

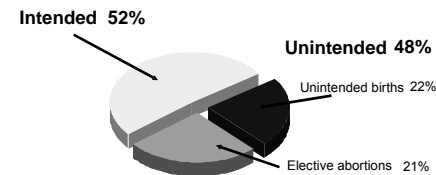
Contraceptive Update

Jan Shepherd, M.D.

Objectives

- Discuss the re-emergence of intrauterine contraception and recently expanded eligibility requirements
- Describe the new contraceptive implant and discuss potential benefits and side effects of the method
- Discuss the effect of Depo Provera on bone density and its clinical implications
- Describe new regimens and dosing schedules for oral contraceptives and discuss their potential benefits

U.S. Pregnancies: Unintended vs. Intended



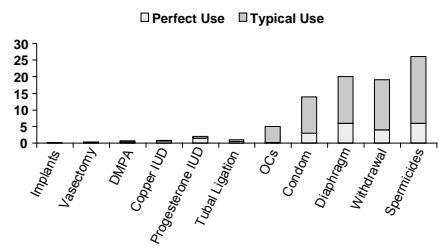
Finer LB et al. Perspectives on Sexual & Reproductive Health 2006;38:90-96.

Contraceptive Use and Unintended Pregnancy

- 40% of unintended pregnancies attributable to 10% of sexually active women who use no method
- 60% of unintended pregnancies — women using some form of birth control

Piccinino LJ, Mosher WD. Fam Plann Perspect. 1998;30:4-10, 46.

First Year Contraceptive Failure Rates: Perfect Use vs Typical Use



Adapted from Hatcher RA. Contraceptive Technology 1998

Current Trends in Contraception

- New delivery systems
- Wider array of options
- Longer-acting methods
- Emphasizing greater success
- Use of emergency contraception

Reproductive Health Plan

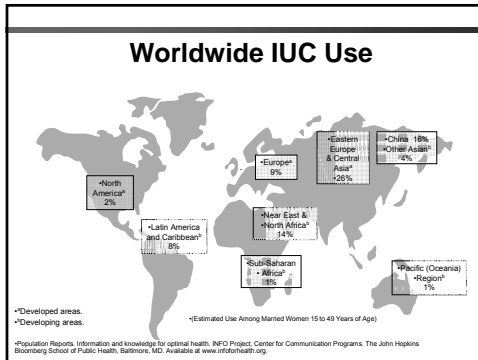
- Regular check-in with patient about plans for having children
 - If not for many years, offer long-term method
 - If soon, offer preconception counseling
- Provides broader view of contraception (not just for this month or this relationship)
- Benefits
 - Prevention of unintended pregnancy
 - Healthier pregnancies

Intrauterine Contraception (IUC)

Levonorgestrel Intrauterine System
Copper T 380A

The Return of the IUD

- Same efficacy in typical and perfect use
- Modern devices proven safe
- A new IUD (IUS) available since 2002



Myths About Intrauterine Contraception

- IUCs are abortifacients
- IUCs cause pelvic inflammatory disease (PID)
- IUCs cause infertility
- IUCs cannot be used in nulliparous women

IUC: Mechanism of Action

- Primary mechanism - Spermicidal
 - Foreign body reaction
- Paragard
 - Heavy metal toxic to sperm
- Mirena
 - Progestin thickens cervical mucous
 - Can inhibit ovulation
- Back-up mechanism
 - Can prevent implantation

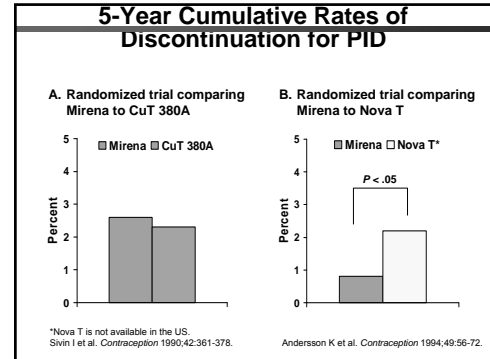
Recovery of Tubal Sperm 2-36 Hours After Midcycle Coitus

	Control (n=30)	Loop IUD (n=30)
Cervical mucus sperm	30	30
Oviductal sperm	14	0

*El-Habashi M, et al. *Contraception*. 1980;22:549.

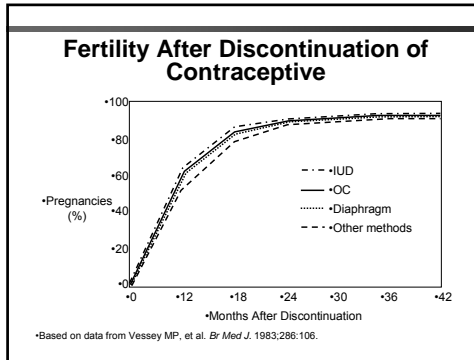
History of IUC Dalkon Shield

- Increased rate of PID, septic abortion, infertility
- Infections related to woven thread
- Off the market for over 30 years
- Modern IUCs are not your grandmother's IUD!



Modern IUCs Do Not Cause PID

- Therefore do not cause infertility
- Therefore can be used by women who have not had children



Copper T 380A (Paragard®)

- On US market since 1988
- High efficacy (failure rate .5-.8% per year)
- Approved for 10 years use
- Changes in menstrual bleeding
 - Can increase flow and cramping
 - Controlled by NSAIDS

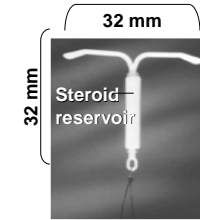
Paragard
September 2005 Labeling Changes

- Contraindications
 - “History of PID” changed to “Patients with current behavior suggesting high risk for PID are not good candidates for IUC”
 - Removed “depressed immune conditions, including HIV”

Paragard
September 2005 Labeling Changes

- Recommended patient profile
 - Removed multiparity
 - Removed mutual monogamy
 - If not mutually monogamous, use condoms to prevent STI
- New patient information materials
- Repeated warning to remove immediately if patient becomes pregnant

Characteristics of Mirena®



- High efficacy (failure rate .2% per year)
- Approved for 5 years use
- Low systemic levels of levonorgestrel
- Changes in menstrual bleeding
 - Irregular spotting at first, then decreased flow or amenorrhea (20%)

Noncontraceptive Benefits of Mirena
(Off-label uses)

- Effective treatment for menorrhagia
 - Increases hemoglobin concentration
 - Acceptable alternative to hysterectomy
- Decreases dysmenorrhea
 - Even in medical conditions
- Provides effective progestin component for Hormone Therapy
- May decrease incidence of endometrial Ca

ACOG Statements

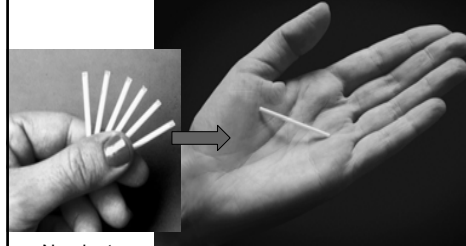
- On IUDs: “IUDs offer safe, effective, long-term contraception and should be considered for *all* women...”
 - On Adolescents: “After thorough counseling regarding contraceptive options, health care providers should **strongly encourage** young women who are appropriate candidates to use this method.”
- Note: *Italics mine***

Which IUC?

- Mirena
 - Woman with heavy flow or cramps
 - Anyone who wants to ↓ menstrual bleeding (over time)
- Paragard
 - Woman who prefers regular predictable cycles
 - Wants to avoid hormonal side effects
 - Prefers longer duration (10 years)
 - Cost issues

The Contraceptive Implant:
(Implanon®)

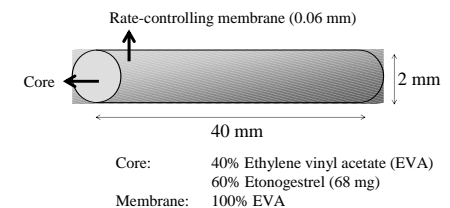
The Contraceptive Implant:
(Implanon®)



Norplant

Implanon

Single-Rod Implant



Advantages

- 3 years of highly effective contraception
- Progestin-only method, can use
 - When estrogen contraindicated
 - If estrogenic side effects with another method
- Insertion and removal easier than Norplant

Mechanism of Action

- **Primarily inhibits ovulation**
 - No ovulation was observed for 30 months
 - Only 2 out of 31 (6.5%) subjects ovulated in year 3, with no resulting pregnancies*
- * Subject 1 = 69.5 kg and ovulated only at month 30
Subject 2 = 57.5 kg and ovulated months 30, 33, and 36
- **Secondarily increases viscosity of cervical mucus**
- **Pearl index ≤ 0.38**

IMPLANON™ [package insert], Roseland, NJ:
Organon USA Inc; 2006.

Incidence of Ovulation

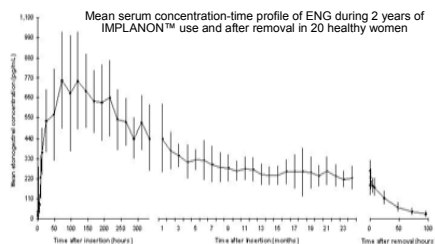
Year	Single-Rod Implant				Norplant®			
	Subjects n/N	%	Cycles n/N	%	Subjects n/N	%	Cycles n/N	%
1	0/62	0	0/244	0	0/16	0	0/164	0
2	0/54	0	0/148	0	0/11	9.1	1/56	1.7
3	2/46	4.3	4/131	3.1	1/3	33.3	1/24	4.1

Efficacy in overweight women

- No clinical trial data
- Women who weighed more than 130% ideal body weight were excluded from the clinical trials
- It is possible that with time IMPLANON™ may be less effective in overweight women
- Clinical judgment required

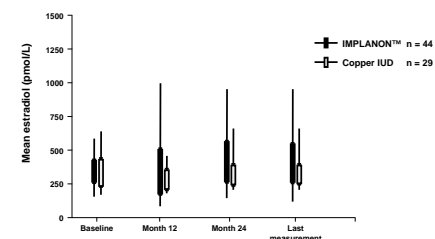
IMPLANON™ [package insert], Roseland, NJ:
Organon USA Inc; 2006.

Quickly Effective, Quickly Reversible



IMPLANON™ [package insert], Roseland, NJ:
Organon USA Inc; 2006.

Estradiol Levels During Treatment



Beerhuizen R, et al. *Hum Reprod.* 2000;15:118-122

Insertion



Implant Insertion and Removal Time (Minutes)

	Implanon®	Norplant®
Insertion	N	659
	Mean	1.1
	SD	0.9
	Median	1.0
	Min-max	0.03-5.0
Removal	N	84
	Mean	2.7
	SD	52.6
	Median	2.0
	Min-max	0.3-20.0

* Insertion time = time needed for incision (if any) and placement;
Removal time = time needed for anesthesia, incision and removal

Discontinuation Rates ($\geq 1\%$) due to Adverse Events

n = 942

Bleeding irregularities *	11.0% (104/942)
Weight gain	2.3% (22/942)
Emotional lability	2.3% (22/942)
Headache	1.6% (15/942)
Acne	1.3% (12/942)
Depression	1.0% (9/942)

* includes frequent, heavy, prolonged, spotting and other patterns of bleeding irregularity

IMPLANON™ [package insert], Roseland, NJ:
Organon USA Inc; 2006.

IMPLANON Bleeding Patterns

- Bleeding can be *light* or *heavy*
- Can be for just a *few days* or *many days* in a row
- Can have many consecutive days or weeks of *no bleeding*
- Patients should be prepared to *experience any of these patterns*
- Patterns can vary *throughout the duration of use*

IMPLANON Bleeding Patterns

- On average, the total amount of bleeding/spotting days is similar to or slightly better than a normal menstruating woman
- The key difference is the irregularity and unpredictability of the bleeding
- Some women may have a slight trend towards lighter and infrequent bleeding or no bleeding at all

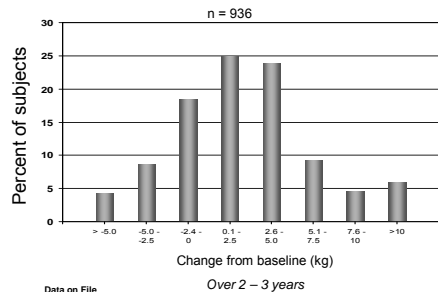
Data on File, Organon USA Inc.

Managing BTB with Implanon

- **COUNSELING**
- Peer support
- Anti-prostaglandins X 5 days
- Estrogen X 10 days
- *Oral contraceptives, if not contraindicated
- Doxycycline 100 mg bid x 5 days

* Contraception 2008;78:106-112.

Weight Changes in Clinical Trials



IMPLANON Removal (From Clinical Trials)

1.7% of Women Experienced Problems at Removal
(n = 15 women out of 900)

Implant Not Palpable
Broken or Damaged Implant
Formation of Fibrosis
Difficult Localization
Slight Migration
Difficult Removal due to Deep Insertion

IMPLANON™ [package insert], Roseland, NJ:
Organon USA Inc; 2006.

Key Point on Insertion

Careful and correct subdermal insertion is one of the keys to successful placement and will facilitate removal.

Depo Provera

Black Box Warning: November 2004:

- Women who use DMPA may lose significant bone mineral density...greater with increasing duration of use and may not be completely reversible.
- Unknown if DMPA during adolescence or early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase the risk of osteoporotic fracture later in life.
- DMPA should be used ...longer than 2 years only if other birth control methods are inadequate

Depo Provera Positive Aspects

- Highly Effective (.3 pregnancy rate)
- Easy to use
not coitus - dependent
no daily administration
- Anonymity
- Can use when estrogen contraindicated
- No drug interactions

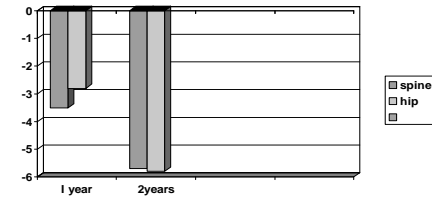
Depo Provera Negative Aspects

- Prolonged pituitary suppression
 - Median time to pregnancy is 9–10 mos
 - Up to 18 months is within normal limits
- Bone density
- Vaginal dryness
- Adverse effect on lipids

Estradiol Levels after 1 Year on Depo Provera

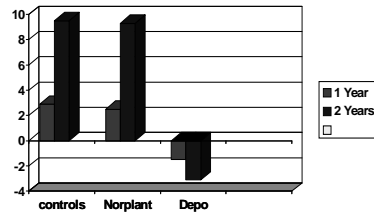
- 80% of women < 50 pg/ml
(50 pg = level needed to maintain bone)
- 20% of women < 20 pg/ml
(10-20 pg = postmenopausal range)

Bone Density on Depo Provera (178 Women ages 18 – 35)

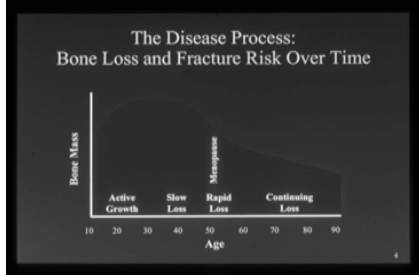


Fertil Steril 2004;82:1580.

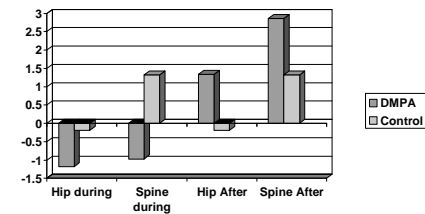
Bone Density of Adolescents on Depo Provera



The Disease Process: Bone Loss and Fracture Risk Over Time

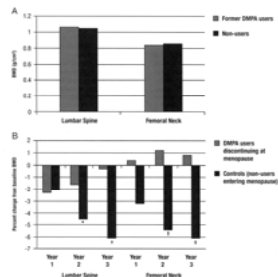


Change in Bone Density among Adolescents Using and Stopping DMPA



Arch Pediatr Adolesc Med 2005;159:139

Change in Bone Density in Perimenopausal Women After DMPA



Contraception 2008;77:67-76.

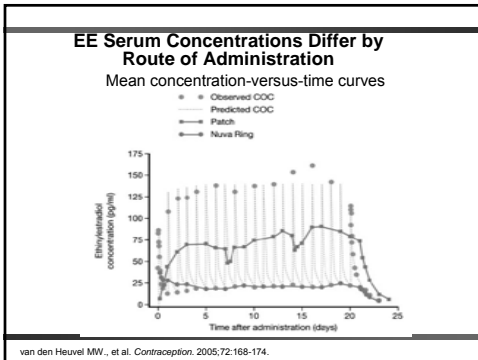
Depo Provera Recommendations

- Discuss bone density risks with clients
- Inform about other contraceptive options
- Recommend calcium and weight-bearing exercise
- In high-risk patients or after 2 years of use
 - Discuss why client feels DMPA is optimal contraceptive choice
 - Consider estrogen supplements
 - Consider BMD (only in perimenopausal women)

Contraceptive Patch

Application of the Transdermal Patch on Abdomen





Data on Risk of VTE with the Patch

Comparator	Odds Ratio
Norgestimate/35 mcg EE ¹	0.9
Norgestimate/35 mcg EE ²	2.4
17 more months data from database used in first study ³	1.1
Levonorgestrel/30 mcg EE	2.0

*No increased risk of heart attack or stroke but too rare to ascertain estimates

1. *Contraception* 2006;73:223-8. 2. *Obstet Gynecol* 2007;109:339-46.
3. *Contraception* 2007;76:4-7.

Incidence of VTE in Women of Reproductive Age

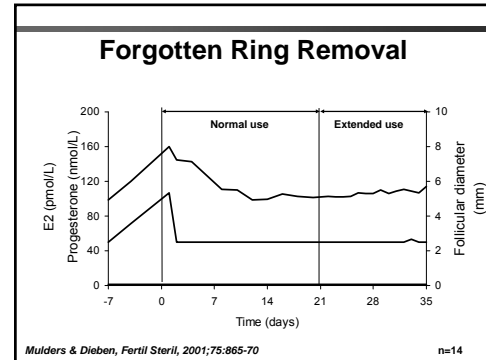
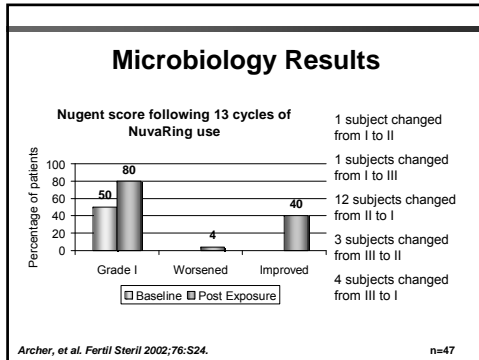
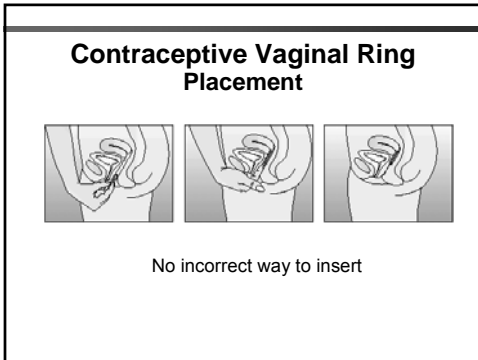
Controls	Estimated Incidence of VTE (per 10,000 Woman-Years)
OC users	1
Pregnancy	3
	6

Farmer, Preston. *J Obstet Gynaecol*. 1995;15:195.

- ### Newest Package Labeling for Patch (under Warnings)
- “Average concentrations at steady state for EE are ~ 60% higher (than on OCPs)”
 - “Peak concentrations are ~ 25% lower”
 - “It is not known whether there are changes in the risk of serious adverse events ...in women using Ortho Evra compared with women using OCs”
 - Increased estrogen exposure may increase the risk of adverse events, including VTE
 - All 4 studies are now described in the insert

- ### Contraceptive Ring and Patch
- More convenient for many women
 - Same hormones as oral contraceptives
 - Similar efficacy
 - Similar side effects
 - Same risks ?
 - SAME CONTRAINDICATIONS

- ### Contraceptive Vaginal Ring Characteristics
- Very low dose
 - 120 µg/day etonogestrel
 - 15 µg/day ethinyl estradiol
 - Flexible
 - Transparent
 - Outer diameter: 54 mm
 - Thickness: 4 mm
 - One ring per cycle 3 weeks ring-in 1 week ring-free
-



Contraceptive Ring and Patch

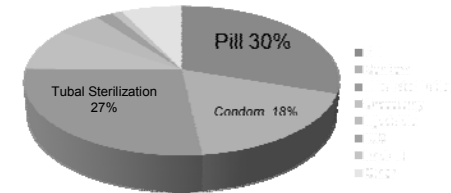
- More convenient for many women
- Same hormones as oral contraceptives
 - Similar efficacy
 - Similar side effects
 - Same risks
 - SAME CONTRAINDICATIONS

What's New with Oral Contraceptives?

Besides a chewable, flavored pill



Contraceptive Use in the US



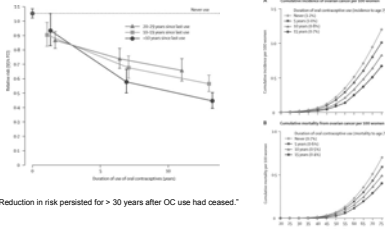
www.cdc.gov/nchs/data/ad/ad350.pdf

OCs Decrease Ovarian Cancer Risk

- 40% to 80% decrease in risk¹
- Protection conferred by OCs
 - Begins with 1 year of use¹
 - Increases with increasing duration of use¹
 - Persists from 10 to 19 years after OCs are stopped^{1,2}
- Consider OC use for ovarian cancer prophylaxis³

¹. CASH. *N Engl J Med*. 1987;316:650.
². Rosenberg et al. *Am J Epidemiol*. 1994;139:654.
³. Grimes. *JAMA*. 1993;270:2855.

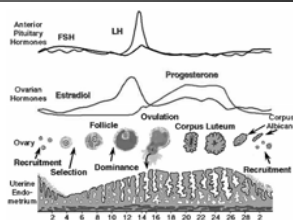
New Data (Lancet Jan. 26, 2008)



Conclusion: OCs "have already prevented some 200,000 ovarian cancers and 100,000 deaths from the disease, and over the next few decades the number of cancers prevented will rise to at least 30,000 per year."

Extended-Regimen Oral Contraceptive (Seasonique®)

- 0.15 mg levonorgestrel/30 µg ethinyl estradiol
- 84 active tablets followed by 7 placebos
- Four periods/year
- Proven safe and similar non-menstrual side effect profile to 21 day regimens



Estrogen → ↑ growth of uterine lining
 Progestin → stops growth
 All OCPs are progestin-dominant

Extended OC Regimens

- Reduce/prevent symptoms during the pill-free interval
 - bleeding, cramping
 - headaches
- May improve correct and consistent use, increase efficacy
- More initial breakthrough bleeding
 - 7.7% (vs 1.8%) discontinue for this reason
- About equal days of bleeding over time

Newest Oral Contraceptives

- Loestrin® 24 Fe
 - 24 days on, 4 days off
- Yaz®
 - 24 days on, 4 days off
- Seasonique®
 - 84 days on, 7 days 10 µg ethinyl estradiol
- Lybrel®
 - Continuous use
- You can replicate any of these regimens with any monophasic OCP

Quick-Start (Off Label)

- The patient takes her first pill in the office, no matter where she is in her cycle
 - Obtain UCG if LMP uncertain
 - Give EC if intercourse \leq 120 hours ago
 - Advise to use back-up x 7 days
 - Advise RTC if no withdrawal bleed first cycle
- Safety issues
 - We know of no harm if a pregnancy is exposed
 - No increase in adverse events
 - No increase in side effects or BTB

1. Obstet Gynecol 2007;109:1270-6.

Quick-Start

- Advantages
 - Avoids complicated instructions
 - Higher patient satisfaction¹
 - Improved adherence to method¹
- Now reported using
 - Vaginal Ring – even less BTB than with OCP¹
 - Depo-Provera²

1. Obstet Gynecol 2005;106:89-96. 2. Contraception 2007;75:84-87.

Emergency Contraception Efficacy

If 100 women have unprotected sex once in the second or third week of their cycle

- 8 will become pregnant without treatment
- 2 will become pregnant following use of combined ECPs (a 75% reduction)
- 1 will become pregnant following use of progestin-only ECPs (an 88% reduction)
- 1 (0.1%) will become pregnant following emergency insertion of copper IUC

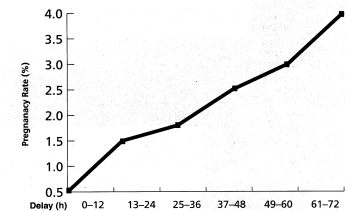
Emergency Contraception Mechanism of Action

- Newest study (Plan B): "Little or no effect on post-ovulation events but highly effective when taken before ovulation" ¹
- Anovulation documented on ultrasound
- International Consortium: "EC is effective only before the ovum is released from the ovary and before the sperm fertilizes the ovum." ²

1. Contraception 2007;75:112-118. 2. <http://www.cecinfo.org>

Efficacy decreases with time after intercourse EC is taken

FIGURE 1. Pregnancy Rate by Delay in Initiating Use of Emergency Contraceptive Pills*



*Adapted from Pezzullo JC, von Hertzen H, Givens DA, Van Look PL. Timing of emergency contraception with levonorgestrel or the Yuzpe regimen. Sex Transm Dis Reproductive Health Methods of Family Planning. October 1998;75:212.

Newer EC Protocols

- Provision "the sooner the better"
- Some efficacy up to 120 hours after intercourse
- Can take both doses at the same time (vs 2 doses 12 hours apart)

Now available "Behind the Counter"

- Must be 18 years of age (show ID)
 - Large chain pharmacies more likely to stock and dispense¹
- Encourage patients to obtain and keep in medicine cabinet with other emergency supplies
- Offer prescription to all women under 18

1. Am J Obstet Gynecol 2008;199:478-80.

Goals and Recommendations

- The U.S. Department of Health and Human Services: "reduce unintended pregnancy to \leq 30% of all pregnancies in the United States"
- The Institute for Medicine Committee on Unintended Pregnancy 1995: "All pregnancies should be intended—that is, they should be consciously and clearly desired at the time of conception."
- Malcolm Potts: "Everything we can do to give women control over their...fertility enhances health and changes the world for the better."