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

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• Barbara Clark, PA-C, MPAS
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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

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

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


Unintended
New Developments in Contraception:
The Single Rod Implant
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Cost of Unintended Pregnancy

<table>
<thead>
<tr>
<th>Cost Burden</th>
<th>Unintended pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>$5 billion</td>
<td></td>
</tr>
</tbody>
</table>

Contraceptive use

Cost Savings $19 billion

Risk of Unintended Pregnancy

Proportion of women at risk for unintended pregnancy

Increase of 1.43 million women

1995: 5.2%
2002: 7.4%


6.3 million pregnancies

Intended

Unintended

Birth 22%
Abortion 20%
Fetal Loss 7%

Contraceptive Use (2002)

% of US women ages 15-44 by method type

Sterilization 23%
Male Condom 19%
OC 11%
Withdrawal 3.3%
IUD 2.5%
Other Non-hormonal 1.3%
Other Hormonal 0.8%

Contraceptive Misuse

1 million pregnancies/year due to misuse or discontinuation of OCs

Month 3 and 3 Pills Missed

Satisfaction with Contraceptive Methods

% Satisfied

Vaginal Ring

Female Condom

Injection

Prel

Condoms

Other

Most satisfied

4.6

4.5

4.1

4.1

3.9

3.6

3.8

Least satisfied

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Typical Vs. Perfect Use

% of Women w/ Unintended Pregnancy within 1st Year of Use

<table>
<thead>
<tr>
<th>Method</th>
<th>Typical use</th>
<th>Perfect use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined Pill</td>
<td>8.0%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Patch (Ortho-Evra)</td>
<td>8.0%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Ring</td>
<td>8.0%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Injectable Depo-Provera</td>
<td>3.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>ParaGard (Copper T)</td>
<td>0.3%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Implant (Norplant)</td>
<td>0.6%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Female Sterilization</td>
<td>0.5%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>


High Rate of OC Discontinuation

18% of OC users discontinued by 6 months

Method-Related Problems
- Other 17%
- Side Effects 46%
- No Need for Contraception 23%
- Other 14%


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

Women Want Reversible Methods

Regret Sterilization


World Health Organisation. 2003
More Options are Better

Unmet Need for Contraceptive Method

History of Implants

Contraceptive Implant Track Record

Contraceptive Implant Track Record (continued)
Contraceptive Implant Use Today

Norplant
Jadelle or Norplant II (2 rods)
Implanon (single rod)
Others

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

Features of Contraceptive Implants (continued)

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

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

One rod 4 cm x 2 mm
- Core
  - 40% ethylene vinyl acetate (EVA)
  - 60% etonogestrel (68 mg)
- Rate-controlling membrane
  - 100% EVA

Single-Rod Implant

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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
<table>
<thead>
<tr>
<th>Class</th>
<th>Progestin-only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>Subdermal</td>
</tr>
<tr>
<td>Formulation</td>
<td>Implantable rod; 68 mg etonogestrel</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>~100%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic via CYP3A4</td>
</tr>
<tr>
<td>Half-life</td>
<td>~ 25 h</td>
</tr>
<tr>
<td>Excretion</td>
<td>Primary urine; some fecal</td>
</tr>
</tbody>
</table>

Pharmacokinetics

Mechanism of Action
- Suppresses ovulation
- Increases cervical mucus viscosity
- Alters endometrium

Metabolic Clearance

ENG Levels undetectable within 1 week

Rapid Return to Fertility
- Ovulation measured by ultrasound and serum progesterone levels
- Majority by 3 weeks
- 94% by 3 months
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The Single-Rod Implant: Efficacy

<table>
<thead>
<tr>
<th>Year</th>
<th>Cycles</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10,867</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>8585</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>3492</td>
<td>0</td>
</tr>
</tbody>
</table>

6 pregnancies occurred shortly after removal

Efficacy-Real Life Experiences

Number of Pregnancies

<table>
<thead>
<tr>
<th>Australia N=204,486</th>
<th>1% N=417</th>
<th>1% N=106</th>
<th>1% N=330</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence = 0.359/10³</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>


Ectopic Pregnancy

“Be alert to the possibility of an ectopic pregnancy”

Patni S. J Fam Plann Reprod Health Care. 2006

Body Weight Distribution and Efficacy

<table>
<thead>
<tr>
<th>≤1 Yr (n)</th>
<th>1–2 Yrs (n)</th>
<th>2–3 Yrs (n)</th>
<th>Pregnancies (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 110 lb</td>
<td>182</td>
<td>157</td>
<td>127</td>
</tr>
<tr>
<td>111–132 lb</td>
<td>539</td>
<td>423</td>
<td>292</td>
</tr>
<tr>
<td>133–150 lb</td>
<td>442</td>
<td>344</td>
<td>239</td>
</tr>
<tr>
<td>151–176 lb</td>
<td>201</td>
<td>151</td>
<td>109</td>
</tr>
<tr>
<td>177–198 lb</td>
<td>42</td>
<td>35</td>
<td>21</td>
</tr>
<tr>
<td>&gt;190 lb</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Total n = 3,312

Organon data on file.

Implanon Physician Insert, 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

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

Women Having Acne Changes While Using Implant

- 61% Improved
- 32% No Change
- 8% Worsened


Non-Contraceptive Benefit: Dysmenorrhea Improvement

Women Experiencing Changes in Dysmenorrhea While Using Implant

- 81% Improved/Resolved
- 14% No Change
- 5% Increased


Changes in Bleeding Pattern

"Irregularly irregular" cycles, including:
- Frequent irregular bleeding
- Heavy menstrual flow
- Prolonged bleeding
- Amenorrhea
- Spotting
- Unpredictability of bleeding pattern over time


Bleeding Patterns are Unpredictable

US Data

- n=330

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

Bleeding Does Not Result in Anemia
Mean Hgb (g/dL)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>24 Months</th>
<th>36 Months</th>
</tr>
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<tbody>
<tr>
<td>N=926</td>
<td>N=663</td>
<td>N=535</td>
<td></td>
</tr>
</tbody>
</table>


Drug-drug Interactions

<table>
<thead>
<tr>
<th>Potent Inhibitors</th>
<th>Moderate Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>amiodarone (Cordarone)</td>
<td>amprenavir (Agenerase)</td>
<td>carbamazepine (Tegretol)</td>
</tr>
<tr>
<td>atazanavir (Reyataz)</td>
<td>aprepitant (Emend)</td>
<td>efavirenz (Sustiva)</td>
</tr>
<tr>
<td>cisapride (Propulsid)</td>
<td>ciprofloxacin (Cipro)</td>
<td>nevirapine (Viramune)</td>
</tr>
<tr>
<td>darfotrionycyn (Blasivin)</td>
<td>diltiazem (Cardizem)</td>
<td>phenytoin (Dilantin)</td>
</tr>
<tr>
<td>iraconazole (Nizoral)</td>
<td>erythromycin</td>
<td>phenobarbital</td>
</tr>
<tr>
<td>nefazodone (Serzone)</td>
<td>fluconazole (Diflucan)</td>
<td>rifabutin (Mycobutin)</td>
</tr>
<tr>
<td>nefilnavir (Viracept)</td>
<td>fluvoxamine (Luvox)</td>
<td>rifampin (Rifadin)</td>
</tr>
<tr>
<td>ritonavir (Norvir)</td>
<td>fosamprenavir (Lexiva)</td>
<td>St. John’s Wort</td>
</tr>
<tr>
<td>tipiluromycin (Ketai)</td>
<td>grapefruit juice</td>
<td>verapamil (Calan)</td>
</tr>
<tr>
<td>torkeandomycin (TAD)</td>
<td>nefazodone (Noroxin)</td>
<td>&gt; 100 mg/d</td>
</tr>
<tr>
<td>voriconazole (Vfend)</td>
<td>verapamil (Calan)</td>
<td></td>
</tr>
</tbody>
</table>

ANON. Obstet Gynecol. 2007  
Rothbard 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.

Insertion Site Symptoms

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>48</td>
<td>3.4</td>
</tr>
<tr>
<td>Redness</td>
<td>6</td>
<td>0.4</td>
</tr>
<tr>
<td>Swelling</td>
<td>5</td>
<td>0.4</td>
</tr>
<tr>
<td>Hematoma</td>
<td>4</td>
<td>0.3</td>
</tr>
<tr>
<td>Expulsion</td>
<td>0</td>
<td>0</td>
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N = 1,409

Organon data on file.
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Adverse Effects

<table>
<thead>
<tr>
<th></th>
<th>N=942</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All Studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding irregularities¹</td>
<td>11.0%</td>
<td></td>
</tr>
<tr>
<td>Emotional Lability²</td>
<td>2.3%</td>
<td></td>
</tr>
<tr>
<td>Weight Increase</td>
<td>2.3%</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1.6%</td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>1.3%</td>
<td></td>
</tr>
<tr>
<td>Depression³</td>
<td>1.0%</td>
<td></td>
</tr>
</tbody>
</table>

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.

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

No Increased Risk of Deep Vein Thrombosis (DVT)

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

Ovarian Cysts

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

Hidalgo, 2006

Continuation ‘Real-Life’

The Single-Rod Implant:
• Patient Selection
• Timing
• Counseling


Hidalgo, MM. Contraception. 2006
Implanon Physician Insert, 2006.
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Discontinuation ‘Real-Life’
Reasons given for Implanon removal before completion of the 3-year period (n=60)

- Amenorrhea 9%
- Planning pregnancy 15%
- Contraceptive no longer needed 7%
- Weight gain 10%
- Mood swings 10%
- Other 15%
- Bleeding irregularly 46%

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

Implanon Physician Insert, 2006.

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.

Patient Counseling

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

2008
Reproductive Health
Education • Research • Advocacy

more…
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Patient Counseling: Efficacy

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

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

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…

more…

more…
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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...

Insertion Timing (continued)

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

‘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

‘Quick Start’ Method

Short Insertion and Removal Time

Insertion
< 1 minute

Removal
< 3 minutes

Components of the Single-Rod Implant Insertion System

Preparation Tips

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

More

‘Quick Start’ Method

Short Insertion and Removal Time

Components of the Single-Rod Implant Insertion System

Preparation Tips

More...
**Insertion Steps Overview**

- Mark site and sterilize
- Inject local anesthetic just under skin
- Remove applicator, maintain sterility
- Verify implant is within needle of applicator
- Remove needle cover

**Insertion Steps Overview (continued)**

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

**Insertion Steps Overview (continued)**

- Turn obturator 90 degrees and fix with one hand (c)
- With other hand, pull needle out (d)
- 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**

- Locate rod and mark site (a)
- Sterilize site
- Inject local anesthetic under distal end of rod (b)
- Press down on proximal end of rod

**Removal Steps Overview (continued)**
Removal Steps Overview (continued)

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

Trouble Shooting: Removals

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

In Summary

Dispelling Misperceptions

Realities about Contraceptive Implants

1. Insertion and removal are not time-consuming or hard to learn
2. Bleeding patterns are accepted by most women
3. No higher risk of litigation than other forms of contraception

No Higher Risk of Litigation

Number of implants withdrawn from market by regulatory agency

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


In Summary

In Summary

Dispelling Misperceptions

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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

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

Disadvantages (continued)

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

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

(continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
<th>Location</th>
</tr>
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<tbody>
<tr>
<td>Mitchell Creinin, MD (chair)</td>
<td>University of Pittsburgh</td>
<td>Pittsburgh, PA</td>
</tr>
<tr>
<td>Phillip Darney, MD, MSc</td>
<td>University of California</td>
<td>San Francisco, CA</td>
</tr>
<tr>
<td>Wendy Grobe, MSN, CRNP</td>
<td>University of Pennsylvania</td>
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</tr>
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<td>Patricia Murphy, CNM, DrPH</td>
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<td>Lee Shulman, MD</td>
<td>Northwestern University</td>
<td>Chicago, IL</td>
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