New Developments in Contraception: The Single-Rod Implant

Association of Reproductive Health Professionals
www.arhp.org

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Faculty Disclosure

- Lee Shulman, MD: Receives grants/research support from Barr Pharmaceuticals
- Consultant for Barr Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Ortho Women's Health and Urology

Faculty Disclosure (cont)

- Speaker for Barr Pharmaceuticals, Bayer HealthCare Pharmaceuticals, GlaxoSmithKline, Merck and Co. Inc., Ortho Women's Health and Urology, Wyeth Pharmaceuticals, Ther-Rx Corporation

Note: Additional disclosure information is located within the program

Expert Medical Advisory Committee

- David F. Archer, MD
- Kurt Barnhart, MD, MSCE
- Barbara Clark, PA-C, MPAS
- Mitchell D. Creinin, MD (chair)

more…

Expert Medical Advisory Committee
(continued)

- Philip D. Darney, MD, MSc
- Wendy Grube, MSN, CRNP
- Patricia Murphy, CNM, DrPH
- Lee Shulman, MD

Learning Objectives

- List three advantages of the contraceptive implant
- List three selection criteria for appropriate candidates for the contraceptive implant
- Identify two possible side effects of the contraceptive implant

more…

Learning Objectives (continued)

- Discuss the clinical expectations and management of bleeding with this method
- Describe the steps for insertion and removal of the contraceptive implant

Program Agenda

- Rationale for Implants
- History of Implant (Why 'misperceptions' prevail)
- Single-Rod Implant: Efficacy
- Single-Rod Implant: Clinical Management

more…

Program Agenda (continued)

- Single-Rod Implant: Safety
- Patient Selection, Timing, Counseling, and Follow-up
- Insertion and Removal

Rationale

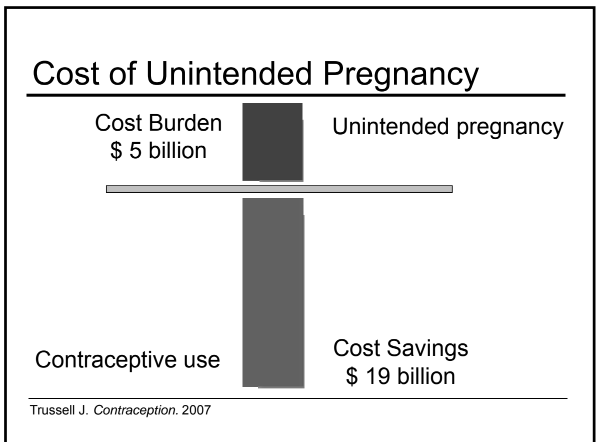
- Why contraception?
- Why another contraceptive method?
- Why implantable contraception?
- Why is it among the most effective?

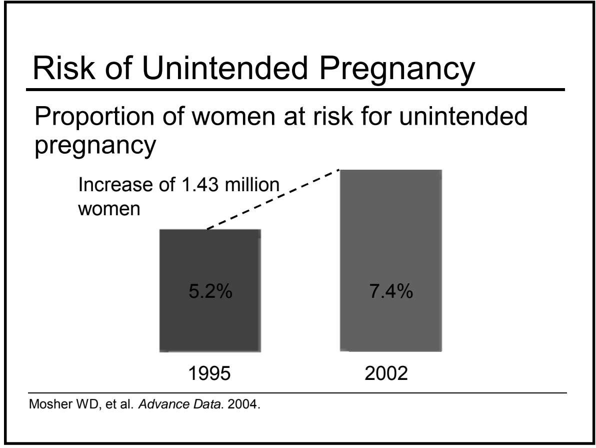
Why contraception?

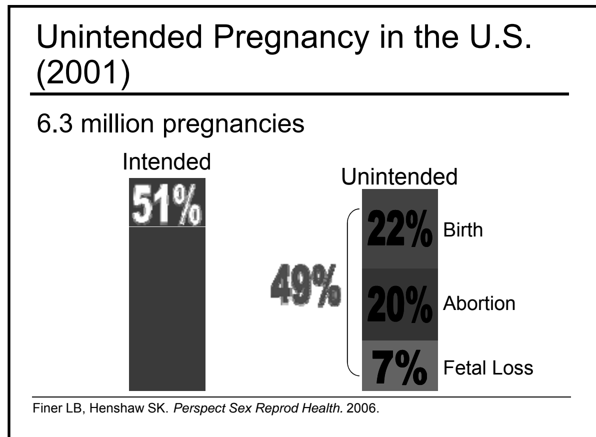
Of the 6.3 million pregnancies

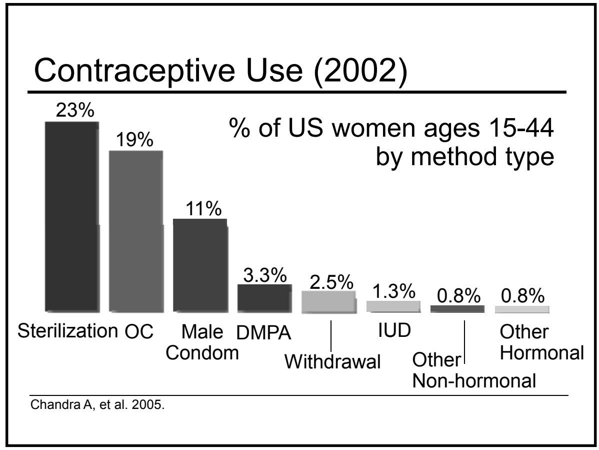
1/2 Unintended

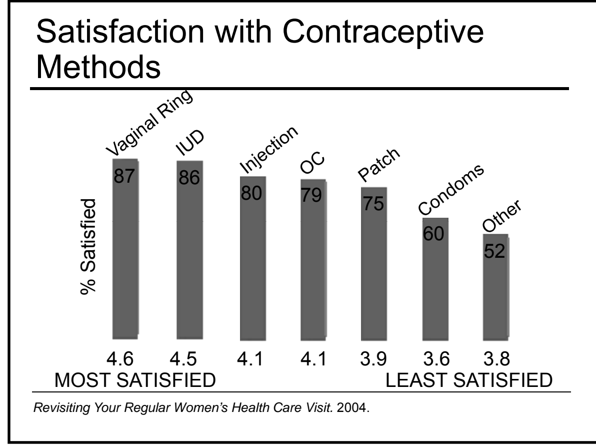
CDC. 2003;52(7):1-16; Varney SJ. Pharmacoeconomics. 2004; Henshaw S. Fam Plan Perspect. 1998.

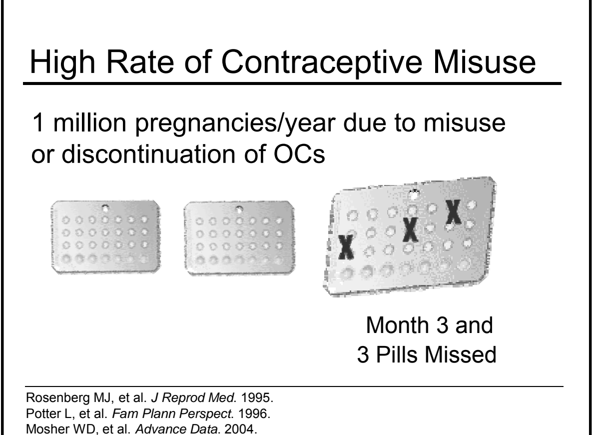

Cost of Unintended Pregnancy
Cost Burden
$ 5 billion
Unintended pregnancy
Contraceptive use
Cost Savings
$ 19 billion
Trussell J. Contraception. 2007


Risk of Unintended Pregnancy
Proportion of women at risk for unintended pregnancy
Increase of 1.43 million women
5.2%
7.4%
1995
2002
Mosher WD, et al. Advance Data. 2004.

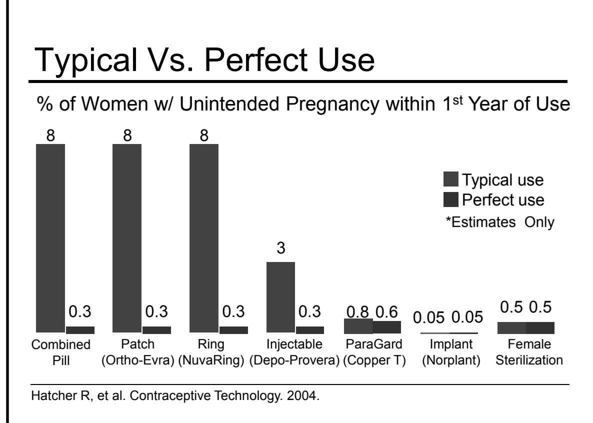

Unintended Pregnancy in the U.S. (2001)
6.3 million pregnancies
Intended
51%
Unintended
49%
22%
Birth
20%
Abortion
7%
Fetal Loss
Finer LB, Henshaw SK. Perspect Sex Reprod Health. 2006.

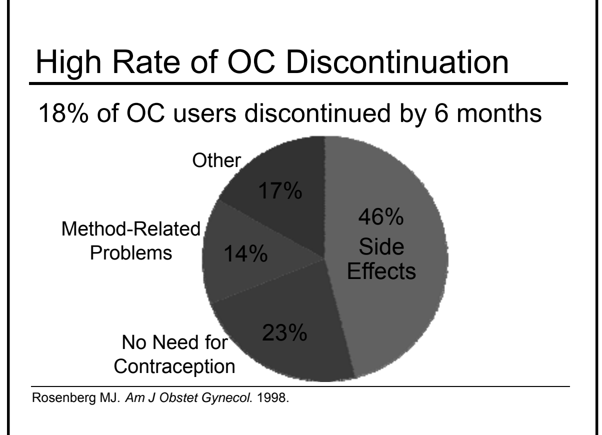

Contraceptive Use (2002)
% of US women ages 15-44 by method type
23%
19%
11%
3.3%
2.5%
1.3%
0.8%
0.8%
Sterilization
OC
Male Condom
DMPA
Withdrawal
IUD
Other Non-hormonal
Other Hormonal
Chandra A, et al. 2005.


Satisfaction with Contraceptive Methods
% Satisfied
Vaginal Ring
IUD
Injection
OC
Patch
Condoms
Other
87
86
80
79
75
60
52
4.6
4.5
4.1
4.1
3.9
3.6
3.8
MOST SATISFIED
LEAST SATISFIED
Revisiting Your Regular Women's Health Care Visit. 2004.


High Rate of Contraceptive Misuse
1 million pregnancies/year due to misuse or discontinuation of OCs
Month 3 and
3 Pills Missed
Rosenberg MJ, et al. J Reprod Med. 1995.
Potter L, et al. Fam Plann Perspect. 1996.
Mosher WD, et al. Advance Data. 2004.

2008
Reproductive Health
Education • Research • Advocacy





Why Another Contraceptive Method?

CHOICE

Varney SJ. Pharmacoeconomics. 2004

Why Implantable Contraception?

- Long duration of action
- Not patient dependent
- Continuous steady state steroid levels
- Avoidance of first-pass effect from GI absorption and hepatic metabolism
- High bioavailability

Why is it among the most effective?

"Implants constitute one of the safest and most effective forms of contraception that exist."

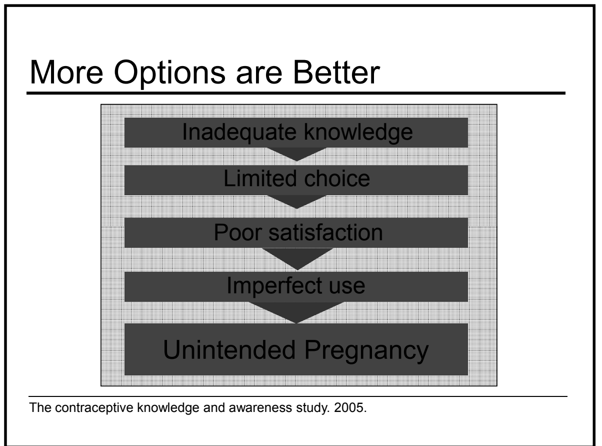
WHO, 2003

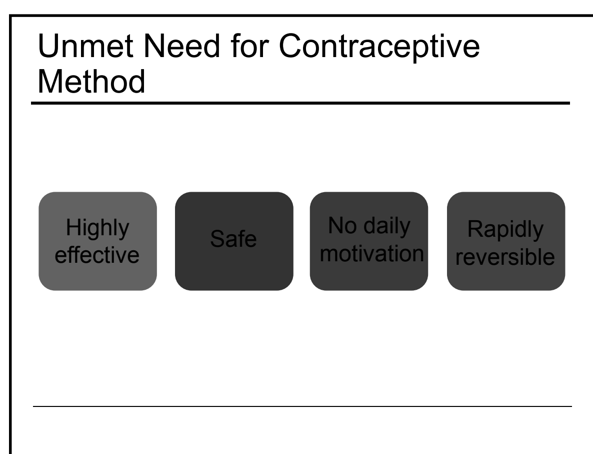
World Health Organization. 2003

Women Want Reversible Methods

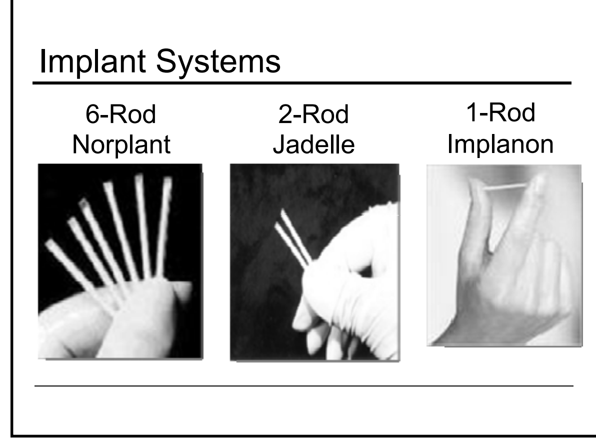
Regret Sterilization

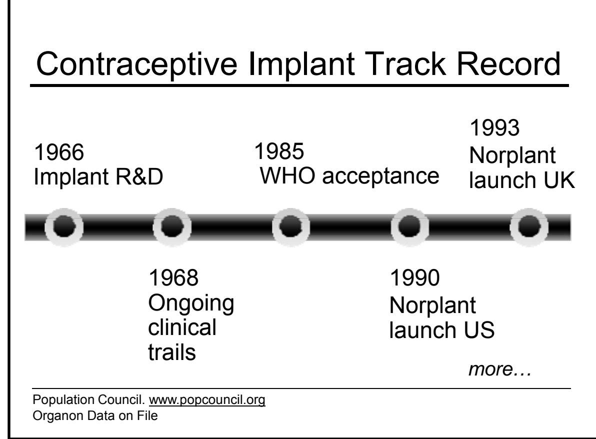
Hillis SD, et al. *Obstet Gynecol.* 1999.

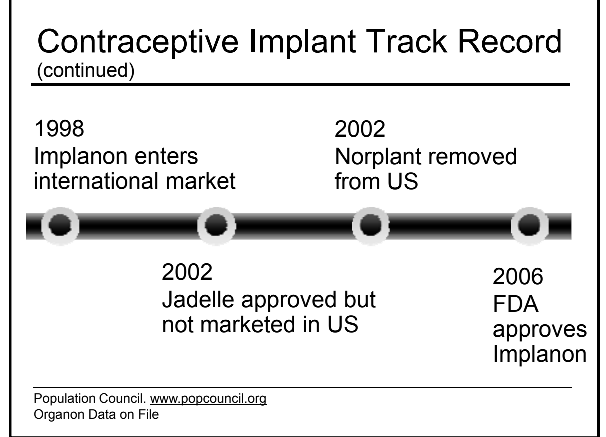




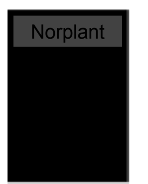
History of Implants

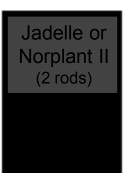


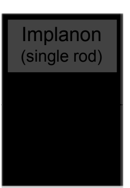




Contraceptive Implant Use Today







Population Council www.popcouncil.org
Organon Data on File

Features of Contraceptive Implants

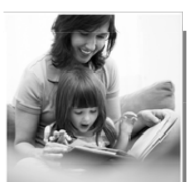
- Highly effective
- Not motivation dependent
- Can be used during lactation
- Discreet, virtually invisible
- Rapidly reversible

more…

Reinprayoon D, et al. *Contraception.* 2000.
Diaz S. *Contraception.* 2000.

Features of Contraceptive Implants
(continued)

- Stable hormone levels
- Extended protection
- Contain no estrogen
- Safe



Reinprayoon D, et al. *Contraception.* 2000.
Diaz S. *Contraception.* 2000.

Limitations of Contraceptive Implants

- Can cause irregular bleeding
- Requires clinician visits for insertion and removal
- Does not protect from STDs

The Single-Rod Implant: Characteristics

Single-Rod Implant

One rod 4 cm x 2 mm

- Core
  - 40% ethylene vinyl acetate (EVA)
  - 60% etonogestrel (68 mg)
- Rate-controlling membrane
  - 100% EVA

Long-acting Protection

- Indicated for the prevention of pregnancy
- Long-acting; up to 3 years
- New implant can continue beyond 3 years
- Reversible at any time

Pharmacology

Class	Progestin-only
Route	Subdermal
Formulation	Implantable rod; 68 mg etonogestrel
Bioavailability	~100%
Metabolism	Hepatic via CYP3A4
Half-life	~ 25 h
Excretion	Primary urine; some fecal

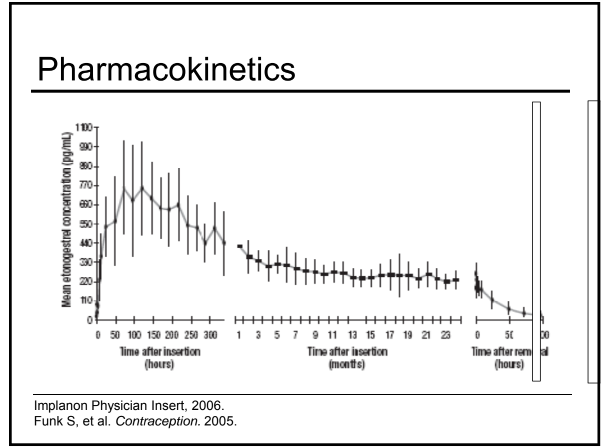
ANON. *Obstet Gynecol.* 2007

Mechanism of Action

- Suppresses ovulation
- Increases cervical mucus viscosity
- Alters endometrium

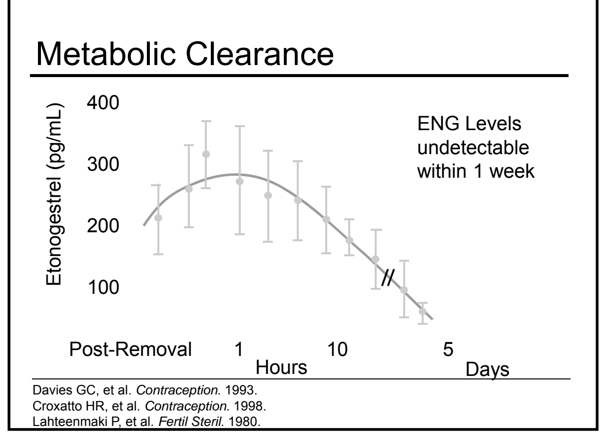
IMPLANON™ Physician insert, 2006

Pharmacokinetics



Implanon Physician Insert, 2006.
Funk S, et al. *Contraception.* 2005.

Metabolic Clearance



Davies GC, et al. *Contraception.* 1993.
Croxatto HR, et al. *Contraception.* 1998.
Lahteenmaki P, et al. *Fertil Steril.* 1980.

Rapid Return to Fertility

Ovulation measured by ultrasound and serum progesterone levels

Majority by 3 weeks

94% by 3 months

Croxatto HB. *Contraception.* 1998.
Lahteenmaki P, et al. *Fertil Steril.* 1980.

The Single-Rod Implant: Efficacy

Efficacy

Year	Cycles	Pregnancy
1	10,867	0
2	8585	0
3	3492	0

6 pregnancies occurred shortly after removal

Implanon Physician Insert, 2006

Efficacy-Real Life Experiences

Number of Pregnancies

Australia	France	Mexico City	UK	US
200	39	0	0	0
1% N=~204,486	Incidence = $0.359/10^3$	N= 417	N=106	N=330

Harrison-Woolrych M. *Contraception.* 2005; Otero Flores JB. *Int J Gynecol Obstet.* 2005, Funk S. *Contraception.* 2005; Agrawal A, *J Fam Plann Reprod.* 2005; Bensouda-Grimaldi L. *Gynecol Obstet Fertil*, 2005

Body Weight Distribution and Efficacy

	≤1 Yr (n)	1–2 Yrs (n)	2–3 Yrs (n)	Pregnancies (n)
< 110 lb	182	157	127	0
111– 132 lb	539	423	292	0
133–150 lb	442	344	239	0
151–176 lb	201	151	109	0
177–198 lb	42	35	21	0
>190 lb	5	2	1	0

Total n = 3,312

Organon data on file.
Implanon Physician Insert, 2006.

Ectopic Pregnancy

"Be alert to the possibility of an ectopic pregnancy"

Patni S. J Fam Plann Reprod Health Care. 2006

The Single-Rod Implant: Clinical Management

Clinical Expectations

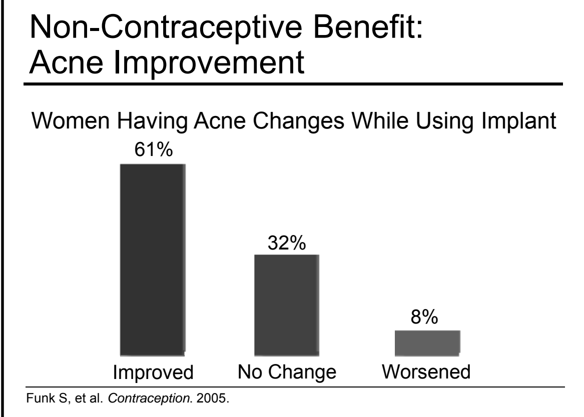
- No anemia
- No reduction in bone mineral density
- No increased risk of DVT
- Little pain at insertion site
- Changes in bleeding pattern
- Drug-drug interactions

more…

Clinical Expectations (continued)

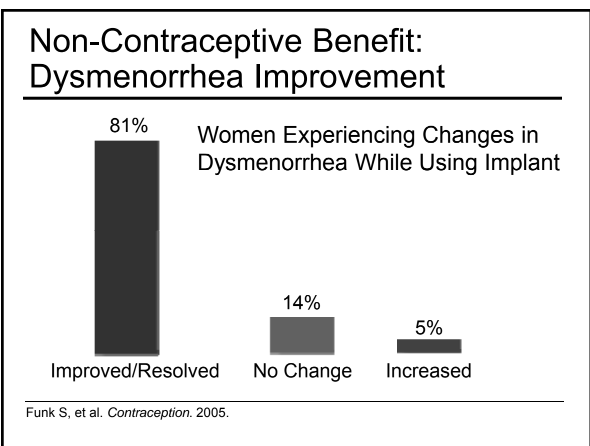
- Associated non-contraceptive benefits
  - Acne may decrease
  - Dysmenorrhea may improve
- Minor weight change
- Mild side effects:
  - Breast pain
  - Headache

Non-Contraceptive Benefit: Acne Improvement



Funk S, et al. *Contraception.* 2005.

Non-Contraceptive Benefit: Dysmenorrhea Improvement



Funk S, et al. *Contraception.* 2005.

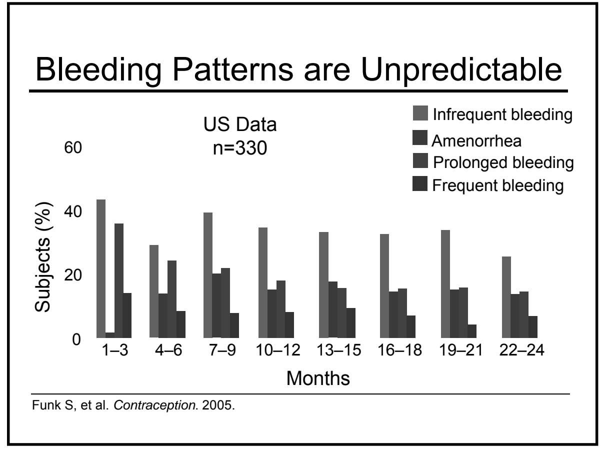
Changes in Bleeding Pattern

"Irregularly irregular" cycles, including:

- Frequent irregular bleeding
- Heavy menstrual flow
- Prolonged bleeding
- Amenorrhea
- Spotting
- Unpredictability of bleeding pattern over time

Affandi B. *Contraception.* 1998.
Zheng SR, et al. *Contraception.* 1999.

Bleeding Patterns are Unpredictable



Funk S, et al. *Contraception.* 2005.

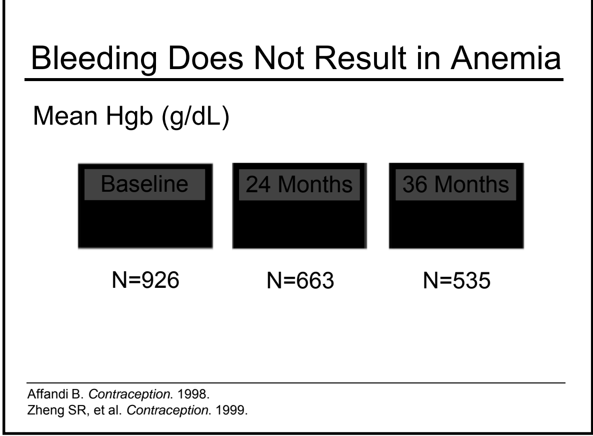
Management of Bleeding

- Few data available
- Considerations
  - Ethinyl estradiol
  - NSAIDs
  - Combination OCs
  - Watchful waiting

Meirik O. *Hum Reproduct Update.* 2003
Weisberg E. *Hum Reprod.* 2006

Bleeding Does Not Result in Anemia

Mean Hgb (g/dL)



Affandi B. *Contraception.* 1998.
Zheng SR, et al. *Contraception.* 1999.

Drug-drug Interactions

Some CYP3A Inhibitors and Inducers

Potent Inhibitors	Moderate Inhibitors	Inducers
amiodarone *(Cordarone)*	amprenavir *(Agenerase)*	carbamazepine *(Tegretol)*
atazanavir *(Reyatz)*	aprepitant *(Emend)*	efavirenz *(Sustiva)*
cisapride *(Propulsid)*	ciprofloxacin *(Cipro)*	nevirapine *(Viramune)*
clarithromycin *(Biaxin)*	diltiazem *(Cardizem)*	phenytoin *(Dilantin)*
itraconazole *(Sporanox)*	erythromycin	phenobarbital
ketoconazole *(Nizoral)*	fluconazole *(Diflucan)*	rifabutin *(Mycobutin)*
nefazodone *(Serzone)*	fluvoxamine *(Luvox)*	rifapentine *(Priftin)*
nelfinavir *(Viracept)*	fosamprenavir *(Lexiva)*	rifampin *(Rifadin)*
ritonavir *(Norvir)*	grapefruit juice	St. John's Wort
telithromycin *(Ketek)*	norfloxacin *(Noroxin)*	topiramate *(Topamax)*
troleandomycin *(TAO)*	verapamil *(Calan)*	> 100 mg/d
voriconazole *(Vfend)*		

ANON.Obstet Gynecol. 2007
Schindlbeck C. *Arch Gynecol Obstet.* 2006.

Minor Weight Change

Mean weight change less than 4 pounds

At year 1 = 2.8 lbs
At year 2 = 3.7 lbs

Implanon Physician Insert, 2006

The Single-Rod Implant: Safety

Insertion Site Symptoms

Condition	n	%
Pain	48	3.4
Redness	6	0.4
Swelling	5	0.4
Hematoma	4	0.3
Expulsion	0	0

N = 1,409

Organon data on file.

Adverse Effects

All Studies	N=942
Bleeding irregularities[1]	11.0%
Emotional Lability[2]	2.3%
Weight Increase	2.3%
Headache	1.6%
Acne	1.3%
Depression[3]	1.0%

[1] Includes frequent heavy, prolonged spotting and other patterns of bleeding irregularity.

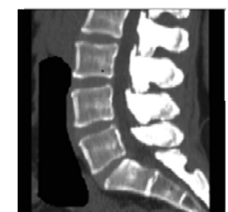
[2] Among US subjects, 6.1% experienced emotional lability that led to discontinuation.

[3] Among US subjects, 2.4% experienced depression that led to discontinuation.

Implanon Physician Insert, 2006

Bone Mineral Density Improves

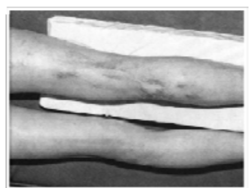
- Changes in bone mineral density similar in study of 44 women with single-rod implant and 29 with non-medicated IUD
- Lumbar spine BMD improved with single-rod



Beerthuizen R, et al. *Hum Reprod.* 2000.

No Increased Risk of Deep Vein Thrombosis (DVT)

- No DVT in 13 clinical trials
- Total of 4,103 woman-years of exposure



Urbancsek J. *Contraception.* 1998.

Ovarian Cysts

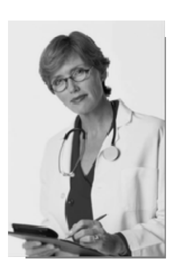
"Finding ovarian cysts during the first year of use is common and transient and should not be interpreted as pathologic."

Hidalgo, 2006

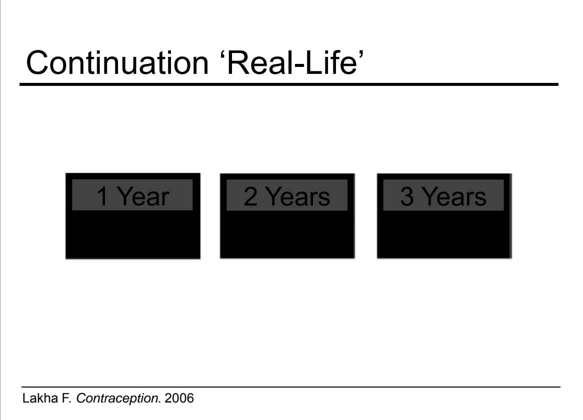
Hidalgo, MM. *Contraception.* 2006
Implanon Physician Insert, 2006

The Single-Rod Implant:

- Patient Selection
- Timing
- Counseling

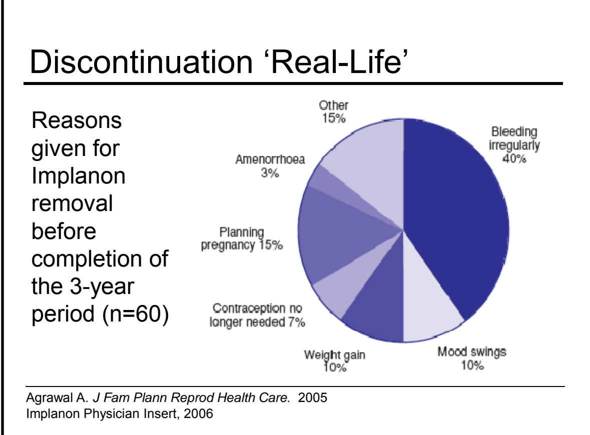


Continuation 'Real-Life'



Lakha F. *Contraception.* 2006

Discontinuation 'Real-Life'



Reasons given for Implanon removal before completion of the 3-year period (n=60)

Agrawal A. *J Fam Plann Reprod Health Care.* 2005
Implanon Physician Insert, 2006

Patient Selection

Women who desire
- Long-term contraception
- High effectiveness
- Rapid reversibility
- Estrogen-free contraception

Contraindications

- Known or suspected pregnancy
- Current or past history of thrombosis or thromboembolic disorders
- Hepatic tumor or active liver disease

more…

Implanon Physician Insert, 2006.
World Health Organization. 2004.

Contraindications (continued)

- Undiagnosed abnormal genital bleeding
- Known or suspected carcinoma of the breast or history of breast cancer
- Hypersensitivity to the components of the implant

Implanon Physician Insert, 2006.
World Health Organization. 2004.

Patient Counseling

PATIENT CONSENT FORM

I understand the Patient Labeling for IMPLANON™. I have discussed IMPLANON™ with my healthcare provider who answered all my questions. I understand that there are benefits as well as risks from using IMPLANON™. I understand that there are other birth control methods and that each has its own benefits and risks.

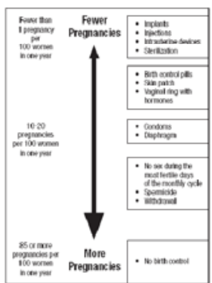
I also understand that this Patient Consent Form is important. I understand that I need to sign this form to show that I am making an informed and careful decision to use IMPLANON™, and that I have read and understand the following points.

- IMPLANON™ helps to keep me from getting pregnant.
- No contraceptive method is 100% effective, including IMPLANON™.
- IMPLANON™ is made of a hormone mixed in a plastic rod.
- It is important to have IMPLANON™ inserted at the

Patient Counseling Topics

- Description of implant
- Efficacy
- Return to fertility
- Bleeding patterns
- Managing potential side effects
- Overview of insertion and removal
- Follow-up

Patient Counseling: Efficacy



Implanon Physician Insert, 2006

Patient Follow-up

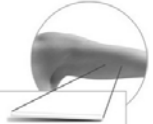
- Expect bleeding irregularities
- Plan on removal after 3 years, or at anytime
- Make sure the implant is palpable
- Report any adverse effects immediately

more…

Patient Follow-up (continued)

- Discuss use of interacting medications now and in future
- Encourage healthy lifestyle
- Safe sex (does not prevent STIs/HIV)
- No smoking

The Single-Rod Implant: Insertion & Removal



Insertion Timing

- Standard or new start
- Insertion within 5 days of initiation of menses
- Switching from combined OC
- Insertion within 7 days of last active tablet

more…

Insertion Timing (continued)

- Switching from progestin-only method
- Insertion any day with progestin only-pill
- Same day as IUD or implant removal
- On due date for next contraceptive injection

more…

Insertion Timing (continued)

- After abortion
- Within 5 days of 1st trimester abortion
- Within 6 weeks of 2nd trimester abortion
- After childbirth
- Within 6 weeks

more…

Implanon physician Insert
Reinprayoon D, et al. *Contraception.* 2000.
Diaz S. *Contraception.* 2002.

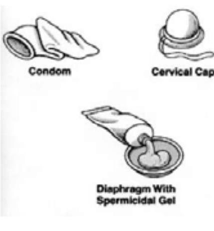
Insertion Timing (continued)

- Considered safe with lactation after 6 weeks
- Clinical study: low concentrations present in milk; no associated adverse events

Implanon physician Insert
Reinprayoon D, et al. *Contraception.* 2000.
Diaz S. *Contraception.* 2002.

‘Quick Start’ Method

- Inserted at any time during menstrual cycle
- Use of back-up barrier contraception for 7 days
- If inserted when emergency contraception is used, do urine pregnancy test in 3 weeks



Short Insertion and Removal Time

Insertion

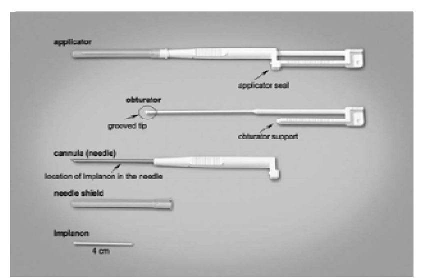
< 1 minute

Removal

< 3 minutes

Zheng SR, et al. *Contraception.* 1999.

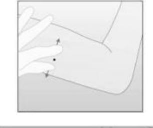
Components of the Single-Rod Implant Insertion System

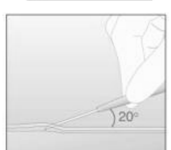


Funk S. *Contraception.* 2005

Preparation Tips

- Supine position
- Nondominant arm, flexed and externally rotated
- Subdermal groove
- Hold applicator up (vertical) before insertion





Insertion Steps Overview

1. Mark site and sterilize
2. Inject local anesthetic just under skin
3. Remove applicator, maintain sterility
4. Verify implant is within needle of applicator
5. Remove needle cover

more…

Insertion Steps Overview (continued)

6. Stretch skin at insertion site (a)
7. Lift or tent skin with needle tip while inserting and insert needle to full length (b)
8. Press the obturator support to break seal of applicator

more…

Insertion Steps Overview (continued)

9. Turn obturator 90 degrees and fix with one hand (c)
10. With other hand, pull needle out (d)

11. Palpate to verify correct insertion

Trouble Shooting: Insertion

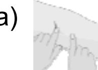
- Non-insertion
- Deep insertion
- Migration

Removal Tips

- Inject local anesthetic under rod
- Incision over distal end
- Use sharp or blunt dissection if encapsulated
- Insert new implant through same incision or opposite arm

Removal Steps Overview

1. Locate rod and mark site (a)



2. Sterilize site
3. Inject local anesthetic under distal end of rod (b)

4. Press down on proximal end of rod

more…

Removal Steps Overview (continued)

5. Use scalpel to make 2–3 mm incision over distal end (c)
6. Gently push rod toward incision, then grasp with mosquito forceps (d)
7. Close with steri-strip closure

Trouble Shooting: Removals

- Unrecognized non-insertion
- Deep placement
- Significant weight gain
- Migration

James P. *Aust N Z J Obstet Gynecol.* 2006.
Piessens SG. *Aust N Z J Obstet Gynecol.* 2005.

In Summary

Dispelling Misperceptions

Realities about Contraceptive Implants

Insertion and removal are not time-consuming or hard to learn

Bleeding patterns are accepted by most women

No higher risk of litigation than other forms of contraception

No Higher Risk of Litigation

Number of implants withdrawn from market by regulatory agency

Sandra J.P. Dennis, Esq. Washington, DC.

Misperceptions Corrected

- Practically invisible
- Not painful to insert
- Infection rare
- No long-term health problems
- No health problems in children conceived after use
- Decrease in libido rarely occurs

Gwinnell E. *J Fam Plann Reprod Health Care.* 2005.

Advantages

- High contraceptive effectiveness
- No need for user compliance
- Long life-span
- Minimal requirement for medical follow-up
- Low, stable serum hormone levels minimizing metabolic effects
- Rapid reversibility

Power J. *Cochrane Database Syst Rev.* 2007

Disadvantages

- High initial cost
  - Counsel properly to prevent early discontinuation
- Insertion/removal requires visit to trained clinician
  - All prescription contraceptives (OCs, Injections, Rings, Patches, IUDs) also need health care provider visit

more…

Power J. *Cochrane Database Syst Rev.* 2007

Disadvantages (continued)

- Misperceptions surrounding implant history
  - Proven track record of single-rod implant has overcome past obstacles

Power J. *Cochrane Database Syst Rev.* 2007

In Conclusion…

- Advancement in contraceptive options
- New option that fulfills unmet need
- Safe, highly effective, and rapidly reversible
- Offers women another choice
- Contraceptive implants widely used worldwide
- Most reproductive-age women are candidates

Resources

- Contact the manufacturer for training sessions for insertion and removal
- www.arhp.org

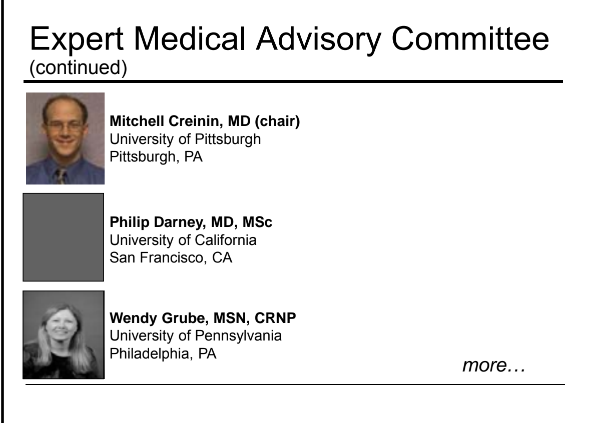
Expert Medical Advisory Committee

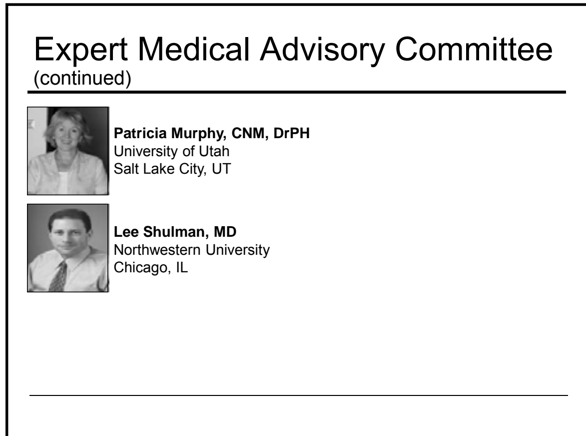
David F. Archer, MD
CONRAD Clinical Research Center
Norfolk, VA

Kurt Barnhart, MD, MSCE
University of Pennsylvania
Philadelphia, PA

Barbara Clark, PA-C, MPAS
Knox OB/GYN
Galesburg, IL

more…


Expert Medical Advisory Committee
(continued)
Mitchell Creinin, MD (chair)
University of Pittsburgh
Pittsburgh, PA
Philip Darney, MD, MSc
University of California
San Francisco, CA
Wendy Grube, MSN, CRNP
University of Pennsylvania
Philadelphia, PA
more…


Expert Medical Advisory Committee
(continued)
Patricia Murphy, CNM, DrPH
University of Utah
Salt Lake City, UT
Lee Shulman, MD
Northwestern University
Chicago, IL

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