Opportunities of prospective observational ENTIS studies

Corinna Weber-Schoendorfer
Pharmakovigilanzzentrum Embryonaltoxikologie, Charité-Universitätsmedizin Berlin, Germany
European Network of Teratology Information Services

30 Services in 19 countries
ENTIS → three core areas

Counselling

Information

www.enties-org.eu

Research
Selection of recent ENTIS studies

- Pregnancy outcomes in women on metformin for diabetes or other indications among those seeking teratology information services
- Pregnancy outcome following maternal exposure to mirtazapine: A multicenter, prospective study
- Pregnancy outcome after methotrexate treatment for rheumatic disease prior to or during early pregnancy
- Methylphenidate in pregnancy: A multicenter, prospective, comparative, observational study
- Pregnancy outcomes after maternal varenicline use: analysis of surveillance data collected by the European Network of Teratology Information Services
STROBE (2007)

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies

Erik von Elm, Douglas G Altman, Matthias Egger, Stuart J Pocock, Peter C Gøtzsche, Jan P Vandenbroucke, for the STROBE initiative

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration

Jan P. Vandenbroucke¹, Erik von Elm²,³, Douglas G. Altman⁴, Peter C. Gøtzsche⁵, Cynthia D. Mulrow⁶, Stuart J. Pocock⁷, Charles Poole⁸, James J. Schlesselman⁹, Matthias Egger²,¹⁰ for the STROBE Initiative

Using observational cohort data for studying drug effects on pregnancy outcome—Methodological considerations

Christof Schaefer\textsuperscript{a,*}, Asher Ornoy\textsuperscript{b}, Maurizio Clementi\textsuperscript{c}, Reinhard Meister\textsuperscript{d}, Corinna Weber-Schoendorfer\textsuperscript{a}

\textsuperscript{a} Pharmakovigilanz- und Beratungszentrum für Embryonaltoxikologie (BBGes), Berlin Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy, Spandauer Damm 130, Haus 10, 14050 Berlin, Germany
\textsuperscript{b} Israel Teratogen Information Service, Ministry of Health and Hebrew University, Hadassah Medical School, Jerusalem, Israel
\textsuperscript{c} CEPIC, Servizio di Genetica Medica, Dipartimento di Pediatria, Università Padova, Padova, Italy
\textsuperscript{d} Department of Mathematics, Technische Fachhochschule Berlin (University of Applied Sciences), Berlin, Germany

\textbf{A R T I C L E   I N F O}

Article history:
Received 29 February 2008
Received in revised form 15 April 2008
Accepted 29 May 2008
Available online 7 June 2008

Keywords:
Pregnancy
Pregnancy outcome
Abnormalities, Drug-induced
Observational studies
Teratology information service
Epidemiology
Risk assessment
Human

\textbf{A B S T R A C T}

Clinical data are urgently needed to specify the risk and safety of drug use during pregnancy. For several reasons pregnant women are usually excluded from clinical studies. Therefore, observational data are the main source of knowledge, cohort studies as well as case-control studies. Disadvantages of cohort studies based on observational data have been repeatedly discussed. However, being involved in individual risk characterisation of pregnant women it is the experience of clinical teratologists that even reports on small cohorts should not be disregarded if no other data are available. The recently published “Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement” underlines the value of observational data and provides a checklist regarding the most important inherent methodological problems. Our article describes how Teratology Information Services (TIS) document and evaluate their observations on pregnant women exposed to various drugs and discusses methodological problems and – considering the STROBE statement – how these could be addressed.

© 2008 Elsevier Inc. All rights reserved.
Requests 1995-2012 (n = 146,489)

Requests reg. fluoroquinolones (n = 2,694)

Maternal exposition in pregnancy (n = 1,866)

Study criteria fulfilled (n = 1,128)

Follow-up completed (n = 969)

Fluoroquinolone Study

Not study relevant (n = 828)
- Lactation (n = 605)
- General requests (n = 194)
- Paternal exposure (n = 29)

Study criteria not fulfilled (n = 738)
- Local therapy (n = 148)
- Not 1st trimester (n = 390)
- Retrospective requests (n = 18)
- Follow-up not possible/initiated (n = 182)

Follow-up not completed (n = 159)
- „Lost to follow up“ (n = 159)

Process of data mining

- Diagnosis of pregnancy
- Counselling
- Pregnancy outcome
- Follow-up
- Data export & Evaluation
Data acquisition

Initial contact:
- Detailed exposure assessment
- Maternal characteristics

Follow-up:
- Update of exposure data
- Pregnancy course
- Pregnancy outcome
Advantages – TIS studies

1. Prospective design
2. All possible pregnancy outcomes recorded
3. Unexposed comparison sample
4. Control of a variety of confounders
5. Realtime documentation of real drug intake
6. Low lost-to-Follow-up rate
7. TIS studies are cost-saving
8. Providing early information on newly medications
All pregnancy outcomes

Advantages – TIS studies

1. Prospective design
2. All possible pregnancy outcomes recorded
3. Unexposed comparison cohort
4. Control of a variety of confounders
5. Real-time documentation of real drug intake
6. Low lost-to-Follow-up rate
7. TIS studies are cost-saving
8. Providing early information on newly medications
Advantages – TIS studies

1. Prospective design
2. All possible pregnancy outcomes recorded
3. Unexposed comparison cohort
4. Control of a variety of confounders
5. Real-time documentation of real drug intake
6. Low lost-to-Follow-up rate
7. TIS studies are cost-saving
8. Providing early information on newly medications
Advantages – TIS studies

1. Prospective design
2. All possible pregnancy outcomes recorded
3. Unexposed comparison cohort
4. Control of a variety of confounders
5. Real-time documentation of real drug intake
6. Low lost-to-Follow-up rate
7. TIS studies are cost-saving
8. Providing early information on newly medications
Advantages – TIS studies

1. Prospective design
2. All possible pregnancy outcomes recorded
3. Unexposed comparison cohort
4. Control of a variety of confounders
5. Real-time documentation of real drug intake
6. Low lost-to-Follow-up rate
7. TIS studies are cost-saving
8. Providing early information on newly medications
Advantages – TIS studies

1. Prospective design
2. All possible pregnancy outcomes recorded
3. Unexposed comparison cohort
4. Control of a variety of confounders
5. Real-time documentation of real drug intake
6. Low lost-to-Follow-up rate
7. TIS studies are cost-saving
8. Providing early information on newly medications
Advantages – TIS studies

1. Prospective design
2. All possible pregnancy outcomes recorded
3. Unexposed comparison cohort
4. Control of a variety of confounders
5. Real-time documentation of real drug intake
6. Low lost-to-Follow-up rate
7. TIS studies are cost-saving
8. Providing early information on newly medications
Disadvantages – TIS studies

• Limited to follow-up periods
• Small to moderate sample sizes
• No randomized controlled study. BIAS!
Bias

- Selection bias
- Information bias
- Detection bias
- Bias by confounder
Bias by confounder

Birth defect rate etc. can be adjusted for several confounders

• Maternal age
• Parity
• Previous pregnancies with malformed fetuses/infants
• Smoking, alcohol, illicit drugs
• Schooling
• BMI
# Major birth defects

<table>
<thead>
<tr>
<th>Cohorts</th>
<th>Odd Ratio Crude [95%CI]</th>
<th>Odd Ratio Adjustiert [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α Inhibitors vs. „Healthy controls“</td>
<td>3.5 [1.8–6.3]</td>
<td>2.2 [1.01–4.8]</td>
</tr>
<tr>
<td>MTX after conception vs. „healthy controls“</td>
<td>2.3 [0.9–5.2]</td>
<td>3.1 [1.03–9.5]</td>
</tr>
</tbody>
</table>

Conclusions

• Prospective observational cohort studies are an essential source for the risk assessment of drugs during pregnancy
• STROBE should be standard requirement
• We can correct for important confounders
• There are more strengths than limitations