Special Considerations for Epilepsy in Women

Anumeha S. Sheth, MD

Hartford HealthCare Ayer neuroscience institute

Program director, Epilepsy fellowship U Conn/HHC

Assistant professor, U Conn School of Medicine

Objectives

- Pregnancy, Maternal, and neurodevelopmental outcomes in women with epilepsy (WWE)

Epilepsy and Fertility

- 55 – 65% of pregnancies in WWE are unintended
- Birth rates among WWE are lower than the general population
- Low birth rates do not translate directly into infertility.
- Women with epilepsy seeking pregnancy without prior known infertility or related disorders have similar likelihood of achieving pregnancy, time to pregnancy, and live birth rates compared with their peers without epilepsy

Seizures in Pregnancy

- ASMs are one of the most frequent chronic teratogen exposures.
- Used to treat psychiatric disorders, pain disorders and epilepsy.
- Approximately 2% of women take ASMs during their pregnancy.
- EURAP: Seizure frequency during 1,956 pregnancies (prospective data)
  - Unchanged ~64%
  - Increased~ 17%
  - Decreased~16%

Anti Seizure Medication (ASM) Pharmacokinetics in Pregnancy

- Causes of decreased ASM levels during pregnancy:
  - Increased clearance
  - *PHT, PB, CBZ, LTG, LEV, OXC, TPM*
    - Maximal clearance of LEV is reached in first trimester, OXC and TPM in second trimester
  - Larger volume of distribution
  - Alterations in drug absorption
  - Non-compliance

Individual ASMs in Pregnancy

Pharmacokinetic Changes During Pregnancy

AED	Increase in Clearance
Levetiracetam	**243%**
Lamotrigine	**65-230%**
Oxcarbazepine	**56-163%**
Phenobarbital	**60%**
Phenytoin	**19-117%**
Free Phenytoin	**25%**

* Evidence for a change in clearance or levels of **VPA, PRM, ESX,** CBZ is conflicting or lacking.

Pennell PB, Hovinga C. *Int Rev Neurobiol* 2008; Harden CL, et al. *Neurology* 2009.

Lamotrigine in Pregnancy

- Primarily eliminated via hepatic glucuronidation
- Free and total clearance is increased during all 3 trimesters
- Seizure frequency significantly increased when *LTG* levels decreased to 65% (of preconceptual)
- Rapid decrease in *LTG* clearance during the early postpartum period can cause symptomatic toxicity

ASM Dosing in Pregnancy

- Target concentration of AED should be determined in preconception phase
- Monitor levels q1-2 months Increase dose if free levels fall or if clinically indicated
- Therapeutic level recommended prior to delivery
- Dose should be adjusted, and levels followed during post partum period

ASMs in Pregnancy

- Pregnancy category C: known risk in animals, unknown risk in humans

  Levetiracetam, lamotrigine, gabapentin, lacosamide, zonisamide, oxcarbazepine

- Pregnancy category D: definite risk in humans

  Phenytoin, Carbamazepine, Valproate, Topiramate

Labor and Delivery Outcomes

- North American Pregnancy Registry
- 9819 ASM exposed women from 1997 – 2017
  - Increased risk of SGA, low birth weight *(ZNS, TPM)* and head circumference, preterm birth
- Nationwide inpatient sample
- Delivery hospitalizations from 69 385 WWE and 20 449 532 WWOE from 2007-2011
  - Increased maternal mortality, preeclampsia preterm labor, stillbirth, increased health care utilization (cesarean delivery and prolonged length of hospital stay (>6 days))

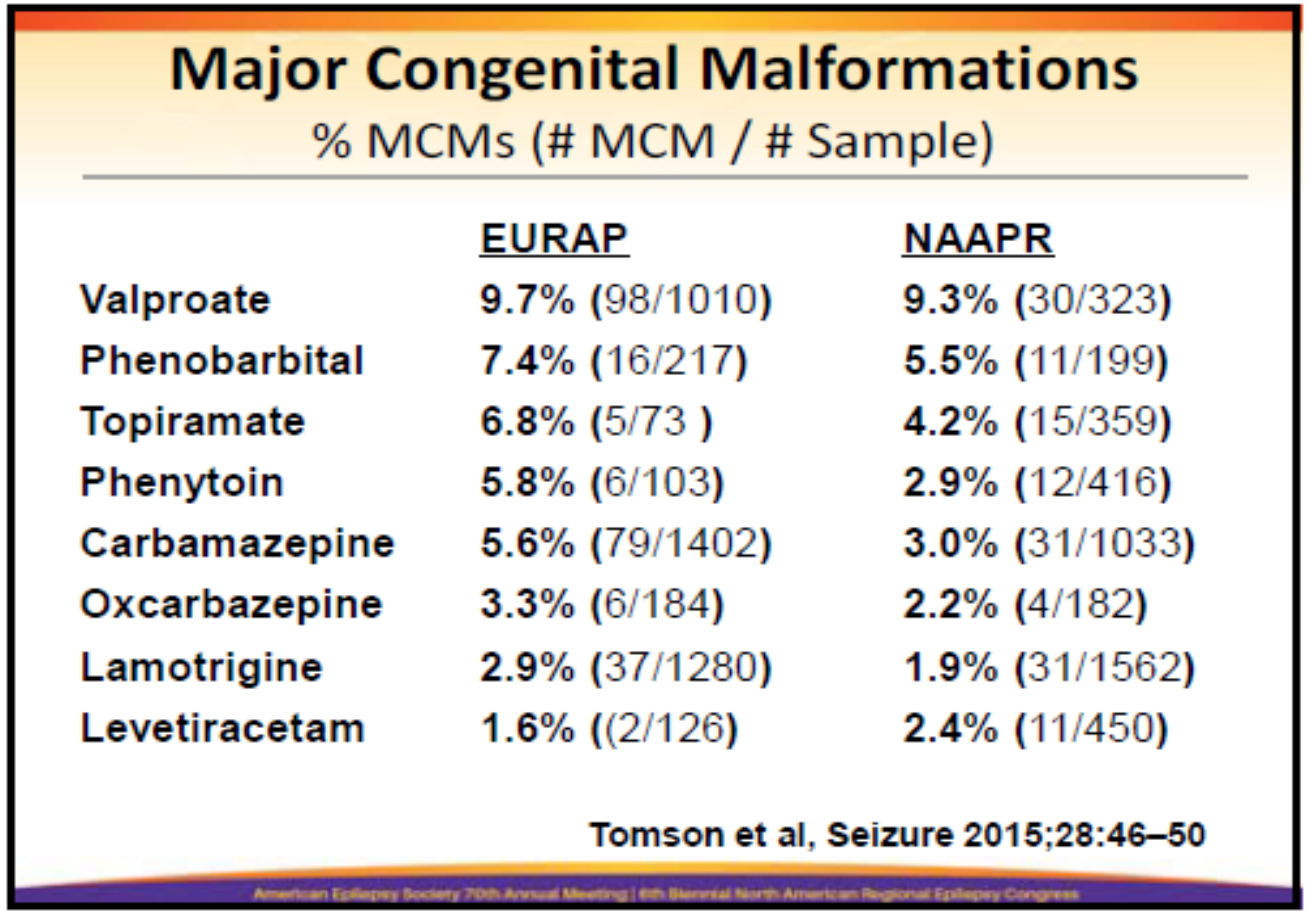
Teratogenicity

- Major congenital malformations (MCM):
  - Neural tube defects, congenital heart disease, oral clefts, skeletal abnormalities, intestinal atresia, urogenital defects
  - General population: 1.6 -3.2%
  - AED exposures: 3.1 - 9%
- Minor malformations (facial dysmorphism, digital anomalies)
  - General population: 4-10%
  - AED exposures: 10-30%

Teratogenicity

- MCM risk is ~2 – 9% with any first trimester monotherapy AED exposure
- MCM risk is ~ 6.5 -19 % with any first trimester polytherapy ASM exposure
- *VPA* as monotherapy (9.3%) or part of any polytherapy regimen has higher risk
- Dose dependent MCM risk with *VPA*

MCM Data


Major Congenital Malformations
% MCMs (# MCM / # Sample)
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)
Tomson et al, Seizure 2015;28:46–50

Teratogenicity - Valproic Acid

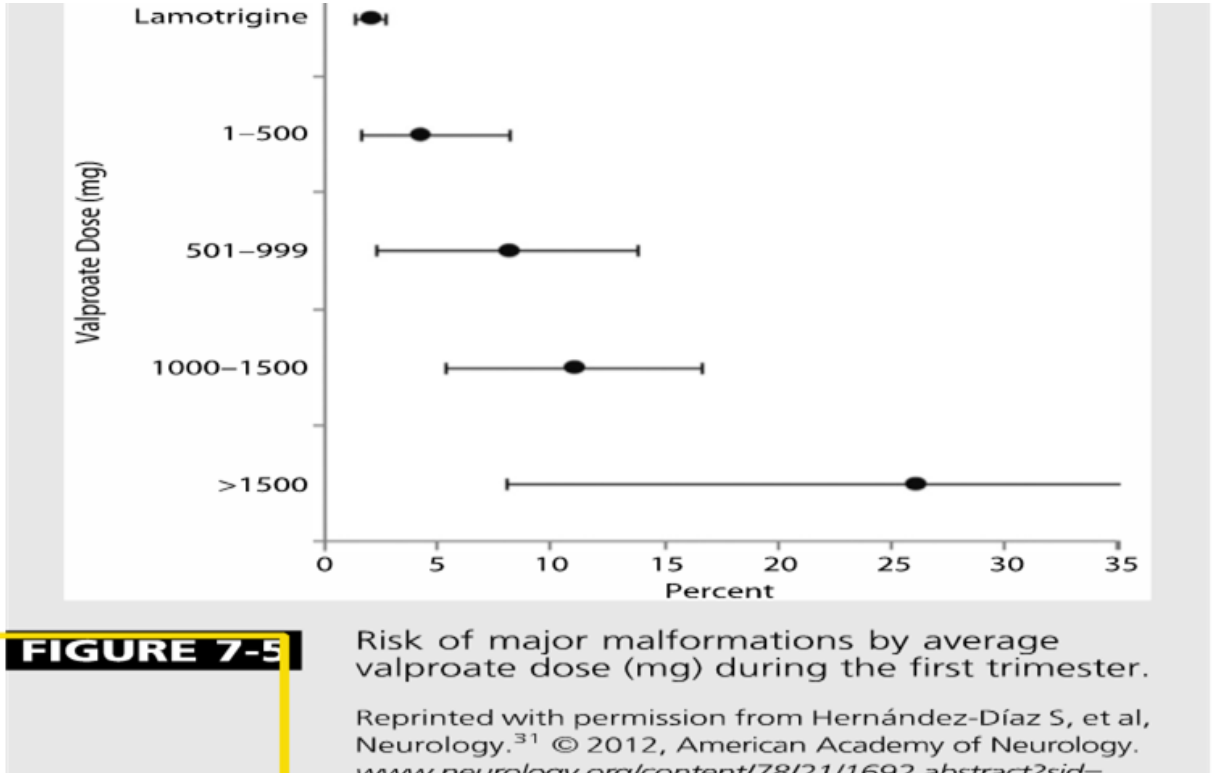


FIGURE 7-5 Risk of major malformations by average valproate dose (mg) during the first trimester.

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Topiramate

- Association of first trimester exposure with increased risk of oro-facial clefts
- Changed from pregnancy category C to D in March 2011
- ~10-fold risk of oral clefts
- Some association with hypospadias
- Lower IQ scores across several domains as well as poorer motor and visual spatial skills.

NEAD

Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study

*Kimford J Meador, Gus A Baker, Nancy Browning, Morris J Cohen, Rebecca L Bromley, Jill Clayton-Smith, Laura A Kalayjian, Andres Kanner, Joyce D Liporace, Page B Pennell, Michael Privitera, David W Loring, for the NEAD Study Group**

Summary

Background Many women of childbearing potential take antiepileptic drugs, but the cognitive effects of fetal exposur are uncertain. We aimed to assess effects of commonly used antiepileptic drugs on cognitive outcomes in children u to 6 years of age.

NEAD

- Prospective, observational, multicenter study in the US and UK.
- Assessed the neurodevelopmental effects of in-utero exposure to four ASM monotherapy groups (*CBZ, VPA, PHT, and LTG*)
- The primary outcome was IQ at age 6 - adjusted for maternal IQ, ASM type and standardized dose, gestational age at birth, and use of peri conceptional folate.

NEAD – Results

- Lower IQ at age 6 in children exposed to *VPA* (6-10 points) as compared to *CBZ, LTG, or PHT*
- High doses of *VPA* were negatively correlated with IQ, verbal & nonverbal ability, memory and executive function
- Decline in social skills and the presence of hyperactive behaviors, suggesting a risk for the development of ADHD in valproate exposed children

NEAD – Results

- Dose dependent outcomes with *VPA*, other ASMs - no dose effect.
- **Mean FSIQ of 6-year-old children whose mothers reported periconceptional folic acid use was higher than the mean FSIQ of those who were not exposed to supplementation early in pregnancy, even after controlling for other factors such as maternal IQ

Autism and Divalproex

- School age children prenatally exposed to *VPA* prenatally more likely to receive a formal diagnosis of autism or autism spectrum disorders
- Absolute risk of autism in the *VPA* exposed cohort was 2.9% and autism spectrum disorders was 4.42% as compared with 0.48 and 1.53 % in general population
- Lower daily living and socialization skills
- Increased need for educational intervention

MONEAD - Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs

- NIH funded, Prospective, observational, multi-center investigation of pregnancy outcomes for mother (WWE) and child (2012 – 2016)
- Primary outcomes (i.e., seizures, obstetric complications, depression, and neurodevelopmental outcomes)
- PWE, 2 control groups: Healthy pregnant women (HPW) and nonpregnant WWE (NPWWE)
- 14 - 45 years
- Gestational age <20 weeks
- IQ >70 points

MONEAD: Changes in Prescribing Patterns

- 351 PWE, 105 HPW and 109 NPWWE (controls), 345 infants.
- Most prescribed ASMs
- Monotherapy
  - *LTG* (42%) and *LEV* (37.5%)
- Polytherapy.
  - *LTG* + *LEV* (42.9%)
- Changes in ASM doses more frequent in PWE than in NPWE
- No difference between PWE and NPWE in increased focal unaware seizure frequency during pregnancy as compared with postpartum

MONEAD - Severe adverse fetal outcomes (SAO)

- SAO - PWWE (7.9%) compared to HPW (1.9%)
- Fetal loss - no significant differences (2.8% vs 0%)
- Major Congenital malformations (MCMs) – No significant difference (5.2%vs 1.9%)
- The SAOs 9.0% in the NEAD study vs 7.9% in MONEAD
- The MCM rate of 5.2% in MONEAD lower than NEAD (6.6%)
  - Higher than NEAD without *VPA* (3.8%), higher for *LEV* and *LTG*
- No effect of periconceptional folate or ASM levels

MONEAD– Obstetrics

- 331 PWWE, 102 HPW
- No differences in C-section rate, pre-eclampsia, placental abruption, instrumental delivery, peripartum hemorrhage, and other major OB complications
- Higher rate of premature rupture of membranes
- Higher but nonsignificant Preterm delivery and NICU admission rates in polytherapy exposed women.

MONEAD – Neonatal outcomes

- No differences were seen between infants born to PWE vs HPW
- Preterm births, major congenital malformations, 5-minute Apgar <6, NICU admission, gestational age, or any growth measure.
- No difference in the rates of small for gestational age
  - TPM - lower birth weight z scores
  - LTG higher birth weight z scores

MONEAD: Neurodevelopmental outcomes

- There was no significant difference in primary language domains at 2 years of age between children of WWE and children of HPW
- Increased use of newer ASMs - lower risk of affecting the immature brain.
- Language at 2 years of age
  - Higher birth weight
  - Maternal IQ
  - Maternal educational level
  - Female gender

ASMs and the Neonate - Breastfeeding

- Higher protein-bound ASMs will have lower concentration in breast milk – *PHT, VPA*
- *PB* may accumulate (slow metabolism) drowsiness
- *LTG, LEV, TPM, GBP* penetrate breast milk in clinically important amounts
- ASM - Extensive placental transfer
- ASM exposure via breast milk is substantially lower than fetal exposure during pregnancy

ASMs and the Neonate

- NEAD
  - No ill effect of ASM exposure through breastmilk on IQ at age 3
  - Higher IQ and verbal ability (by 4 points) at age 6 in breast fed children exposed to *LTG, PHT, VPA* and *CBZ*
- MONEAD
  - ASM concentrations in blood samples of breastfed infants <<< maternal blood concentrations.
  - *LTG* has a higher concentration in breast milk compared to *LEV*

AAP encourages breastfeeding with close observation of the baby

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MONEAD - Depression and Anxiety

- Beck Depression Inventory (BDI) - worse in PWWE
- Beck Anxiety Inventory (BAI) - worse in PWWE
- Decreased from pregnancy to postpartum
- Structured Clinical Interview for DSM-IV (SCID) Major depressive episode – No difference
- Factors associated w/ MDE in PWWE
  - >1 seizure/90 days, ASM polytherapy, unplanned pregnancy, h/o mood disorders

AAN Practice Parameters for Women with Epilepsy - 2009

- If WWE have been seizure free for 2-5 years, and have single seizure type, normal IQ and exam, and normalized EEG, discontinuation of treatment may be considered
- AED withdrawal should be completed at least 6 months before conception

Practice Parameters for WWE, Continued

- For stable patients, monitor free ASM levels prior to conception and at start of each trimester
- Additional levels as indicated
- Monitored through the 8 postpartum week or till levels are stable
- Breast feeding is not contraindicated

Practice Parameters for WWE, Continued

- The choice of ASM should be that deemed most appropriate for the seizure type
- Monotherapy should be the aim of treatment
- Change to an alternate ASM should not be undertaken for the sole purpose of reducing teratogenic risk*

Practice Parameters for WWE, Continued

- Folate supplementation of no less than 0.4 mg/day (4mg/day per ACOG) should be instituted in all WWE having reproductive potential and continued throughout pregnancy