Living with Epilepsy
Community Education Conference
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Epilepsy and Pregnancy

Hill Physicians Medical Group
Epilepsy and Pregnancy

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*Items with asterisk involve income > $10,000 for recent years.
Historical Background

- 1850s – 1st Antipileptic Drug (AED) discovered
- 1956 – 18 USA states with sterilization for people with epilepsy
- 1960s – 1st reports of malformations & AEDs
- 1980 – last US state law repealed forbidding people with epilepsy to marry
- 1980s – 1st AED specific defect: Spina bifida & Valproate
- 1980s – Animal studies suggests AEDs could have behavioral teratogenesis
- 2000s – Human studies show differential AED risks for both anatomical & behavioral teratogenesis
Childbearing in Women with Epilepsy: Clinical Dilemma

- Drugs generally contraindicated in pregnancy.
- Most women with epilepsy are unable to stop using AEDs due to risks of seizures.
  - Injury, Death, Miscarriage, Developmental delay, & Loss of job or driving
- As a group, both somatic & functional neurodevelopment are reduced.
- Majority of the children are normal.

AEDs = antiepileptic drugs
<table>
<thead>
<tr>
<th>Lower hormone levels</th>
<th>No significant effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Carbamazepine</td>
<td>• Clonazepam</td>
</tr>
<tr>
<td>• Clobazam</td>
<td>• Ethosuximide</td>
</tr>
<tr>
<td>• Eslicarbazepine</td>
<td>• Ezogabine</td>
</tr>
<tr>
<td>• Felbamate</td>
<td>• Gabapentin</td>
</tr>
<tr>
<td>• Oxcarbazepine (&gt;1200mg)</td>
<td>• Lacosamide</td>
</tr>
<tr>
<td>• Perampanel</td>
<td>• Lamotrigine*</td>
</tr>
<tr>
<td>• Phenobarbital</td>
<td>• Levetiracetam</td>
</tr>
<tr>
<td>• Phenytoin</td>
<td>• Pregabalin</td>
</tr>
<tr>
<td>• Primidone</td>
<td>• Tiagabine</td>
</tr>
<tr>
<td>• Rufinamide</td>
<td>• Valproate**</td>
</tr>
<tr>
<td>• Topiramate (&gt;200mg)</td>
<td>• Vigabatrin</td>
</tr>
<tr>
<td></td>
<td>• Zonisamide</td>
</tr>
</tbody>
</table>

* Estradiol lowers lamotrigine level  
** Valproate can interact with other drugs but not OCPs
AED Levels Change in Pregnancy

- “Reasoned” Noncompliance
- Malabsorption
- Change in Volume of Distribution
- Increased AED Elimination
  - Increase in peak clearance (drug removal):
    - 191% Lamotrigine
    - 207% Levetiracetam
    - 12% Carbamazepine
- Highly variable across individual women & across repeat pregnancies

*Reisinger et al, Epilepsy Behav 2013
Congenital Malformations

- General Population = 2 - 3%

- Infants of Mothers with Epilepsy = 4 - 8% (Range = 1.25 - 18.6%)

**Major Malformations**: Heart Defects, Orofacial Clefts, Skeletal, Urological & Neural Tube Defects (VPA= 1.5%, CBZ< 0.5%)

CBZ=carbamazepine; VPA=valproate
<table>
<thead>
<tr>
<th>Drug</th>
<th>EURAP</th>
<th>NAAPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>9.7% (98/1010)</td>
<td>9.3% (30/323)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>7.4% (16/217)</td>
<td>5.5% (11/199)</td>
</tr>
<tr>
<td>Topiramate</td>
<td>6.8% (5/73)</td>
<td>4.2% (15/359)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>5.8% (6/103)</td>
<td>2.9% (12/416)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>5.6% (79/1402)</td>
<td>3.0% (31/1033)</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>3.3% (6/184)</td>
<td>2.2% (4/182)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>2.9% (37/1280)</td>
<td>1.9% (31/1562)</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1.6% ((2/126)</td>
<td>2.4% (11/450)</td>
</tr>
</tbody>
</table>

Tomson et al, Seizure 2015;28:46–50
## EURAP: Dose Dependent Effects on MCMs

<table>
<thead>
<tr>
<th>Antiepileptic Drug</th>
<th>N</th>
<th>% Seizure Free</th>
<th>% Malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cabamazepine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;400 mg/d</td>
<td>148</td>
<td>64%</td>
<td>3.4%</td>
</tr>
<tr>
<td>400 to &lt;1000 mg/d</td>
<td>1047</td>
<td>67%</td>
<td>5.3% *</td>
</tr>
<tr>
<td>≥1000 mg/d</td>
<td>207</td>
<td>62%</td>
<td>8.7% *</td>
</tr>
<tr>
<td><strong>Lamotrigine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;300 mg/d</td>
<td>836</td>
<td>67%</td>
<td>2.0%</td>
</tr>
<tr>
<td>≥300 mg/d</td>
<td>444</td>
<td>68%</td>
<td>4.5% *</td>
</tr>
<tr>
<td><strong>Phenobarbital</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;150 mg/d</td>
<td>166</td>
<td>71%</td>
<td>5.4% *</td>
</tr>
<tr>
<td>≥150 mg/d</td>
<td>51</td>
<td>69%</td>
<td>13.7% *</td>
</tr>
<tr>
<td><strong>Valproate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;700 mg/d</td>
<td>431</td>
<td>71%</td>
<td>5.6% *</td>
</tr>
<tr>
<td>700 to &lt;1500 mg/d</td>
<td>480</td>
<td>66%</td>
<td>10.4% *</td>
</tr>
<tr>
<td>≥1500 mg/d</td>
<td>99</td>
<td>61%</td>
<td>24.2% *</td>
</tr>
</tbody>
</table>

* More MCMs than LTG<300mg/d

Tomson et al., Lancet Neurol 2011;10: 609-17
**EUROCAT**

**European Surveillance of Congenital Anomalies**

- **Case-control study**
  98,075 cases with malformations among 3.8 million births in Europe
  14 countries from 1995 – 2005

- **Valproate**
  **Odds Ratio** (ie, increased risk)
  - Spina bifida: 12.7
  - Atrial septal defect: 2.5
  - Cleft palate: 5.2
  - Hypospadius: 4.8
  - Polydactyly: 2.2
  - Craniosynostosis: 6.8

- **Carbamazepine**
  - Spina bifida: 2.6

Conclusions: Anatomical Teratogenesis

- Valproate poses special risk (9.3%)
- Possible dose dependent risks for all AEDs
- Spina Bifida:
  - Valproate = 12.7 X, Carbamazepine = 2.6 X
- Phenobarb (5.5%), Topiramate (4.2%)
- Risks of most AEDs and specific polytherapy combination are uncertain
- North American AED Pregnancy Registry
  - 1-888-233-2334
In Utero AEDs & Behavioral Neurodevelopment in Animals

- Phenobarb reduces brain weight & impairs behavior in mice.
- Phenytoin impairs coordination & learning in rats.
- Phenytoin can cause hyperactivity in monkeys.
- Neurobehavioral effects also found for valproate.

Neurodevelopment in Children of Women with Epilepsy

- Maternal seizure type
- # of seizures during pregnancy
- IQ & education of parents
- AEDs & other drugs
- Other environmental factors
Fetal valproate exposure associated with lower IQ.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean IQ</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>98</td>
<td>6</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>101</td>
<td>9</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>99</td>
<td>7</td>
</tr>
<tr>
<td>Valproate</td>
<td>92</td>
<td></td>
</tr>
</tbody>
</table>

Meador et al. NEJM 2009;360:1597-605

IQ = intelligence quotient

Funded by NIH/NINDS #2RO1 NS 38455 and #1 R01050659
Fetal Exposure to Valproate Associated with Lower IQ at Age 6

Mean IQs (95% Difference CIs from VPA) adjusted for maternal IQ, AED dose, gestational age & folate:

<table>
<thead>
<tr>
<th></th>
<th>CBZ</th>
<th>LTG</th>
<th>PHT</th>
<th>VPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IQ</td>
<td>105 *</td>
<td>108 *</td>
<td>108 *</td>
<td>97</td>
</tr>
<tr>
<td>Difference</td>
<td>7</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td># Children</td>
<td>93</td>
<td>100</td>
<td>56</td>
<td>62</td>
</tr>
</tbody>
</table>

* Significantly better than VPA.

CBZ=carbamazepine, LTG=lamotrigine, PHT=phenytoin, VPA=valproate

Dose Dependent Effects of Valproate

The higher the dose of valproate during pregnancy, the worse the child’s performance on:

- IQ
- Verbal abilities
- Visuospatial abilities
- Memory
- Executive Functions
Distribution of IQ scores: Controls & Low/High Valproate Groups

Child General Cognitive Ability

Control (n=210)

Valproate low dose (n=21)

Valproate high dose (n=30)

<800mg/day

>800mg/day

Baker et al, Neurology 2014
Fetal Valproate: Autism, Autism Spectrum Disorder (ASD), & ADHD

Christensen et al, JAMA 2013. Population-based Danish register study
ASD 4.4%
Autism 2.5%

Wood et al, Epilepsia 2015. Small prospective study reporting increased scores in Childhood Autism Rating Scale at 6-8 years if exposed to VPA polytherapy (n=15)

Cohen et al, Epilepsy Behav 2013. Prospective NEAD study at 6 years. Children exposed to valproate had:
- Greater risk of diagnosis of ADHD
- Lower General Adaptive Composite scores
Child IQ & Periconceptional Folate

Folate = 108 (106, 111)  No Folate = 102 (98, 104)


Effect of Treatment Type and Preconception Folate Use on Year 6 IQ

- CBZ
- LTG
- PHT
- VPA

○ = Folate
○ = No Folate
### Fetal Levetiracetam & Topiramate: Cognition at 5-9 years old

<table>
<thead>
<tr>
<th></th>
<th>No AED</th>
<th>TPM</th>
<th>LEV</th>
<th>VPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>55</td>
<td>27</td>
<td>42</td>
<td>47</td>
</tr>
<tr>
<td>FSIQ*</td>
<td>100</td>
<td>100</td>
<td>99</td>
<td>96</td>
</tr>
<tr>
<td>VIQ</td>
<td>102</td>
<td>99</td>
<td>101</td>
<td>94</td>
</tr>
</tbody>
</table>

*Mean Full Scale IQ (standard deviation).

VIQ = verbal IQ

N = # children.

Bromley et al, Neurology 2016;87:1-11
Conclusions: Behavioral Teratogenesis

• Present studies suggest that valproate poses a special risk for behavioral as well as anatomical teratogenesis.

• Reasons for individual variability are unclear.

• Risks for many AEDs and polytherapies are uncertain.
Possible Mechanisms of AED Effects on Fetal Development

- Reactive Intermediates
  - Free Radicals
  - Arene Oxides (epoxides)
- Neuronal Apoptosis & Neuronal Dysfunction
  - NMDA antagonist & GABA agonist
  - Antagonism of neutropins & signal proteins
AEDs and Apoptosis in Developing Brain

- Widespread neural apoptosis (cell death) in young rats:
  - **Present** for clonazepam, diazepam, phenobarb, phenytoin, valproate, & vigabatrin\(^1,2\)
  - **Absent** for carbamazepine, lamotrigine, levetiracetam, & topiramate monotherapy\(^3-8\)

Conclusions: Mechanisms

- Mechanisms and reasons for individual variance are unknown.
- Neonates may also be at risk given the common use of benzodiazepines and phenobarbital in neonates.
Known Positive Effects of Breastfeeding

- Beneficial for the infant and mother.
- Child: reduced risk of severe lower respiratory tract infections, atopic dermatitis, asthma, acute otitis media, non-specific gastroenteritis, obesity, type 1 and 2 diabetes, leukemia, SIDS, enterocolitis, and possibly cognition.
- Mother: reduced risk for type 2 diabetes, breast cancer, ovarian cancer, and maternal postpartum depression.

Cognitive Effects of Breastfeeding

• General Population: Positive Cognitive Effects.

• Controversy Remains.

• Age 3 Outcomes in Children Breastfed on AEDs.

No adverse effects found.
Effects of Breastfeeding when on AEDs

IQ scores at age 6 yrs across all AEDs:

Breastfed 108
Non-breastfed 104

Mean Difference 4 (significantly higher)

181 children, 43% breastfed, mean duration of 7.2 mos.

Clinical Implications

- Most children born to WWE are normal.
- WWE of childbearing potential should be taking folate.
- WWE should receive informed consent outlining risks PRIOR to conception.
- Valproate is a poor 1st choice AED for most WWE of childbearing potential. If used, dose as low as possible.
- Breastfeeding on AEDs appears safe.
- Risks for many AEDs uncertain.

WWE=Women with epilepsy
Further research needed to:

• Delineate cognitive effects of fetal & neonatal exposure for other AEDs.
• Establish relations based on AED blood levels.
• Determine AEDs effects on cerebral lateralization.
• Confirm effects of periconceptional folate.
• Determine risks for maternal outcomes.
• Determine reasons for individual variability.
• Explore underlying mechanisms.
MONEAD Study
Maternal Outcomes & Neurodevelopmental Effects of Antiepileptic Drugs

https://web.emmes.com/study/monead/
Funded by NIH/NINDS #2U01-NS038455 and U01-NS050659
MONEAD Study

• MATERNAL OUTCOMES:
  Risks in WWE during pregnancy
  • Seizures
  • OB Complications
  • Depression (pregnancy & postpartum)

• OUTCOMES in CHILDREN of WWE:
  • Neurodevelopment Cognitive & behavioral
  • Neonatal Outcomes
  • Breastfeeding Effects if WWE taking AED.

• Pharmacokinetics: Relation of AED exposure & outcomes

AEDs=Antiepileptic Drugs; WWE=Women with Epilepsy
Women and Children in MONEAD Study

- Pregnant Women with Epilepsy 351
- Pregnant Healthy Women 106
- Children born to these women 451
- Non-pregnant Women with Epilepsy 109

Most of the Women with Epilepsy were on Lamotrigine or Levetiracetam or both.

Other common AEDs included Carbamazepine, Oxcarbazepine, Topiramate, and Zonisamide.
Seizure Changes during Pregnancy

Trimester-specific / Postpartum SzFreq in PWWE, and similar time intervals in NPWWE

PWWE = pregnant women with epilepsy; NPWWE = Non-pregnant women with epilepsy; TM1 = First Trimester
Preliminary Findings from MONEAD

- Postpartum depression more common in PWWE.
- Many AEDs have a marked lowering of their blood levels in pregnancy, but it is very variable across women.
- OB complications are not increased in PWWE.
- C-sections for seizures rare.
- Overall, no increased risk for neonatal problems (e.g., small for gestation age, but it may occur with topiramate).
- AED blood levels are low in nursing children when mothers take AED.

AED = antiepileptic drug; PWWE = pregnant women with epilepsy
Conclusions - 1

- Valproate is poor 1st choice for women of childbearing potential. If used, dose low.
- Phenobarbital & Topiramate: intermediate risks.
- Risks for many AEDs remain uncertain.
- Lamotrigine and Levetiracetam are now most commonly prescribed AEDs, and Valproate use markedly reduced in tertiary centers, but Rxs in general population unclear.
- Additional research needed to provide data to improve our care of epilepsy in pregnancy.

AED = antiepileptic drug
Conclusions - 2

• Most children born to WWE are normal.
• WWE of childbearing potential should be taking folate (dose: 0.4 – 4.0 mg/d).
• WWE should receive informed consent outlining risks PRIOR to conception (i.e., when the 1st Rx is written). Half of pregnancies not planned!
• Informed consent should include known relative anatomical & behavioral teratogenesis, the unknowns, contraceptive, and pregnancy & postpartum issues.

WWE = women with epilepsy