Nordic initiative to improve knowledge about Medication Safety in Pregnancy and Lactation

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Disclaimer: This presentation presents my personal opinions and experience. I have no conflict of Interest.

Disposition

1. The Nordic registries
2. Secondary data - examples
   • Methodological challenges
   • Paternal exposure to valproate - NDDs
   • Maternal exposure to topiramate - NDDs
3. Primary data collection
   • The MoBa birth cohort
Nordic countries:
27 million inhabitants
280,000 births per year

France:
>700,000 births per year

Cecarian section: 16% - 20%
Preterm birth: 4.8% - 6%
Smoking: 1.2% - 5.5%
Malformations: 2.7% - 2.9%
Infant mortality: 0.19% - 0.22%

Nordic perinatal statistics 2020 (julkari.fi)
www.europeperistat.com
Long tradition of perinatal Nordic collaboration

- Medical birth registries
- Prescription registries
- Patient registries
- Cancer registries

The risk of distortion of the information from infant to coded data is great …

Bengt Kallen, Epidemiology of Human Reproduction, CRC 1988
Critical assessment – perinatal pharmacoepidemiology: The same as any pharmacoepi study

Material and Methods
- Data source
- Exposure measurement
- Selection of comparison groups
- Measurement of outcome
- Confounders
- Handling of missing data
- Statistical method
- Sensitivity analysis

Results & interpretation
- Magnitude and precision of effect estimates
- Robustness of results – sensitivity analyses
- Absolute risk

In practice, some especially challenging:
- Sample size requirements
- Capturing early miscarriages and terminations (see fig. below)
- Definition and classification of malformations
- Measuring long-term neurodevelopmental outcomes
How do we measure malformations?

- **Definitions differ between birth registries:**
  Example: Swedish MBR use "weeded malformation". Exclude some common, mild conditions: preauricular tag, tongue tie, patent ductus arteriosus at preterm birth, single umbilical artery, undescended testicles at preterm birth, unstable hip, and nevus.

- **What is the validity of malformations in the birth registries?**

- **What is a major malformation?**
  - Cryptorchidism with/without surgery?
  - Ventricular septal defects (VSD) that often close spontaneously?
  - Patent ductus arteriosus (IQ25) if gestational age < 37 weeks

- **Minor malformations are often excluded:**
  → Are minor malformations not important?

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**Example**


- Danish registries
- European surveillance of congenital anomalies (EUROCAT) classification system.

- Validation study: → Correct for 89-90% of cardiac malformations
Time of detecting malformation - information recorded in the Swedish Medical Birth Registry

![Graph showing cumulative discovery relative to Birth Register over age (days) from 0 days to 900 days, with different lines representing different body systems: Any major congenital malformation, Nervous system, Ear, face and neck, Digestive system, Eye, Ear, face and neck, Respiratory, Oro-facial clefts, Abdominal wall defects, Limb, Any cardiovascular malformations.]

Colourbox
EU RMP category 1 (imposed as condition of marketing authorisation)
EMEA/H/A-31/1454

A post-authorization safety study (PASS) to evaluate the **paternal exposure to valproate and the risk of neurodevelopmental disorders** including autism spectrum disorders as well as congenital abnormalities in offspring - a population-based retrospective study

Nordic registries – NO-SE-FI

Sanofi press release March 2023:
• HR for NDDs: 1.47 (95% CI: 1.10, 1.96)
• Paternal valproate group: 5.6 – 6.3%
• Paternal lamotrigine/levetiracetam monotherapy: 3.6%
EMA review of data on paternal exposure to valproate

Press release 16/06/2023

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) is reviewing data on the potential risk of neurodevelopmental disorders (NDDs) in children conceived by fathers taking valproate medicines.

The review is focusing on data from a retrospective observational study conducted by companies as an obligation following a previous review of valproate use during pregnancy.

This retrospective observational study compared the risk of NDDs (including autism spectrum disorder) in children born to men taking valproate with the risk in children born to men taking lamotrigine or levetiracetam (other treatments for epilepsy). It was carried out using multiple registry databases in Denmark, Norway and Sweden.
SmPC of topiramate reflects risks of birth defects

Section 4.3 (Contraindication) Migraine prophylaxis in pregnancy. In WOCBP, if highly effective method of contraception is not used.

Section 4.6 (Pregnancy)
- Teratogenic in mice, rats and rabbits
- North American Antiepileptic Drug pregnancy registry, infants exposed to monotherapy have:
  - 3-fold higher prevalence of major congenital malformations (4.3%) vs reference group not taking AEDs (1.4%).
  - After 1st trimester exposure: Cleft lip/palate, hypospadias, anomalies various body systems.

Indication epilepsy
- Consider alternative therapeutic options in WOCBP.
- If topiramate used in WOCBP, highly effective contraception recommended (see 4.5), woman fully informed of known risks of uncontrolled epilepsy & potential risks of topiramate to fetus.

Section 4.4 (special warnings) contains warning as well
Association of Prenatal Exposure to Antiseizure Medication With Risk of Autism and Intellectual Disability

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**IMPORATANCE** Women with epilepsy frequently need antiseizure medication (ASM) to prevent seizures in pregnancy. Risk of neurodevelopmental disorders after prenatal exposure to ASMs is uncertain.

**OBJECTIVE** To determine whether children exposed prenatally to ASMs in monotherapy and duotherapy have increased risk of neurodevelopmental disorders.

- Data from Denmark, Finland, Iceland, Norway and Sweden
- More than 24,000 children exposed to at least one anti-epileptic medicine before birth.
- 471 were exposed to topiramate alone, including 246 children born to mothers who had epilepsy.

**Figure 2. Association Between Prenatal Antiseizure Medication (ASM) Exposure and Child Neurodevelopmental Disorder (ND)**

ASD, n = NA, aHR: 2.77 (95% CI 1.35 – 5.65)
**Strengths**

Study design several notable strengths:
- large, well-established, population-based health-care registers from countries with similar health-care & data structure

**Limitations**

Confounding by indication:
- topiramate 2nd/3rd line drug

Study power:
- Children exposed to topiramate: 471 total; 246 mothers in epilepsy
- 12 children autism spectrum disorders; 6 children intellectual disability
- ASD, Epilepsy: n not presented (data protection rules because of low numbers; <5)
- Absolute risk not be estimated/ presented due to low number of events

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**What should we do with ....**

- 1 code of autisme at 6 months
- 1 code of language impairment at 1 year
- 1 code of ADHD at 2 years

**Outcome misclassification ?!**
Primary data collection

- 35 prospective European pregnancy and birth cohorts with > 300 mother-child pairs
- > 500,000 live-born European children.
- 19 countries with the majority of cohorts located in Northern and Western Europe. [www.birthcohorts.net](http://www.birthcohorts.net)

- The Norwegian Mother, Father and Child Cohort, n=108,000
- Danish MoBa, n= 106,370
Original Investigation | Pediatrics
Analysis of Prenatal Exposure to Opioid Analgesics and Scholastic Skills in Children in Fifth Grade in Norway
Johanne Naper Trannes, MSc, Pharm; Angela Lupattelli, PhD; Eivind Ystrom, PhD; Hedvig Nord

Abstract

IMPORTANCE Few studies have examined the neurodevelopmental consequences of exposure to opioid analgesics. Therefore, it is necessary to gain knowledge to inform decisions for pregnant women with moderate to severe pain.

Findings In this cohort study of 64,256 children, exposure to opioid analgesics in the first trimester or during two to three 4-week intervals during pregnancy was associated with lower scores in literacy and numeracy tests, compared with no prepregnancy exposure. However, the differences may not be clinically relevant.

Data collection in MoBa

<table>
<thead>
<tr>
<th>GW 17</th>
<th>GW 22</th>
<th>GW 30</th>
<th>Birth</th>
<th>6 mths</th>
<th>18 mths</th>
<th>36 mths</th>
<th>5 yrs</th>
<th>7 + 8 yrs</th>
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Ultrasound

Child

Mother

Father

GW=gestational week

Methods
Concluding remarks

• Long tradition of perinatal Nordic collaboration using linked registry data
• Regulatory decisions are often based on perinatal observational studies with linked registry data from the Nordic registry data

As with all observational studies, there are important methodological considerations

• If these limitations are not well understood and addressed, studies based on these data sources can misinform risk-benefit decisions for drugs