Malformation risks of antiepileptic drugs in pregnancy: an update from the UK Epilepsy and Pregnancy Register

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- Ian Robertson, Preston Obstetrics & Gynaecology
- Beth Irwin, Belfast Epilepsy Nurse Specialist
- Norman Delanty, Dublin Neurology
- Patrick Morrison, Belfast, Genetics
<table>
<thead>
<tr>
<th>Study</th>
<th>Exposed No</th>
<th>%MCM</th>
<th>Controls No</th>
<th>%MCM</th>
</tr>
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<tbody>
<tr>
<td>Samren et al, 1997</td>
<td>1221</td>
<td>9.0</td>
<td></td>
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<tr>
<td>Olafsson et al, 1998</td>
<td>266</td>
<td>5.7</td>
<td>82,483</td>
<td>2.2</td>
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<td>Canger et al, 1999</td>
<td>444</td>
<td>9.7</td>
<td></td>
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<tr>
<td>Kaneko et al, 1999</td>
<td>885</td>
<td>9.0</td>
<td></td>
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<tr>
<td>Samren et al, 1999</td>
<td>1441</td>
<td>3.7</td>
<td>2000</td>
<td>1.5</td>
</tr>
<tr>
<td>Holmes et al, 2001</td>
<td>223</td>
<td>4.5</td>
<td>508</td>
<td>1.8</td>
</tr>
</tbody>
</table>
Which AEDs are associated with higher rates of MCM?

Which types of malformations are associated with individual AEDs?
Major congenital malformations (2)

- Is dose important?
- Does dosing schedule influence MCM rate?
- What about polytherapy?
- What is the protective role of folic acid?
Do you have epilepsy and are pregnant or planning a pregnancy?

Around 2,500 women with epilepsy will have a baby each year in the UK. If you could be one of these women, find out how you can help improve the health of babies born to pregnant women with epilepsy in the future.

UK epilepsy & pregnancy Register

Pregnancy is an exciting time in a woman’s life. For pregnant women with epilepsy, a potential concern may be whether their anti-epileptic treatment will cause harm to their unborn child.

There is a major study in the UK investigating which epilepsy treatments show the lowest risk to a baby’s health.

The aim is to find out which type of epilepsy treatment women are taking while they are pregnant, and to collect information on the health of their babies after delivery.

By agreeing to register, your valuable contribution will help doctors give the best advice possible to you and to other women who are thinking of becoming pregnant.

If you wish to register, or would like further information about the pregnancy register, please visit www.epilepsyandpregnancy.co.uk or call: Freephone 0800 389 1248

All calls will be answered in confidence by experienced healthcare professionals.
Epilepsy and Pregnancy Registers

- Pharmaceutical company (GSK, UCB)
- National (USA, UK, Australia)
- Multi-national (EURAP)

Potential disadvantages
- Not randomised
- No control population
- Selective reporting
- Heterogeneous population

Potential advantages
- Prospective / observational
- Reflect current practice
- Broad based
- Adequate numbers recruited
- Homogeneous population
Methodology

- Prospective, observational registration and follow-up study

- Case - woman with epilepsy
  - on AED in any combination
  - or not on AED
  - identified before outcome of pregnancy known
- General demographic information
- Epilepsy details
  - Age at onset
  - Cause of epilepsy
  - Seizure type and frequency
- AED exposure
  - 3 months before conception and during pregnancy up to the date of referral
  - Any changes made
  - Other drug exposures e.g. folic acid
• Outcome data collected 3 months after expected delivery
  - Changes to AED during pregnancy
  - Previous pregnancy details
  - Relevant family history
  - Current pregnancy outcome
  - Prenatal test results
Results – 31st January 2012

- Number of registrations – 8820
- Number with full outcome data – 7402
- Incomplete registrations – 1418 (16%)
- AED details (full outcome)
  - No AED = 516 (6.9%)
  - Monotherapy = 5395 (72.8%)
  - Polytherapy = 1491 (20.1%)
Major congenital malformation

- **Definition:**
  - An abnormality of an essential embryonic structure requiring significant treatment and present at birth or discovered during the first six weeks of life

- **Grading of abnormal outcomes**
  1. Major malformation
  2. Minor malformation
  3. Pregnancy loss
  4. Gene/chromosomal abnormality
MCM rate calculated as:

\[
\frac{\text{(Total number of live births with an MCM)} + \text{(total number of pregnancy losses with an MCM)}}{\text{(Total number of live births)} + \text{(Total number of pregnancy losses with an MCM)}}
\]
<table>
<thead>
<tr>
<th>Group</th>
<th>n.</th>
<th>%</th>
<th>(95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AED</td>
<td>500</td>
<td>2.8</td>
<td>(1.7% – 4.6%)</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>5127</td>
<td>3.3</td>
<td>(2.8% – 3.8%)</td>
</tr>
<tr>
<td>Polytherapy</td>
<td>1380</td>
<td>5.1</td>
<td>(4.1% – 6.4%)</td>
</tr>
<tr>
<td>Total Exposed Group</td>
<td>6507</td>
<td>3.7</td>
<td>(3.3 – 4.2%)</td>
</tr>
</tbody>
</table>
Monotherapy exposures
## MCM rate for monotherapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of outcomes</th>
<th>MCM rate (%)</th>
<th>95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>1497</td>
<td>2.56</td>
<td>1.85 - 3.53</td>
</tr>
<tr>
<td>LTG</td>
<td>1587</td>
<td>2.25</td>
<td>1.61 – 3.15</td>
</tr>
<tr>
<td>VAL</td>
<td>1129</td>
<td>6.16</td>
<td>4.84 – 7.84</td>
</tr>
<tr>
<td>LEV</td>
<td>197</td>
<td>0.00</td>
<td>0.0 – 1.9</td>
</tr>
<tr>
<td>DPH</td>
<td>103</td>
<td>7.14</td>
<td>3.41–14.98</td>
</tr>
<tr>
<td>TOP</td>
<td>94</td>
<td>5.80</td>
<td>2.42 -13.97</td>
</tr>
<tr>
<td>GBP</td>
<td>42</td>
<td>2.63</td>
<td>0.37–18.69</td>
</tr>
<tr>
<td>Drug</td>
<td>No.Inform-ative Outcomes</td>
<td>N.T.D.</td>
<td>Facial Cleft</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------</td>
<td>--------</td>
<td>--------------</td>
</tr>
<tr>
<td>No AED</td>
<td>463</td>
<td>2 (0.4%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>CBZ</td>
<td>1497</td>
<td>4 (0.3%)</td>
<td>6 (0.4%)</td>
</tr>
<tr>
<td>VPA</td>
<td>1129</td>
<td>13 (1.2%)</td>
<td>13 (1.2%)</td>
</tr>
<tr>
<td>LTG</td>
<td>1587</td>
<td>4 (0.3%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Poly-therapy</td>
<td>1328</td>
<td>7 (0.5%)</td>
<td>7 (0.5%)</td>
</tr>
</tbody>
</table>
Are there differences in Major malformation rates following AED exposure during first trimester?

Kennedy et al. ECE 2010
MCM rate (%) by dose.

- CBZ < 400mg, NaVal < 600mg, LTG < 100mg.
- CBZ 400-1000mg, NaVal 600-1000mg, LTG 100-200mg
- CBZ > 1000mg, NaVal > 1000mg, LTG > 200mg
LTG Dosage update

- Obvious birth defect
- Major congenital malformation

Dose in mg
- 0 - 100
- >100 & <200
- >=200 & <400
- >=400

Graph showing the number of cases for each dose range.
Does polytherapy increase MCM rate?

(The UK & Ireland Epilepsy and Pregnancy Register)
MCM rate for Polytherapy

MCM rates for any combination including:

CBZ (n=584): 3.94% (95% CI 2.62 – 5.93)

LTG (n=714): 4.34% (95% CI 3.05 – 6.17)

VAL (n=476): 7.77% (95% CI 5.63 – 10.72)
Results are generally reassuring – overall low rates of MCMs.
The generally low rates of MCM reinforces the need for very large prospective studies.
If need to continue on AED treatment then monotherapy should be the preferred practice.
Women taking VPA appear to carry higher relative risk (PHT)(particularly, as part of a polytherapy regime).
For other agents data on safety in pregnancy (CBZ and LTG) reassuring.
Dysmorphic features

- How common?
- Association with major malformations?
- Association with cognitive / behavioural problems?
Retrospective study of 249 children born to mothers with epilepsy

Recruitment from Manchester and Liverpool.

VPA (41), CBZ (52), PHT (21), Polytherapy (49), Unexposed (80).

Major malformations in VPA group 14% (Unexposed 4%)

Children exposed to VPA had significantly lowered Verbal IQs
Distribution of Verbal IQ (VIQ) According to Monotherapy Drug Exposure In Utero Compared to the Expected Score in the General Population

Distribution of verbal IQ
- Above average (>110)
- Average (90–109)
- Low average (80–89)
- Low (70–79)
- Exceptionally low (<69)

<table>
<thead>
<tr>
<th></th>
<th>Above average (&gt;110)</th>
<th>Average (90–109)</th>
<th>Low average (80–89)</th>
<th>Low (70–79)</th>
<th>Exceptionally low (&lt;69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>50</td>
<td>25</td>
<td>16</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Unexposed Carbamazepine</td>
<td>43</td>
<td>24</td>
<td>17</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Valproate</td>
<td>54</td>
<td>17</td>
<td>17</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>
COGNITIVE FUNCTION AT 3 YEARS OF AGE AFTER FETAL EXPOSURE TO ANTIEPILEPTIC DRUGS

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Neurodevelopmental of children exposed in utero to lamotrigine, sodium valproate and carbamazepine.

Abstract

OBJECTIVE: Children born to women with epilepsy (WWE), exposed in utero to levetiracetam (LEV, n = 51), were assessed for early cognitive development and compared to children exposed to sodium valproate in utero (VPA, n = 44) and a group of children representative of the general population (n = 97).

METHODS: Children were recruited prospectively from 2 cohorts in the United Kingdom and assessed using the Griffiths Mental Development Scale (1996), aged <24 months. Information regarding maternal demographics were collected and controlled for. This is an observational study with researchers not involved in the clinical management of the WWE.

RESULTS: On overall developmental ability, children exposed to LEV obtained higher developmental scores when compared to children exposed to VPA (p < 0.001). When compared, children exposed to LEV did not differ from control children (p = 0.62) on overall development. Eight percent of children exposed to LEV in utero fell within the below average range (DQ score of <84), compared with 40% of children exposed to VPA. After controlling for maternal epilepsy and demographic factors using linear regression analysis, exposure to LEV in utero was not associated with outcome (p = 0.67). Conversely, when compared with VPA exposure, LEV exposure was associated with higher scores for the overall developmental quotient (p < 0.001).

CONCLUSION: Children exposed to LEV in utero are not at an increased risk of delayed early cognitive development under the age of 24 months. LEV may therefore be a preferable drug choice, where appropriate, for WWE prior to and of childbearing age.
Summary

- 1800 - 2400 first trimester AED exposures in the UK/annum.
- AEDs increases major congenital malformation (MCM) risk from background 1-2% to 4-9%.
- International registries led to a better appreciation of individual AED teratogenicity.
- Has increased awareness resulted in a changed prescribing practice?
- If so, has this impacted on outcomes?
Change in treatment groups over the time period of the study

- **Monotherapy**
- **Polytherapy**
- **No AEDs**

Time periods:
- 1995-2000
- 2001-2005
- 2006-2010
Distribution of treatment as a proportion of the total, over time.

- **LTG**
- **VPA**
- **CBZ**
- **MISC**
Total MCM rates through time

- 1995-2000: 5.5%
- 2001-2005: 4%
- 2006-2010: 3.5%
Economic analysis – the costs

- If 2400 UK children exposed to AEDs per annum.
- A reduction in MCM rate: 4.5% (108) v 3.2% (77) = 31 less children born with a MCM per year.
- If VPA is major culprit:
  - 5 less Neural tube defects  Savings in Health care
  - 8 less Cleft lip/palate      alone
  - 7 less hypospadias         ~ £3-4 million
  - 4 less cardiac (ASD/VSD/etc) per annum
  - 7 less skeletal, Gastrointestinal.
  - Cognitive/developmental delay (£……………?)
The Future

- Continue to collect data for UK & Ireland registers
- Publication of Short paper - JNNP
- Epilm/Epilm Chrono paper accepted by seizure
- Sibs study/ Obstetric paper
- Update on Keppra paper & follow up neurodevelopmental paper
- Keppra audit (seizure control in pregnancy)
- Continued collaboration (Neurodevelopmental studies & Pharmacogenetic study)
Thank you for listening