Evaluation of observational data in human teratogenicity studies of the Berlin Embryotox project

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Berlin Embryotox

Tasks
• Risk information to HCP and pregnant women
• Pharmacovigilance pregnancy on behalf of Federal Institute for Drugs and Medical Devices
• Research

Multidisciplinary team,
  i.e. obstetrics/gynaecology, paediatrics, human genetics, internal medicine, anaesthesiology, pharmacy, biometrics
To improve mother-child health

- Prevention of birth defects
- Avoidance of non-prescription or non-compliance
- Prevention of terminations of pregnancies due to overestimated drug risks
Embryotox drug risk information via

- Open access information database [www.embryotox.de](http://www.embryotox.de) (~1 200 000 visitors/year or ~4 000/d)
Embryotox drug risk information via

- Open access information database www.embryotox.de (~1 200 000 visitors/year or 4 000/d)
- Individual consultation via phone, email, online questionnaire or letter (~14 000 consultations/year or ~70/d)
  ➔ followed by structured protocol of pregnancy outcome
Consultations - gestational week at 1st contact

Weeks of gestation

No.

- 2011
- 2012
- 2013
Individual consultations for

- Psychiatrische Erkrankungen
- Infektionen und parasitäre Erkrankungen
- Chirurgische und medizinische Eingriffe
- Erkrankungen des Nervensystems
- Erkrankungen des Gastrointestinaltrakts
- Skelett- und Bindegewebs- und Knochenerkrankungen
- Erkrankungen der Haut und des Unterhautzellschleimhaut
- Erkrankungen der Atemwege, des Brustraums und Mediastinums
- Gefäß- und Gefäßerkrankungen
- Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen
- Erkrankungen des Immunsystems
- Endokrine Erkrankungen
- Untersuchungen
- Allgemeine Erkrankungen und Beschwerden am Verabreichungsort
- Schwangerschaft, Wochenbett und perinatale Erkrankungen
- Augenerkrankungen
- Stoffwechsel- und Ernährungsstörungen
- Gutartige, boesartige und unspezifische Neubildungen...
- Erkrankungen der Geschlechtsorgane und der Brustdrüse
- Kongenitale, familiäre und genetische Erkrankungen
- Soziale Umstände
- Herzerkrankungen
- Erkrankungen des Blutes und des Lymphsystems
- Erkrankungen der Nieren und Harnwege
- Erkrankungen des Ohres und des Labyrinths
- Leber- und Gallenerkrankungen
Sources of information re. drug effects in (human) pregnancy?

Observational data, evaluated

• case by case
• cohort studies (e.g. Embryotox patient database)
• case-control-studies (e.g. birth defect registries)
• prescription studies
Embryotox-patient database

• ~50 000 exposed pregnancies with complete follow-up
• ~4 000 annual increment

Maternal data:
Age, education, (obstetric) history, family history
Gestational week at 1st contact
Drugs incl. hormones, social drugs, X-ray, fever, weight loss
Fertility problems etc.

Follow-up:
Course of pregnancy (and of chronic diseases)
Prenatal diagnostics
Pregnancy outcome:
  Gestational week and fetopathology if miscarriage
  Status of newborn until week 5
Embryotox - cohort studies: comparison groups

- **Disease-comparison group**: Similar disease but no medication or other than study group
- **Comparison group II**: no teratogens and fetotoxicants:
  - Acitretin
  - Isotretinoin
  - MTX
  - Mycophenolate
  - Thalidomide
  - Valproic acid
  - Angiotensin-II receptor blockers (sartanes) (only when used in 2\(^{nd}\) or 3\(^{rd}\) trimester)
  - ACE inhibitors (only when used in 2\(^{nd}\) or 3\(^{rd}\) trimester)

Excluded treatment indication:
- Malignancies (MedDRA code: Malignant or unspecified tumors (SMQ 20000091), ICD-10: C00-D09)
- Malignancy related conditions (MedDRA: SMQ 20000092), ICD-10: C00-D09)
2nd generation antipsychotics
(Habermann et al. J Clin Psychopharmacol 2013)
Publication selected for Mitchell B. Balter Award 2013

• In spite of frequent use in pregnancy insufficient experience
# 2nd generation antipsychotics

(Habermann et al. J Clin Psychopharmacol 2013)

<table>
<thead>
<tr>
<th></th>
<th>SGA</th>
<th>FGA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pregnancies</strong></td>
<td>561</td>
<td>284</td>
<td>1122</td>
</tr>
<tr>
<td>Exposure at least during</td>
<td>513</td>
<td>256</td>
<td></td>
</tr>
<tr>
<td>1\textsuperscript{st} trimester</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure at least until delivery</td>
<td>235</td>
<td>99</td>
<td></td>
</tr>
</tbody>
</table>
2nd generation antipsychotics
(Habermann et al. J Clin Psychopharmacol 2013)

<table>
<thead>
<tr>
<th>SGA</th>
<th>FGA</th>
<th>2nd generation antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>Haloperidol</td>
<td>129 Pipamperone 14</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Promethazine</td>
<td>101 Fluspirilene 8</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Flupentixol</td>
<td>66 Zuclopenthixol 8</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Chlorprothixene</td>
<td>37 Prothipendyl 7</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Melperone</td>
<td>29 Thioridazine 6</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Sulpiride</td>
<td>29 Triflupromazine 6</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>Fluphenazine</td>
<td>20 Perphenazine 5</td>
</tr>
<tr>
<td>Zotepine</td>
<td>Levomepromazine</td>
<td>18 Pimozide 5</td>
</tr>
<tr>
<td></td>
<td>Perazine</td>
<td>16 Clopenthexiol 1</td>
</tr>
</tbody>
</table>
## 2nd generation antipsychotics
(Habermann et al. J Clin Psychopharmacol 2013)

<table>
<thead>
<tr>
<th>Category</th>
<th>SGA</th>
<th>FGA</th>
<th>Controls</th>
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</thead>
<tbody>
<tr>
<td><strong>Miscarriages</strong></td>
<td>24%</td>
<td>16%</td>
<td>20%</td>
</tr>
<tr>
<td>cumulative incidence</td>
<td>95% CI</td>
<td>14% - 39%</td>
<td>10% - 26%</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>568</td>
<td>289</td>
</tr>
<tr>
<td><strong>ETOP</strong></td>
<td>17%</td>
<td>21%</td>
<td>3%</td>
</tr>
<tr>
<td>cumulative incidence</td>
<td>95% CI</td>
<td>13% - 23%</td>
<td>14% - 31%</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>568</td>
<td>289</td>
</tr>
<tr>
<td><strong>Preterm children</strong></td>
<td>9.1%</td>
<td>15.1%</td>
<td>8.7%</td>
</tr>
<tr>
<td>gestation wk &lt; 37</td>
<td>95% CI</td>
<td>6.5% - 12.1%</td>
<td>10.8% - 20.3%</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>453</td>
<td>238</td>
</tr>
<tr>
<td><strong>Birth weight</strong></td>
<td>median</td>
<td>3400 g</td>
<td>3380 g</td>
</tr>
<tr>
<td>term births</td>
<td>25Q/75Q</td>
<td>3080 - 3750</td>
<td>2959 - 3710</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>398</td>
<td>190</td>
</tr>
</tbody>
</table>
### 2nd generation antipsychotics
(Habermann et al. J Clin Psychopharmacol 2013)

Major birth defects:

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Type</th>
<th>OR</th>
<th>CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGA vs. FGA</td>
<td>adj.</td>
<td>1.27</td>
<td>0.57 – 2.82</td>
</tr>
<tr>
<td>(430/213)</td>
<td>crude</td>
<td>1.22</td>
<td>0.55 – 2.70</td>
</tr>
<tr>
<td>SGA vs. Controls</td>
<td>adj.</td>
<td>2.17</td>
<td>1.20 – 3.91</td>
</tr>
<tr>
<td>(430/1014)</td>
<td>crude</td>
<td>2.13</td>
<td>1.20 – 3.83</td>
</tr>
<tr>
<td>FGA vs. Controls</td>
<td>adj.</td>
<td>1.71</td>
<td>0.78 – 3.79</td>
</tr>
<tr>
<td>(213/1014)</td>
<td>crude</td>
<td>1.75</td>
<td>0.80 – 3.80</td>
</tr>
</tbody>
</table>
# 2nd generation antipsychotics
(Habermann et al. J Clin Psychopharmacol 2013)

<table>
<thead>
<tr>
<th>Neonatal adverse effects</th>
<th>SGA</th>
<th>FGA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15.6%</td>
<td>21.6%</td>
<td>4.2%</td>
</tr>
<tr>
<td></td>
<td>(37/237)</td>
<td>(22/102)</td>
<td>(43/1014)</td>
</tr>
</tbody>
</table>
Embryotox – methods, e.g.
Cumulative incidences of pregnancy outcomes

To be considered:
• delayed study entry, depends on recognition of being pregnant and contact to the study center (Embryotox)
• Abortion and ETOP are “competing” events
Methods: Cumulative incidences of pregnancy outcomes

Competing risks/events:
- Spontaneous abortion
- ETOP
- Live birth

Delayed study entry (left truncation)

<table>
<thead>
<tr>
<th>Weeks of gestation</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>20</th>
<th>30</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancies at risk</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>
Methods: Cumulative incidences of pregnancy outcomes

<table>
<thead>
<tr>
<th></th>
<th>Exposed</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live birth</td>
<td>0.53</td>
<td>0.91</td>
</tr>
<tr>
<td>Induced abortion</td>
<td>0.22</td>
<td>0.02</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>0.25</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Meister et al. Reprod Toxicol 2008
Methods: Cumulative incidences of pregnancy outcomes

<table>
<thead>
<tr>
<th>Causes of end of pregnancy</th>
<th>Exposed</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live birth</td>
<td>0.53</td>
<td>0.91</td>
</tr>
<tr>
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<td>0.07</td>
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</tbody>
</table>

Meister et al. Reprod Toxicol 2008
Low dose MTX: Cumulative incidences for abortions

Weber-Schoendorfer et al. Rheumatologic MTX. Arthritis Rheumatol 2014
### Tabelle 3.16 Fehlbildungsrisiken nach Expositionszeit (Odds Ratios und Konfidenzintervalle).

<table>
<thead>
<tr>
<th>Expositionsbeginn (SSW)</th>
<th>Gesamte Fehlbildungen</th>
<th>Große Fehlbildungen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>KI (95%)</td>
</tr>
<tr>
<td>2+0 bis 2+6</td>
<td>0.92</td>
<td>0.49–1.72</td>
</tr>
<tr>
<td>3+0 bis 3+6</td>
<td>1.09</td>
<td>0.61–1.96</td>
</tr>
<tr>
<td>4+0 bis 4+6</td>
<td>0.70</td>
<td>0.32–1.52</td>
</tr>
<tr>
<td>5+0 bis 5+6</td>
<td>0.54</td>
<td>0.20–1.47</td>
</tr>
<tr>
<td>6+0 bis 6+6</td>
<td>0.78</td>
<td>0.24–2.53</td>
</tr>
<tr>
<td>7+0 bis 7+6</td>
<td>1.81</td>
<td>0.64–5.18</td>
</tr>
<tr>
<td>Ab 8+0</td>
<td>0.44</td>
<td>0.06–3.24</td>
</tr>
</tbody>
</table>

KI: Konfidenzintervall; SSW: Schwangerschaftswoche.

Padberg, Dissertation 2014
sent a major teratogenic risk in early pregnancy. Similar to published case reports, there is no indication of coumarin embryopathy in our large cohort of those live births (n=235) exclusively exposed ≤ week 8 (see Table 3). There seems to be a stronger risk for (major) birth defects when exposure has taken place (exclusively) after week 8 (OR 10.53; 95% CI 2.47–44.93). However, this OR should be carefully interpreted because there were only a few cases in this group (n=23). The rate of major birth defects

Limitations of Embryotox patient database

- Selected population may not be representative for all pregnant women under index treatment/exposure:
  - Self selection by HCP or patient
  - Better education and pregnancy care, i.e. at lower risk
- Paediatric reports of heterogeneous quality
- Exposed cohorts too small to investigate associations with specific rare birth defects
Advantages of Embryotox patient database

- Pre-existing infrastructure (for consultation)
- High quality real-time ascertainment of exposure data
- Motivated “respondents”, only 20% non-responders
- Spontaneous abortions and ETOPs included
- Fetopathology included
- Plausibility control and call backs to involved HCP
- Comparison cohorts
Drugs During Pregnancy and Lactation
Treatment Options and Risk Assessment

Edited by
Christof Schaefer, Berlin Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy, Charité-University Clinic Berlin, Berlin, Germany
Paul Peters, Department of Obstetrics, University Medical Center Utrecht (UMCU), Utrecht, The Netherlands
Richard K. Miller, University of Rochester School of Medicine and Dentistry, Rochester, New York, USA

Drugs During Pregnancy and Lactation, Third Edition is a quick and reliable reference for all those working in disciplines related to fertility, pregnancy, lactation, child health and human genetics who prescribe or deliver medicinal products, and to those who evaluate health and safety risks. Each chapter contains twofold information regarding drugs that are appropriate for prescription during pregnancy and an assessment of the risk of a drug when exposure during pregnancy has already occurred. Thoroughly updated with current regulations, references to the latest pharmacological data, and new medicinal products, this edition is a comprehensive resource covering the latest knowledge and findings related to drugs during lactation and pregnancy.

Key Features
• Provides evidence-based recommendations to help clinicians make appropriate recommendations
• Uniquely organized and structured according to drug class and treatment indications to offer authoritative clinical content on potential adverse effects
• Highlights new research developments from primary source about working mechanism of substances that cause developmental disorders

Related Titles
Mattison/Clinical Pharmacology During Pregnancy, 2013, 978-0-12-386007-1
Gupta/Reproductive and Developmental Toxicology, 2012, 978-0-12-392032-7