Evolving strategies for generating evidence on medication safety in pregnancy

Marianne Cunnington, GSK Epidemiology and on behalf of the ConcePTION consortium
Disclaimer

• The speaker is an employee of GlaxoSmithKline (GSK) and holds stock in GSK

• The speaker is a member of the ConcePTION consortium and speaking on behalf of the broader consortium with content developed and approved by the ConcePTION Managing Board
Overview:

- Background: information gap
- Traditional approaches and their limitations
- Leveraging developments in real world evidence generation to fill the gap
  - Example of IMI ConcePTION
The need for information on medication safety in pregnancy

- Globally 200 million women get pregnant each year, 5 million in EU
- Many women have chronic illness requiring continued medication use or become ill during pregnancy
- Medication use in pregnancy is high estimated at 57-97%* of pregnancies across European countries
- But the majority of newly approved medicines are of unknown teratogenic potential
  - 2011 EMA review found 94.6% products reviewed had restricted use in pregnancy and 71% had no information on use in pregnancy

Challenges in understanding medication safety in pregnancy

Reproductive toxicology in animals

Reproductive safety in human
- Usually no pregnant women actively included
- Follow-up of pregnancies occurs during trial

Postmarketing:
- Routine and additional pharmacovigilance
- Routine pharmacovigilance
- Epidemiology studies including:
  - Pregnancy registries
  - Prospective cohorts
  - Retrospective cohorts (routine health data)
  - Case control
  - Systematic reviews/meta analyses

Discovery

Preclinical

Clinical development

Exploratory development

Full development

Post approval

Phase I

Phase II

Phase III

Phase IV

Candidate seeking

Filing

LSHTM Pregnancy Talk 2020
Pregnancy registries approaches have evolved

Healthcare Providers (HCPs)/women ring toll free number to report exposure and enroll in registry

HCPs provide key information on exposure: medication, dose, timing in pregnancy, expected date of delivery

Registry contacts HCP close to time of delivery to ascertain outcome

Outcomes reviewed by expert panel. Independent panel also reviews data and develops conclusions

Methodological improvements over time:

- Internal comparator groups:
  - Unexposed
  - Exposed to other medications

- Consent for medical record release

- Collection of birth outcomes beyond malformations, including longer term follow up after birth

But challenges remain:

- Voluntary enrolment linked to:
  - Selection bias
  - Low enrolment
  - High loss to follow up
  - Limited power to detect all but signal for major teratogenicity
Variable experience from GSK sponsored pregnancy registries

<table>
<thead>
<tr>
<th>Drug registry</th>
<th>Date</th>
<th>Comparator</th>
<th>No. MBD</th>
<th>Total 1st trimester exposures</th>
<th>% MBD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiretroviral</td>
<td>1/1/1989-1/31/2019</td>
<td>Internal, other antiretrovirals</td>
<td>271</td>
<td>9854</td>
<td>2.8%</td>
<td>2.4-3.1%</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>9/1/1992–3/31/2010</td>
<td>None</td>
<td>35</td>
<td>1558</td>
<td>2.2%</td>
<td>1.6-3.1%</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>1/1/1996-9/19/2012</td>
<td>None</td>
<td>20</td>
<td>478</td>
<td>4.2%</td>
<td>2.6-6.5%</td>
</tr>
<tr>
<td>Bupropion</td>
<td>9/1/1997-3/31/2008</td>
<td>None</td>
<td>24</td>
<td>675</td>
<td>3.6%</td>
<td>2.3-5.3%</td>
</tr>
<tr>
<td>Menveo</td>
<td>9/30/2014-present</td>
<td>None</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

1 Lamotrigine and Antiretroviral exclude chromosomal defects; 2 Registry is closed: data from final report
Potential to leverage existing healthcare and surveillance datasources

Healthcare databases in Europe for studying medicine use and safety during pregnancy


1 Department of Pharmacy and Pharmacology, University of Bath, Bath, UK
2 IMER (Emilia-Romagna Registry of Birth Defects), Azienda Ospedaliero-Universitaria di Ferrara, Ferrara, Italy
3 Department of Nursing, College of Human and Health Sciences, Swansea University, Swansea, Wales, UK
4 Institute of Clinical Physiology, National Research Council (IFC-CNR), Pisa, Italy
5 Pharmacologie, Medicale, Faculte de Medicine, Universite de Toulouse III, ISERM UMR1027, Toulouse, France
6 Medical Birth Registry of Norway, The Norwegian Institute of Public Health, Oslo, Norway
7 Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
8 Section of Social Medicine, Department of Public Health, University of Copenhagen, Copenhagen, Denmark
9 Hospital Lillebaelt, Kolding, Denmark
10 Agenzia Regionale di Sanita della Toscana, Florence, Italy
11 Pharmacoepidemiology and Pharmacoecconomics Unit, Department of Pharmacy, University of Groningen, Groningen, The Netherlands
12 Drug Policy Service, Emilia-Romagna Region Health Authority, Bologna, Italy
13 Institute of Life Science, College of Medicine, Swansea University, Swansea, Wales, UK

Key strengths
- Large populations
- Objectively captured medication exposure
- Multiple exposures and outcomes exposures
- Potential for longer term follow up
- Internal comparators
- Information on confounders

Some limitations
- Time lag
- % mother and babies linked
- Prescription medication only
- No outcome adjudication
- Completeness of some confounders e.g. smoking

investigating pregnancies without recorded outcomes in the Clinical Practice Research Datalink / London School of Hygiene and Tropical Medicine Pregnancy Register, with the aim of improving validity.

Date of ISAC Approval: 15/02/18
Pregnancy registries remain an important tool for safety data collection in the postmarketing setting because of the prospective design and the ability to collect detailed patient level data. However, because of the recurring challenges of achieving sufficient enrollment, pregnancy registries generally are not sufficient by themselves to assess the safety of products during pregnancy; therefore, other study methods capable of appropriately assessing the occurrence of specific major congenital malformations (MCMs) (e.g., birth defects and congenital anomalies) and other pregnancy outcomes are needed. In addition, use of complementary approaches may help address the limitations inherent to a specific study design and provide greater confidence in the conclusions.

Preferably and if feasible, epidemiological studies should be carried out using existing data sources (i.e. secondary data use) and be designed in such a way as to minimise bias and confounding (see P.III.B.4.2.3.). Given the usually limited exposure to medicines in pregnancy and the low incidence of causally related adverse outcomes (see P.III.A.1.3.), it is usually necessary to include participants from more than one country in order to achieve adequate power.
The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking ConcePTION grant nº 821520

IMI ConCePTION project:

Building and testing a pan-European ecosystem for generating, monitoring, and providing robust and rapid real world evidence on medication safety in pregnancy and breastfeeding

Scientific & ethical Advisory Board

WP1: Data Beyond registries

WP2: reported pregnancies

WP3: in-vitro, and in-vivo models

WP4: Human breast milk biobank

WP5: dissemination and education to the public

WP6: stakeholder engagement

WP7: IT, Governance/ethics, data quality and harmonization

WP8: Management & sustainability

WP1, WP2, WP3, WP4, WP5, WP6, WP7, WP8

Building and testing a pan-European ecosystem for generating, monitoring, and providing robust and rapid real world evidence on medication safety in pregnancy and breastfeeding.
The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative Joint Undertaking under the grant agreement nº821520.
ConcePTION data catalogue

• **FAIR**: Findable Accessible Interoperable Re-usable (EU rules)

• **Catalogue features**
  • Meta-data (descriptors) of organization and datasource
  • Storage of documentation (dictionary/governance/ETL scripts)
  • Negotation service to contact data access providers for participation
  • Querying option of data quality indicators
# ConcePTION data access

Organizations with access to relevant data sources (DAP) are being asked to participate

<table>
<thead>
<tr>
<th>Country</th>
<th>Area</th>
<th>Source population (million)</th>
<th>Total births captured per year (thousands)</th>
<th>Type of data sources</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population based data sources</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>Tuscany</td>
<td>3.7</td>
<td>25</td>
<td>Record linkage of regional/national health services data and registries</td>
</tr>
<tr>
<td></td>
<td>Caserta</td>
<td>0.9</td>
<td>6</td>
<td>Record linkage of health services data</td>
</tr>
<tr>
<td></td>
<td>Emilia Romagna</td>
<td>4.4</td>
<td>35</td>
<td>Record linkage of regional/national health services data and registries</td>
</tr>
<tr>
<td>Norway</td>
<td>Entire country</td>
<td>5.4</td>
<td>60</td>
<td>Record linkage of health insurance data and registries</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Sample</td>
<td>4.4</td>
<td>15</td>
<td>Record linkage of health insurance data and registries</td>
</tr>
<tr>
<td>Denmark</td>
<td>Entire country</td>
<td>5.6</td>
<td>60</td>
<td>Record linkage of health insurance data and registries</td>
</tr>
<tr>
<td>UK</td>
<td>Scotland</td>
<td>5</td>
<td>50</td>
<td>Record linkage of medical records and registries</td>
</tr>
<tr>
<td></td>
<td>Wales</td>
<td>3.7</td>
<td>33</td>
<td>Record linkage of medical records and registries</td>
</tr>
<tr>
<td>Spain</td>
<td>Catalunya</td>
<td>5.8</td>
<td>40</td>
<td>Record linkage of health insurance GP data and registries</td>
</tr>
<tr>
<td></td>
<td>Valencian Region</td>
<td>5</td>
<td>50</td>
<td>Record linkage of health insurance data and registries</td>
</tr>
<tr>
<td>Finland</td>
<td>Entire country</td>
<td>1.9</td>
<td>60</td>
<td>Record linkage of health insurance data and registries</td>
</tr>
<tr>
<td>France</td>
<td>Entire country</td>
<td>66</td>
<td>700</td>
<td>Health insurance, hospital data</td>
</tr>
<tr>
<td></td>
<td>Haute Garonne</td>
<td>1.4</td>
<td>10</td>
<td>Cohort &amp; linkage to health insurance data</td>
</tr>
<tr>
<td>Germany</td>
<td>sample</td>
<td>16</td>
<td>100</td>
<td>Health insurance data</td>
</tr>
<tr>
<td>Multiple countries</td>
<td>EUROmediCAT</td>
<td>Approx. 75 million</td>
<td>750 000</td>
<td>Congenital anomaly registries in EUROCAT surveillance</td>
</tr>
</tbody>
</table>
The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking ConcePTION grant nº821520.

ConcePTION data & analytics harmonization

Low level CDM
Syntactic harmonization

Generation of variables (semantic harmonization) & results

DAP: data access providers
Optimizing methods and demonstrating scientific robustness of ConcePTION approach

PHARMACOEPIDEMIOLOGY DEMONSTRATION STUDIES

- For each area: Drug utilization, Disease impact and Medication Safety

<table>
<thead>
<tr>
<th>Therapeutic Area in Pregnancy</th>
<th>Methodology to be addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic pain</td>
<td>Methods for controlling <strong>confounding by indication</strong></td>
</tr>
<tr>
<td>Mental Health Disorders (Psychotropics)</td>
<td>Effect of time varying confounding factors on <strong>long-term childhood outcomes</strong></td>
</tr>
<tr>
<td>Multiple sclerosis and Systemic lupus erythematosus</td>
<td>Novel statistics/Bayesian techniques to handle <strong>small sample sizes/rare disease</strong></td>
</tr>
<tr>
<td>Migraine</td>
<td>Studying <strong>intermittent medication exposures</strong> for episodic manifestations during pregnancy</td>
</tr>
<tr>
<td>Breast cancer</td>
<td><strong>Accurate identification</strong> of an incident case.</td>
</tr>
</tbody>
</table>
Sustainable evidence generation to inform and empower choices of pregnant women

- WP1 Data beyond registries
- WP2 Pregnancy reports
- WP3 in vitro, in vivo models
- WP4 Human breast milk biobank
- WP5 Knowledge bank
- WP6 Stakeholder engagement
- WP7 Stakeholder engagement
- WP8 Sustainability

Includes regulatory qualification

Dissemination and education for public

Long term evidence generation solution

The research leading to these results has received support from the EU/EFPIA Innovative Medicines Initiative (2) Joint Undertaking ConCePTION grant nº 821520
With thanks to ConcePTION?

- **Management team:**
  - Michael Steel, Miriam Sturkenboom, Pieter Stolk, Marie Teil

- **Managing Board (WP leads):**
  - Amanda Neville, Anja Geldof, Laura Yates, David Lewis, Isabelle Huys, Michele Bouisset-Leonard, Mats Hansson, Marie Teil, Stephanie Tcherny-Lessenot, Agnes Kant, Dipak Kalra, Christine Allan, Miriam Sturkenboom, Marianne Cunnington, Pieter Stolk, Ida Niklson, Hildrun Sundseth

**Participants:**

- > 200 persons from 88 organizations including the European Medicines Agency, drug manufacturers, academia, small medium enterprises, public health organizations, women’s health and teratology networks