



# Potential abortifacient effects of the Birth Control Pill and the Morning After Pill: Science and Ethics

Bioethics Summer Course 2008

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## Outline

- Ethical Analysis
- Contraception: mechanisms of action
  - ◆ Birth Control Pill (BCP)
  - ◆ Morning After Pill (MAP)
  - ◆ IUD, RU 486 (Romano)
- Potential Abortifacient effects
  - ◆ BCP
  - ◆ MAP
- Conclusions



## Ethical Analysis



- Contraception is an intrinsic evil (HV)
  - Definition
    - Couples wants to have sex
    - The couples do not want to have children from this union
    - The couples put in some means to prevent ii. from happening
  - Protestant vs Catholic stance
- Abortion is an intrinsic evil
- Use of “contraceptives” in case of rape
  - Not contraception by definition
- If abortifacient, is it an added sin?

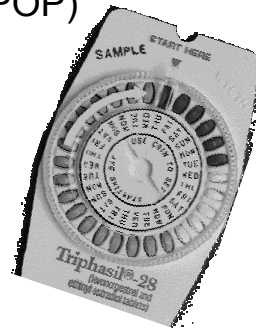
## Ethical Analysis



- Does % make a difference?
  - Always wrong: Russian roulette
  - Acceptable negligible risks, like vaccines.
  - Accumulated effect: 60 million BCP users worldwide, even 0.1% = 60,000 abortions
- Double Effect
  - To treat gynecological diseases (irregularity, dysmenorrhea, endometriosis?)
  - For family planning?
- Implications for prescribing physicians, dispensing pharmacists
  - Objection of conscience
- Informed consent

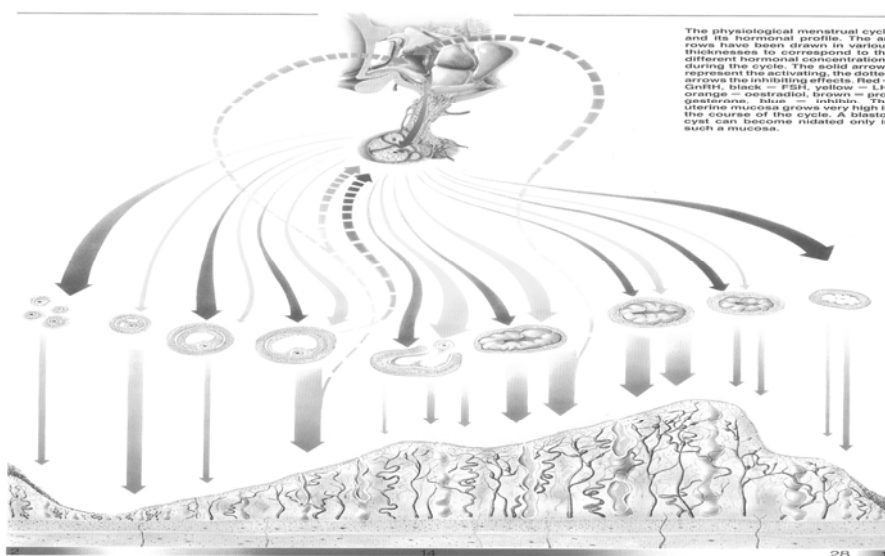
## Different types of “Contraceptives”

- Combined Oral Contraceptive (COC)
  - High Dose 50 mcg Estrogen (before 1989 = 150mcg)
  - Low Dose <25 mcg Estrogen (before 1989 < 50mcg)
- Progestin Only Pill or Mini-pills (POP)
- Depo-Provera (DP)
- Norplant
- Morning After Pill, Plan B (MAP)
- Intrauterine Device (IUD)
- RU 486



## BCP mechanism of action

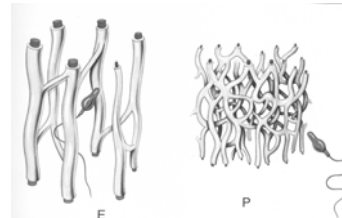
### Representation of the physiological cycle



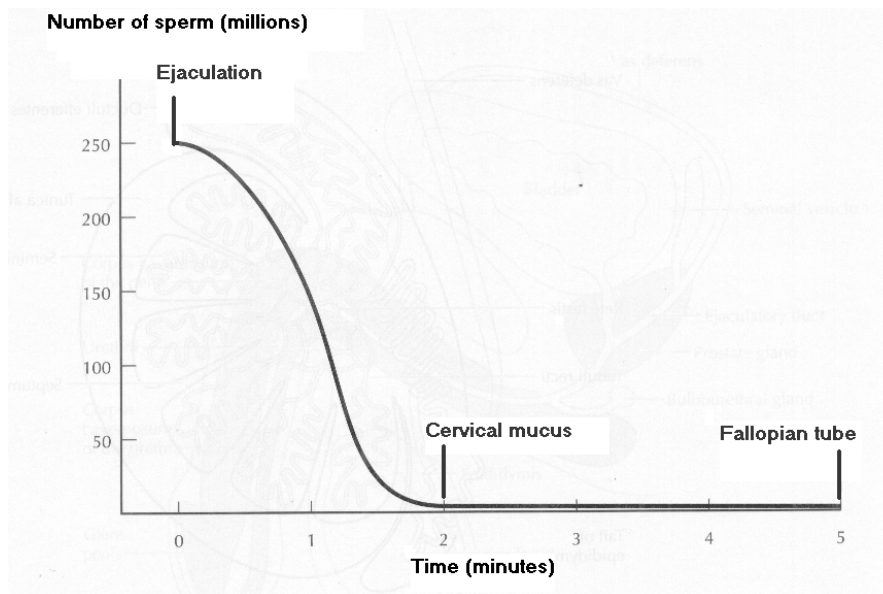
## BCP mechanism of action

### ● Physician Desk Reference

- Prevent ovulation
- Alter peristalsis of fallopian tube
- Alter cervical mucus, making it hostile to sperm penetration
- Alter endometrium, hostile to implantation and/or sustained pregnancy

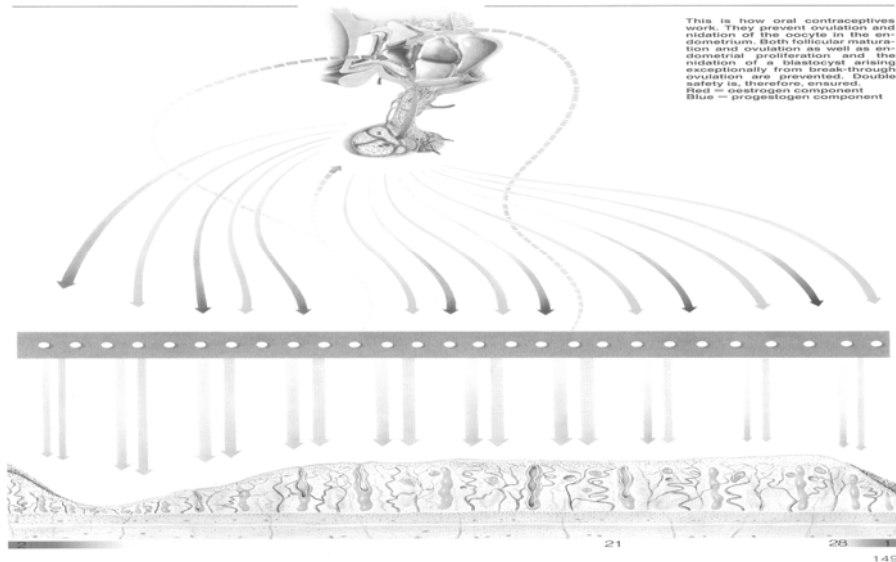


## BCP mechanism of action

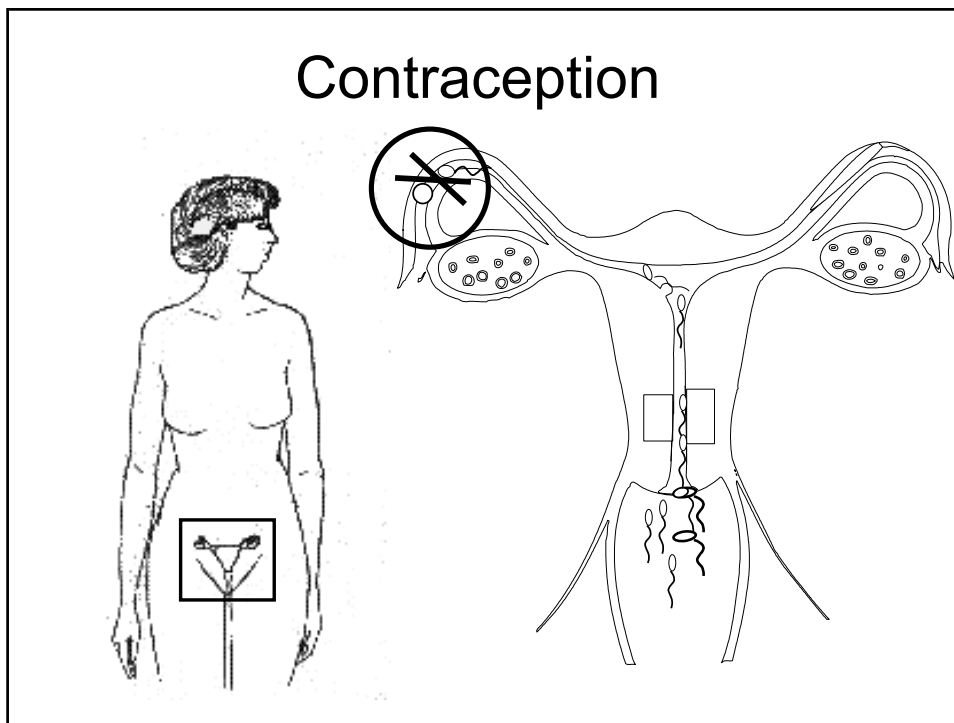


# BCP mechanism of action

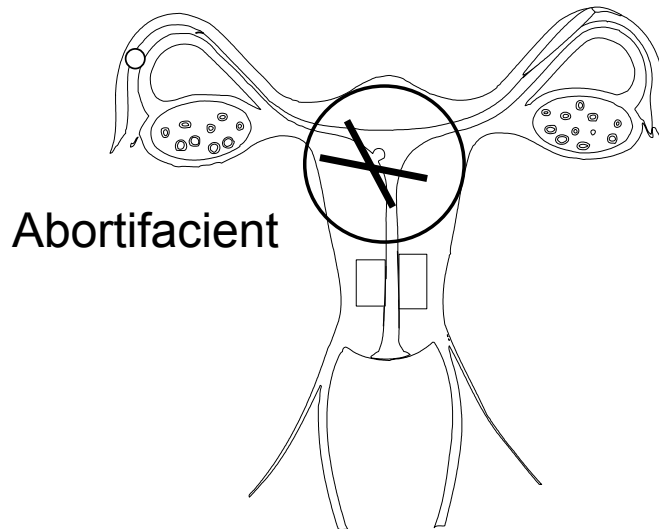
## Cycle during oral contraception



## Contraception



## Interception or contragestation



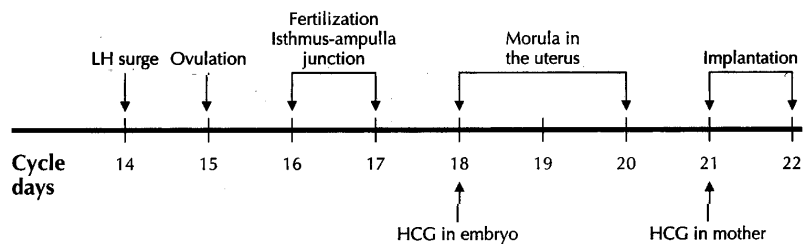
## Abortifacient effect

- Definition of conception: not at implantation! (pre-embryo)
- Breakthrough ovulation while on the pill.
- Sperm pass through mucus barriers
- Fertilization took place
- But: Implantation rates sub-normal
  - Ectopic pregnancies increased
  - Cannot implant
  - Cannot sustain implantation

## Abortifacient effect

### ● Direct Evidence

- No test to detect presence of fertilized egg (embryo) before implantation
- Candidates: Early Pregnancy Factor, sensitive  $\beta$ -HCG, etc.



## Abortifacient effect

### ● Indirect evidence

- FDA, Physician Desk Reference Manufacturers
- Breakthrough ovulation
- Hostile Endometrium
- Implantation factors: Integrins
- Increased proportion of ectopic / tubal pregnancies
- Statistical extrapolation



## Abortifacient effect: Physician Desk Reference

- The Food and Drug Administration–approved product information for OCs in the Physicians' Desk Reference states, “Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus, which increase the difficulty of sperm entry into the uterus, and changes in the endometrium, which reduce the likelihood of implantation.”
- Objections: legal protection, cover all the bases.

## Breakthrough ovulation rates

- Perfect vs typical vs sloppy use
- Missed days
- Poor digestion, vomiting, diarrhea, drug interactions
- Walter L. Larimore, Joseph B. Stanford, “Postfertilization Effects of Oral Contraceptives and Their Relationship to Informed Consent”, *Arch Fam Med.* 2000;9:126-133.

	Breakthrough ovulation
COC	1.7-6%
POP	33-56%

## Abortifacient effect: Hostile Endometrium

- Women on BCP has thinner endometrium,
  - Magnetic Resonance imaging: 1.1mm, 58% of normal women (5-13mm)
  - Atrophied glands, histological changes, vascular changes.
  - Very scanty menstrual flow
- Thickness and implantation rates
  - From in vitro fertilization studies
  - "Endometrial thickness is related to functional receptivity of the endometrium." (Larimore - Stanford. 2000)
  - Average thickness necessary for implantation and maintenance of pregnancy is 5-13 mm
- Women off pill recommended to wait a few cycles before trying to get pregnant

## Abortifacient effect: Hostile Endometrium

- **Objections:** Crocket, Susan; DeCook, Joseph; Harrison, Donna; Hersh, Camilla. "Hormone Contraceptives: Controversies and Clarifications." Fennville, MI: ProLife Obstetricians, April 1999; Goodnough, Joel. "Redux: Is the Oral Contraceptive Pill an Abortifacient?" Ethics & Medics (Spring 2001) 17 (1):37 -51.
  - Endometrium is always thin, only increases in thickness after ovulation, even in the case of breakthrough ovulation of women on pill, when the corpus luteum produces progesterone.
    - But: No studies to demonstrate this sudden rebound.
    - Menstrual flow in women on BCP takes a few cycles to return to normal

## Abortifacient effect: Hostile Endometrium objections

- Embryos can implant in very hostile environment: tubes, ovaries, intestines.
  - But the question is on decreased probability of implantation...
- Women asked to wait because it is easier to calculate the estimated date of confinement (delivery), as one cannot know accurately last menstrual period once off the pill.
- Only one study showed this effect directly.  
 Chowdhury V, Joshi UM, Gopalkrishna K, Betrabet S, Saxena BN.  
 'Escape' ovulation in women due to the missing of low dose combination oral contraceptive pills. *Contraception*. 1980;22:241-247.

## Abortifacient effect: Implantation factors

- Many signaling factors are present that the embryo communicates to the endometrium, to prepare for a successful implantation.  
 (Space shuttle analogy) Wilks, John. "The Impact of the Pill on Implantation Factors-New Research Findings." *Ethics & Medicine* (2000) 16(1):15-22.
  - Interleukins, especially IL-1 $\beta$
  - Platelet-Activating Factor (PAF)
  - Insulin-Like Growth Factor (IGF)
  - Integrins (Somkuti, S.C., Fritz, M.A., et al., "The Effect of Oral Contraceptive Pills on Markers of Endometrial Receptivity," *Fert Steril*. 65:3 (1996), 484-8.)
- These factors are diminished in BCP users.

## Abortifacient effect: Ectopic pregnancies

- If the BCP has post-fertilization (abortifacient) effects on the embryo, then, the ratio of ectopic pregnancies vs. intrauterine pregnancies would increase compared to those not on BCP.
- This is demonstrated definitively in POP, partly also because of its effect on tubal peristalsis
- However in COC's this is also demonstrated.
- Objections: controls are pregnant (in the studies above) vs. non-pregnant (no difference shown).

## Abortifacient effect: Statistical extrapolation

	Breakthrough ovulation	Pregnancy perfect use	Pregnancy typical use	Pregnancy rate adjusted for elective abortions
COC	1.7-6%	0.1-3/100	3/100	4% good compliers 8% poor compliers 29% some users
POP	33-56%	0.5-1/100	3-7/100	

## Abortifacient effect: Statistical extrapolation

- Maria Luis Di Pietro and Roberto Minacori, "Sull'abortività della pillola estrogenogestinica e di altri 'contraccettivi'", *Medicina e Morale* 5 (1996), 863-900.
  - In mono, bi and triphasic combined estrogen-progesterone pills, there is a 6.48 per 200 cycles of breakthrough ovulation.
  - 50/200 sperm penetration,
  - 20% alteration of endometrial wall hostile to implantation.
  - Normal fertilization 25% of the times
  - Thus, chance of fertilization while on pill = 1.55 per 200 cycles
  - Chance of pregnancy on pill 0.07-0.5% (mean 0.28%)
  - All this adds up to a Pearl index of 1.5 abortions per 200 cycle use, or 1 abortions in 10 years of pill use.

## Abortifacient effect: Statistical extrapolation

- In POP or mini-pill, there is a 20-40% (higher in Stanford studies) breakthrough ovulation, but has greater effect on sperm penetration and tubal motility, and this translates to a Pearl Index of 1.5% abortions per cycle, or 3.2 abortions in 15 years of use or 1 abortion every 5 years.



## Abortifacient effect: Statistical extrapolation

- “The results of the study show that the current research in the field of birth control is mainly directed towards products with an abortifacient action and that there is an attempt, also by the international literature, to make the public opinion accept them, by disguising or mystifying the ‘abortion’ aspect. In a situation like this semantic and scientific reality is more necessary than ever, otherwise people can be subject to manipulation while they think they are free.” (op. cit. 900)

## Ethical Analysis

- Contraception is an intrinsic evil (HV)
- If abortifacient, is it an added sin?
- COC 0.75 - POP 1.5% abortifacient rate (PI): One abortion every 10 or 5 years of use.
  - Always wrong
  - Acceptable negligible risks, like vaccines?
  - Accumulated effect: 60 million users worldwide = 9 million chemical abortions per year. (American Life League 14 million in US)

## Ethical Analysis

- Intention to contracept vs. to abort.
- Double Effect
  - To treat gynecological diseases (irregularity, endometriosis?)
  - Alternatives: NFP, NaProTechnology  
[www.fertilitycare.org](http://www.fertilitycare.org)
- Implications for prescribing physicians, dispensing pharmacists
  - Objection of conscience

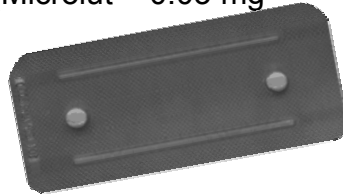
## Ethical Analysis

- Informed consent for patients (Larimore - Stanford 2000)
  - Patients's religious and values system should be respected.
  - Some may consider this unacceptable, even if incidence of abortion is low.
  - Possible psychological impact if she finds out later.
  - Rare complications in medical procedures are reported. Eg. Death in anesthesia < 1/25,000.
  - Truly informed consent, autonomy...



## Morning After Pill

- Emergency Contraception (EC), Morning After Pill (MAP), Post-coital pills
  - <72 h after unprotected intercourse (<120h?)
  - Yuzpe (0.1 mg Estradiol + 0.5 mg LNG)
  - Levonorgestel (LNG) (P only)
    - Plan B, Norlevo
    - 0.75 mg x 2, or 1.5 mg x 1 (Microlut = 0.03 mg LNG)



## Indications for use (according to manufacturer)

- Ruptured condom
- Forgot BCP
- IUD expelled
- Misplaced diaphragm
- Unsuccessful coitus interruptus
- Sexual relation during fertile period in natural methods
- Rape



## Principles

- Abortion is intrinsically evil
- Contraception is intrinsically evil
- Rape is evil
- In the case of rape, if conception has occurred, it is wrong to cause an abortion.
- In the case of rape, if conception has NOT occurred, it is acceptable to prevent conception from taking place.

## Use as BCP

- Prevent Unwanted pregnancies and abortions?
  - 50% reduction in abortion rates. J. Trussell *et al.*, "Emergency Contraception: A Simple Proposal to Reduce Unintended Pregnancies," *Family Planning Perspectives* 24 (Nov/Dec 1992): 6.
  - 23 published studies from 10 countries published between 1998 and 2006 disprove this claim. Easier access to EC fails to achieve *any* statistically significant reduction in rates of unintended pregnancy and abortion. E. Raymond *et al.*, "Population Effect of Increased Access to Emergency Contraceptive Pills," *Obstetrics & Gynecology* 109 (2007): 181-8.

## Rape Victims

- National Victim Center estimates more than 1 million rapes per year in US
- FBI estimates 1 in 3 women will be raped in their lifetime.
- 83% of those raped are under the age of 25,
- 60% of rapes perpetrated by a male friend, relative, or neighbor.
- 13% of college women indicate that they have been forced to have sex in a dating situation. Rapes are frequently facilitated by drug use, chiefly alcohol.
- There is a 4% or less chance of pregnancy from a rape.

## Rape Victims

- “Compassionate and understanding care should be given to a person who is the victim of sexual assault. Health care providers should cooperate with law enforcement officials and offer the person psychological and spiritual support as well as accurate medical information. A female who has been raped should be able to defend herself against a potential conception from the sexual assault. If, after appropriate testing, there is no evidence that conception has occurred already, she may be treated with medications that would prevent ovulation, sperm capacitation, or fertilization. It is not permissible, however, to initiate or to recommend treatments that have as their purpose or direct effect the removal, destruction, or interference with the implantation of a fertilized ovum.”

USCCB “Ethical and Religious Directives for Catholic Health Care Services,” 4th edition (NCCB / USCC, June 15, 2001), no. 36,

## Possible mechanisms of action

### ● Affects ovulation

- “follicle maturation;
- the ovulatory process;

### ● Affects fertilization

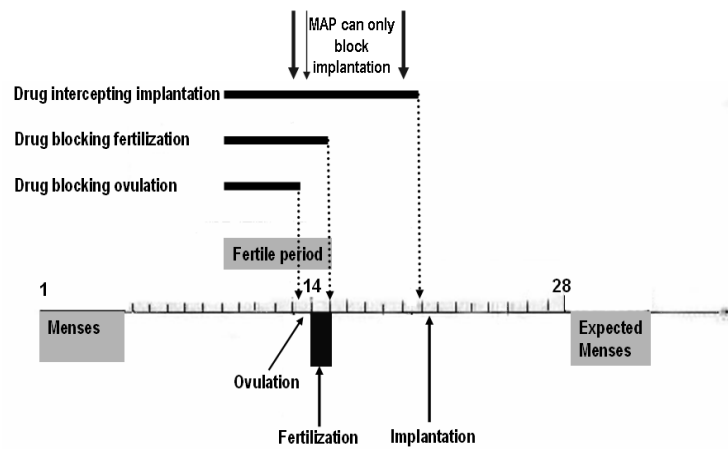
- sperm migration into and through the fallopian tube, including adhesion of spermatozoa to the epithelium needed to acquire and maintain their fertilizing capacity;
- fertilization;
- zygote development in the fallopian tube;
- zygote transport through the fallopian tube;

## Possible mechanisms of action

### ● Affects Implantation of embryo

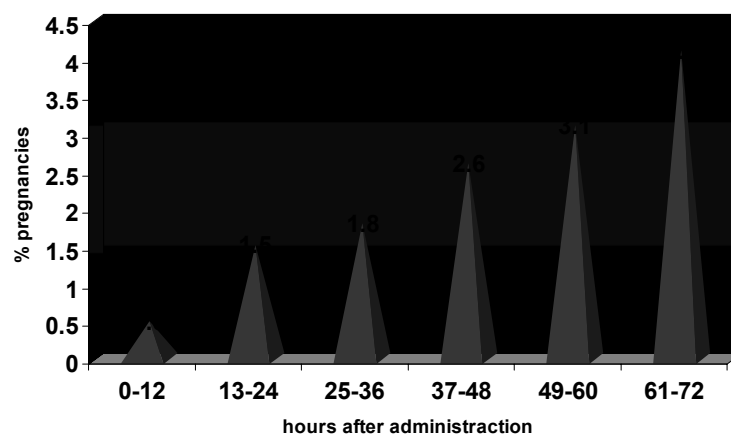
- preimplantation development within the uterus;
- uterine retentiveness of the free laying morula or blastocyst;
- endometrial receptivity;
- blastocyst signaling, adhesion and invasiveness;
- corpus luteum sufficiency and responsiveness to hCG.”

Horacio B. Croxatto, Luigi Devoto, Marta Durand, “Mechanism of action of hormonal preparations used for emergency contraception: a review of the literature,” *Contraception* 63, no. 3 (March 2001): 111-121.

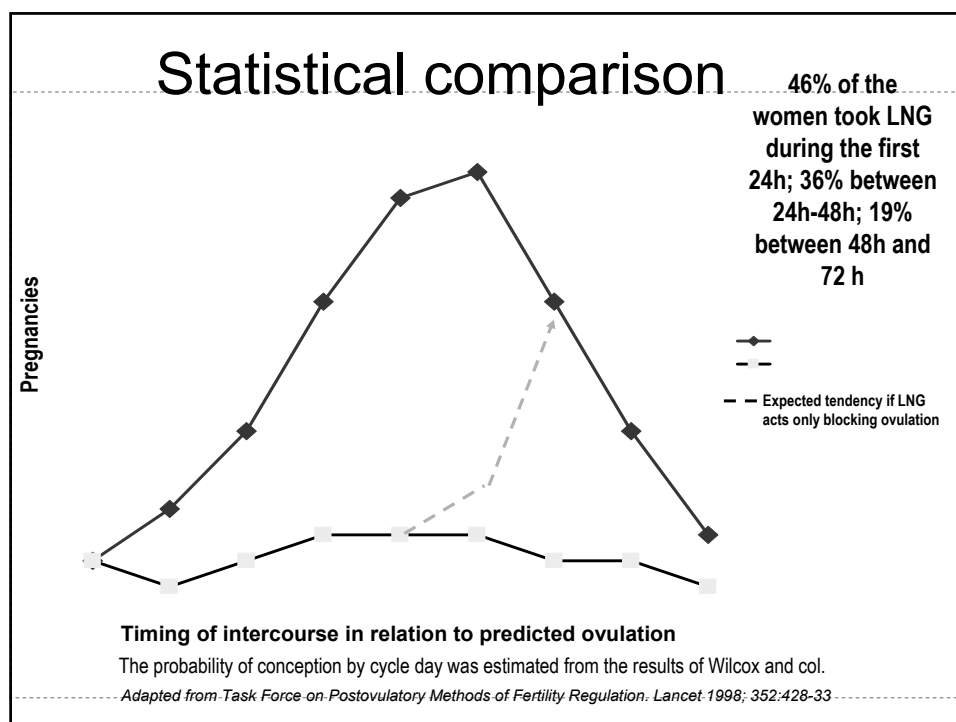


**The mechanism of action of emergency contraceptive drugs depends on the period of the menstrual cycle in which they are taken.**  
 Adapted from H von Hertzen and PA van Look Fam Plann Perspect. 1996 Mar-Apr; 28(2): 52-7, 88.


## Pregnancy rates



Van Look P.F.A., 8<sup>th</sup> World Congress of Gynecological Endocrinology, 2000



## Efficacy 60-85%



Ho PC, Kwan MS. <i>Hum Reproduction</i> 1993;8:389-92.	Reported efficacy	60%*
WHO Task Force on Postovulatory Methods of Fertility Regulation. <i>Lancet</i> 1998;352:428-33	Reported efficacy	85%
Von Hertzen H, et al 2002 <i>Lancet</i> 360, 1803-1810.	Reported efficacy:	80%
Hamoda H, et al <i>Obstet Gynecol</i> 2004;104:1307-13.	Reported efficacy	64%
Wai Ngai S, et al <i>Hum Reprod</i> 2005 Jan;20(1):307-3	Reported efficacy	72-75%
Expected pregnancy calculated with other historical control		

## Efficacy

- “[W]e can be 95% confident that it reduces pregnancy risk by more than 23%. But just how much more remains poorly defined; the published efficacy figures ... – on average, approximately 80% – may overstate actual efficacy, possibly quite substantially. Clearly, if the method is weakly efficacious, it is unlikely to produce a major reduction in unintended pregnancy no matter how often women use it.”

**E. Raymond *et al.*, *Obstetrics & Gynecology*, op cit., at 187.**

## Potential abortifacient effects

- Emergency “Contraception”?
- Post-fertilization effects
- Plan B insert
  - “Plan B® works like a birth control pill to prevent pregnancy mainly by stopping the release of an egg from the ovary. It is possible that Plan B® may also work by preventing fertilization of an egg (the uniting of sperm with the egg) or by preventing attachment (implantation) [of what?] to the uterus (womb), which usually occurs beginning 7 days after the release of the egg from the ovary.”



## Evidence of Potential abortifacient effects of LNG

- Extrapolation from BCP data
  - Ovulation after MAP
  - Effects on endometrium: thickness, histology, integrins, prostaglandins
- Preclinical studies
  - Animal studies
  - *In vitro* studies
  - Basic science studies (IL- $\beta$ , etc)
- Epistemological studies
  - Statistical comparison of efficacy with historical control
  - Clinical evidence
  - Pilot studies
  - NO DIRECT EVIDENCE TO DATE (double blind controlled trials)
    - Timing of Intercourse
    - Timing of ovulation
    - Timing of MAP

## Animal studies

- Cebus monkey (Ortiz 2004)
  - Unknown fertile window (humans days -5 to 1)
- Rats (Croxatto, 2003)
  - Ovulation occurs 12 h after coitus
  - Doses higher than clinical EC
  - Lack of statistical difference





## Pilot Studies

- Three-dimensional endometrial construct
- *In vitro* implantation rates in the presence of mifepristone or LNG with controls
- Mifepristone, but not levonorgestrel, inhibits human blastocyst attachment to an *in vitro* endometrial three-dimensional cell culture model

P.G.L. Lalitkumar, S. Lalitkumar, C.X. Meng et al. Hum 2007,Reprod. 22;11: 3031

- In vivo vs in vitro
- Mid-luteal phase endometrium samples, but luteal defects not excluded.

	N° of Embryos	N° of embryos attached to Cell culture
Control	17	10 (59%)
LNG	14	6 (43%) NS
Mifepristone	15	0 (p 0.01)

## Durand 2001

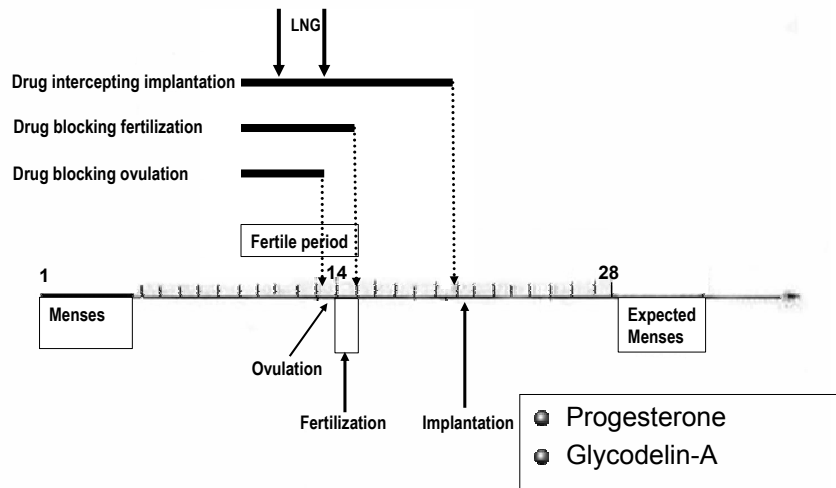
- Marta Durand, Ma. del Carmen Cravioto, Elizabeth G. Raymond, and others, "On the mechanisms of action of short-term levonorgestrel administration in emergency contraception," *Contraception* 64, no. 4 (Oct. 2001): 227-234
- No histological differences in endometrium
- But did not measure thickness
- When LNG taken in follicular phase
  - Ovulation suppressed 80%
  - Defective E2 and P4
- When LNG taken -3d before LH surge
  - Ovulation can take place (20%)
  - Defective Corpus Luteum, Decreased progesterone production
  - Defective luteal phase and endometrium development
- When LNG taken on LH surge and after
  - No effect on ovulation or endometrium



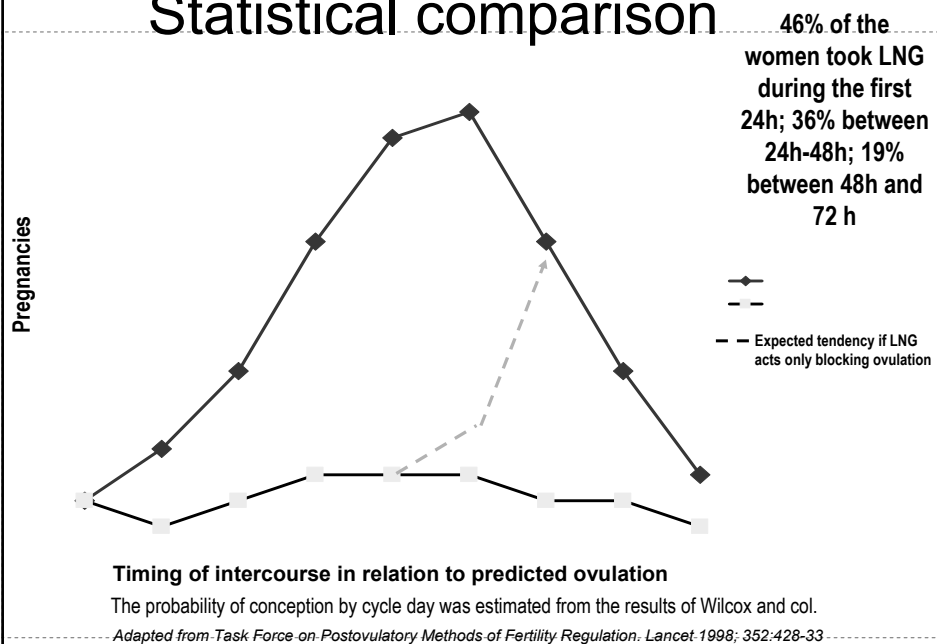
## Durand 2005

- Durand, Marta, Markku Seppälä, Ma. del Carmen Cravioto, Hannu Koistinen, Riitta Koistinen, José González-Macedo, Fernando Larrea. "Late follicular phase administration of levonorgestrel as an emergency contraceptive changes the secretory pattern of glycodeclin in serum and endometrium during the luteal phase of the menstrual cycle." *Contraception* 71, no. 6 (June 2005): 451-457.
- Decreased Glycodeclin-A secretion in endometrium
  - a potent inhibitor of sperm-zona binding
  - also believed to play a role in feto-maternal defense mechanisms
  - through its inhibitory activity on immune cells
- Can therefore adversely affect implantation

# Potential abortifacient effects



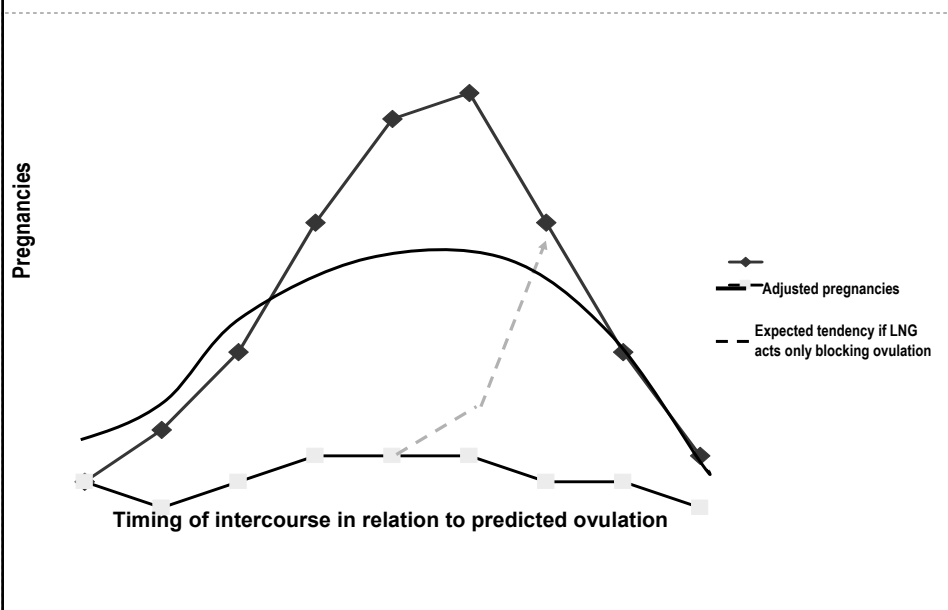
## Statistical comparison



## Statistical comparison

- Stanford, Joseph B., "Emergency contraception: Overestimated effectiveness and questionable expectations." *Clinical Pharmacology & Therapeutics* 83, no. 1 (Jan. 2008): 19-21.
- E. Raymond *et al.*, "Population Effect of Increased Access to Emergency Contraceptive Pills," *Obstetrics & Gynecology* 109 (2007): 181-8.
- Day of ovulation by LMP and self-reporting of women
- All previous randomized control trials had this error

## Statistical comparison



## Novikova 2007

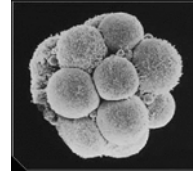
Natalia Novikova, Edith Weisberga,b, Frank Stanczyk, Horacio Croxatto et al., "Effectiveness of levonorgestrel emergency contraception given before or after ovulation — a pilot study", *Contraception* 75 (2007) 112– 118

Cycle day of intercourse	Probability of clinical pregnancy (%)	N° of women who had sexual Intercourse on each cycle day.	Expected pregnancies	Observed pregnancies
-5	4	7	0,28	0
-4	13	9	1,17	0
-3	8	12	0,96	0
-2	29	6	1,74	0
-1	27	<b>11</b>	<b>2,97</b>	<b>1</b>
<b>0</b>	8	<b>6</b>	<b>0,48</b>	<b>2</b>
<b>Total</b>		<b>51</b>	<b>7,6</b>	<b>3</b>

## Novikova 2007

- "The small number of participants in our study does not enable us to make a definitive statement on the hypothetical postfertilization effect of the ECP."
- "A larger study is needed to prove our hypothesis that the LNG ECP has a major contraceptive effect when taken prior to but not after ovulation and that it does not interfere with postfertilization events."

## MAP Summary



- Indirect evidence

- LNG taken in follicular phase prevents ovulation 80%
- LNG taken in day -3 – day 0 of ovulation may cause luteal and endometrial defects
- LNG taken post-ovulation not shown to have post-fertilization effects.

- “It is unlikely that this question can ever be unequivocally answered, and we therefore cannot conclude that ECPs never prevent pregnancy after fertilization.”

James Trussell and B. Jordan, “Mechanism of action of emergency contraceptive pills”, *Contraception* 74 (2006), 87-89.

## Further investigations

- No Clinical trials to demonstrate definitively if MAP is abortifacient.

- Unethical: Catholic—embryo loss
- Secular—cause unwanted pregnancy

- Studies that analyze timing of ovulation, MAP and coitus

- Mikolajczyk, Rafael T. and Joseph B. Stanford. “Levonorgestrel emergency contraception: a joint analysis of effectiveness and mechanism of action.” *Fertility and Sterility* 88, no. 3 (Sept. 2007): 565-571.
- Ultrasound measurements of follicles
- Measurement of mucus ferning to identify ovulation
- EPF or sensitive  $\beta$ HCG to identify fertilized ovum.

- Seek morally acceptable alternatives

- Delay ovulation with GnRH antagonist: Ganirelix, Cetrorelix



## Ethical Debate

### ● Catholic Hospitals

- Peoria protocol
  - Pregnancy test
  - Ovulation test (LH urine)
- Connecticut hospitals forced to give MAP to all rape victims without ovulation test
- CMA: should MAP be given even in rape victims? Especially if they are available over the counter?



## Ethical Analysis

### ● Use of “contraceptives” in case of rape

- Not contraception by definition
- Uncertainty about abortifacient effects.
- Rare but not impossible.
  - 4% pregnancy from rape, 89% women on BCP, 6/28 fertile, 3/28 luteal effect...
- Moral certitude
  - Burden of the proof lies in proving that it is not abortifacient
  - More stringent than use of BCP, because MAP is used post-coitally, intention to abort even if necessary
  - Ovulation test, though not perfect, gives greater guarantee that Catholic hospitals are not collaborating with abortion.





## Ethical Analysis

- Culture of Life, scandal of caving into pressure, losing the moral high ground, especially when pharmaceutical companies claimed potential abortifacient effect.
- Objection of conscience. Hospitals, staff, church, pharmacists.
- Informed consent
- Nicanor Pier Giorgio Austriaco, "Is Plan B an abortifacient? A critical look at the scientific evidence." *National Catholic Bioethics Quarterly* 8, no. 1 (Winter 2007): 703-707.
- Patrick Yeung, Erica Laethem, and Joseph Tham, "Is Plan B abortifacient?" *National Catholic Bioethics Quarterly* 8, no. 2 (Spring 2008): 217-219.

