Fecundity, ART & Birth Defects: Can DAGs Help with Causal Thinking

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Today’s Talk

- Understanding the ‘causal’ pathway between fecundity, treatment & birth defects
  - Weight of evidence
  - Methodologic considerations
  - DAGs & risk communication
Definitions

- **Fecundity**
  - Biologic capacity of men & women for reproduction irrespective of pregnancy intentions

- **ART**
  - Manipulation of oocytes and sperm outside the body to establish a pregnancy (IVF, ICSI, GIFT, ZIFT, ET)

Weight of Evidence

- Impaired fecundity associated with greater likelihood of pregnancy complications & adverse perinatal outcomes including birth defects
  - (Ghazi et al., 1991; Williams et al., 1991; Joffe & Li 1994; Henriksen et al., 1997; Basso & Baird 2003; Axmon & Hagmar 2005)
  - (Helmerhorst et al., 2004; Jackson et al., 2004; Rimm et al., 2004; McGovern et al., 2004)
ART & Perinatal Risks

Jackson et al., 2004

Infertility and Pregnancy Outcomes

Basso & Baird 2003
Infecundity vs. Treatment*

<table>
<thead>
<tr>
<th>Birth weight (grams)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1500-2500</td>
<td>1.7 (1.4-2.0)</td>
</tr>
<tr>
<td>&lt;1500</td>
<td>2.7 (1.8-4.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gestation (weeks)</th>
<th></th>
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<tbody>
<tr>
<td>32-37</td>
<td>1.6 (1.3-1.9)</td>
</tr>
<tr>
<td>&lt;32</td>
<td>2.2 (1.4-3.3)</td>
</tr>
</tbody>
</table>

*IVF singletons vs. natural conception among subfertile women; Kapiteijn et al., 2006

Infertility & Birth Defects

- Population based studies suggest ≈30% increase in risk of birth defects for ART (largely IVF or ICSI)
  - Bower et al., 2005; Ericson and Kallen, 2001; Hansen et al., 2002, 2005; Helmerhorst et al., 2004; Rimm et al., 2004; Shiota & Yamada 2005
**ART & Birth Defects, Western Australia**

Hansen et al., 2002

![Graph showing birth defects by ART method](image)

**ART & Birth Defects, Sweden**

- IVF significantly associated with:
  - NTDs (RR = 2.9)
  - Anal atresia (RR = 3.1)
  - Esophageal atresia (RR = 3.5)
  - Omphalocele (RR = 3.3)
  - Hypospadias (RR = 1.5; 95% CI = 1.0-2.1)

Ericson and Kallen, 2001
National Birth Defects Prevention Study*

- ART significantly associated with:
  - Septal heart defects (AOR = 2.1)
  - Cleft lip with/without palate (AOR = 2.4)
  - Esophageal atresia (AOR = 4.5)
  - Anorectal atresia (AOR = 3.7)
  - Hypospadias, 2° or 3° (AOR 2.1; 95% CI 0.9-5.2)

*Reefhuis et al., 2009

Interpreting the Findings

- “...distinguish whether these risks are due to the underlying infertility or to the drugs & procedures used to overcome it....” (Mitchell 2002)

- “...difficulty distinguishing between the effects of underlying subfertility & the infertility treatment used...” (Reefhuis et al., 2009)
Does ART 'cause' birth defects?

- If no, what is causing the relation?
  - Underlying infecundity
  - Unmeasured confounders

 Infertility $\rightarrow$ ART $\rightarrow$ Birth Defects

- If yes, what aspect of ART is causal?
  - Fertility drugs
  - Manipulation of gametes
  - Culture
  - Incubation

Reproductive & Developmental Toxicity of ART

- Role of culture
  - Type associated with varying rates of fertilization, embryo cleavage, implantation, pregnancy loss
  - Type affects embryonic genetic expression in mice, sheep and cows (Ho et al., 1994; Young et al., 2001; Wrenzycki et al., 2001)
  - Alterations in [single component] of culture medium induces changes in expression (Ho et al., 1994)
Methodologic Considerations - How good are the data?

Data & Measurement Error

- **Exposure**
  - Retrospective time-to-pregnancy, infertility Hx, & infertility Rx
    - SAQs, birth certificates, linkages
    - Largely maternal report

- **Outcome**
  - Birth defects registries
    - Birth prevalence
    - Active vs. passive surveillance
    - Major malformations
Validity of Retrospective TTP

- Probability of conception for women exposed to unprotected sexual intercourse in the absence of lactational anovulation, pregnancy or sterility (Gini 1924)
  - Conception delay (>6 months)
  - Infertility (≥12 months)
- Do couples report TTP accurately?
  - Knowledge of fertile window
  - Timing of intercourse

Validity of TTP (in months)*

<table>
<thead>
<tr>
<th>Exact Agreement</th>
<th>17%</th>
</tr>
</thead>
<tbody>
<tr>
<td>+1 months</td>
<td>41%</td>
</tr>
<tr>
<td>+2 months</td>
<td>65%</td>
</tr>
<tr>
<td>+3 months</td>
<td>72%</td>
</tr>
</tbody>
</table>

*33% of women could not remember

Cooney et al., 2009
Prevalence Infertility, US*

*NSFG, 1995
### Accuracy Infertility Rx

**Birth Certificate**

<table>
<thead>
<tr>
<th></th>
<th>Neither</th>
<th>FD only</th>
<th>ART only</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neither</td>
<td>26%</td>
<td>2%</td>
<td>2%</td>
<td>0.5%</td>
</tr>
<tr>
<td>FD only</td>
<td>1%</td>
<td>10%</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>ART only</td>
<td>0.4%</td>
<td>1%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Both</td>
<td>4%</td>
<td>5%</td>
<td>27%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Lynch et al. (in preparation)

### Couples' Fecundity Status

- **Fecund**
- **Infecund**
- **Impaired Fecundity**
  - Conception Delay
Dx Subtypes of Infertility

Causes of Infertility

- Male Factor (40%)
- Female Factor (40%)
- Couple Factor (10%)
- Unknown 10%

Genetic
Environmental

Tubal
Ovulatory
Uterine
Other

What may affect validity of retrospective TTP?
<table>
<thead>
<tr>
<th>Design</th>
<th>Wilcox et al. 2000</th>
<th>Fehring et al. 2006</th>
<th>Keulers et al. 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>-213 population volunteers</td>
<td>-165 clinical volunteers</td>
<td>-212 couples having fertility evaluation</td>
</tr>
<tr>
<td>Fertile Window</td>
<td>-696 cycles with urinary E/P ratio as proxy for ovulation</td>
<td>-1,060/1,335 cycles with &quot;peak&quot; monitor reading</td>
<td>-U/S confirmed ovulation</td>
</tr>
<tr>
<td>Findings</td>
<td>-6-day window</td>
<td>-6-day window</td>
<td>-Fertile window varies 1 to 5 days</td>
</tr>
<tr>
<td></td>
<td>30% women had fertile window within days 10-17</td>
<td>25% women had fertile window within days 10-17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10% ovulated day 14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Probability of Being in Fertile Window by Cycle Length**

- 33% ♀ with short vs. 7% ♀ long reached fertile window by 7 days

Wilcox et al., 2000
Probability Clinical Pregnancy by Couple's Age & Intercourse

Dunson et al., 2002

% Infertile Women by Age & Frequency of Intercourse

<table>
<thead>
<tr>
<th>Female Age (in years)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercourse - twice weekly</td>
<td></td>
</tr>
<tr>
<td>19-26</td>
<td>8</td>
</tr>
<tr>
<td>27-34</td>
<td>13-14</td>
</tr>
<tr>
<td>35-39</td>
<td>18</td>
</tr>
<tr>
<td>Intercourse - once weekly</td>
<td></td>
</tr>
<tr>
<td>19-26</td>
<td>15</td>
</tr>
<tr>
<td>27-34</td>
<td>22-24</td>
</tr>
<tr>
<td>35-39</td>
<td>29</td>
</tr>
</tbody>
</table>

European Fecundability Study (Colombo & Masarotto 2000; Dunson et al., 2004)
Getting answers... overcoming methodologic barriers...

Experimental Approach

- Couples randomized to receive ART or not
Observational Approach

- Develop conceptual paradigm for research question including identification of relevant covariates
  - Assumes we know determinants of couple fecundity, yet ≈14% variance in TTP explained by OC use prior to attempting, menstrual cycle length, age, & parity in Swedish women born 1960 or later (Axmó et al., 2006)
  - Assumes no difference in couples by ART care seeking behavior, antenatal testing or decision to deliver an affected pregnancy
- Recognize measurement error (bias)
- Consider DAGs
  - Illustrating the research question
  - Formalizing modeling assumptions
  - Interpreting the data

Directed Acyclic Graphs (DAGs)

- Causal diagrams that allow investigators to specify the “causal question” in the context of other variables, whether they are measured or unmeasured, for reducing bias.
  - Decompose total causal effects so you can assess factors in the pathway.
- Not a statistical technique that yields estimates, but a method for conceptualizing & controlling for confounding (causation vs. association)

Pearl 1995; Shrier & Platt 2008
**Direct & Indirect Effects**

\[
\text{BD} = \alpha + \beta_3 \text{ART} + \beta_4 \text{I}
\]

**Note of Caution**
- If there is no causal path between infertility and birth defects, adjusting for it in the context of ART will underestimate the ART effect.
- Model specification - role of (un)measured confounders
  - Collider stratification bias (also called selection bias, collider bias or confounding)
**Collider Stratification Bias***

*U introduces a (biased) association between E & U

**Summary**

- DAGs represent theoretical method for assessing causality
  - Research question
  - Modeling assumptions
  - Analytic plan appropriate for model
- Communicating risk & uncertainty
  - Within assumptions underlying DAG (and what’s missing)

*Transdisciplinary research team to draw the DAG!*
Birth defects researchers cannot escape consideration of human fecundity...

In my beginning is my end... T.S. Eliot
% Agreement

- Summary of agreement:
  - 47% fully concordant
  - 43% partially concordant
  - 10% fully discordant

- Most frequent error:
  - Underreporting of FD use on the birth certificates of children born from both FD and ART

Lynch et al. (in preparation)

Assessing Direct & Indirect Effects

Total effect of $E$ \[ D = \alpha + \beta_1 E \]
Direct effect of $C$ \[ D = \alpha + \beta_2 C \]
Direct & indirect effect of $E$ \[ D = \alpha + \beta_3 E + \beta_4 C \]
### Direct & Indirect Effects

**Indirect Path**

Infertility → ART → Birth Defects

**Direct Path**

- Direct ART effect: $BD = \alpha + \beta_2 \text{ART}$
- Total infertility effect ($I$): $BD = \alpha + \beta_1 I$
- Direct & indirect infertility effect: $BD = \alpha + \beta_3 \text{ART} + \beta_4 I$

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### Collider Stratification Bias*

**Collider** $U$ introduces a (biased) association between $E$ & $U$

- Total infertility effect: $BD = \alpha + \beta_1 \text{Infertility}$
- Direct & indirect infertility effect: $BD = \alpha + \beta_3 \text{ART} + \beta_4 \text{Infertility}$

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* $U$ introduces a (biased) association between $E$ & $U$
Probability of Being in the Fertile Window

- 2% on day 4
- 17% on day 7
- 54% on days 12-13

Wilcox et al., 2000