# Different study designs for signal detection and evaluation in pregnancy

**ENCePP Plenary Meeting**

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# Drug use in pregnancy…….Concerns?

## Outcomes of interest

- Conception (infertility) and contraception (OC failure).

- Pregnancy loss (15% spontaneous abortions).

- Health of the mother (preeclampsia).

- <u>Health of the offspring (preterm, **congenital malformations**)</u>.
    - Preterm Delivery, 6-10%
    - <u>Major Congenital Malformations</u>, 3-4%

- Long-term effects (neurodevelopment, late-diagnosis).

# What do we know before a drug is marketed?

- **Animal studies**
  - rarely predict human teratogenicity
- **Premarket human trials**
  - usually exclude pregnant women
  - too small to detect teratogenesis
- **Pharmacology**
  - teratogenic mechanisms largely unknown
  - teratogenicity often unrelated to a drug's therapeutic action or clinical toxicity

# Congenital Anomalies

– Teratogenic effects are often specific, i.e., a drug does not increase the risk of ALL malformations.

Valproic acid & NTD

Paroxetine & heart defects

Lithium & Ebstein anomaly

– Need to consider specific congenital anomalies.

- Major Malformations, 3-4 per 100
- Specific Major Malformations, 1 per 1,000 or lower

# Prevalence of congenital anomalies

Any malformation          3-4%

Spina bifida              0.1-0.05%
Congenital heart disease  0.7%
  – VSD                   0.2%
Orofacial clefts          0.1-0.2%
Musculo-skeletal          0.08%
  – Craniosynostosis      0.014%

# Lumping or splitting

Birth defects
- Taking all MCM together can dilute the effect
- Lumping is sometimes justified in case BDs originate from the same teratogenic mechanism (vit A derivates and cranial neural crest cells disruption)
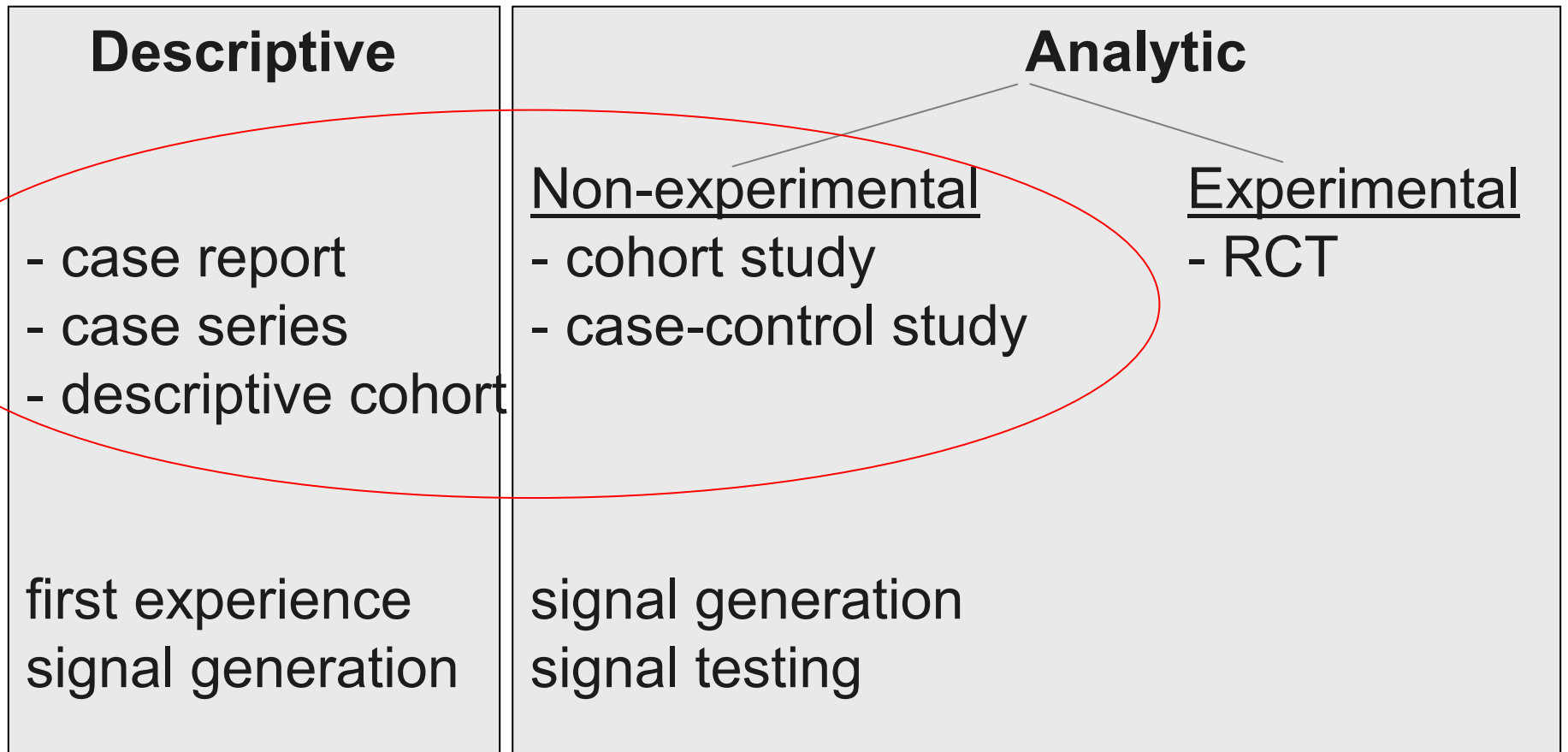
Drugs
- Taking all SSRIs will result in no effect while specific drugs can have an effect.
- Lumping is sometimes possible example: all folic-acid antagonists together is justified and therefore will give more power.

# Teratogenic mechanisms associated with medical drug use

- Folate antagonism
- Neural crest cell disruption
- Endocrine disruption
- Oxidative stress
- Vascular disruption
- Receptor- or enzyme-mediated teratogenesis

# Observational study designs

| Descriptive | Analytic | |
|---|---|---|
| | Non-experimental | Experimental |
| - case report | - cohort study | - RCT |
| - case series | - case-control study | |
| - descriptive cohort | | |
| | | |
| first experience | signal generation | |
| signal generation | signal testing | |

# Observational epidemiologic studies

- Cohorts
  - Identify persons exposed to selected drugs
    and then identify outcomes.
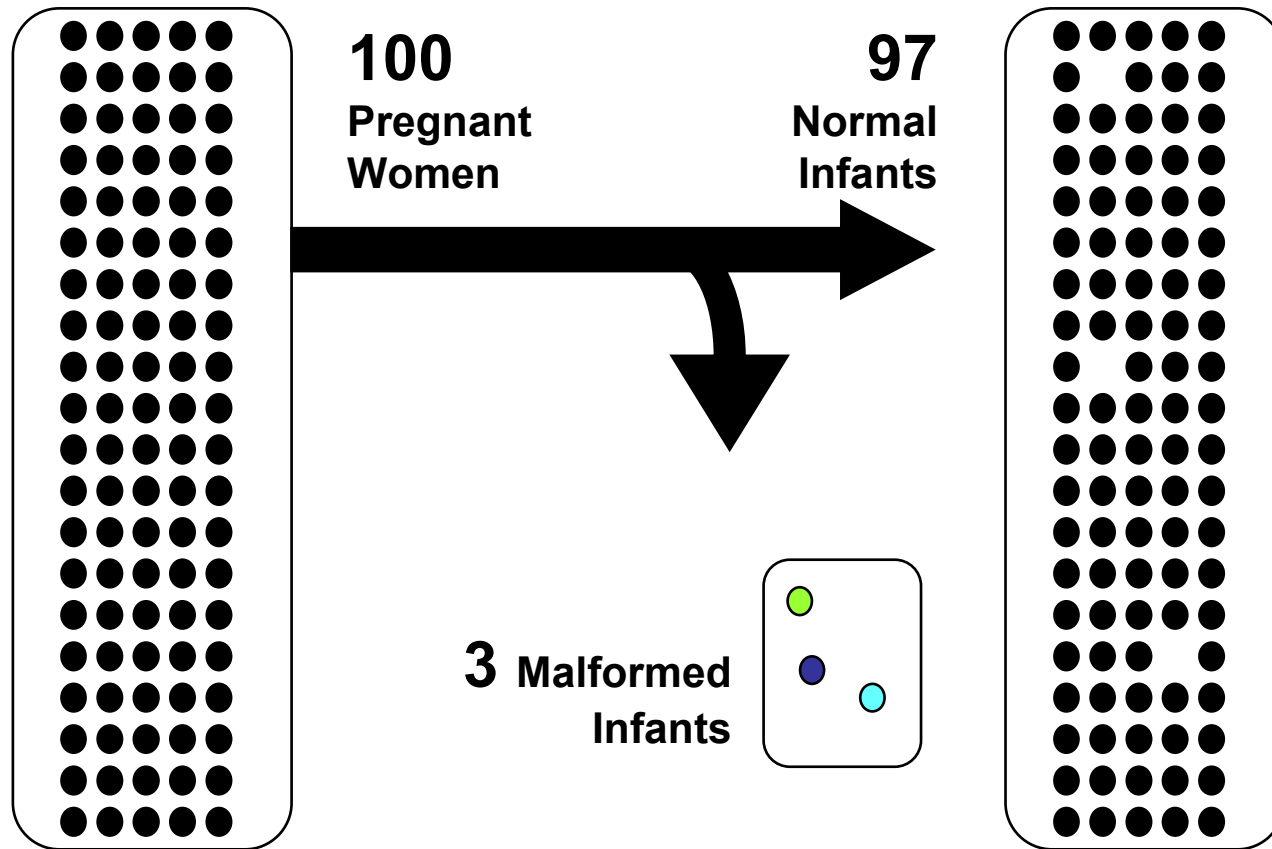    Prospective or retrospective

- Case-control study:
  - Identify adverse event and
    then identify specific exposure of interest.

- Case-control surveillance:
  - Multiple case-control studies in one
    infrastructure for birth defects (as  ICBDSR, EUROCAT,
    Slone, CDC,……)

# Cohort Design

**100**
**Pregnant**
**Women**

**97**
**Normal**
**Infants**

**3 Malformed**
**Infants**

# Pregnancy registries of drug companies

**1:1000**

acyclovir ('84-'98)  (n=581)                    15x

lamotrigine ('92-04) (n=831)                    10x
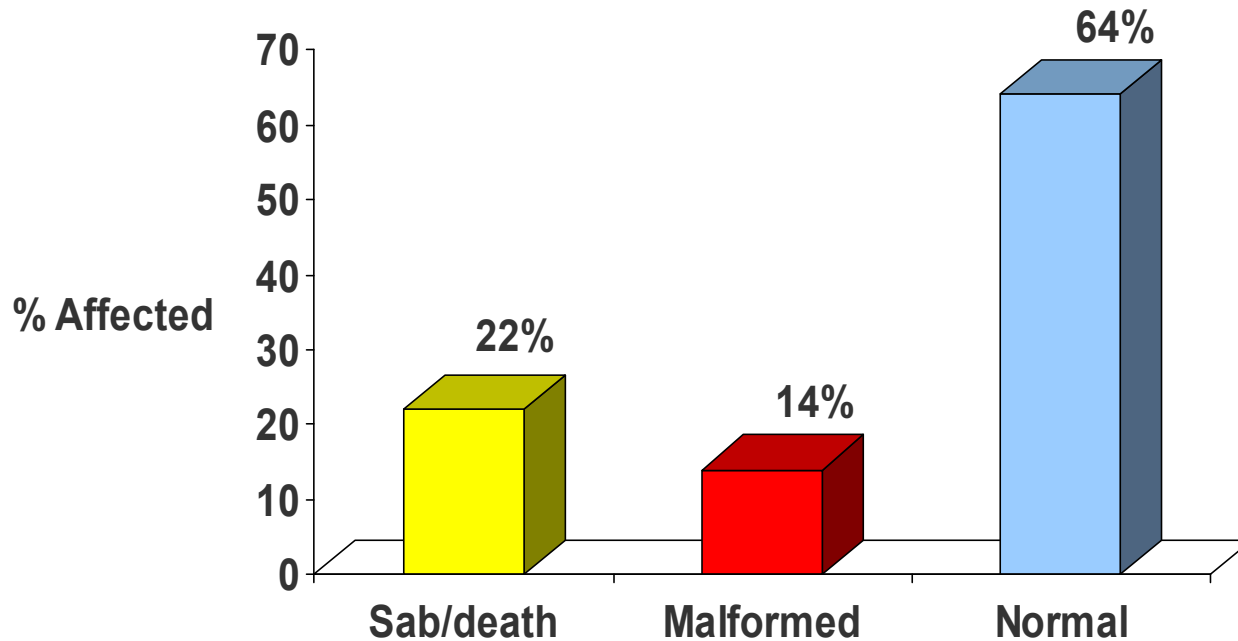
sumatriptan ('96-'98) (n=183)                   20x

to put this in a context:
- – phenytoine may cause a 2-3 fold increase in BDs
- – valproic acid increases the prevalence of spina bifida by about 10-fold.

**Cohort studies are important to detects high and moderate teratogens**

# Cohort: Isotretinoin
## Prospectively Enrolled Pregnancies (n=36)

**% Affected**

- Sab/death: 22%
- Malformed: 14%
- Normal: 64%

**Specific malformations:**

face / skull defects                              145 x increased

# Cohort Studies

**For a relatively common defect such as oral cleft (baseline 1 per 1,000 births):**

| To identify a risk of at least | Need to follow: | | |
| --- | --- | --- | --- |
| | Exposed | Not exposed | Total |
| 20-fold | 150 | 300 | 450 |
| 12-fold | 300 | 600 | 900 |
| 5-fold | 2,000 | 4,000 | 6,000 |

**alpha = 0.05, beta = 0.20.**

# Cohort Studies

**For a rare defect, affecting 1 per 10,000 births:**

| To identify a risk of at least | Need to follow: | | |
|---|---|---|---|
| | **Exposed** | **Not exposed** | **Total** |
| **20-fold** | 1,500 | 3,000 | 4,500 |
| **12-fold** | 3,000 | 6,000 | 9,000 |
| **5-fold** | 20,000 | 40,000 | 60,000 |

**alpha = 0.05, beta = 0.20.**

# Detection of teratogens after being on the market

|  | on market | detected as teratogen |
|---|---|---|
| thalidomide | 1958 | 1961 |
| isotretinoin | 1980s | within 1 year |
|  |  |  |
| phenytoine | 1938 | 1968, confirmed 1973 |
| valproic acid | 1960s | 1982 |
| carbamazepin | 1960 (trig neur) | 1991 |
|  | 1970 (epilepsia) |  |
| DES | 1950 | 1971 |

# Small cohort (2 examples)

1. Leflunomide:

   an immuno-modulator to treat Multiple Sclerosis (MS)

   A prospective small cohort study   (Chambers 2010)


2. Mycophenolate:

   An immuno-suppressant drug used to prevent organ rejection after transplantation

   A descriptive prospective small cohort   (Hoeltzenbein 2012)

# Leflunomide

- Teratogenic and embryotoxic effects in animal studies

- Post-approval **prospective** cohort study conducted by the Teratology Counseling Services (US, Canada) OTIS (2000-2008)

- 64 pregnant women with RA treated with leflunomide

  and two comparative groups:

  - 108 pregnant women with RA **not** treated with leflunomide and

  - 78 healthy pregnant women.

- Information collected via interviews with mothers, review medical record and specialized physical examination of children

|  | Leflunomide **64** | RA comp. **108** | Healthy comp. **78** |  |
|---|---|---|---|---|
| Live births | 56 (88%) | 95 (88%) | 72 (92%) | ns |
| Spontaneous abortion | 5 (8%) | 8 (7%) | 3 (4%) | ns |
| Stillbirth | 0 | 1 | 0 |  |
| Elective termination | 1 | 0 | 0 |  |
| Lost to follow-up | 1 | 2 | 3 |  |
| Major Cong. Anom. | 3/63 (5%) * | 7/93 (7%) | 3/75 (4%) | ns |

\* Occult spinal dysraphism, utero-pelvic dysjunction, microcephaly

# Conclusion of this study

Although the sample size is small, these data do **not support** the notion that there is a substantial increased risk of adverse pregnancy outcomes due to leflunomide exposure among women who undergo cholestyramine elimination procedure early in pregnancy.

These findings can provide some reassurance to women who inadvertently became pregnant while taking leflunomide and undergo wash-out procedure

**Chambers C Arthritis Rheum. 2010;62:1494-1503**

# Mycophenolate

- An immunosuppressant drug used to prevent organ rejection after transplantation and prescribed for systemic lupus erythematosus (SLE) and other auto-immune diseases

- Teratogenic effect shown in rats and rabbits at doses comparable with those in humans

- Post-marketing from pharmaceutical company and transplantation registries have suggested a high risk for adverse pregnancy outcomes
  At least 19 cases with congenital anomalies are documented. The pattern of anomalies consist of microtia, atresia of external auditory canal, orofacial clefts, heart defects, eye anomalies.

- Some cases have been published repeatedly and most were retrospective reports

# Prospective descriptive cohort identified by ENTIS

- Objective:  to estimate the prevalence of major congenital anomalies and to further confirm its teratogenicity

- From 1998-2011, 72 pregnancies with mycophenolate  exposure were identified by members of ENTIS
  - 14 were reported retrospectively (not included)
  - 58 were prospectively of whom 1 ongoing
  - **57 pregnancies included in the study**

- Treatment indications were organ transplantation (22 women) SLE (23) and other auto-immune  diseases (12).

- All exposed during the first trimester, median dose approx 1g/day. 75% stopped therapy before week 8 of pregnancy. 43 women had additional immunosuppressive therapy.

# Outcome of these 57 pregnancies

- 16 spontaneous abortion (16/57= 28%)
- 12 elective terminations (8 personal reasons, 2 because of the disease and 2 late due to multiple anomalies)
- 29 liveborn  of whom 6 with major congenital anomalies

Of the 31 informative pregnancies (29 + 2 ETOP) 8 fetuses/infants with a major congenital anomaly (26%)

The pregnancy outcome of women who discontinued treatment before week 6 of pregnancy:
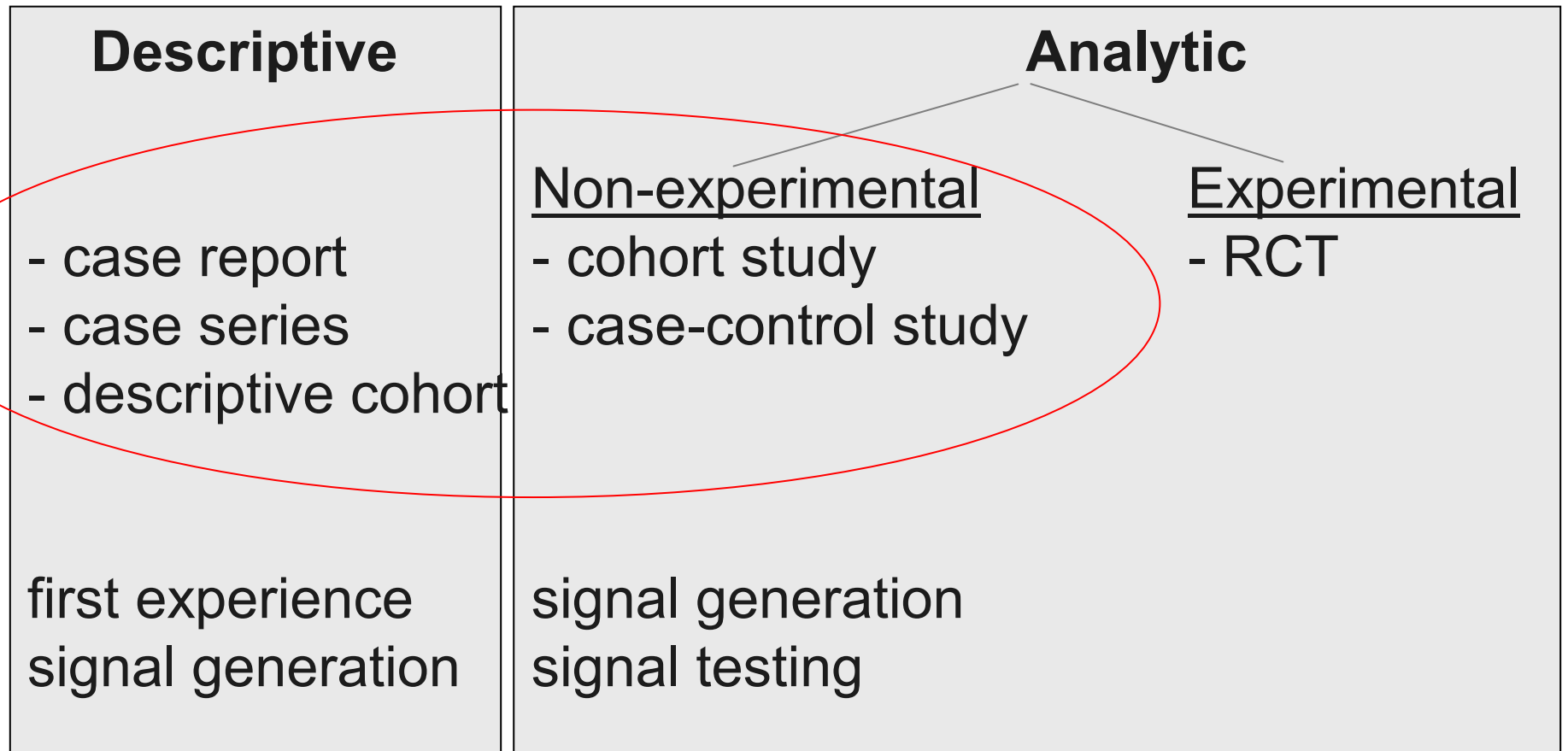
17 livebirths (1 meningocele)

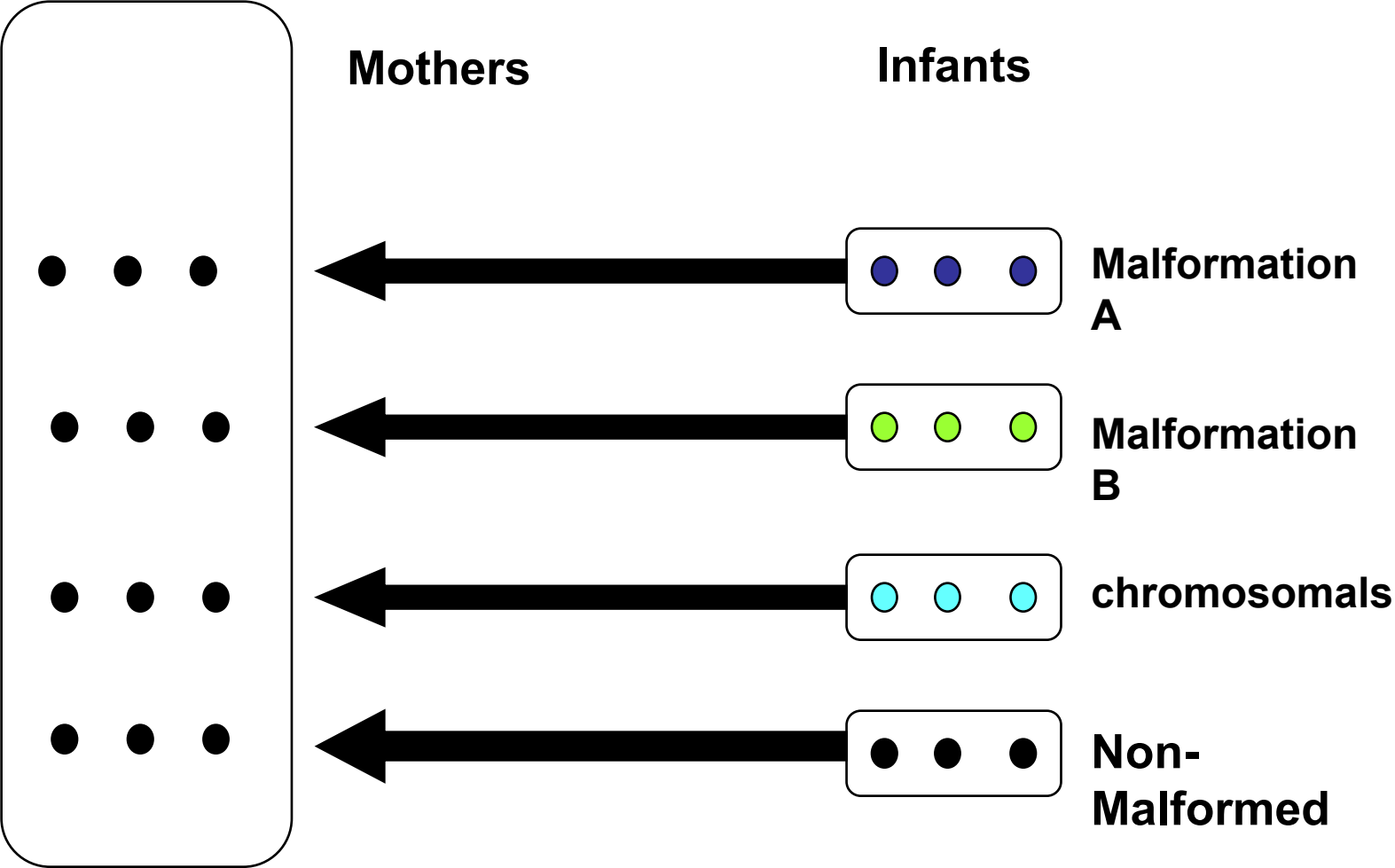9 spontaneous abortions

5 terminations

# Conclusions of this cohort

- The authors confirm the high risk for congenital anomalies not yet reported for other immunosuppressive drugs

- Specific features of mycophenolate embryology

- Increased risk especially when exposure last longer that 7 wk of pregnancy

Hoeltzenbein M et al  Am J of Med Genet Part A 2012; 158A:588-596 :

# Observational study designs

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| | | |
| first experience | signal generation | |
| signal generation | signal testing | |

# Case-Control Design

**Mothers**          **Infants**

Malformation A

Malformation B

chromosomals

Non-Malformed

# Historical case-control study
# DES and 'clear cell' cancer

**clear cell cancer**

|  | | yes | no |
|---|---|---|---|
| | yes | 7 | 2 |
| Exposed to DES during pregnancy | | | |
| | no | 1 | 30 |

Odds ratio : 7/1 : 2/30 = 210/2 = 105

# SSRIs and pulmonary hypertension in the newborn

|  |  | pulmonary hypertension | |
|---|---|---|---|
|  |  | yes | no |
| Exposed to SSRIs after 20 weeks | yes | 14 | 6 |
|  | no | 361 | 812 |

Odds ratio = 14/361 : 6/812 = 6.1 (2.2-15.5)

# Case-Control monitoring system

**Mothers**          **Infants**

Malformation A

Malformation B

chromosomals

Non-Malformed
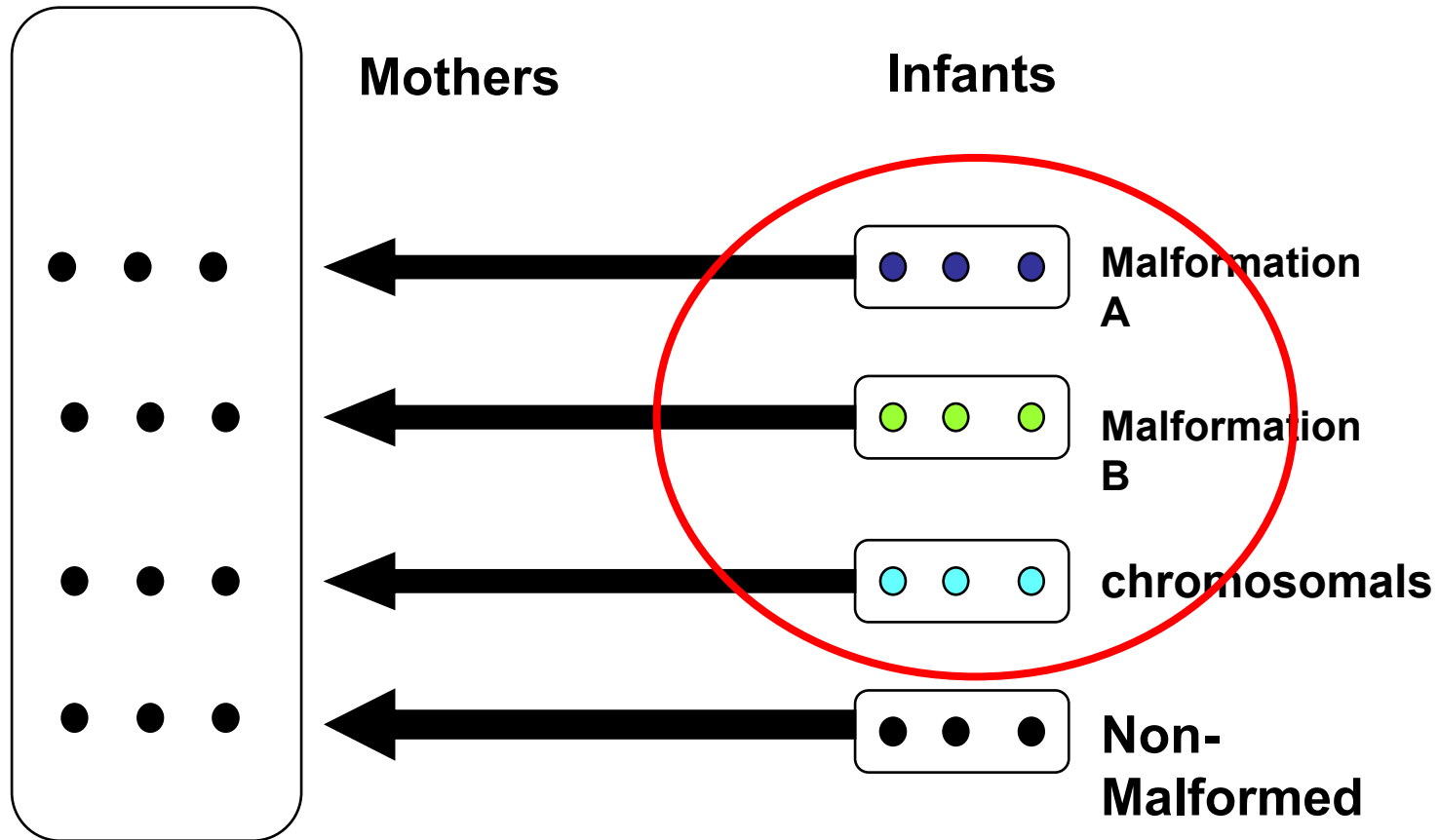
EUROCAT: network of population-based birth-defect registries and can be used to test signals of specific BDs related to specific drugs.

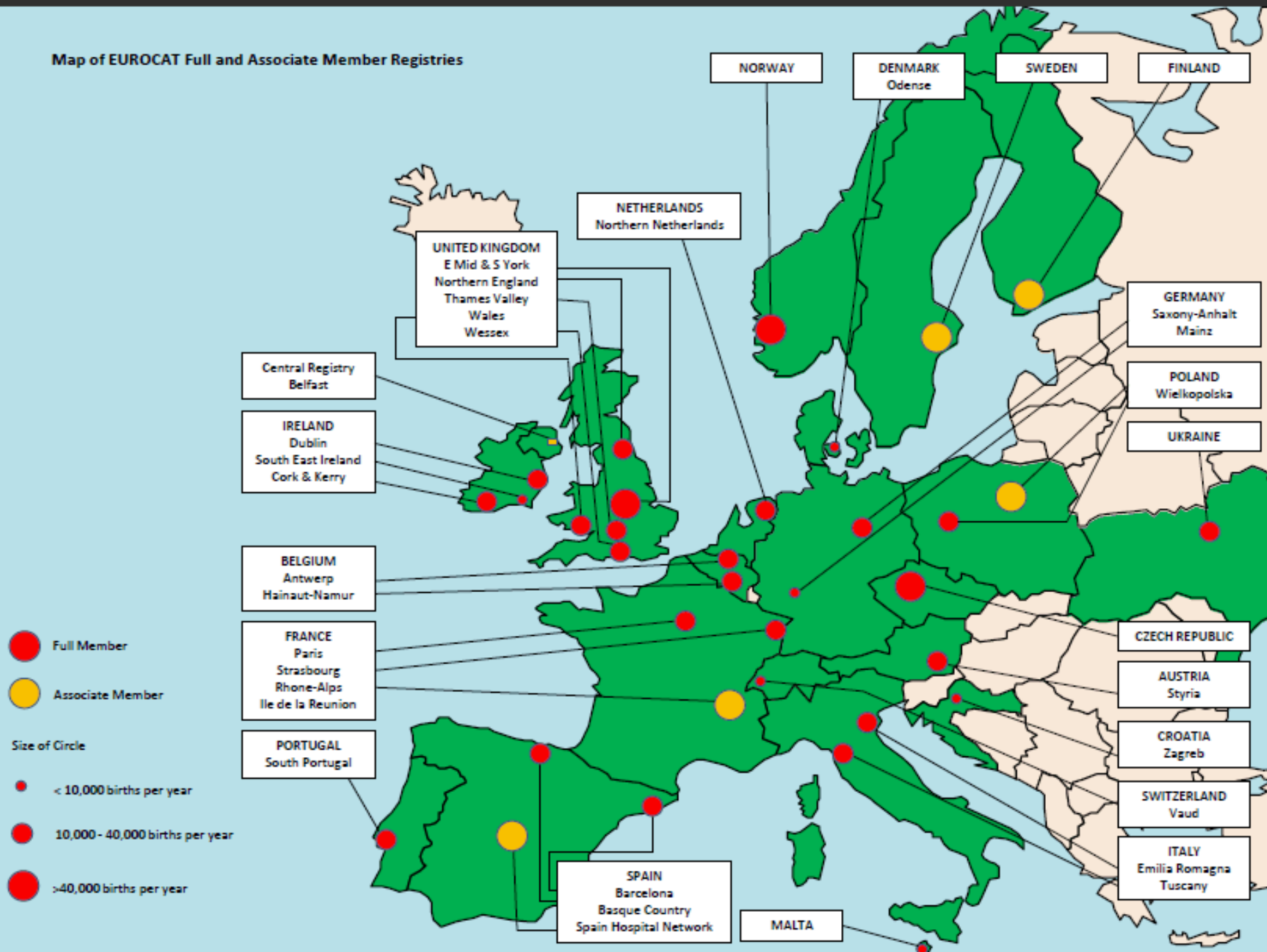EUROmediCAT is the dataset with detailed information of drug exposure

# EUROCAT

- European network of population-based congenital anomaly registries across Europe.
  - Live births, still births, fetal deaths and termination after prenatal diagnoses
  - Standardised classification system for malformations (ICD-9/10 ) and drugs (ATC-codes) (EUROCAT Guide 1.3)
  - Minor anomalies are excluded

- Established in 1979 for surveillance of congenital birth defects.
  - To provide essential epidemiologic information on congenital birth defects (prevalence, trends by region, over time).
  - To serve as early warning system for new teratogenic effects
  - To assess impact of new prevention/screening programs

- Consists of 43 member registries across 20 countries

- Coverage of registries varies e.g. at regional/country level

- EUROCAT network covers 1.5 million births each year
    - 1/3 of all births in Europe

# Map of EUROCAT Full and Associate Member Registries



**NORWAY**

**DENMARK**
Odense

**SWEDEN**

**FINLAND**

**NETHERLANDS**
Northern Netherlands

**UNITED KINGDOM**
E Mid & S York
Northern England
Thames Valley
Wales
Wessex

**GERMANY**
Saxony-Anhalt
Mainz

**POLAND**
Wielkopolska

**UKRAINE**

**Central Registry**
Belfast

**IRELAND**
Dublin
South East Ireland
Cork & Kerry

**BELGIUM**
Antwerp
Hainaut-Namur

**CZECH REPUBLIC**

**FRANCE**
Paris
Strasbourg
Rhone-Alps
Ile de la Reunion

**AUSTRIA**
Styria

**CROATIA**
Zagreb

**SWITZERLAND**
Vaud

**PORTUGAL**
South Portugal

**ITALY**
Emilia Romagna
Tuscany

**SPAIN**
Barcelona
Basque Country
Spain Hospital Network

**MALTA**

● **Full Member**

● **Associate Member**

**Size of Circle**

· < 10,000 births per year

● 10,000 - 40,000 births per year

● >40,000 births per year

# EUROCAT, limitations

- Data on exposure to drugs in the **first trimester** collected through maternal interviews or linkage to pharmacy registries
  - Captures up to five drug exposures
  - ATC codes

- Data on drug exposure in pregnancy are not available in all registries, Chronic drugs use is well documented (antiepileptics, insuline, …)

- Additional covariates of interest available include maternal age, gestational age, maternal illness before and during pregnancy No info about smoking and alcohol use!!

# EUROCAT AED-study Database

- FDA alert based on Holmes findings of a 17-fold increased risk of orofacial clefts after lamotrigine exposure (2007)

- EUROCAT created a EUROCAT Antiepileptic Study Database including data from 19 registries, 1995-2005.
  - Inclusion of registries only where AED exposure recorded for at least 3 per 1000 malformed infants
  - Inclusion of registries only with complete drug name or 7-digit ATC code for at least 80% AED exposed infants

- This dataset was used to conduct a population-based case-control study with malformed controls evaluating the risk of orofacial clefts related to lamotrigine exposure (**hypothesis driven study**).

# Risk of orofacial clefts related to lamotrigine exposure

**Final dataset**

85,563 registrations:

- 5,511 non-syndromic orofacial clefts (isolated and multiple)
  of whom 1969 cleft palate
- 4571 isolated non-syndromic orofacial clefts
  of whom 1532 isolated cleft palate

- 80,052 controls (malformed controls)

495 AED exposed registrations
- Over 80% monotherapy
- AED exposure 5.8/1000 registrations

# Lamotrigin & orofacial clefts:  **power calculation**

Power calculation

  – 4571 isolated orofacial clefts

  – Exposure rate of lamotrigine monotherapy 0.44 per 1000

  – We will include at least 10 controls per case

  – Power of 80%, alpha 0.05

We can detect an odds ratio of 3.3

For isolated cleft palate we can detect an odds ratio of 6.6

# Results ..no increased risk

We evaluated the signal:  lamotrigine and orofacial clefts in a population-based case-control study with malformed controls
Lamotrigine monotherapy compared with no AED-use

|  | LTG monotherapy vs no AED $OR_{adj}$  95%CI | |
|---|---|---|
| orofacial cleft (I) | **0.80** | [0.11-2.85] |
| orofacial cleft (I+M) | **0.67** | [0.10-2.34] |
| cleft palate (I) | **1.01** | [0.03-5.57] |
| cleft palate (I+M) | **0.79** | [0.03-4.35] |

No confirmation of the increased risk noted in the alert.

# Discussion

- Study demonstrates the issue of studying a rare outcome and a rare exposure.

- Among 3.9 million births, we only captured ~70 LTG exposures among case and control groups.

- Numbers were still adequate to rule out threefold increase in risk.

- We continued to use this data also for evaluating :
  - The risk of  valproic acid and various specific birth defects related to the use of other antiepileptic drugs
  - And carbamazepin and various birth defects

# Valproic acid and specific birth defects

- **Study population**
  19 EUROCAT registries: 3.8 million births covered
  including 98,075 malformed

- **Study design:**
  - Literature review to find signals
  - Test these signals in case-control study

    - Control groups:     -non-chromosomal
                          -chromosomal

    - Exposure:           -VPA mono vs. no AED
                          -VPA mono vs. other AED mono

- All these 8 studies presented a case-list of specific birth defects

- In 3 cases we contacted the first author of the study for more detailed info about the specific birth defect

- Based on this information we calculated the prevalence of specific birth defects among the 1565 valproic acid exposed pregnancies

- We compared that with the prevalence of these specific birth defects in the general EUROCAT population

- When the prevalence of a specific birth defect among valproic acid exposed pregnancies was sign. higher than in the general population it was regarded as a signal.

These signals were tested in a case- malformed control design.

# Included studies, literature review

| Study | Valproic acid monotherapy exposed | | |
|---|---|---|---|
| | number | Malformed | Rate (95%CI) |
| Samrén 1997 | 184 | 16 | 8.7%  [5.4-13.7] |
| Kaaja 2003 | 61 | 4 | 6.6%  [2.6-15.7] |
| Sabers 2004 | 30 | 2 | 6.7%  [1.9-21.3] |
| Vajda 2004 | 89 | 15 | 16.9%  [10.5-26.0] |
| Wide 2004 | 268 | 26 | 9.7%  [6.7-13.8] |
| Wyszinsky 2005 | 149 | 16 | 10.7%  [6.3-16.8] |
| Meador 2006 | 69 | 12 | 17.4%  [10.2-28.0] |
| Morrow 2006 | 715 | 44 | 6.2%  [4.6-8.2] |
| Total | 1565 | 135 | 8.6%  [7.3-10.1] |
| Total MCM* | 1565 | 188 | 7.5%  [6.3-9.0] |

* According to the EUROCAT classification (based on ICD-10) 17 were only minor and therefore excluded

# 14 signals of specific BDs identified

|  | Literature | | EUROCAT | | |
|---|---|---|---|---|---|
|  | number | prev./1000 | number | prev./1000 | P-value |
| Spina bifida | 22 | 14.1 | 1933 | 0.5 | P<0.0000 |
| microcephaly | 2 | 1.3 | 745 | 0.2 | P=0.0296 |
| VSD | 12 | 7.7 | 1189 | 3.1 | P<0.0000 |
| ASD | 11 | 7.0 | 8428 | 2.2 | P=0.0001 |
| Tetralogy of Fallot | 3 | 1.9 | 991 | 0.3 | P=0.0010 |
| Pulmonary valve atresia | 3 | 1.9 | 339 | 0.1 | P<0.0000 |
| Hypoplastic right heart | 1 | 0.6 | 99 | 0.03 | P=0.0225 |
| Cleft palate | 13 | 8.3 | 2338 | 0.6 | P<0.0000 |
| Diaphragmatic hernia | 4 | 2.6 | 766 | 0.2 | P<0.0000 |
| gastroschisis | 2 | 1.3 | 807 | 0.2 | P=0.0407 |
| hypospadias | 22 | 14.1 | 541 | 1.4 | P<0.0000 |
| Club foot | 8 | 5.1 | 3847 | 1.0 | P<0.0000 |
| polydactyly | 8 | 5.1 | 3594 | 0.9 | P<0.0000 |
| Craniosynostosis | 5 | 3.2 | 551 | 0.1 | P<0.0000 |
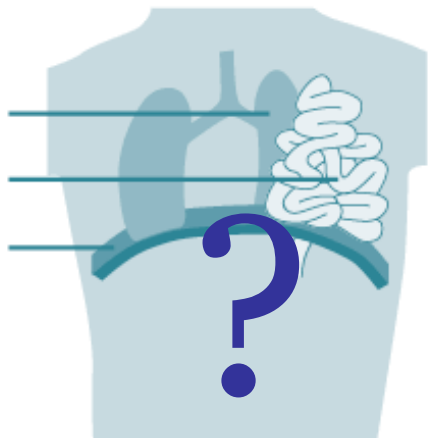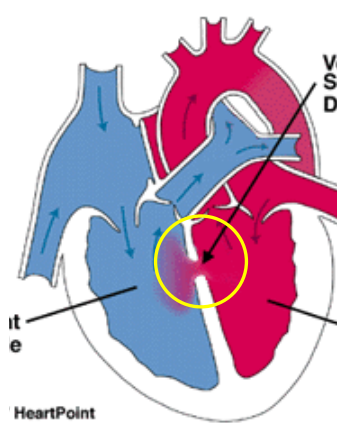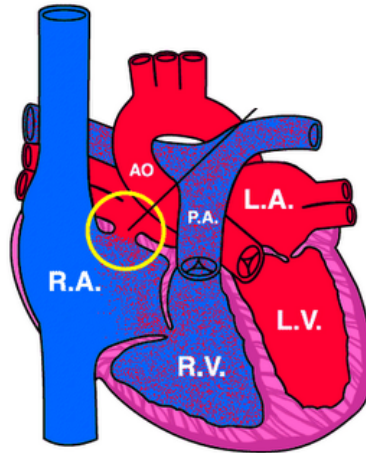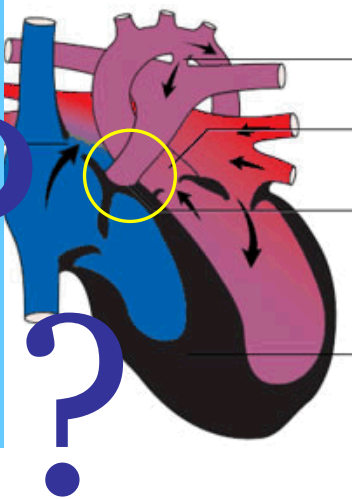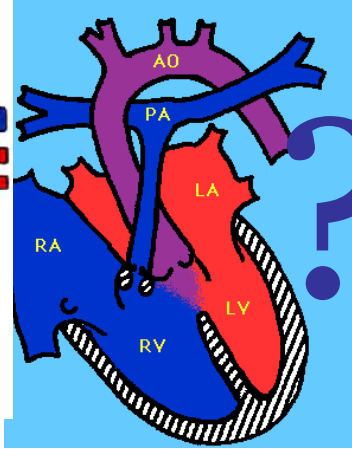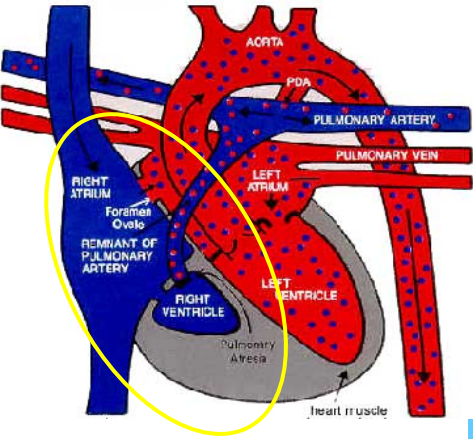
Does 1ˢᵗ trimester VPA exposure increase the risk for all these defects??
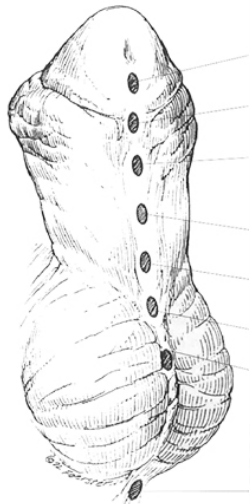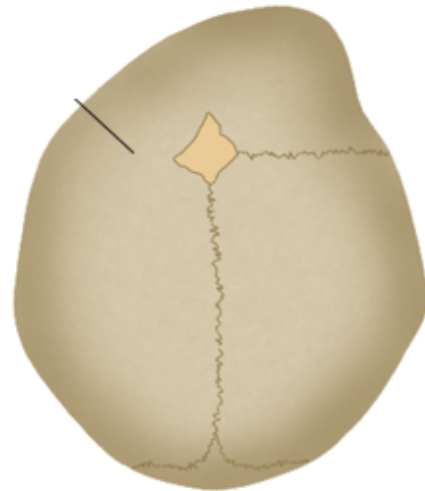
# Results summarised

- 14 signals identified in literature

- 6 confirmed:        comp. with no AED-exp
  - spina bifida:        OR=12.7 (7.7-20.7)
  - ASD:                 OR=2.5 (1.4-4.4)
  - cleft palate:        OR= 5.2 (2.8-9.9)
  - hypospadias:        OR=4.8 (2.9-8.1)
  - polydactyly:        OR= 2.2 (1.0-4.5)
  - craniosynostosis: OR= 6.8 (1.8-8.8)

- 4 non-significantly increased (OR 2-4):
  - microcephaly                OR=2.5 (0.3-9.7)
  - tetralogy of Fallot         OR=2.8 (0.6-8.6)
  - pulmonary valve atresia     OR=2.8 (0.1-16.7)
  - diaphragmatic hernia        OR=2.3 (0.3-9.0)

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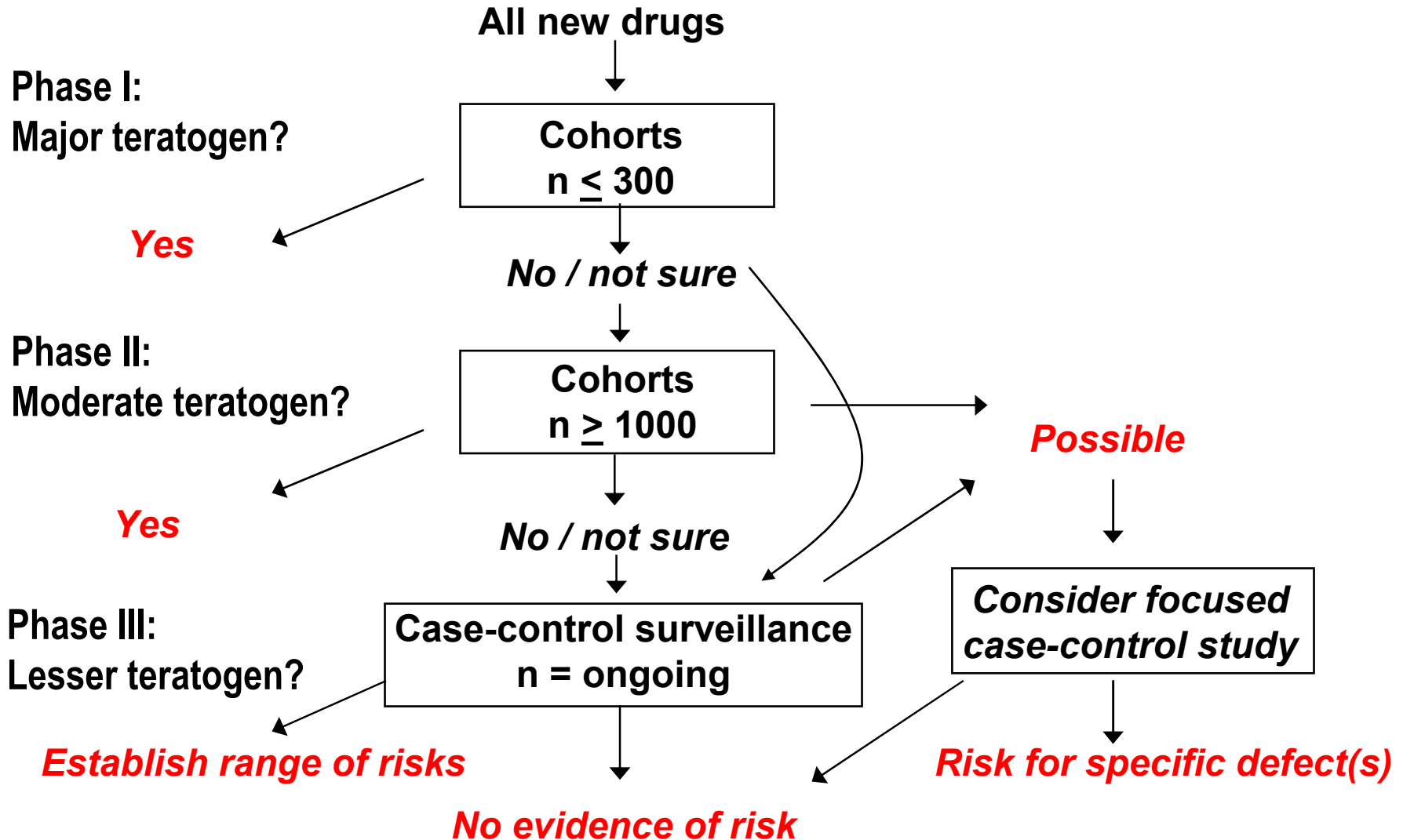
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- 6 confirmed:          comp. with no AED-exp          comp with other AED monoth.
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  - ASD:                 OR=2.5 (1.4-4.4)            3.2 (1.5-7.0)
  - cleft palate:        OR= 5.2 (2.8-9.9)           3.0 (1.2-7.4)
  - hypospadias:         OR=4.8 (2.9-8.1)            6.7 (2.9-15.2)
  - Polydactyly:         OR= 2.2 (1.0-4.5)           7.1 (1.8-28.4)
  - Craniosynostosis:    OR= 6.8 (1.8-8.8)           4.9 (0.7-55.2)

- 4 non-significantly increased (OR 2-4):
  - Microcephaly              OR=2.5 (0.3-9.7)
  - tetralogy of Fallot       OR=2.8 (0.6-8.6)
  - pulmonary valve atresia   OR=2.8 (0.1-16.7)
  - diaphragmatic hernia      OR=2.3 (0.3-9.0)

Jentink J et al Valproic acid monotherapy in pregnancy and major congenital malformations N EnglJ Med 2010;362:2185-2193

# To remind

- **General birth defects** is not a single outcome, so ideally you have to look at specific birth defects

- **Teratogenicity** should be studied in each individually drug

- **Small cohorts** are sufficient to identify high-risk teratogens, which affect a large proportion of exposed pregnancies……..

- **Case-Control Studies / Surveillance** facilitates to study all individual major birth defects in relation to all drug exposures and are efficient to identify moderate-risk teratogens
  - Potential for recall bias
  - Moderate risks of uncommonly used drugs may take a long time to identify and small risks of such drugs may escape detection.

A Possible Approach (Dr. A. Mitchell)

All new drugs

Phase I:
Major teratogen?

Cohorts
n ≤ 300

Yes

No / not sure

Phase II:
Moderate teratogen?

Cohorts
n ≥ 1000

Possible

Yes

No / not sure

Phase III:
Lesser teratogen?

Case-control surveillance
n = ongoing

Consider focused
case-control study

Establish range of risks

No evidence of risk

Risk for specific defect(s)

# Case-Control Studies

For a drug used by 5% of controls:

| To identify a risk of at least | Need to identify: | | |
|---|---|---|---|
| | Cases | Controls | Total |
| 20-fold | 10 | 20 | 30 |
| 5-fold | 50 | 100 | 150 |

alpha = 0.05, beta = 0.20.

# Case-Control Studies

For a drug used by 0.1% of controls:

| To identify a risk of at least | Need to identify: | | |
|---|---|---|---|
| | Cases | Controls | Total |
| 10-fold | 700 | 1,400 | 2,100 |
| 5-fold | 2,000 | 4,000 | 6,000 |

alpha = 0.05, beta = 0.20.