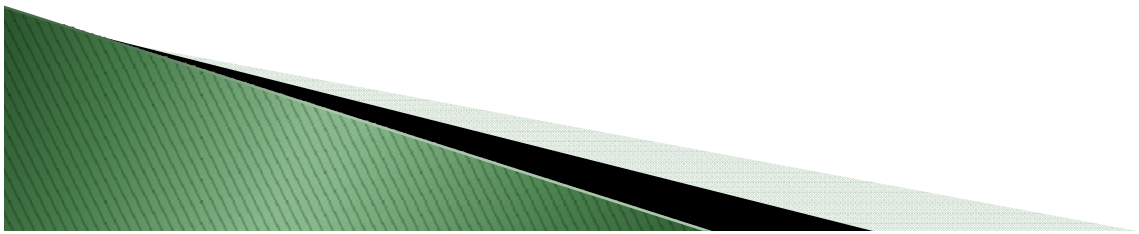
Seizures During Pregnancy

- Seizures due to acute medical conditions during pregancy:
  - Eclampsia
  - CNS infxn
  - Cerebral venous sinus thrombosis
- Gestational Epilepsy:
  - Seizures occurring only during pregnancy, with seizure freedom btw pregnancies.
  - Incidence is unclear.



Fertility and WWE

- 30-60% decrease in fertility rates
- Multifactorial:
  - Social isolation
  - Woman's choice
  - Sexual dysfuntion
  - Reproductive endocrine disorders related to AED
    - Increase rate of anovulation (VA)
    - Polycystic Ovarian Syndrome (VA)



Antenatal Care

- Teratogenicity Risk
  Pregnancy Registry
  AED serum monitoring
  Vitamin K

Case example

- 32 year old woman with epilepsy since age 26
  - Left frontal lobe epilepsy
    - EMU showing seizures from left frontal lobe, and independent right temporal spikes
    - comorbid non-epileptic seizures
  - Last seizure was 2008 (during EMU admission)
- Presents to epilepsy clinic at 20 week gestation
  - She had decreased her Topamax 100mg BID to take it once daily.
- What are your recommendations?

Embryonic Organogenesis and Major Congenital Malformations

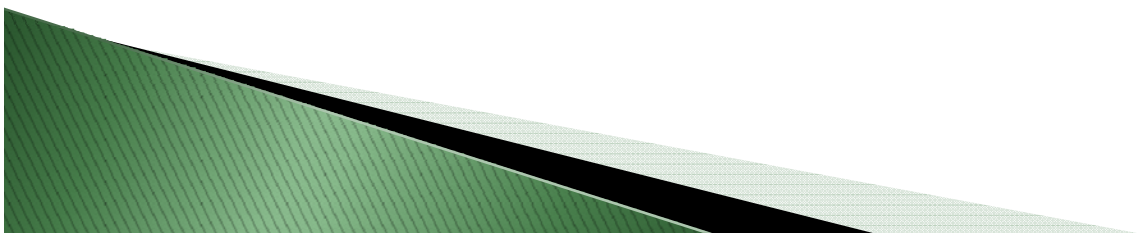
Organ System	MCM	Conception Age (days)
CNS	NTD	28
Face	Cleft lip & palate	36 and 70
Cardiovascular	VSD	42
Urogenital	Hypospadias	56

Relative prevelance in general population of MCM is 1.3%

Teratogenesis of AED

- Less than 10% of WWE receive information about teratogenesis of AED from their physicians

- Several mechanisms postulated in etiology

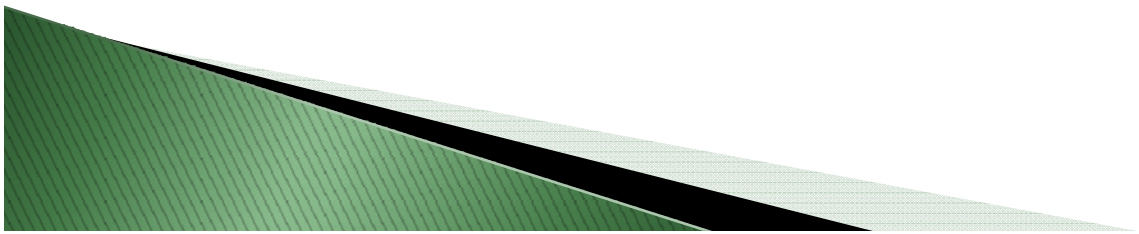


Teratogenesis: Potential mechanisms of AED

- ANTIFOLATE EFFECT
  - Phenytoin, Phenobarb, Carbamazepine, Valproate
  - Decrease absorption and increased clearance of folate
- TOXIC INTERMEDIARY METABOLITES (unstable epoxides)
  - CBZ + enzyme inducers → increase conversion to epoxide
  - VPA inhibits epoxide hydrolase
  - Genetic susceptibility (regulation of epoxide hydrolase)

Teratogenesis: Potential mechanisms

- OTHER MECHANISMS:
  - FREE RADICAL INTERMEDIATES generated by use of certain AEDs
  - Inhibition of protein synthesis and binding
  - Interference with lipid metabolism
  - Sequestration of trace metals.



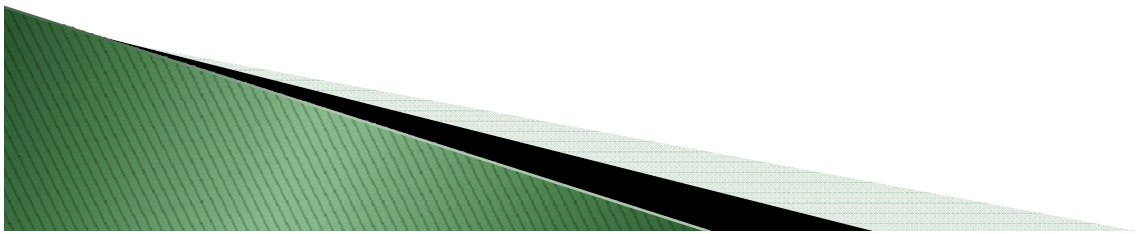
Teratogenicity: Other things to consider…

- Genetics:
  - Maternal trait of epilepsy
  - Severity of the disease (maternal seizure during pregnancy)
- Environment
  - Falls/injuries secondary to seizures
  - Lower socio-economic status

CONGENITAL MALFORMATIONS

NEURAL TUBE DEFECTS

Valproate	1-2%
Carbamazepine	0.5-1%
Phenytoin	0.3-0.4%
Phenobarbital	0.3-0.4%
Non-epileptic women	0.15%



Conclusions about Teratogenicity

- AED taken in 1st trimester increase risk of MCM.
  - Unclear if it's due to all or some of the AEDs
- Intrauterine 1st trimester valproate has higher risk of major congenital malformations than other AEDs.
  - Avoid valproate as monotherapy and as part of polytherapy
- Polytherapy probably contributes to development of MCM as compared to monotherapy (only one class I study).

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Conclusions about Teratogenicity : specific AEDs

- PHT → cleft palate (one Class II study).
- CBZ → posterior cleft palate (one Class II study).
- VPA → neural tube defects and facial clefts (one Class I study)
- VPA → hypospadias (one Class II study).
- Phenobarbital (PB) → cardiac malformations (two Class III studies).

- Cognition:
  - VPA, PHT, and PB → increase risk of poor cognitive outcomes.

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Toparimate – Now Pregnancy Category D

- MGH registry abstract, 2010 (289 pt on TPM)
  - Prevalence of MCM of those exposed to topiramate in 1st trimester is 3.8% (vs. 1.3% in general population)
  - Prevelance of oral clefts (1.4% – 4 patients) vs other AEDs (0.38 to 0.55%) vs. no maternal epilepsy and no AED (0.07%).
  - Previous report by European registry in 2008
- 1st trimester exposure to LTG, OXC, TPM, LEV, or GBP vs. no exposure was not associated with an increased risk of major birth defects
  - Danish study. Small sample size.
  - Molgaard-Nielsen & Hviid, JAMA, 2011

AED Pregnancy Registry
Mass General Hospital

Women who are currently pregnant and taking AEDs for any reason.

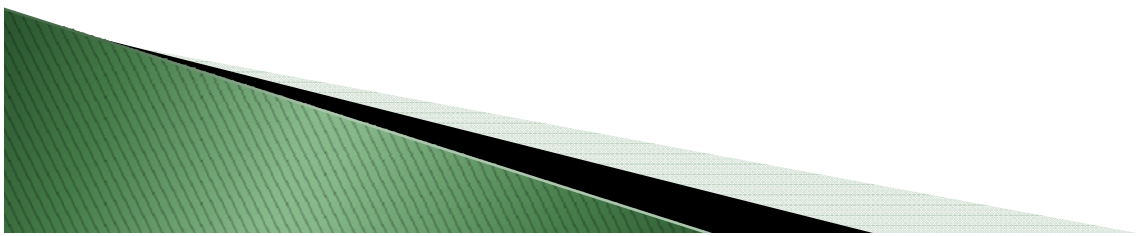
1-888-233-2334

3 brief telephone interviews:

- Enrollment
- @ 7months
- Few months after delivery

AED level monitoring during pregnancy

- Minimum requirements of drug monitoring:
  - @ preconception levels
  - @ beginning of each trimester
  - In the last month of pregnancy
  - During 2 months of postpartum



Monitoring AEDs during pregnancy: specific AEDS

- LTG: increase clearance → decrease levels → increase in seizure frequency
- CBZ: decrease levels
  - 9% in 2nd trimester
  - 12% in 3rd trimester
- PHT: increase clearance→ decrease levels
- OXC metabolite monohydroxy derivative: decrease levels
- LVT: decrease levels
- Lack of evidence for other AEDs, but this should not discourage monitoring

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Hemorrhagic complications in the newborns of WWE taking AEDs

- Vitamin K 20mg PO Qday in the last 2-4 weeks????
  - Insufficient evidence to support or refute the increase risk of neonatal hemorrhagic complications
  - Inadequate evidence to determine if prenatal vitamin K supplementation reduces neonatal hemorrhagic complications
- ***All neonates (offsprings of WWE taking AED or not) receive vitamin K at delivery!!
  - Vitamin K 1mg IM at birth

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Postnatal Care

- Follow AED levels
  Seizure precautions
  Breastfeeding
  More counseling

Seizure precautions

- Depends on type of seizures
- In general, nothing that would cause harm to baby should mom has an episode of loss of consciousness
  - Sponge bath rather than water bath
  - Changing on floor rather on table.
  - Reinforce driving restrictions
- Warn about sleep deprivation and increase tendency for seizures

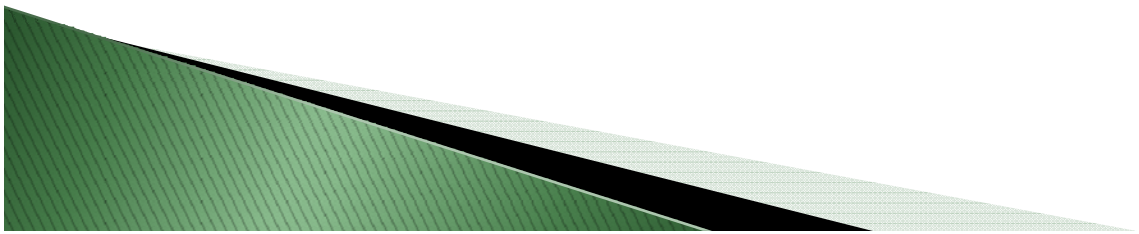
Breastfeeding

- More AED crosses the placenta than into milk

BUT

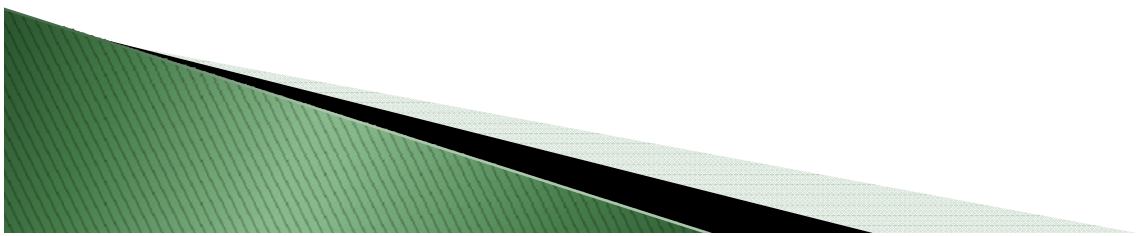
- In utero AED exposure cannot be avoided, ex utero AED exposure is voluntary.

- Other factors:
  - In utero AED occurs while brain is forming..and hence greatest impact occurs at this time.



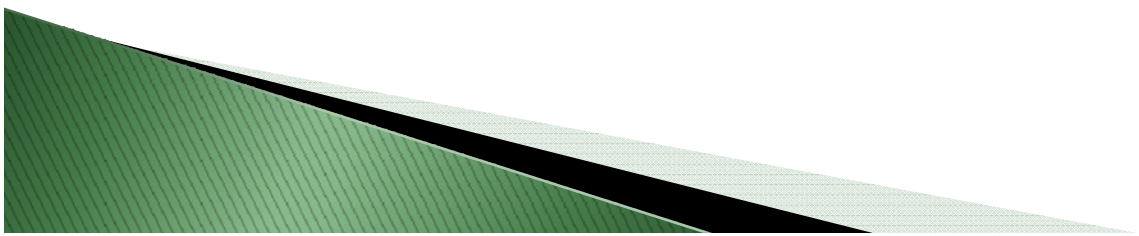
Breastfeeding: exposure to infant

- Several variables:
  - Maternal plasma concentration of drug
  - Fraction of AED transferred to the breast milk
    - Increase accumulation in AEDs with
      - Low protein binding
      - Low molecular weight
      - High lipophilicity
  - Infant absorption and elimination
    - Typically efficient with very low levels detected in few reported cases.



Breastfeeding

- Transfer of AED into milk difficult to study:
  - Frequency and amount of milk child breastfeeds varies.
  - Time of collection is not standard.
  - Foremilk and Hindmilk have different protein, fat, and carbohydrate proportion resulting in different medication binding and secretion.
  - Enrolment issue → few studies



Quatifing AED Exposure:

AED and Protein binding	Breast milk: Maternal plasma ratio	Maternal : Infant plasma ratio
CBZ/moderate	0.4–0.6	n/a
ESX/none	0.9	n/a
GBP/none	0.7–1.3	0.06 (1 case report)
LTG/moderate	0.4–0.7	0.18–0.36
LEV/none	0.85–1.55 (1 case of 3.09)	Very low – undetectable
OXC/moderate	0.5	n/a
PB/moderate	0.4–0.6	n/a
PHT/High	0.18–0.45	n/a
PR/moderate	0.7–0.9	n/a
TPM/moderate	0.7–1.1	Very low – undetectable
VPA/High	0.01–0.10	n/a
ZNS/moderate	0.41–0.93	n/a

Ohman et al. 2002, Pennel et al. 2003, Kristensen el al. 2006, Johannessen et al. 2005, Westin el al. 2008

Breastfeeding: transfer to milk

- PRM and LVT probably penetrate into breast milk in potentially clinically important amounts (one Class I study and a supporting Class II study or two Class II studies).
- GBP, LTG, and TPM possibly penetrate into breast milk in potentially clinically important amounts (one Class II study each).
- VPA, PB, PHT, and CBZ probably do not penetrate into breast milk in potentially clinically important amounts (one Class I study and a supporting Class II study or two Class I studies).

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Breastfeeding: long-term effects

- There is no evidence to determine if indirect exposure to maternally ingested AEDs has symptomatic effects on the newborns of WWE

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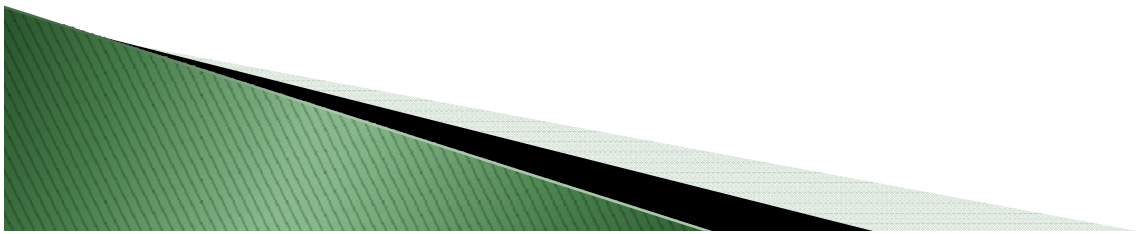
- CBZ, LTG, PHT, and VPA exposure during breastfeeding has no effect on IQ at age 3. (Meador et al. 2010 – NEAD study)



Summary

- Before Pregnancy:
  - Frequent Family planning conversations in WWE
  - Establish lowest effective dose, avoid valproate, add folate, and determine optimal AED plasma concentration
- During Pregnancy:
  - Meaesure AED plasma levels and maintain stabilility
  - emphasizing pregnancy registry
- After Pregnancy:
  - Measure AED plasma levels until stability is re-established.
  - Seizure precautions.