Clinical Teratology: In Bed With The Devil?

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In Bed With The Devil

- We will never know how many babies have been saved by teratology studies done in animals, *in vitro* or *in silico*.
In Bed With The Devil

- The only way we ever know that an exposure is teratogenic in humans is to recognize that it causes birth defects in babies.

In Bed With The Devil

- Clinical teratology research is all about recognizing when we have harmed babies as quickly and as effectively as possible.
In Bed With The Devil

• Clinical teratology counselling depends on learning from our own failures.

Kinds of Human Data

• Case reports
• Clinical series
• Pregnancy registries
• Cohort studies
• Case-control studies
• Record linkage studies
Case Reports

- Where the recognition of many human teratogenic exposures starts
- Get no respect because most associations observed are much more likely to be coincidental than causal

Clinical Series

- How most exposures that are teratogenic in humans and all teratogenic syndromes have been recognized
Clinical Series

- Most are epidemiological nightmares
  - Biased ascertainment
  - No appropriate comparison group
  - Cannot be used to provide quantitative estimate of risk

Pregnancy Registries

- Clinical series of outcomes among women who have taken a particular drug or drugs during pregnancy
- Natural approach for post-marketing surveillance of prescription drugs
Pregnancy Registries

- Best used to look for major effects; insensitive to more subtle or rare effects
- Collection of high-quality outcome data difficult (but critical)

Pregnancy Registries

- Subject to problems of all clinical series
  - Ascertainment bias in spades if not prospective
  - Often inappropriately compared to rigorously collected birth defects registry data
Cohort Studies

• Compare frequency of birth defects among children born to women treated or not treated with an agent during pregnancy

Cohort Studies

• Can estimate risk and statistical significance
• Can assess many different outcomes simultaneously
• Two flavours:
  - Birth cohorts
  - Exposure cohorts
Birth Cohort Studies

- Insensitive to rare exposures and outcomes
- Quality of exposure and outcome (birth defect diagnosis) data critical
- Very big, very expensive, and infrequently done

Exposure Cohort Studies

- Use existing TIS infrastructure
- Efficient for uncommon exposures
- Exposure and outcome data of varying quality
- Often underpowered for robust conclusions
Quality of Information on Birth Defects


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Quality of Information on Birth Defects

- “Did [your child] have a health problem at birth or a birth defect that was diagnosed in the first year of life?”
Quality of Information on Birth Defects

- Sensitivity (case mothers responding “yes”) = 61%
- PPV (mothers responding “yes” whose baby had a major birth defect) = 47%

Power

The chance of finding an association that really exists
Power Depends On

- Sample size
- Frequency of outcome
- Strength of association between treatment and outcome

Power Depends On

- How exposure is defined
  - Drug or class
  - Dose (amount, route, duration)
  - Timing of exposure
- How adverse outcome is defined
### 80% Power: 100 Births

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<th>Unexposed</th>
<th>Exposed</th>
<th>RR</th>
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\( \alpha = 0.05, 1 \text{ control per case, 2 tails} \)

### 80% Power: 250 Births

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<td>3.0%</td>
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\( \alpha = 0.05, 1 \text{ control per case, 2 tails} \)
Case-Control Studies

- Compare frequency of maternal treatment during pregnancy among children with or without birth defects

Case-Control Studies

- Can estimate risk and statistical significance
- Quality of exposure and outcome (birth defect diagnosis) data critical
Case-Control Studies

- Insensitive to rare exposures
- Can only be used to look for association with birth defects present in cases

What Teratogenic Effects Should We Look For?

- Congenital anomalies (structural)
  - Major anomalies
  - Multiple anomalies
  - Minor anomalies
Congenital Anomalies

- Teratogens do not affect all congenital anomalies
- Unlikely:
  - Monogenic disorders (inherited)
  - New dominant mutations
  - Chromosomal abnormalities

Congenital Anomalies

- Teratogenic exposures usually produce characteristic patterns of congenital anomalies.
Characteristic Patterns of Anomalies

- Not standard ICD-10 classifications
- Not restricted to an anatomic system
- Minor anomalies often most characteristic

What Teratogenic Effects Should We Look For?

- Birth weight
- Birth length
- Head circumference
- Growth during childhood
### What Teratogenic Effects Should We Look For?

- Premature delivery
- Spontaneous abortion
- Late fetal death/ stillbirth
- Infant death
- Death in later childhood

### What Teratogenic Effects Should We Look For?

- Functional defects
  - Mental retardation
  - Deafness
  - Blindness
  - Autism
  - Others
What Teratogenic Effects Should We Look For?

- Transplacental carcinogenesis
- Other adult-onset diseases
- Second-generation reproductive effects

Case-Control Studies

- Can provide excellent power for rare outcomes
  - Greatest strength
  - Greatest weakness
Statistical significance and clinical significance are not the same thing.

Statistical Significance

• An expression of how likely an association is to have occurred by chance alone
• What gets a paper published in the *New England Journal of Medicine*
Clinical Significance

- What matters to a pregnant woman and her physician.
  - Can I take this medicine if I am pregnant?
  - Should I consider an abortion?
  - Do I need prenatal diagnosis?

Two Dimensions of Risk

Magnitude

Severity
Two Dimensions of Risk

- Severity
- Magnitude

- Statistical Significance

Two Dimensions of Risk

- Magnitude
- Severity

- Clinical Significance
Two Dimensions of Risk

Severity

Magnitude

Thalidomide

Two Dimensions of Risk

Magnitude

Severity

• Tetracycline
Two Dimensions of Risk

- Is easiest to demonstrate in a subgroup with the most “effective” exposure and/or most characteristic outcome
  - Multiple anticonvulsant therapy
  - Toxic methyl-Hg exposure
  - Attempted abortion with misoprostil

Statistical Significance
In the real world, we usually do not know which birth defects will occur in excess.

Generally look broadly first (e.g., at all birth defects), then more narrowly (e.g., by kind of birth defect).
Subgroup Analysis

Birth Defect Subgroup
- 9.7%

Controls
- 3.3%

Subgroup Analysis

Specific Birth Defect
- 18%

Controls
- 3.3%

Exposure

0% 10% 20% 30%
“Selective reporting of post hoc subgroup observations, which are generated by the data rather than tested by them, is analogous to betting on a horse after watching the race.”

Rothwell: Lancet 365:176, 2005
Record Linkage Studies

- Use existing records or databases to identify both exposures and outcomes
- May be analyzed as cohort studies or case-control studies (or both)

Record Linkage Studies

- Often cost effective
- Information on potential confounders often limited
- Quality of exposure and/or outcome data may be poor
Estimating teratogenic risk for an individual patient always requires extrapolation beyond the available data.

The more you have to extrapolate, the greater the uncertainty.
Uncertainty of the Risk Estimate

% Malformed

Uncertainty of the Risk Estimate

% Malformed
Reducing Uncertainty

- Consider all relevant data
- Weigh evidence on basis of quality, consistency and clinical relevance
- Integrate all available information into the clinical assessment

Interpreting Information from Multiple Studies

- Formal meta-analysis
- Expert consensus
- Flying by the seat of your pants
Formal Meta-analysis

- Systematic approach to identifying, evaluating, synthesizing and combining the results of relevant studies in a particular area

Formal Meta-analysis

- May permit quantitative conclusions that cannot be drawn from individual studies to emerge from multiple studies
- Effects of biases and limitations of individual studies can be assessed
Formal Meta-analysis

- “Statistical alchemy for the 21st century”
  ...Alvan Feinstein
  - Garbage in, garbage out
  - Mixing apples and oranges
  - The file drawer problem

Expert Consensus

- Can simultaneously evaluate studies of different types, sizes, and quality, including non-epidemiological studies
Expert Consensus

- Consensus is qualitative, not rigorously quantitative
- Consensus depends on who is making it

TERIS
The Teratogen Information System
Flying by the Seat of Your Pants

- Quality depends on who is doing the flying
- Can be done quickly and cheaply (often not well)
- Difficult and time consuming to do well

The Problem

Clinical teratologists and epidemiologists speak different languages and dance to different tunes.
Clinical Teratologists Like

- Lots of data
- Statements of absolute risk
- No “ifs”, “ands” or “buts”
- Good news (no adverse effect)

Epidemiologists Like

- Novel problems (no data)
- Statements of relative risk
- Consideration of possible bias, interaction and effect modification (“ifs”, “ands” and “buts”)
- Bad news (large effects)
The Epidemiologist’s World

The Clinical Teratologist’s World
Uncertainty of the Risk Estimate

- Uncertainty is greatest when no information on the teratogenic risk is available

Lack of Knowledge Is a Problem

- Many teratogenic risks remain unrecognized
- Babies and their mothers are being harmed unnecessarily
Lack of Knowledge Is a Problem

- Pregnant women may be advised or choose to terminate their pregnancies to avoid risk

- Pregnant women may not receive treatments that benefit their own health or that of the fetus
Lack of Knowledge Is a Problem

- Teratogenic risk of 468 drugs approved 1980-2000 evaluated by TERIS expert Advisory Board
- Risk undetermined for 427 (91.2%) of treatments

Lo & Friedman, Obstet Gynecol 100:465-73, 2002

Not Using the Knowledge We Have Is Also a Problem

- Many preventable birth defects continue to occur
Prevention of Teratogenic Exposures

- Physician information and education
- Public education
- Regulation
- Folic acid fortification / supplementation

Prevention of Teratogenic Exposures

- Immunization
  - Rubella
  - Varicella
- Recognition of affected child
  - Recurrent exposure
  - Genetic predisposition
Prevention of Teratogenic Exposures

- We can’t prevent teratogenic exposures until we know what they are.
- We don’t know what exposures are teratogenic in humans until babies have been harmed.

How Should We Look For Teratogenic Effects?

- Case reports
- Clinical series
- Pregnancy registries
- Cohort studies
- Case-control studies
- Record linkage studies
If You Are in Bed With The Devil...

Make The Most of It!