

Contraceptive Update

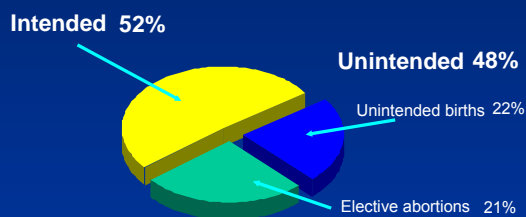
With Emphasis on Long-Acting Reversible Contraception

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



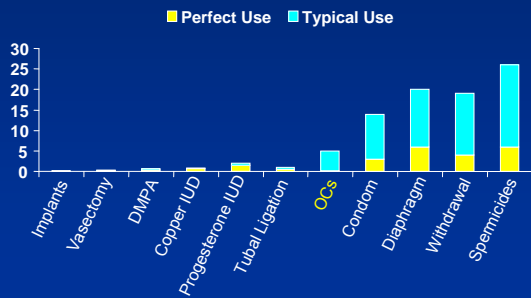
Finer LB et al. *Perspectives on Sexual & Reproductive Health* 2006;38:90-96.

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 L.J, Mosher WD. *Fam Plann Perspect.* 1998;30:4-10, 46.

First Year Contraceptive Failure Rates: Perfect Use vs Typical Use



Current Trends in Contraception

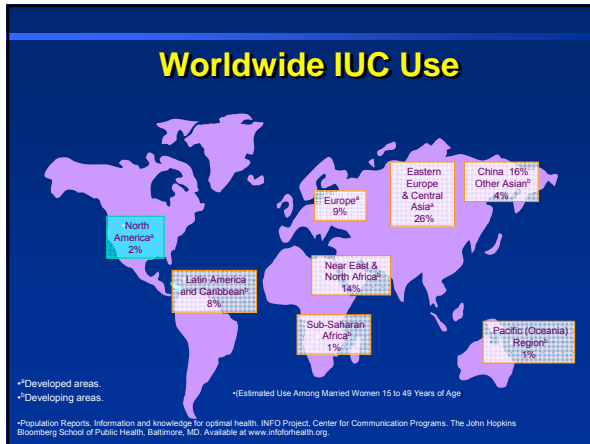
- New delivery systems
- Wider array of options
- Longer duration of action
 - Increasing ease of adherence to method
 - “Reproductive Health Plan”
- Emphasizing greater success
- Use of emergency contraception

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.

Annual Ectopic Pregnancy Rate per 100 Women Using IUD

	Total Pregnancy Rate	Ectopics/100 Pregnancies	Ectopic Pregnancy Rate	Relative Risk Ectopic vs No Method
• No contraception ¹	40-50	1.4	0.3-0.5	1.0
• Cu T 380 ¹	0.3	6	0.02	0.1
• Levonorgestrel-release	Insufficient data			

¹ Sivin I. *Obstet Gynecol.* 1991;78:291.

History of IUC Dalkon Shield

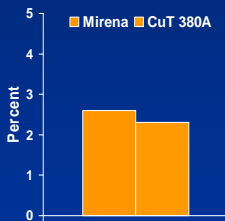
- Increased rate of PID, septic abortion, infertility
- Infections related to woven thread
- Off the market for over 30 years
- Modern IUCs are not your grandmother's IUD!



Modern IUCs Do Not Cause PID

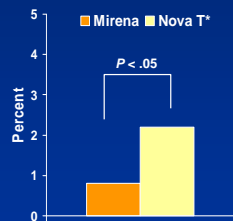
5-Year Cumulative Rates of Discontinuation for PID

A. Randomized trial comparing Mirena to CuT 380A



*Nova T is not available in the US.
Sivin I et al. *Contraception* 1990;42:361-378.

B. Randomized trial comparing Mirena to Nova T

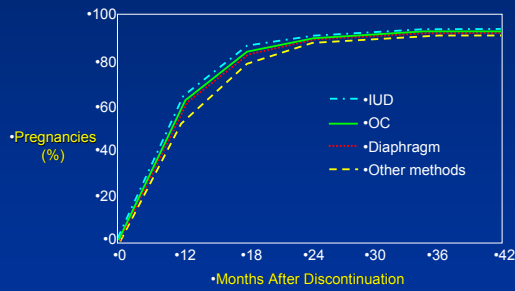


Andersson K et al. *Contraception* 1994;49:56-72.

Modern IUCs Do Not Cause PID

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

Fertility After Discontinuation of Contraceptive



Based on data from Vessey MP, et al. *Br Med J.* 1983;286:106.

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 STDs
- New patient information materials
- Repeated warning to remove immediately if patient becomes pregnant

Characteristics of Mirena®



levonorgestrel
20 µg/day

- 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

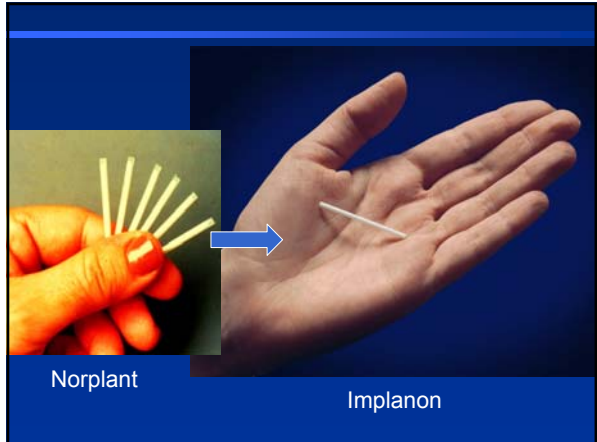
- On IUDs: “IUDs offer safe, effective , long-term contraception and should be considered for **all** women...”
- On Adolescents: “After thorough counseling regarding contraceptive options, health care providers should **strongly encourage** young women who are appropriate candidates to use this method.”

Note: Italics mine

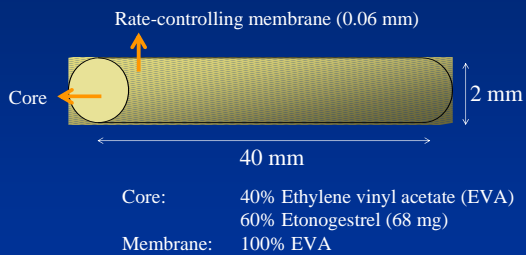
Which IUC?

- 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®)



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

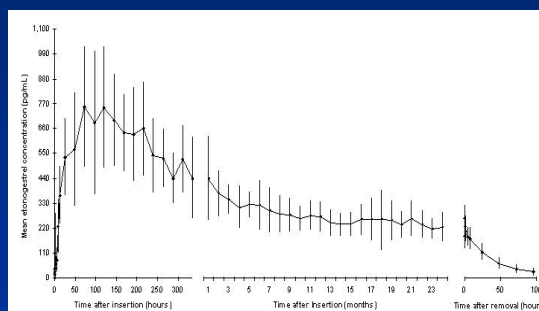
Year	Single-Rod Implant				Norplant®			
	Subjects n/N	%	Cycles n/N	%	Subjects n/N	%	Cycles n/N	%
1	0/62	0	0/244	0	0/16	0	0/164	0
2	0/54	0	0/148	0	0/11	9.1	1/56	1.7
3	2/46	4.3	4/131	3.1	1/3	33.3	1/24	4.1

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

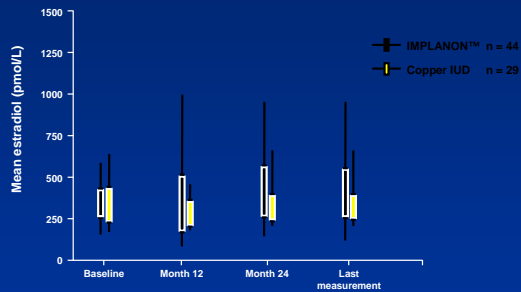
IMPLANON™ [package insert], Roseland, NJ:
 Organon USA Inc; 2006.

Quickly Effective, Quickly Reversible



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

Estradiol Levels During Treatment



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

Insertion



Implant Insertion and Removal Time (Minutes)

		Implanon®	Norplant®
Insertion	N	659	655
	Mean	1.1	4.2
	SD	0.9	2.1
	Median	1.0	4.0
	Min-max	0.03-5.0	0.8-18.0
Removal	N	175	84
	Mean	2.7	11.3
	SD	52.6	9.3
	Median	2.0	8.0
	Min-max	0.3-20.0	2.0-50.0

* 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

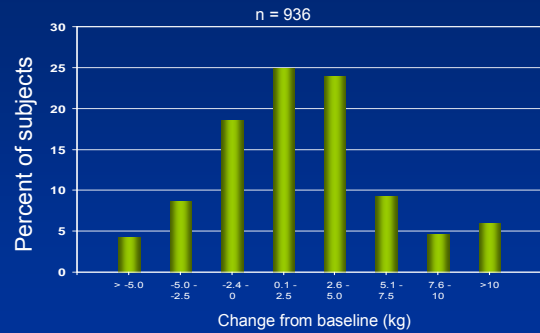
Data on File. Organon USA Inc.

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

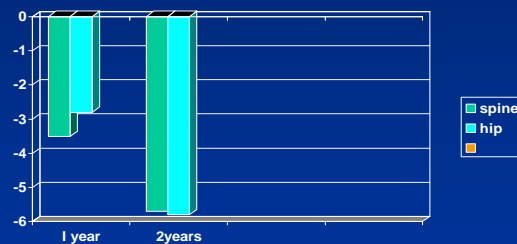
Depo Provera Negative Aspects

- 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

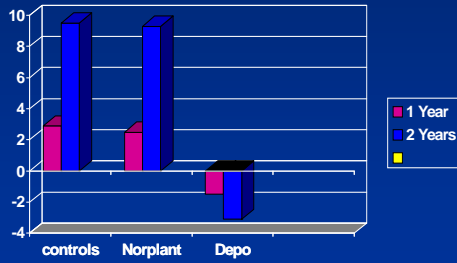
- 80% of women < 50 pg/ml
(50 pg = level needed to maintain bone)
- 20% of women < 20 pg/ml
(10-20 pg = postmenopausal range)

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

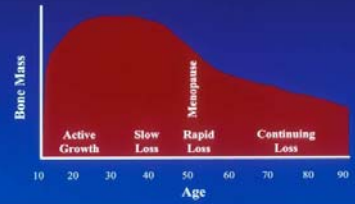


Fertil Steril 2004;82:1580.

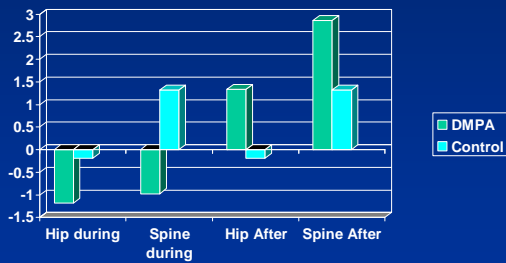
Bone Density of Adolescents on Depo Provera



The Disease Process: Bone Loss and Fracture Risk Over Time

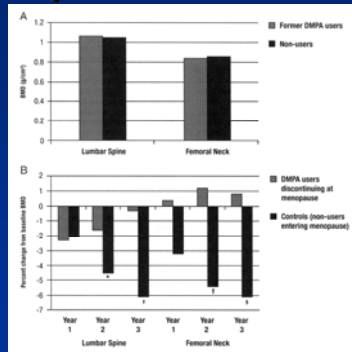


Change in Bone Density among Adolescents Using and Stopping DMPA



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)

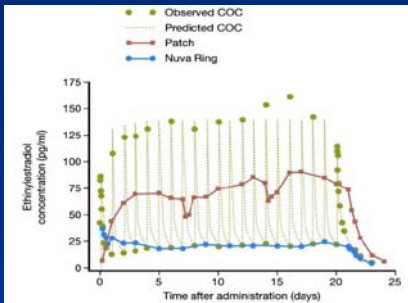
Contraceptive Patch

Application of the Transdermal Patch on Abdomen



EE Serum Concentrations Differ by Route of Administration

Mean concentration-versus-time curves



van den Heuvel MW., et al. *Contraception*. 2005;72:168-174.

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

*Estimated Incidence of VTE
(per 10,000 Woman-Years)*

Controls	1
OC users	3
Pregnancy	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

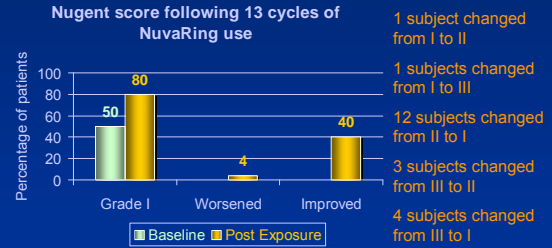


Contraceptive Vaginal Ring Placement



No incorrect way to insert

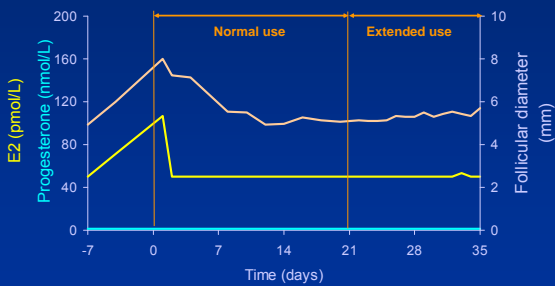
Microbiology Results



Archer, et al. *Fertil Steril* 2002;76:S24.

n=47

Forgotten Ring Removal



Mulders & Dieben, *Fertil Steril*, 2001;75:865-70

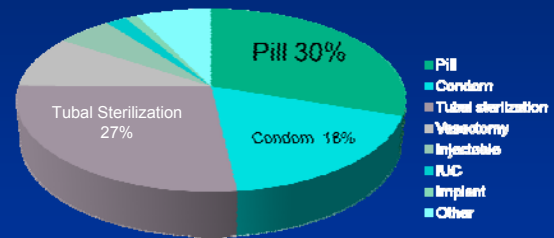
n=14

Contraceptive Ring and Patch

- More convenient for many women
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 - Similar side effects
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 - SAME CONTRAINDICATIONS

How Can We Increase the Efficacy of Oral Contraceptives?

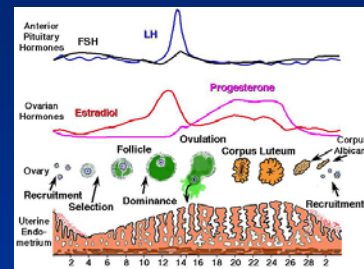
Contraceptive Use in the US



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

Extended-Regimen Oral Contraceptive (Seasonale®)

- 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
 Progesterin → 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

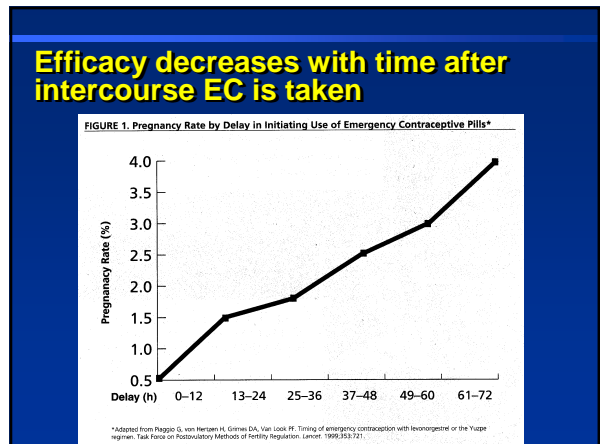
If 100 women have unprotected sex once in the second or third week of their cycle

- 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>



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.

Elicit and Respect Patient Choice

- Giving a woman her method of choice facilitates contraceptive continuation¹
 - Within medical guidelines, patient priorities must be our priorities
- ↓
- Listen to patient
 - Encourage HER decision making
 - Avoid personal biases

1. Pariani S, et al. *Stud Fam Plann.* 1991;22:384.

Goals and Recommendations

- The U.S. Department of Health and Human Services: “reduce unintended pregnancy to ≤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.”