

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

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## Today's Talk

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

## Definitions

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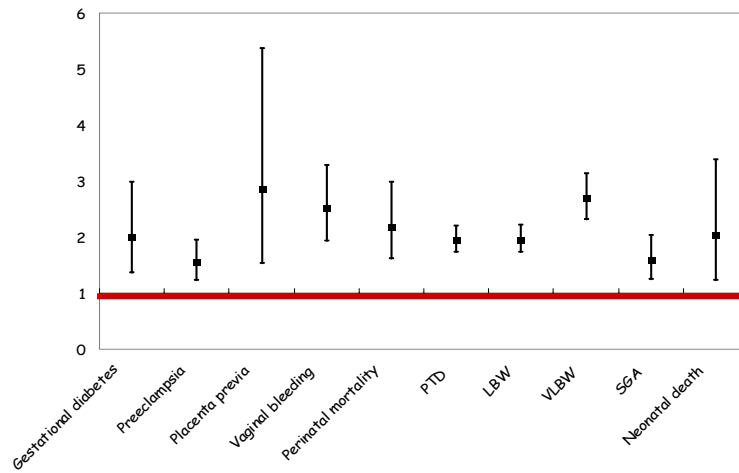
- Fecundity
  - Biologic capacity of men & women for reproduction irrespective of pregnancy intentions
- ART
  - Manipulation of oocytes and sperm outside the body to establish a pregnancy (IVF, ICSI, GIFT, ZIFT, ET)

## Weight of Evidence

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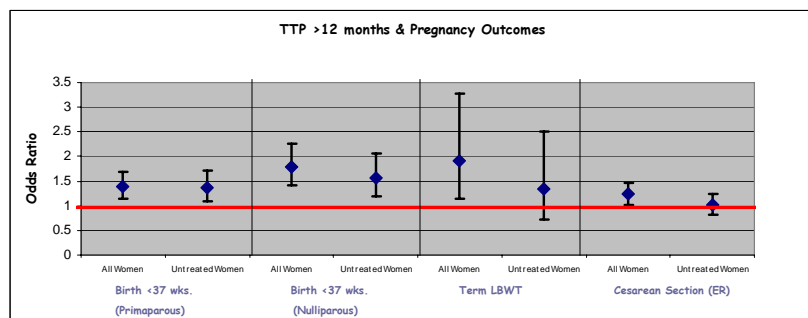
- **ART** Impaired fecundity associated with greater likelihood of pregnancy complications & adverse perinatal outcomes including birth defects
  - (Ghazi et al., 1991; Williams et al., 1991; Joffe & Li 1994; Henriksen et al., 1997; Basso & Baird 2003; Axmon & Hagmar 2005)
  - (Helmerhorst et al., 2004;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

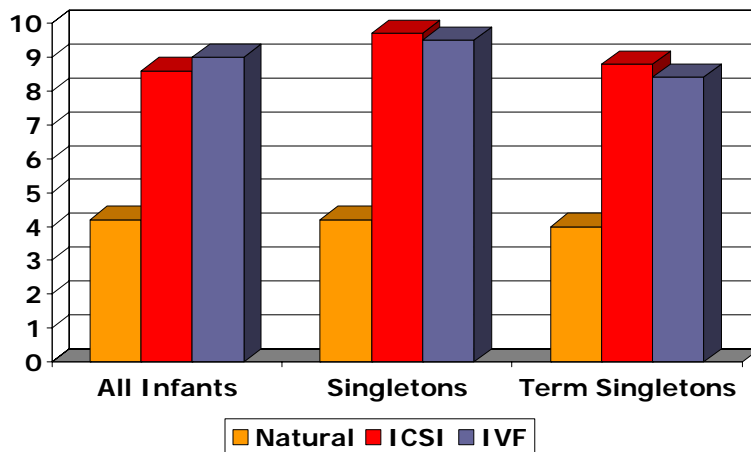
Birth weight (grams)	
1500-2500	1.7 (1.4-2.0)
<1500	2.7 (1.8-4.1)
Gestation (weeks)	
32-37	1.6 (1.3-1.9)
<32	2.2 (1.4-3.3)

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

## Infertility & Birth Defects

- Population based studies suggest  $\approx 30\%$  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

## 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\*

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- 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

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- "...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
- } Male, female, couple



### □ If yes, what aspect of ART is causal?

- Fertility drugs
  - Manipulation of gametes
  - Culture
  - Incubation
- } Rx toxicant

## 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)

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## Methodologic Considerations - How good are the data?

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## 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

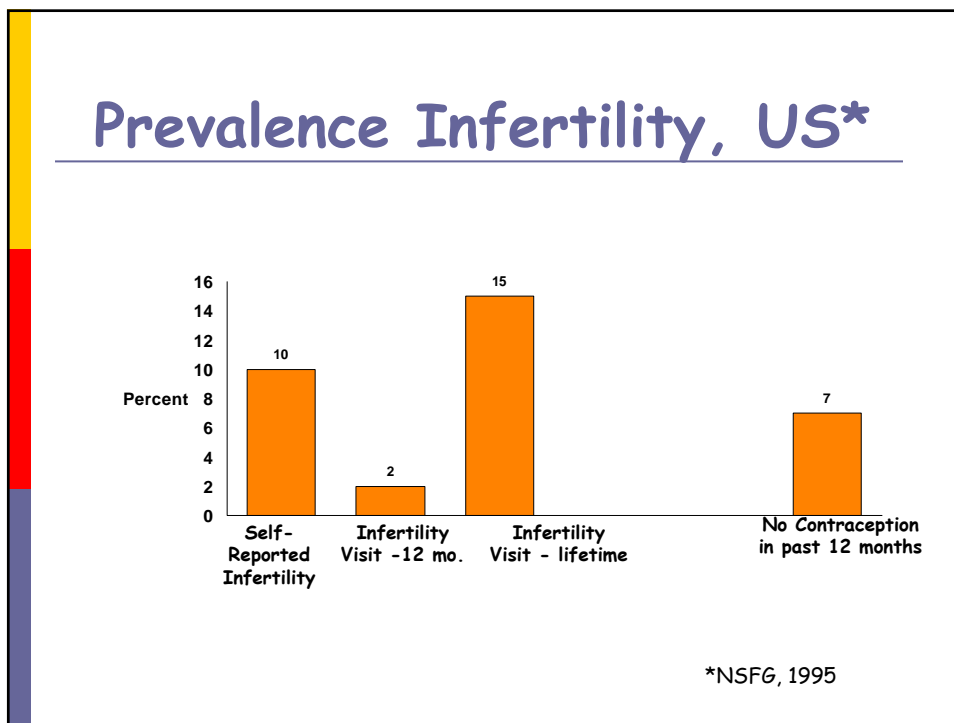
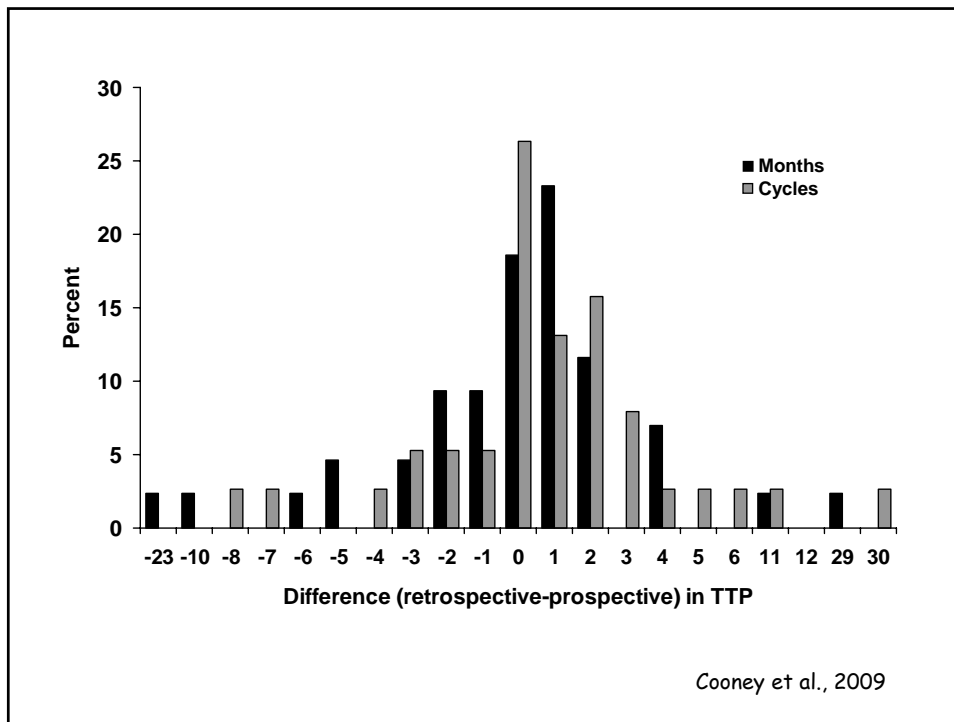
- Probability of conception for women exposed to unprotected sexual intercourse in the absence of lactational anovulation, pregnancy or sterility (Gini 1924)
  - Conception delay (>6 months)
  - Infertility ( $\geq$ 12 months)
- Do couples report TTP accurately?
  - Knowledge of fertile window
  - Timing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

## Validity of TTP (in months)\*

<b>Exact Agreement</b>	<b>17%</b>
<b>+1 months</b>	<b>41%</b>
<b>+2 months</b>	<b>65%</b>
<b>+3 months</b>	<b>72%</b>

\*33% of women could not remember

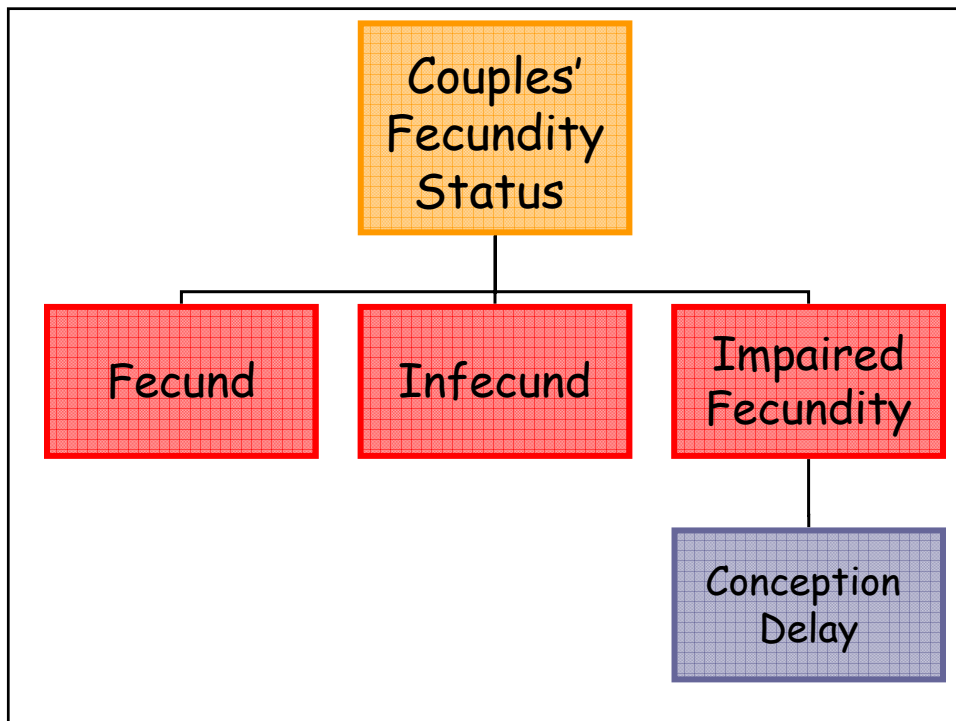
Cooney et al., 2009



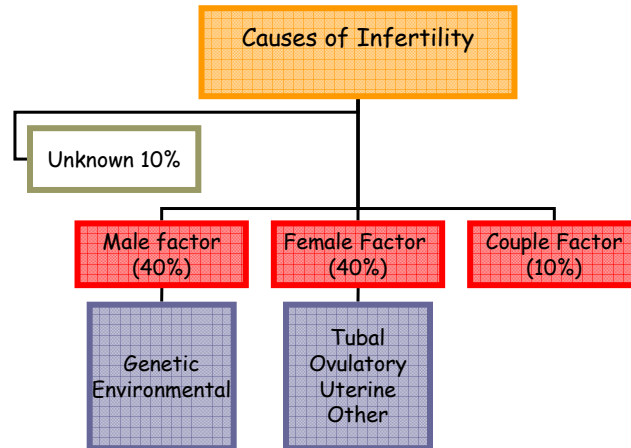
# Accuracy Infertility Rx

		Birth Certificate			
		Neither	FD only	ART only	Both
Mother's Report	Neither	26%	2%	2%	0.5%
	FD only	1%	10%	6%	2%
	ART only	0.4%	1%	3%	1%
	Both	4%	5%	27%	9%

Lynch et al. (in preparation)



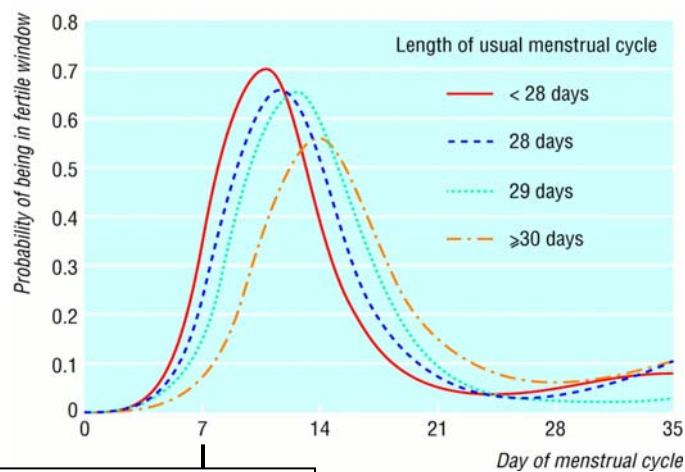
## Dx Subtypes of Infertility



What may affect validity of retrospective TTP?

	Wilcox et al. 2000	Fehring et al. 2006	Keulers et al. 2007
<b>Design</b>	Women desiring pregnancy	Women avoiding pregnancy	Subfecund couples
<b>Sample</b>	•213 population volunteers	•165 clinical volunteers	•212 couples having fertility evaluation
<b>Fertile Window</b>	•696 cycles with urinary E/P ratio as proxy for ovulation	•1,060/1,335 cycles with "peak" monitor reading	•U/S confirmed ovulation
<b>Findings</b>	<ul style="list-style-type: none"> <li>•6-day window</li> <li>•30% women had fertile window within days 10-17</li> <li>•10% ovulated day 14</li> </ul>	<ul style="list-style-type: none"> <li>•6-day window</li> <li>•25% women had fertile window within days 10-17</li> </ul>	<ul style="list-style-type: none"> <li>•Fertile window varies &lt;1 to &gt;5 days</li> </ul>

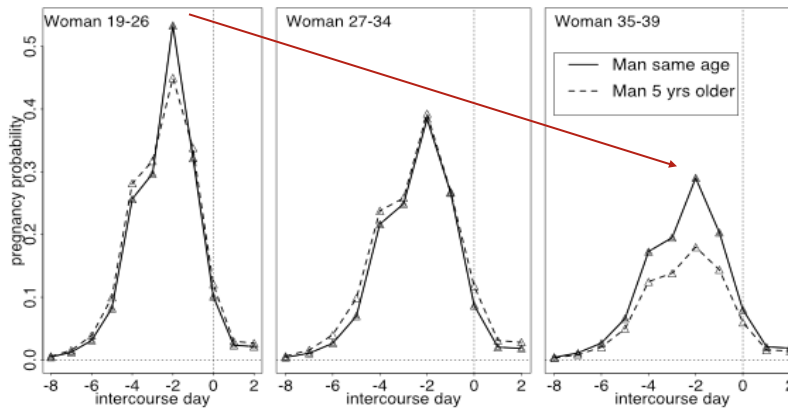
## Probability of Being in Fertile Window by Cycle Length



≈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

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

European Fecundability Study (Colombo & Masarotto 2000; Dunson et al., 2004)



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Getting answers... overcoming  
methodologic barriers...



## Experimental Approach

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- 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  $\approx 14\%$  variance in TTP explained by OC use prior to attempting, menstrual cycle length, age, & parity in Swedish women born 1960 or later (Axmon 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

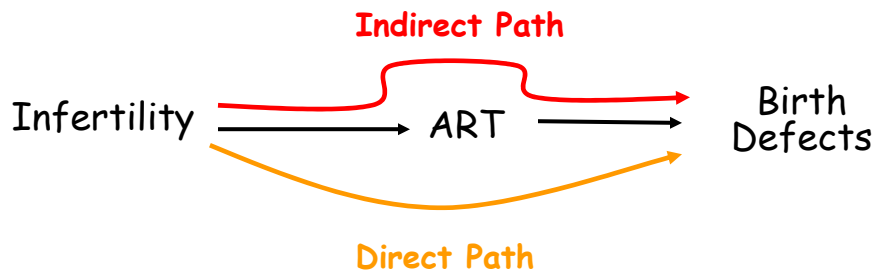
## Directed Acyclic Graphs (DAGs)

- 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

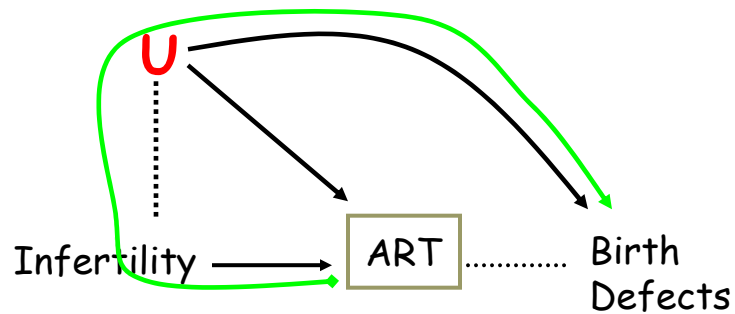


Direct & indirect infertility effect  $BD = \alpha + \beta_3 ART + \beta_4 I$

## 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!**

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Birth defects researchers  
cannot escape consideration of  
human fecundity...



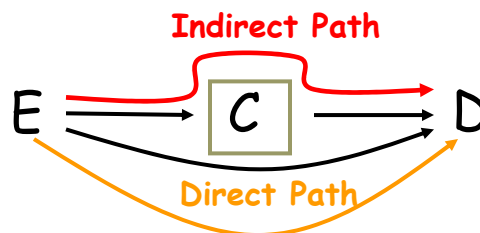
In my beginning is my  
end... T.S. Eliot

## % 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

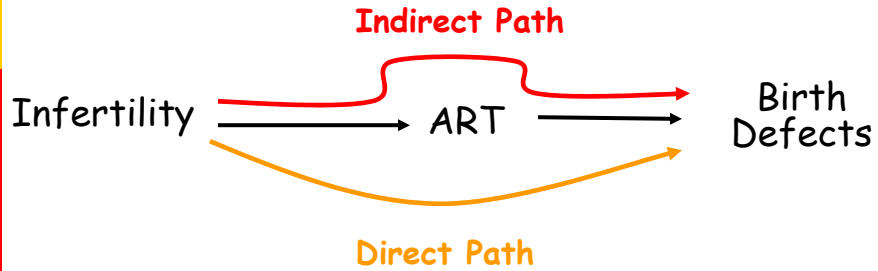


Total effect of E  $D = \alpha + \beta_1 E$

Direct effect of C  $D = \alpha + \beta_2 C$

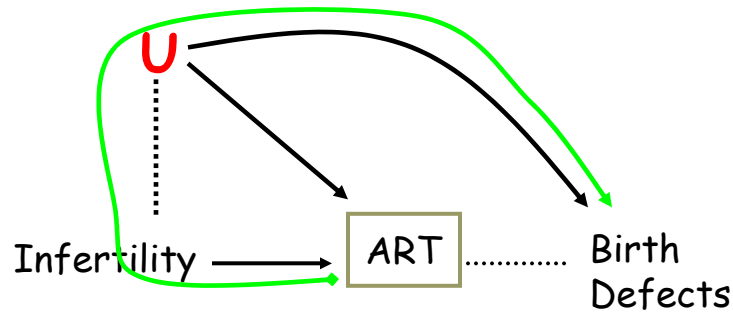
Direct & indirect effect of E  $D = \alpha + \beta_3 E + \beta_4 C$

## Direct & Indirect Effects



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

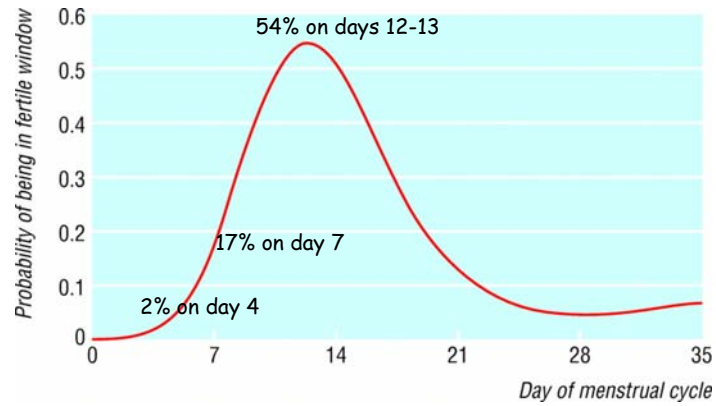
## Collider Stratification Bias\*



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

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

## Probability of Being in the Fertile Window



Wilcox et al., 2000