High Hopes versus Harsh Realities
The Population Impact of ECPs

James Trussell, PhD
Office of Population Research
Princeton University
Disclosures

• Advisory Boards: Merck and Teva
• Consultant: Bayer
Learning Objectives

• After seeing this presentation, participants will be able to:
  – State that easy access to emergency contraceptive pills has not reduced unintended pregnancies
  – Describe the evidence for this conclusion
  – Describe reasons why no reduction has been found
The Hope

Widespread use of ECPs could prevent HALF of all unintended pregnancies and abortions in the US each year

—Trussell, Stewart et al. 1992

Trussell et al. Fam Plann Perspect 1992
The Reality – 20 Years Later

Fifteen studies have examined the impact of increased access to ECPs on pregnancy and abortion rates.

Only one has shown any benefit

Raymond et al. Obstet Gynecol 2007;
Polis et al. Cochrane Rev 2010;
Shaaban et al. Contraception 2013
The great tragedy of science—the slaying of a beautiful hypothesis by an ugly fact

TH Huxley, *Collected Essays*, 1894
Agenda Today

• Review these studies
• Discuss possible explanations for disappointing findings
• Consider the role of ECPs in the contraceptive method mix
The Fifteen Studies

- Conducted 1998-2011
- 14 randomized trials, 1 cohort study
  - Total of 12,804 women enrolled
- 1 demonstration project
  - >17,831 women given ECPs
- Followed women up to one year
- Compared increased access to standard access
Common Study Design

• Women assigned to one of two groups:
  – Advance Provision (intervention): given a supply of ECPs for later use should the need arise
  – Standard Provision (control): obtain ECPs from a clinic in the regular way
## Selected Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Regimen</th>
<th>% Pregnant</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glasier</td>
<td>1083</td>
<td>Yuzpe</td>
<td>5%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Lo</td>
<td>1030</td>
<td>LNG</td>
<td>1%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Hu</td>
<td>2000</td>
<td>mife</td>
<td>4%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Raine</td>
<td>1228</td>
<td>LNG</td>
<td>8%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Raymond</td>
<td>1490</td>
<td>LNG</td>
<td>9%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Shaaban</td>
<td>1158</td>
<td>LNG</td>
<td>0.8%</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>
The Single Exception

- Women using LAM in Egypt
- Lower pregnancy rate appears to be due to better uptake of regular contraception
- Authors argue that women used EC to buy time to get to a family planning clinic

Shaaban et al. Contraception 2013
Explanations for Negative Results

1. Flaws in studies
Problems with the Studies

- Small sample size (50-2868 women)
- Huge loss to follow-up (1-62%)
- Weak intervention
- Good access in comparison group
- Low baseline risk of pregnancy – little room for improvement with EC
- Not randomized
None of the 14 studies had all of these problems —

Indeed, some were very good!

Consistency of findings hard to ignore
Explanations

1. Flaws in studies
2. Increased risk taking
ECPs and Risk Taking

- No evidence of increase in unprotected sex or decrease in use of regular contraception with enhanced ECP access
- Some suggest “improved” behavior (but most data self-reported)
- 4 studies showed no effect on STIs

Polis et al. Cochrane Rev 2010
However...

• Reanalysis of one of the randomized trials suggests that easier access to ECPs
  – may have increased the frequency of coital acts with the potential to lead to pregnancy
  – led to greater substitution of ECPs for condoms or another contraceptive
  – increased repeat use greatest among those with lowest baseline risk of pregnancy

Raymond and Weaver. *Contraception* 2008
Weaver *et al*. *Obstet Gynecol* 2009
Baecher *et al*. *Human Reprod* 2009
Explanations

1. Flaws in studies
2. Increased risk taking
3. Low ECP efficacy
Current Estimates

• ECP efficacy conveys the reduction in pregnancy risk after a single coital act

• Plan B package (LNg regimen): 7/8=88%

• Published literature:
  – LNg regimen: 52% - 100%
  – UPA regimen: 62% - 85%
Methodology

In a group of ECP users, compare:

• observed number of pregnancies
• expected number of pregnancies (number that would have occurred without ECPs)

Calculate the reduction due to the ECPs
Example

WHO 1998 trial of LNG vs. Yuzpe regimen

• 1001 women using LNG regimen
• Pregnancies observed: 11
• Pregnancies expected without EC: 75.3
• Pregnancies prevented: 75.3 - 11 = 64.3
• Efficacy: $\frac{64.3}{75.3} = 85\%$
Expected Pregnancies

- Determine the day of the menstrual cycle when the coital act occurred
- Estimate that day relative to day of ovulation
- Use published probabilities of pregnancy by cycle day to estimate expected pregnancies
Pregnancy Risk by Cycle Day

- Schwartz 1979
- Schwartz 1980
- Bremme 1991
- Weinberg 1998
- Wilcox 1998
- Colombo 2000
Do Any of the Charts Apply?

Women in the charts wanted to be pregnant

ECP users wanted **NOT** to be pregnant.

Possible differences in:

- Fecundity?
- Amount and type (broken condom, withdrawal?) of unprotected sex?
- Accuracy of data?
Do Any of the Charts Apply?

• One study found that in 25 of 69 women seeking EC, no sperm were present in the vagina
• When sperm were present, the number was much lower than in women trying to conceive

Do Any of the Charts Apply?

- Another study found that 99 women were between days -5 and +1 when the day of ovulation was estimated as usual cycle length minus 13.
- Hormonal data indicated that only 51 of these 99 (56%) were in fact between days -5 and +1.

Espinós et al. Contraception 1999
Efficacy: Conclusion

Numbers of expected pregnancies reported by studies are probably too high.

Most published efficacy figures are probably overestimates.
Don’t Give Up…

ECPs do work!

• Physiology studies show effects incompatible with pregnancy
• LNG regimen proven to be more effective than Yuzpe → it must be more effective than nothing
• UPA more effective than LNG

Raymond et al. Contraception 2004
Efficacy of LNG Regimen

Efficacy of Yuzpe

Efficacy of LNG
Efficacy of LNG Regimen

![Graph showing the efficacy of LNG and Yuzpe regimens]

- Efficacy of LNG
- Efficacy of Yuzpe

The graph illustrates the correlation between the efficacy of LNG and the efficacy of Yuzpe. As the efficacy of Yuzpe increases, the efficacy of LNG also increases.
Enhancing the Efficacy of LNg

- Pilot study in 41 women
- Adding meloxicam (Mobic) 15 mg significantly increased the proportion of cycles with no follicular rupture or ovulatory dysfunction (88% versus 66%, $p=0.012$)
- Adding a Cox-2 inhibitor can disturb the ovulatory process after onset of the LH surge

Massai et al. Human Reprod 2007
Ulipristal Acetate

• Meta-analysis of two randomized studies found UPA superior to LNG
  – 0-24 h: OR=0.35 (95% CI 0.11-0.93)
  – 0-72 h: OR=0.58 (95% CI 0.33-0.99)
  – 0-120 h: OR=0.55 (95% CI 0.32-0.93)

• But only after other factors were controlled (study, BMI, time from UPI to ovulation, expected probability of conception, further UPI).

Why is UPA More Effective?

• Levonorgestrel is no more effective than a placebo in preventing ovulation when the leading follicle reaches 15-17 mm

• By the time the leading follicle reaches 18-22 mm, ulipristal acetate prevents follicular rupture within 5 days of administration in 59% of cycles (versus 0% for the placebo)

Croxatto et al. Contraception 2004;70:442-50
Brache et al. Hum Reprod, 2010
Ulipristal Acetate

- Follicular rupture failed to occur within 5 days after treatment with UPA
  - in all women treated before onset of the LH surge
  - in 79% of women treated after the onset of the LH surge but before the LH peak
  - and in 8% of women treated after the LH peak

Brache et al. Hum Reprod 2010
Effectiveness and BMI

• LNG showed a rapid decrease of efficacy with increasing BMI, reaching the point where it appeared no different from pregnancy rates expected among women not using EC at a BMI of 26 kg/m$^2$ compared with 35 kg/m$^2$ for UPA.
New EMA Label for Norlevo 1.5mg
November 2013

• Norlevo 1.5mg identical to Plan B One-Step, Next Choice One Dose and My Way
• “In clinical trials, contraceptive efficacy was reduced in women weighing 75 kg (165 lb) or more and levonorgestrel was not effective in women who weighed more than 80 kg (176 lb)”

http://www.medicines.ie/medicine/11933/SPC/Norlevo+1.5mg+tablet/
EMA Removed from Norlevo 1.5mg Label in July 2014

- European Medicines Agency, after reviewing additional data from three WHO trials that did not find reduced efficacy with increasing weight or BMI, removed that statement from the Norlevo label in July 2014

Explanations

1. Flaws in studies
2. Increased risk taking
3. Low ECP efficacy
4. Insufficient use
Effects of Increased Access

- In nearly all studies increased access resulted in substantially increased use.

But...

- Repeated use was uncommon.
- Many unprotected acts remained uncovered by ECPs.
Effect on Pregnancy

• Among the randomized trials, only three powered to detect a reduction in pregnancy rates

• In the community intervention study in Lothian, Scotland, about 1 in 5 women aged 16-29 got ECPs in advance to take home
Why No Reduction in Trials?

• In San Francisco, 45% of the women in the advance provision (AP) group who had UPI did not use ECPs.

• In Nevada/NC, 33% of women in the AP group had UPI at least once without using ECPs.

Why No Reduction in Abortion Rates in Lothian?

- Women most at risk probably did not get ECPs

Glasier et al. Contraception 2004
Reasons for Non-Use

- Failure to perceive pregnancy risk
- Forgetting
- Lack of motivation to use EC
- Inconvenience

Limits to ECP use in the real world

- Expensive
- Side effects
Fourteen Studies, No Benefit

1. Flaws in studies - but consistency compelling

2. Increased risk taking - evidence mostly against

3. Low ECP efficacy - precise efficacy unknown

4. Insufficient use - definitely a problem
What To Do Now?

- “be most slow to believe what we most wish should be true.” Letter from Samuel Pepys to Balthazar St Michael, 9 October 1679
- Do not promise public health impact: do not oversell by implying ECPs will reduce unintended pregnancy or abortion rates or be cost effective
- Stress efficacy for individuals: everyone deserves a second chance to prevent an unintended pregnancy
The Best Emergency Contraceptive
not-2-late.com

WELCOME. You’ve come to the right place if you want to prevent pregnancy after sex.

Get Emergency Contraception NOW

INFO about Emergency Contraception

Q&A about Emergency Contraception

Info for TEENS

The Emergency Contraception Website

Your website for the "Morning After"

Find a Morning After Pill Provider Near You

ZIP CODE  Submit

This website is operated by the Office of Population Research at Princeton University and by the Association of Reproductive Health Professionals, and has no connection with any pharmaceutical company or for-profit organization.