

# Determinants of Contraceptive Failure

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# Perfect Use *versus* Typical Use

# What is Perfect Use?

- By definition, perfect use of a method requires actual use according to the directions for that method
- Perfect use of a barrier method requires that it be used correctly at every act of intercourse
- Perfect use does not imply no pregnancies

# Logical Error Ingrained in Literature

- Suppose in a contraceptive trial there are 100 years of exposure to risk of pregnancy
- 15 pregnancies occur during a cycle of imperfect use
- 5 pregnancies occur during a cycle of perfect use
- What is the method-related pregnancy rate (pregnancy rate during perfect use)?

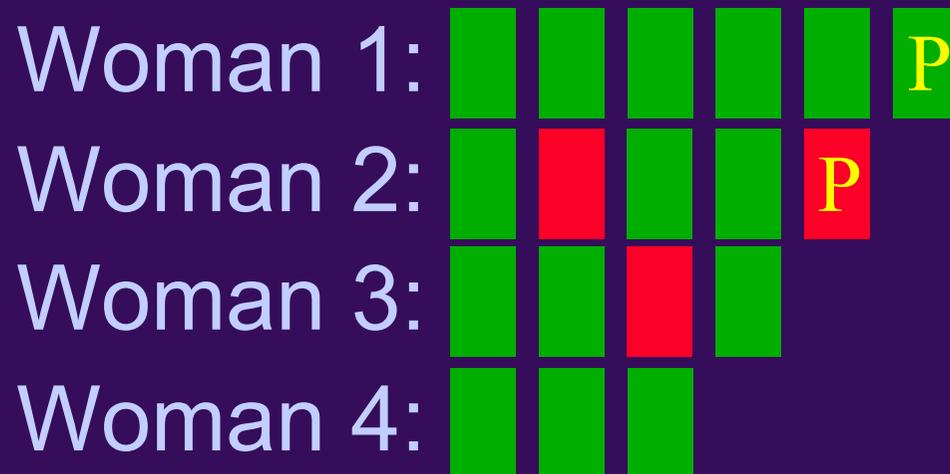
# Method-Related Pregnancy Rate

- Traditional answer
  - $5/100 = 5$  per 100 woman-years of exposure
- Logical error
  - Denominator cannot be all exposure since by definition a method-related pregnancy can occur only during perfect use
  - If there are only 50 woman-years of perfect use, correct answer is  $5/50 = 10$  per 100 woman-years of exposure

# Flaw in Design of Clinical Trials

- Information on perfect (correct and consistent) use is usually obtained only for cycles when pregnancy occurred
- Hence, pregnancy rates during perfect use cannot be estimated in most trials
- Pregnancy rates during perfect use are available only for the male condom, diaphragm, sponge, spermicides, cervical cap, female condom, and three fertility awareness based methods

# Correct Analysis by Cycle



■=imperfect ■=perfect P=pregnancy

Rates: 1/3 and 1/15 and 2/18

# Determinants of Perfect Use

- Coital frequency
- Age: both coital frequency and fecundity decline with age
- Simultaneous use of methods
- BMI?

# Simultaneous Use of Methods

- Probabilities of pregnancy during the first year of perfect use of male condoms and spermicides are estimated to be 2% and 18%
- It is reasonable to assume that during perfect use the contraceptive mechanisms of condoms and spermicides operate independently
- Lack of independence during typical use would most likely be due to imperfect use (either use both methods or not use either)

# Simultaneous Use of Methods

- The annual probability of pregnancy during simultaneous perfect use of condoms and spermicides would be 0.2%
- This is about the same as that achieved by the combined pill (0.3%) and LNg 20 IUD (0.2%) during perfect use

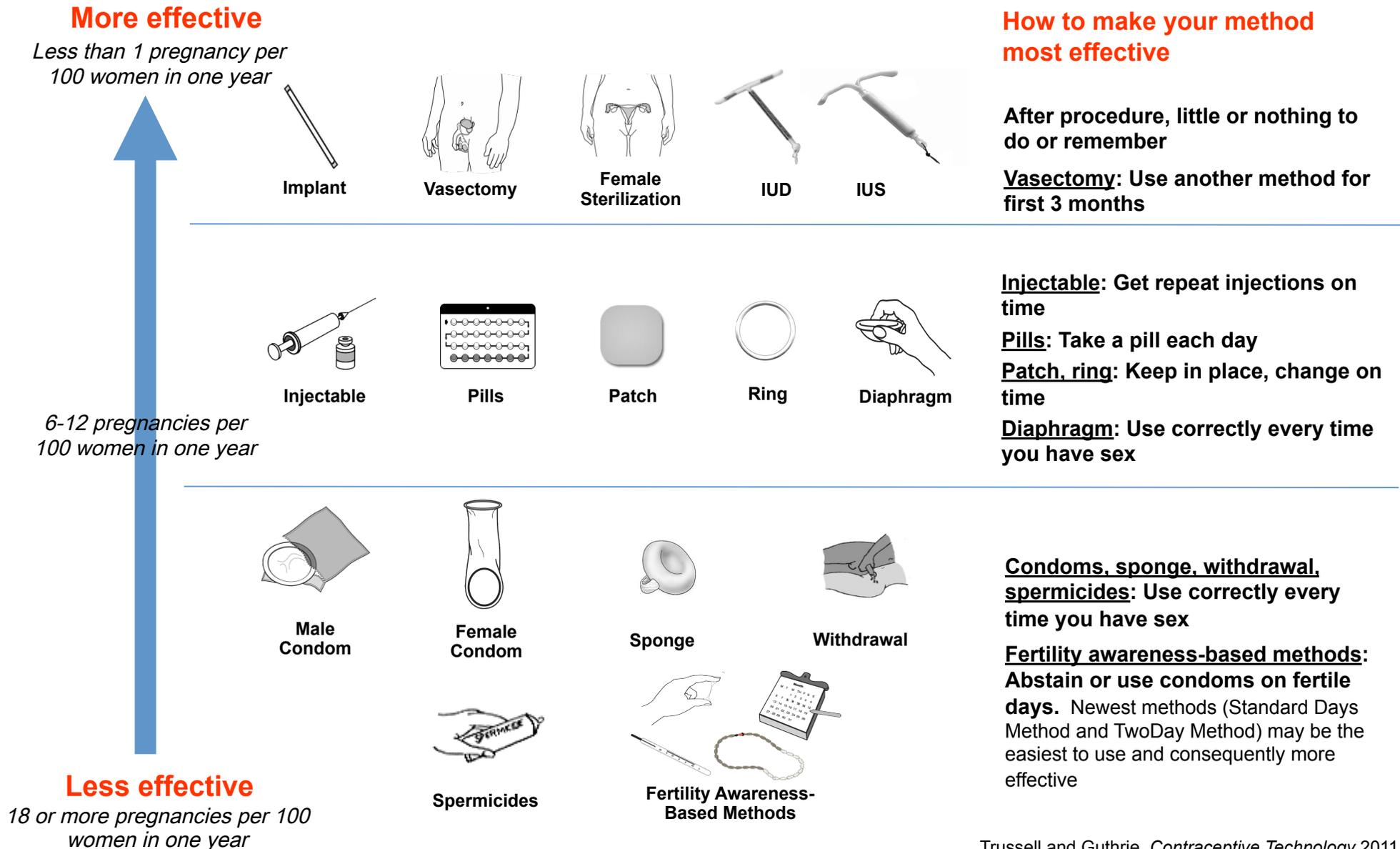
# What is Typical Use?

- By definition, a woman is a user whenever she considers herself to be using a method
- Hence, typical use of a barrier method does not imply that it is actually used at every act of intercourse
- Typical use includes both inconsistent use and incorrect use

# Determinants of OVERALL Contraceptive Failure During Typical Use

- Method mix
- Adherence

# Comparing typical effectiveness of contraceptive methods



# First-Year Typical Use Failure Rates

Method	France	US	Australia
Pill	2	9	2
Condom	3	18	8
Withdrawal	10	22	14
Fertility awareness	8	24	18

Moreau. *Hum Reprod* 2007

Trussell. *Contraceptive Technology* 2011

Bracher. *Fam Plann Perspect* 1992

# Why the Difference?

- Adherence
- Adherence
- Adherence
- Adherence

# The Creeping Pearl in the US

Year approved	Regimen	Pearl Index
1982	EE30/LNg150	0.51
1989	EE30/NGM250	0.96
2003	EE30/LNg150	1.98
2007	EE20/LNg90	2.38
2008	EE20//LNg100	2.74
2013	EE20,25,30/LNg150	3.19

# Why the Creeping Pearl?

- More frequent pregnancy testing with more accurate tests
- Less selected patient populations containing more and more women less likely to be adherent (now required by the FDA)

# The Agile Patch

- Women randomly assigned to either a new low-dose EE–LNg patch or an approved OC containing 20- $\mu$ g EE and 100- $\mu$ g LNg
- Women in the OC arm used OCs for six cycles and then were switched to the patch

# Study Population

- Only 17% switched from another method of hormonal contraception
- Only 57% were White non-Hispanic
- Significant nonadherence was demonstrated by laboratory results

# Pearl Indices

- Patch 4.96
- Pill 4.02
- Difference neither clinically meaningful nor statistically significant

# Implications Are Stark

- In order to insure themselves against results like this, companies will need to conduct adequately powered equivalence studies with an already approved product as a comparator
- Regulatory agencies must recognize that if they insist on more diverse study populations, the rates of contraceptive failure in methods requiring adherence will be much higher than those previously observed

# Further Analysis: Patch vs. OCs

- **Problem statement:** In a Bayer patch study the PI was higher than in 3 previous recent US OC studies
- **Aim:** Explore whether the differences in PI observed could be explained by different subject characteristics as seen within the Patch study
- **Method:** Find comparable (*i.e.* matched) subjects with similar baseline characteristics in Patch study and in OC studies by using the propensity score (for being in the Patch study). Compare PI for matched and unmatched subjects

# Results Propensity Score Model

- Variables included in final propensity score model were
  - previous contraceptive method=pill or patch
  - Hispanic, and
  - ever pregnant
- The main reason for retaining this model over the other models investigated was that it separated the matched from the unmatched patch users well and that included only few explanatory variables
- Of the 1,453 subjects in the Patch study, 1,386 could be closely (caliper size: 0.01) matched to one of the 2,253 subjects from an OC-Study. Thus 67 Patch and 867 OC subjects could not be closely matched

# Results: Pearl Index

	Patch not matched	Patch matched	OC matched	OC not matched
Relevant exposure during complete study (women-years)	39.3	943.3	1009.4	664.6
Pregnancies during treatment (+ 7 days), complete study	4	28	25	6
PI	10.17	2.97	2.48	0.90
95% confidence interval	2.77-26.05	1.97-4.29	1.60-3.66	0.33-1.96

- Matched subjects had a similar PI (~3)
- Unmatched Patch subjects had a higher PI (~10) than unmatched OC subjects (~1)

# Clinical Trials: Europe vs. US

- In OC trials with arms in Europe and the US, lower rates of OC failure have been found in Europe
- The most probable reason for this is that OCs are prone to be used more correctly and consistently in Europe
- Higher failure rates in US trials likely reflect differences in health care systems

# Clinical Trials: Europe vs. US

- Higher failure rates in US trials likely reflect differences in health care systems
- Uninsured women in the US may be inclined to join a clinical trial in order to get the health care provided from the trial and receive compensation for their participation

# Summary

- Contraceptive failure rates powerfully illustrate the need for abortion
- The typical woman in the US will experience >1.3 contraceptive failures from age 15 to age 45



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