New Developments in Contraception: The Single-Rod Implant

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Organon Pharmaceuticals
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Learning Objectives

• Discuss the features of contraceptive implants
• Dispel provider myths about implants
• Discuss characteristics and clinical expectations of the single-rod implant
• Describe steps for insertion and removal
• List counseling topics for discussion with patients
Contraceptive Use, 1988–2002

% Distribution, Women Aged 15–44 Years

- Oral Contraceptives
- Implant
- IUD
- Condom
- Diaphragm
- Female Sterilization

Why Another Contraceptive?

- High unintended pregnancy rate
- High rates of misuse and discontinuation
- Patient interest in alternative methods
- Sterilization regret
- Greater number of safe and effective options allows for better match with individual lifestyle
Risk of Unintended Pregnancy

• Proportion of women at risk for pregnancy increased significantly between 1995 and 2002, from 5.2% to 7.4%
• This represents an increase of 1.43 million women

Mosher. Advance Data No. 350 2004
High Proportion of Pregnancies Are Unintended

<table>
<thead>
<tr>
<th>Age</th>
<th>Proportion Unintended</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–19</td>
<td>78.0%</td>
</tr>
<tr>
<td>20–24</td>
<td>58.5%</td>
</tr>
<tr>
<td>25–29</td>
<td>39.7%</td>
</tr>
<tr>
<td>30–34</td>
<td>33.1%</td>
</tr>
<tr>
<td>35–39</td>
<td>40.8%</td>
</tr>
<tr>
<td>&gt;40</td>
<td>50.7%</td>
</tr>
<tr>
<td>Total</td>
<td>49.2%</td>
</tr>
</tbody>
</table>

Henshaw. Fam Plann Perspect 1998
High Rate of Contraceptive Misuse

• 1 million pregnancies/year are due to misuse or discontinuation of oral contraceptives (OCs)—the most common reversible contraceptive used in the United States today

• > 50% of all OC users miss more than 2 pills by the 3rd cycle

• Based on 2002 data from the NSFG, it appears that teen use of injectable contraceptives has contributed to the decrease in rate of unintended pregnancy

Potter. *Fam Plann Perspect* 1996
Mosher. *Advance Data* No. 350 2004
Typical Use Versus Perfect Use

% of Women Experiencing an Unintended Pregnancy Within the First Year of Use

Orange = typical use
Blue = perfect use

High Rate of OC Discontinuation

• Of 1,657 women initiating or switching to a new OC, 18% discontinued by 6 months

• Reasons:
  – Side effects (46%)
  – No need for contraception (23%)
  – Method-related problems (14%)
  – Other, unspecified (17%)

Interest in Contraceptive Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>% Satisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal Ring</td>
<td>88</td>
</tr>
<tr>
<td>IUD</td>
<td>87</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>86</td>
</tr>
<tr>
<td>Injection</td>
<td>80</td>
</tr>
<tr>
<td>OC</td>
<td>79</td>
</tr>
<tr>
<td>Patch</td>
<td>75</td>
</tr>
<tr>
<td>Condoms</td>
<td>60</td>
</tr>
<tr>
<td>Other</td>
<td>52</td>
</tr>
</tbody>
</table>

Mean (out of 5):
- Vaginal Ring: 4.6
- IUD: 4.5
- Diaphragm: 3.6
- Injection: 4.1
- OC: 4.1
- Patch: 3.9
- Condoms: 3.6
- Other: 3.8

Harris Interactive Poll 2004
Sterilization Regret

- 20% of women who select sterilization at age 30 years or younger later express regret.
- Most common reasons for regret—desire for more children (33%) and divorce/remarriage (24%).
- Reversible methods can be as effective as sterilization.
Impact of Choice

% of Women Discontinuing Contraceptive Use at 1 Year

Choice Granted          Choice Denied

Pariani. Stud Fam Plann 1991
Unmet Need

For a contraceptive method that is

• Highly effective
• Safe
• Not a daily method
• Rapidly reversible
Worldwide History of Contraceptive Implant Use

1950s  Norplant (6 rods) developed
1960s  First used for contraception
1990   Approved in United States
1994   Used by almost 1 million American women
2002   Manufacture discontinued

Today
• Norplant is registered in more than 60 countries
• Norplant II (2 rods) is registered in Europe
• Implanon (single rod) likely to be approved by FDA soon

Planned Parenthood. 2004
Glasier. Contraception 2002
Features of Contraceptive Implants

- Highly effective and rapidly reversible
- Discreet
- Require no daily or coitus-related action
- Provide non-fluctuating hormone levels and extended contraceptive protection
- Contain no estrogen
- Can be used during lactation

Reinprayoon. *Contraception* 2000
Diaz. *Contraception* 2000
Features of Contraceptive Implants (continued)

• Cause unscheduled vaginal bleeding
• Require clinician visits for insertion and removal
Dispelling Provider Myths About Contraceptive Implants

• Insertion and removal are neither time-consuming nor difficult to learn
• Implants are not associated with higher risk of ectopic pregnancy
• Implants are not associated with high litigation risk for providers
Insertion and Removal Are Neither Time-Consuming nor Difficult

<table>
<thead>
<tr>
<th></th>
<th>Single-rod implant</th>
<th>Multiple-rod implant</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insertion time (minutes)</td>
<td>0.61</td>
<td>3.90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Removal time (minutes)</td>
<td>2.18</td>
<td>11.25</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Zheng. Contraception 1999
No Increased Risk of Ectopic Pregnancy

- No pregnancies (intrauterine or ectopic) reported during 4,103 woman-years of use for single-rod implant in 13 clinical trials
- Multiple-rod implant associated with ectopic rate of 0.3 to 0.6 per 1,000 woman-years
- US baseline ectopic rate is 19.7 per 1,000 pregnancies

Glasier. Contraception 2002
CDC. MMWR 1995
Not Associated with High Litigation Risk for Providers

• How many lawsuits lost by Norplant manufacturer?
  – Zero

• How many implants withdrawn from market by regulatory agency?
  – Zero
Single-Rod Implant

• Trade name: Implanon®
• One rod 40 mm x 2 mm
• Core:
  – 40% ethylene vinyl acetate (EVA)
  – 60% etonogestrel (68 mg)
• Rate-controlling membrane: 100% EVA
Single-Rod Implant Study Worldwide

Green = not yet available
Pink = available for use
Components of the Single-Rod Implant Insertion System
Other Implant Systems

- 6-Rod Implant (Norplant)
- 2-Rod Implant (Jadelle)
Release Rate of 3-Ketodesogestrel (ENG)

Release Rate of ENG from Implanon (µg/d)

Initial | After Year 1 | After Year 2 | After Year 3

Huber. Contraception 1998
Pharmacokinetics

![Graph showing etonogestrel concentration (pg/mL) over time after implant insertion (months 0–36) for Thailand (n=15), Europe (n=16), and U.S. (n=20).](image)

Organon Data on File
Mechanism of Action

- Inhibits ovulation
  - No ovulation was observed for 30 months in clinical trials
    - Only 2 out of 31 (6.5%) subjects ovulated in Year 3, with no resulting pregnancies
- Increases viscosity of cervical mucus

Organon Data on File; Implanon™ [package insert]
## Efficacy

<table>
<thead>
<tr>
<th>Year</th>
<th>Subjects with Ovulation</th>
<th>Cycles with Ovulation</th>
<th>Subjects with Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>1</td>
<td>0/47</td>
<td>0</td>
<td>0/177</td>
</tr>
<tr>
<td>2</td>
<td>0/39</td>
<td>0</td>
<td>0/103</td>
</tr>
<tr>
<td>3</td>
<td>2/31</td>
<td>6.5</td>
<td>4/86</td>
</tr>
</tbody>
</table>

*Organon Data on File*
Efficacy from Multiple Sources

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Women</td>
<td>1,117</td>
</tr>
<tr>
<td>No. of Cycles</td>
<td>26,787</td>
</tr>
<tr>
<td>No. of Pregnancies</td>
<td>0</td>
</tr>
</tbody>
</table>

Organon Data on File
## Body Weight Distribution and Efficacy

<table>
<thead>
<tr>
<th>Weight Range</th>
<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; 50 kg</td>
<td>182</td>
<td>157</td>
<td>127</td>
<td>0</td>
</tr>
<tr>
<td>50–60 kg</td>
<td>539</td>
<td>423</td>
<td>292</td>
<td>0</td>
</tr>
<tr>
<td>60–70 kg</td>
<td>442</td>
<td>344</td>
<td>239</td>
<td>0</td>
</tr>
<tr>
<td>70–80 kg</td>
<td>201</td>
<td>151</td>
<td>109</td>
<td>0</td>
</tr>
<tr>
<td>80–90 kg</td>
<td>42</td>
<td>35</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>&gt;90 kg</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Total n = 3,312

Organon Data on File
Return to Fertility

- ENG Levels undetectable within 1 week

Davies. Contraception 1993
Croxatto. Contraception 1998
Lahteenmaki. Fertil Steril 1980
Clinical Management Issues

- No anemia
- No reduction in bone mineral density
- No increased risk of deep vein thrombosis
- Little pain at site

- Associated non-contraceptive benefits
- Changes in bleeding pattern
- Minor weight change
- Mild side effects:
  - Breast pain
  - Headache
Changes in Bleeding Pattern

• “Irregularly irregular” cycles
• Amenorrhea more common
• Patterns include:
  – Frequent irregular bleeding
  – Heavy menstrual flow
  – Prolonged bleeding
  – Amenorrhea
  – Spotting
  – Unpredictability of bleeding pattern over time

Affandi B. *Contraception* 1998
Zheng SR. *Contraception* 1999
Bleeding Patterns

US Data  
n=330

Months

Subjects (%)  

- Orange: Infrequent bleeding
- Cyan: Amenorrhea
- Red: Prolonged bleeding
- Gray: Frequent bleeding

Funk. (in press) Contraception
## Bleeding Pattern Comparison

<table>
<thead>
<tr>
<th></th>
<th>Single Rod n=432</th>
<th>Multiple Rod n=430</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Bleeding-spotting days per 90 days</td>
<td>7.7</td>
<td>10.2</td>
</tr>
<tr>
<td>No. Bleeding days per 90 days</td>
<td>3.3</td>
<td>4.6</td>
</tr>
<tr>
<td>No. Bleeding-spotting episodes per 90 days</td>
<td>1.5</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Affandi. *Contraception* 1998
## Bleeding Pattern Comparison (continued)

<table>
<thead>
<tr>
<th></th>
<th>Single Rod n=432</th>
<th>Multiple Rod n=430</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amenorrhea</td>
<td>40.6%</td>
<td>29.4%</td>
</tr>
<tr>
<td>Infrequent bleeding-spotting</td>
<td>32.2%</td>
<td>33.5%</td>
</tr>
<tr>
<td>Frequent bleeding-spotting</td>
<td>2.5%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Prolonged bleeding-spotting</td>
<td>3.4%</td>
<td>4.5%</td>
</tr>
</tbody>
</table>

Affandi. *Contraception* 1998
Management of Bleeding

• Few data available

• Considerations:
  – Oral estrogen
  – NSAIDs
  – Combination OCs
  – Watchful waiting
Bleeding Does Not Result in Anemia

<table>
<thead>
<tr>
<th></th>
<th>Mean Hgb (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>11.8</td>
</tr>
<tr>
<td>24 mo</td>
<td>12.2</td>
</tr>
<tr>
<td>36 mo</td>
<td>12.4</td>
</tr>
</tbody>
</table>
Minor Weight Change

- Small but steady weight increases seen
- In a comparative analysis, weight increase seen in 21% of women but reported as drug-related in only 6.4%
- A comparative study found mean increase similar to that seen with non-medicated IUD
## Little Pain at Insertion Site

*N = 1,409*

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling</td>
<td>5</td>
<td>0.4</td>
</tr>
<tr>
<td>Redness</td>
<td>6</td>
<td>0.4</td>
</tr>
<tr>
<td>Pain</td>
<td>48</td>
<td>3.4</td>
</tr>
<tr>
<td>Hematoma</td>
<td>4</td>
<td>0.3</td>
</tr>
<tr>
<td>Expulsion</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Organon Data on File*
Mild Side Effects

- Breast pain (9%)
- Headache (8.5%)
No Reduction in Bone Mineral Density

- Open, prospective comparison 2-year study of 44 women with single-rod implant and 29 with non-medicated IUD
- Changes in bone mineral density similar

Beerthuizen. *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. Contraception 1998
Non-Contraceptive Benefit: Acne Improvement

- 61% Acne Improved During Study
- 8% Acne Worsened
- 32% No Change

Funk. (in press) *Contraception*
Non-Contraceptive Benefit: Dysmenorrhea Improvement

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

Funk. (in press) *Contraception*
Reasons for Discontinuation

Number at study initiation = 1,300

Discontinuation (% of Total Subjects)

- Frequent Bleeding: Year 1 (10%), Year 2 (6%)
- Prolonged Bleeding: Year 1 (12%), Year 2 (4%)
- Weight Gain: Year 1 (3%), Year 2 (2%)
- Emotional Lability: Year 1 (1%), Year 2 (1%)
- Acne: Year 1 (2%)

Organon Data on File
Croxatto. *Hum Reprod* 1999
Zheng. *Contraception* 1999
Patient Selection

Women who desire:

• Long-term contraception
• High effectiveness
• Rapid reversibility
• Estrogen-free contraception
Contraindications

- Known or suspected pregnancy
- Active thrombosis or thromboembolic disorders
- Hepatic tumor or active liver disease
- Undiagnosed abnormal genital bleeding
- Known or suspected carcinoma of the breast or history of breast cancer
- Progestogen-dependent tumor
- Hypersensitivity to the components of the implant
Insertion Steps Overview

1. Mark site and sterilize.
2. Inject 1% lidocaine just under skin.
3. Remove applicator from pack, maintaining sterility.
4. Verify implant is within needle of applicator.
5. Remove needle cover.
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.
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.
Insertion Timing

- **Standard start-up**
  - Insertion within 5 days of initiation of menses

- **Switching from combined OC**
  - Insertion within 7 days of last active tablet

- **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
Insertion Timing (continued)

• After abortion
  – Within 5 days of 1\textsuperscript{st} trimester abortion
  – Within 6 weeks of 2\textsuperscript{nd} trimester abortion

• After childbirth
  – Within 6 weeks
  – Considered safe with lactation after 6 weeks
  – Clinical study: low concentrations present in milk; no associated adverse events
‘Quick Start’ Method

- Single-rod implant is inserted at any time during menstrual cycle
- Provider should recommend use of back-up barrier contraception for 7 days
- If Quick Start method is used with emergency contraception, provider should obtain urine pregnancy test in 4 weeks
Removal Steps Overview

1. Locate rod and mark site. (a)
2. Sterilize site.
3. Inject 1% lidocaine *under* distal end of rod. (b)
4. Press down on proximal end of rod.
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 butterfly closure.
Patient Counseling

• Important for all women needing contraception
• May include written materials
• Should be sensitive to literacy level and language requirements
• Must include informed consent
Patient Counseling Topics

- Description of implant
- Efficacy
- Return to fertility
- Bleeding patterns
- Potential side effects
- Tips for dealing with bleeding patterns and other side effects
- Overview of insertion and removal
- Follow-up
Dispelling Common Myths About Contraceptive Implants

- Virtually invisible
- No hair loss or excessive growth
- No breakage or movement in arm
- Insertion not painful
- Infection rare
- No long-term health problems
- No health problems in children conceived after removal
- No effect on libido

Meirik. Obstet Gynecol 2001
Zheng. Contraception 1999
Croxatto. Hum Reprod 1999
Brache. Contraception 2002
The Single Rod Implant

• New method for women that fulfills unmet need
• Advancement in contraceptive options
• Offers women another choice in safe, effective contraception
Resources

Summary

- Contraceptive implants widely used worldwide
- Implants are safe, highly effective, and rapidly reversible
- Majority of reproductive-age women are candidates
- New option for women that fulfills unmet need