International Pregnancy Registries
A Global Approach to a Global Challenge

December 6, 2013
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Karolinska Institutet, Stockholm, Sweden
<table>
<thead>
<tr>
<th>Name of Commercial Interest</th>
<th>Type of Financial Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bial, Eisai, GSK, Novartis, UCB</td>
<td>Research Grants for EURAP and for SUDEP project</td>
</tr>
<tr>
<td>CURE</td>
<td>Research grant for SUDEP project</td>
</tr>
<tr>
<td>GSK</td>
<td>Consultancy fee for SUDEP adjudication</td>
</tr>
<tr>
<td>Bial, Eisai, Sun Pharma, UCB</td>
<td>Speakers’ honoraria</td>
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</tbody>
</table>
Learning Objectives

• To understand the importance of contributing to pregnancy registries
• To become aware of differences in teratogenic potential between different AED treatment options
The Global Challenge

• Approximately 15 million women with epilepsy are of childbearing age in the world
• Every year approximately 600,000 children are born by women with epilepsy
• 1,700 every day
• Unknown proportion exposed to AEDs
• Settings and conditions vary drastically
• Shared objective: uneventful pregnancy and healthy child

IOM 2012, Epilepsy across the spectrum; Yerby Neurology 2000; www.indexmundi.com
The critical question

• Which is the best treatment for my epilepsy during pregnancy?
  – With minimized teratogenic risks
    • Major congenital malformations
    • Cognitive development
    • Behavioural development
    • Growth
  – With maintained efficacy
Teratogenic risks with AEDs

50 years since first clinical report on malformations in a child exposed to AEDs


45 years since first retrospective case series of malformations after AED exposure

Meadow SR Lancet 1968;292;1296
Before The Pregnancy Registries
Malformation rates in 108 studies

mean 7.2% (95% CI 6.4-8.0%)

What we knew 1997

• Increased risk of malformations in offspring of mothers with epilepsy

• Greater risks
  – In offspring of mothers with AED treatment
  – With polytherapy vs. monotherapy

• Association between exposure to valproate and neural tube defects
What we didn’t know 1997

• How teratogenic potential differs between AEDs
• Dose-dependency
• Newer generation AEDs and
  – Teratogenic risks
  – Gestational effects on pharmacokinetics
  – Breast-feeding
• Efficacy during pregnancy
The Methodological Challenges in studies of malformations

• Epilepsy accounts for only 0.3-0.5% of all pregnancies
• Birth defects are uncommon, appr. 2% in the general population, and 3-6% among offspring of women with epilepsy
• There are at least 20 different AEDs in monotherapy and numerous combinations
• Randomized studies unethical and observational studies only option
• Confounding factors may be important
Before Pregnancy Registries

Cohort size in studies of malformations

Urgent need for

• Large scale prospective studies
• Including accurate information on risk factors

# Pregnancy Registries

A method to obtain large cohorts

- **National generic registries**
  - e.g. Scandinavian Medical Birth Registries

- **Epilepsy/AED dedicated**
  - **Industry driven** (e.g. GSK Lamotrigine, UCB Keppra)

<table>
<thead>
<tr>
<th>Independent</th>
<th>Initiated</th>
<th>Pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK &amp; Ireland,</td>
<td>1996</td>
<td>&gt;8,000</td>
</tr>
<tr>
<td>North American,</td>
<td>1997</td>
<td>&gt;8,000</td>
</tr>
<tr>
<td>EURAP,</td>
<td>1999</td>
<td>&gt;19,000</td>
</tr>
<tr>
<td>Australian,</td>
<td>1999</td>
<td>&gt;1,500</td>
</tr>
<tr>
<td>Kerala</td>
<td>1998</td>
<td>&gt;1,800</td>
</tr>
</tbody>
</table>
The Global Opportunity
Distribution by country of 108 publications on pregnancy outcomes

The EURAP World
An International Antiepileptic Drugs and Pregnancy Registry
Including contributions from UK, Australia, and India

>900 collaborators from 44 countries

www.eurapinternational.org
Recruitment of pregnancies over time

www.eurapinternational.org
Lessons from pregnancy registries: All polytherapies are not equal
Lessons from pregnancy registries:
All monotherapies are not equal

<table>
<thead>
<tr>
<th></th>
<th>Valproate</th>
<th>Carbamazepine</th>
<th>Lamotrigine</th>
<th>Phenobarbital</th>
<th>Phenytoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Lamotrigine Pregnancy Registry</td>
<td></td>
<td></td>
<td>35/1588 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finnish Medical Birth Registry and drug prescription databases*</td>
<td>28/263 (11%)</td>
<td>22/80 (3%)</td>
<td>..</td>
<td>..</td>
<td>1/33 (3%)</td>
</tr>
<tr>
<td>Swedish Medical Birth Registry*</td>
<td>29/613 (5%)</td>
<td>35/1318 (3%)</td>
<td>26/867 (3%)</td>
<td>..</td>
<td>8/119 (7%)</td>
</tr>
<tr>
<td>UK Epilepsy and Pregnancy Register*</td>
<td>44/71 (6%)</td>
<td>20/90 (2%)</td>
<td>21/647 (3%)</td>
<td>..</td>
<td>3/81 (4%)</td>
</tr>
<tr>
<td>North American AED Pregnancy Registry*</td>
<td>30/323 (9%)</td>
<td>31/1033 (3%)</td>
<td>31/1532 (2%)</td>
<td>11/199 (6%)</td>
<td>12/416 (3%)</td>
</tr>
<tr>
<td>International Registry of Antiepileptic Drugs and Pregnancy (EURAP)*</td>
<td>98/1010 (10%)</td>
<td>79/1422 (6%)</td>
<td>37/1230 (3%)</td>
<td>16/217 (7%)</td>
<td>6/103 (6%)</td>
</tr>
</tbody>
</table>

Data are number with major congenital malformations/number exposed to antiepileptic drug monotherapy (%). AED = antiepileptic drug. *Källén K, University of Lund, Sweden, personal communication.

Table 1: Rates of major congenital malformations in six different studies

Tomson and Battino Lancet Neurol 2012
Lessons from pregnancy registries: Dose matters

Malformation rate at one year for monotherapy exposure to carbamazepine, phenobarbital, valproic acid and lamotrigine by dose

Tomson et al., Lancet Neurol 2011
Lessons from pregnancy registries: Dose matters

Figure 1: Risk of major malformations by average valproate dose (mg) during the first trimester.
Lessons from pregnancy registries: Continuation needed for assessment of newer AEDs

Combined data from 22 reports with different definitions and methods

Data from Tomson & Battino Lancet Neurol 2012, updated May 2013
Further lessons from pregnancy registries: Co-variates other than AEDs can play a role

Multivariable Logistic Analysis EURAP Data

<table>
<thead>
<tr>
<th>Non-drug covariates</th>
<th>Odd Ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Americas vs Europe</td>
<td>2.1 (0.82-5.33)</td>
<td>0.1227</td>
</tr>
<tr>
<td>South-East Asia vs Europe</td>
<td>1.3 (0.59-2.94)</td>
<td>0.5064</td>
</tr>
<tr>
<td>Western Pacific vs Europe</td>
<td>1.0 (0.67-1.63)</td>
<td>0.8570</td>
</tr>
<tr>
<td>Parental history of major congenital malformations</td>
<td>4.4 (2.06-9.23)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Maternal age</td>
<td>1.0 (0.97-1.04)</td>
<td>0.8209</td>
</tr>
<tr>
<td>Educational level father (low vs medium/high)</td>
<td>1.0 (0.64-1.55)</td>
<td>0.9941</td>
</tr>
<tr>
<td>Educational level mother (low vs medium/high)</td>
<td>1.1 (0.70-1.73)</td>
<td>0.6829</td>
</tr>
<tr>
<td>Generalized tonic-clonic seizures during first trimester</td>
<td>0.6 (0.31-1.11)</td>
<td>0.103</td>
</tr>
<tr>
<td>Folic acid use (appropriate vs inappropriate)</td>
<td>1.4 (1.02-1.82)</td>
<td>0.035</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>1.0 (0.75-1.29)</td>
<td>0.8982</td>
</tr>
<tr>
<td>Idiopathic generalized epilepsy vs localisation-related epilepsy</td>
<td>0.9 (0.62-1.23)</td>
<td>0.4421</td>
</tr>
<tr>
<td>Undetermined/unclassifiable vs localisation-related epilepsy</td>
<td>0.8 (0.47-1.22)</td>
<td>0.2531</td>
</tr>
<tr>
<td>Parity</td>
<td>0.8 (0.67-1.04)</td>
<td>0.1074</td>
</tr>
</tbody>
</table>

Odd ratios for maternal age and parity show the risk associated with an increase of 1 year in age and an increase of 1 point in parity, respectively

Tomson et al., Lancet Neurol 2011
Further lessons from pregnancy registries: The challenge to balance teratogenic risk against seizure control

Hernandez-Diaz Neurology 2012;78:1692-99
Further lessons from pregnancy registries:
Seizure control and treatment changes

Seizure control and treatment changes in pregnancy:
Observations from the EURAP epilepsy pregnancy registry
*Dina Battino, †Torbjørn Tomson, ‡Erminio Bonizzoni, §John Craig, ¶Dick Lindhout, **Anne Sabers, ††Emilio Penucca, ‡‡Frank Vajda, and † for the EURAP Study Group

Battino et al., Epilepsia 2013
Additional Benefit from Pregnancy Registries

• Sub-cohorts can be used for additional studies including
  – Pharmacokinetics of newer AEDs
  – Breast-feeding
  – Cognitive development
  – Pharmacogenomics

• Can increase awareness and promote improved care
The critical question
Not Addressed in Conventional Pregnancy Registries

• Which is the best treatment for my epilepsy during pregnancy?
  – With minimized teratogenic risks
    • Major congenital malformations
    • Cognitive development
    • Behavioural development
    • Growth
  – With maintained efficacy
Lessons yet to learn from Pregnancy Registries

• Newer AEDs and risk of malformations
• Specific AED combinations and risks
• Relative risks with different AEDs and specific types of malformations
• Other adverse pregnancy outcomes, e.g. spontaneous abortions
• Role of folate and other preventive measures
• Prediction of risk based on individual patient characteristics
• Geographical differences in risks
Impact on Clinical Care and Practice

• AED treatment should be critically reviewed and possibly revised before conception
• Valproate should be avoided, when possible, in particular at doses >500 mg/day
• Lowest effective dose should be established before pregnancy regardless of type of AED
Global approaches

• Are useful and feasible
• Can be sustainable
• Rely on efficient communication
• Need networks of dedicated collaborators
• Depend on a common understanding of the importance of the project objectives
## Development since 1963

<table>
<thead>
<tr>
<th>Era</th>
<th>Observations</th>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970’s–80’s</td>
<td>Confirmation of increased risk of birth defects in offspring of WWE</td>
<td>Retrospective case series</td>
</tr>
<tr>
<td>1980’s-90’s</td>
<td>Identification of some specific birth defects with individual AEDs</td>
<td>Case-control studies</td>
</tr>
<tr>
<td></td>
<td>Analysis of the role of AEDs vs. epilepsy</td>
<td>Prospective single centre cohort studies</td>
</tr>
</tbody>
</table>
The critical question

• Which is the best treatment for my epilepsy during pregnancy?
  – With minimized teratogenic risks
    • Major congenital malformations
    • Cognitive development
    • Behavioural development
    • Growth
  – With maintained efficacy
EURAP Core Protocol

• **Primary objective:** To compare risk of major malformations following exposure to different AEDs
• **Inclusion criteria:** AED exposure at time of conception
• Enrolled before foetal outcome is known and at the latest week 16 (prospective cases)
• **Follow-up:** Assessment every trimester and final assessment 1 year after birth
• **Teratogenic endpoint:** Presence or absence of major congenital malformation

www.eurapinternational.org
How it works
The Methodological Challenges in Pregnancy Registries

• Definition of AED exposure
• Information on other risk factors
• Criteria for pregnancy outcomes
  – Definition of major malformation
  – Time window for assessment
  – Inclusion of data from induced abortions
• Comparator?

Tomson et al., Epilepsia 2010
Lessons from pregnancy registries:
Continuation needed for assessment of newer AEDs

Combined data from 22 reports with different definitions and methods.

<table>
<thead>
<tr>
<th>Source</th>
<th>Exposed (n)</th>
<th>MCMs (n)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long 2006</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>UK register</td>
<td>304</td>
<td>2</td>
<td>0.7%</td>
</tr>
<tr>
<td>NAAPR</td>
<td>450</td>
<td>11</td>
<td>2.4%</td>
</tr>
<tr>
<td>French 2001</td>
<td>9</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>UCB Keppra</td>
<td>272</td>
<td>24</td>
<td>8.8%</td>
</tr>
<tr>
<td>EURAP</td>
<td>126</td>
<td>2</td>
<td>1.6%</td>
</tr>
<tr>
<td>AUS register</td>
<td>22</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>ten Berg 2005</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Malformation rate (%)

Data from Tomson & Battino Lancet Neurol 2012, updated May 2013

GBP (328)  TPM (569)  LEV (1190)  OXC (637)  ZNS (100)  LTG (5914)
Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs

Kimford J. Meador, M.D., Gus A. Baker, Ph.D., Nancy Browning, Ph.D., Jill Clayton-Smith, M.D., Deborah T. Combs-Cantrell, M.D., Morris Cohen, Ed.D., Laura A. Kalayjian, M.D., Andres Kanner, M.D., Joyce D. Liporace, M.D., Page B. Pennell, M.D., Michael Privitera, M.D., and David W. Loring, Ph.D., for the NEAD Study Group*
Cognitive function at 6 years

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>Mean age-6 IQ (95% CI)</th>
<th>p value (vs below-median dose valproate)</th>
<th>p value (vs above-median dose valproate)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbamazepine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below group median</td>
<td>28</td>
<td>107 (102-112)</td>
<td>0.3994</td>
<td>0.0002</td>
</tr>
<tr>
<td>Above group median</td>
<td>33</td>
<td>106 (102-110)</td>
<td>0.5990</td>
<td>0.0004</td>
</tr>
<tr>
<td><strong>Lamotrigine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below group median</td>
<td>31</td>
<td>106 (102-111)</td>
<td>0.4854</td>
<td>0.0003</td>
</tr>
<tr>
<td>Above group median</td>
<td>43</td>
<td>109 (105-113)</td>
<td>0.1154</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Phenytoin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below group median</td>
<td>20</td>
<td>108 (103-114)</td>
<td>0.2551</td>
<td>0.0002</td>
</tr>
<tr>
<td>Above group median</td>
<td>20</td>
<td>106 (101-112)</td>
<td>0.5501</td>
<td>0.0011</td>
</tr>
<tr>
<td><strong>Valproate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below group median</td>
<td>23</td>
<td>104 (99-109)</td>
<td>NA</td>
<td>0.0065</td>
</tr>
<tr>
<td>Above group median</td>
<td>26</td>
<td>94 (90-99)</td>
<td>0.0065</td>
<td>NA</td>
</tr>
</tbody>
</table>

Means were adjusted for maternal IQ, gestational age at birth, and folate. IQ=intelligence quotient.

*Table 5: IQ outcomes at age 6 years by median group dose for the age-6-completer sample (n=224)*