Long-acting Contraceptive Methods for Women

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Today’s Presentation

Part I  Contraceptive use worldwide

Part II  Overview of long-acting contraceptives

Part III  Current and future challenges
Most contraceptive users worldwide rely on modern methods.

Large proportion of the world’s couples are using contraception.

Level of contraceptive use is higher in developed regions, highest in Europe and lowest in Africa.

Short-acting and reversible methods are more popular in developed regions.

Longer-acting and highly effective methods are more used in less developed regions.

Source: UN Population Division 2001. World Contraceptive Use
Part II: Long-acting methods

1. Injectable preparations
2. Implantable contraceptives
3. Intrauterine methods
4 long term contraceptives as effective as female sterilization

<table>
<thead>
<tr>
<th>METHOD</th>
<th>TRADE NAME</th>
<th>USE TIME</th>
<th>USERS (in million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCu380A IUD</td>
<td>Paragard(^R)</td>
<td>10-12 years</td>
<td>30-40</td>
</tr>
<tr>
<td>6 Silastic capsules implant</td>
<td>Norplant(^R)</td>
<td>7 years</td>
<td>8</td>
</tr>
<tr>
<td>LNG releasing IUS</td>
<td>Mirena(^R)</td>
<td>5 years</td>
<td>2</td>
</tr>
<tr>
<td>DMPA</td>
<td>Depo Provera(^R)</td>
<td>3 months</td>
<td>12</td>
</tr>
</tbody>
</table>
Injectable contraceptives
Injectable contraceptives (1)

- 1967: first registration of an injectable
- 1992: approved by the US FDA
- Currently registered in > 100 countries
- Used by >10 million women worldwide
Injectable contraceptives (2)

1. Two-to-three monthly: progestogen-only
   - NET-EN  Examples: Noristerat\textsuperscript{R}
   - DMPA  Examples: Depo-Provera\textsuperscript{R}, Megestron\textsuperscript{R}

2. Once-a-month: combined progestogen-estrogen
   - Examples: Cyclophem\textsuperscript{R}, Cycloprovera\textsuperscript{R}, Mesigyna\textsuperscript{R}
Mechanism of action

• Mainly: ovulation inhibition

• Effects on morphology and function of endometrium, Fallopian tubes, cervix
## Combined monthly injectables

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Composition</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perlutal</td>
<td>Dihydroxyprogesterone acetophenide 150 mg + E₂ enanthate 10 mg</td>
<td>Latin America, Spain</td>
</tr>
<tr>
<td>Topasel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclofem</td>
<td>DMPA 25 mg + E₂ cypionate 5 mg</td>
<td>22 c., Latin America, Indonesia, Thailand</td>
</tr>
<tr>
<td>Lunelle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesigyna</td>
<td>NET-EN 50 mg + E₂ valerate 5 mg</td>
<td>Latin America, Turkey, 7 African c., China</td>
</tr>
<tr>
<td>Norigynon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese injectable No1</td>
<td>17α-hydroxyprogesterone caproate 250 mg + E₂ valerate 5 mg</td>
<td>China</td>
</tr>
<tr>
<td>Mego-E</td>
<td>Megestrol acetate 25 mg + 17β E₂ 3.5 mg</td>
<td>China</td>
</tr>
</tbody>
</table>
Combined monthly injectables: Typical pharmacokinetic profile

Adapted from: Fraser & Diczfalusy, 1980
DMPA: Background

- Most commonly used injectable
- 150 mg / 1 ml aqueous solution
- Administered by deep i.m. injection
- Produces depot at site of injection
- Dissolves slowly with high initial serum levels
- Upon discontinuation delayed return of fertility
Pharmacokinetic profiles of hormones administered by different routes and different preparations

![Graph showing pharmacokinetic profiles of hormones](image)
DMPA: Contraceptive effectiveness

- Highly effective for at least 3 months
- Pearl Index 0.3 (pregnancies/ 100 women/ year)
- 3 pregnancies/ 1000 women/ year
- Provided injections are regularly spaced
- Some flexibility in timing of return visits
DMPA
DMPA: Menstrual bleeding disturbances

- **Spotting**: common during first months of use
- **Heavy bleeding**: during first months, rare
- **Amenorrhea**: frequent and increasing over time:
  DMPA: 55% of users at 1 year, 80% at 5 years
- **Highlights importance of good counseling**
### DMPA: Non-menstrual adverse events: Discontinuation rates at 1 year (in %)

<table>
<thead>
<tr>
<th></th>
<th>DMPA</th>
<th>NET-EN</th>
<th>Cyclofem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal discomfort</td>
<td>1.1</td>
<td>0.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Weight gain</td>
<td>2.1</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td>0.7</td>
<td>0.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.9</td>
<td>0.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.2</td>
<td>1.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Headaches</td>
<td>2.3</td>
<td>2.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>0.9</td>
<td>0.6</td>
<td>-</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.5</td>
<td>0.7</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>8.7</td>
<td>9.3</td>
<td>6.3</td>
</tr>
<tr>
<td><strong>Woman-months</strong></td>
<td>20,550</td>
<td>10,361</td>
<td>10,969</td>
</tr>
</tbody>
</table>
DMPA & bone metabolism

- Hypo-estrogenic effect on bone mineral density
- **Adults:** reversible upon discontinuation, no apparent long-term effect
- **Adolescent girls:** peak bone mass not yet attained, slow down of normal bone mass accumulation
- Evidence not conclusive: advantages outweigh concerns

Implantable contraceptives
Which role do implants play in the worldwide method mix?
World Contraceptive Use 2001: Share of Implants in the method mix

## Implants: Numbers on Current Use

<table>
<thead>
<tr>
<th></th>
<th>World</th>
<th>No. of countries where licensed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norplant</td>
<td>4 million</td>
<td>62</td>
</tr>
<tr>
<td>Jadelle</td>
<td>15,000</td>
<td>11</td>
</tr>
<tr>
<td>Implanon</td>
<td>1 million</td>
<td>25</td>
</tr>
</tbody>
</table>
Implants: Regulatory Approvals

1983  Finland first country to approve Norplant
1984  US FDA approves Norplant for 5 years
1996  US FDA first to approve Jadelle for 3 years
1997  Finland approves Jadelle for 3 years
1998  Indonesia first to approve Implanon
## Implant Contraceptives for Women

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Type of progestin</th>
<th>Number of Units</th>
<th>Life span (in years)</th>
<th>Current status of approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norplant</td>
<td>Levonorgestrel</td>
<td>6 capsules</td>
<td>7</td>
<td>Approved</td>
</tr>
<tr>
<td>Jadelle</td>
<td>Levonorgestrel</td>
<td>2 rods</td>
<td>5</td>
<td>Approved</td>
</tr>
<tr>
<td>Implanon</td>
<td>Etonogestrel</td>
<td>1 rod</td>
<td>3</td>
<td>Approved</td>
</tr>
<tr>
<td>Nestorone</td>
<td>Nestorone</td>
<td>1 rod</td>
<td>2</td>
<td>Under development</td>
</tr>
<tr>
<td>Elcometrine</td>
<td>Elcometrine</td>
<td>1 capsule</td>
<td>0.5</td>
<td>Licensed in Brazil</td>
</tr>
<tr>
<td>Uniplant</td>
<td>Nomegestrol ac.</td>
<td>1 capsule</td>
<td>1</td>
<td>Not available on the market</td>
</tr>
</tbody>
</table>

Norplant
Jadelle
Norplant & Jadelle
Norplant & Jadelle

Norplant (6 capsules)
- 216 mg LNG
- Silastic medical adhesive
- Silastic tubing
- Levonorgestrel
  - 36 mg free crystals
  - 75 mg crystals in silicone copolymer

Jadelle (2 rods)
- 150 mg LNG
- 2.4 mm
Implanon
Implanon

Sterile disposable applicator
Obturator
Cannula with needle
Needle shield
Rod
Implanon

Single-rod implant with 68 mg etonogestrel (ENG, 3-ketodesogestrel)

- EVA copolymer rod covered by a thin EVA membrane
- 68 mg ENG embedded in EVA copolymer

40 mm

2.0 mm
Insertion & Removal

- Minor surgery under local anaesthesia
- Inner aspect of the non-dominant upper arm
- Subdermal placement
- Implanon: surgery only for removal
- Norplant: difficult and time consuming removals
- Provider-dependent method
- Differences in mean insertion & removal times
## Insertion & Removal

### Mean duration (in minutes)

<table>
<thead>
<tr>
<th></th>
<th>Insertion</th>
<th>Removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norplant</td>
<td>4.3 (0.8 - 18.0)</td>
<td>10.2 (1.3 - 50.0)</td>
</tr>
<tr>
<td>Jadelle</td>
<td>2.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Implanon</td>
<td>1.1 (0.03 - 5.0)</td>
<td>2.6 (0.2 - 20.0)</td>
</tr>
</tbody>
</table>

Source: Mascarenhas L. Contraception 1998;58:79S.
Serum Levels of Levonorgestrel (LNG) One Week following insertion

Serum Levels of Levonorgestrel (LNG)

One Year after insertion

Serum Levels of Levonorgestrel (LNG)

First 3 years of use

Serum Levels of Levonorgestrel (LNG)

5 years of use
Contraceptive Effectiveness: Norplant and Jadelle (1)

- Annual pregnancy rates
  - year 5: < 1/100 Norplant & Jadelle
  - year 7: < 1/100 Norplant
  - year 7: 2.0/100 Jadelle

- Cumulative pregnancy rates
  - year 5: 1.1/100 Norplant & Jadelle
  - year 7: 1.9/100 Norplant

Contraceptive Effectiveness: Norplant and Jadelle (2)

- Identical clinical performance through year 5
- **Norplant**: remains highly effective through year 7
  - equal to tubal ligation
- **Jadelle**: highly effective through year 5
  - remove at end of year 5

Contraceptive Effectiveness: Implanon

- 13 studies with 1,700 women in 10 countries
- 4100 woman-years of observation
- Pregnancy rate over 3 years: zero
- Pregnancy rate over 4 years (2 studies): zero
- In 175 women with body weight >70 kg: zero

Menstrual Bleeding Disturbances

Norplant and Jadelle
- prolonged or irregular bleeding
- spotting between periods
- amenorrhoea

Implanon
- prolonged or irregular bleeding
- amenorrhoea

### Non-menstrual Adverse Events

<table>
<thead>
<tr>
<th>Symptom</th>
<th>% users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>10-30</td>
</tr>
<tr>
<td>Weight gain</td>
<td>4-22</td>
</tr>
<tr>
<td>Acne</td>
<td>3-22</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4-11</td>
</tr>
<tr>
<td>Mood changes</td>
<td>1-9</td>
</tr>
<tr>
<td>Hair loss</td>
<td>2-5</td>
</tr>
</tbody>
</table>

**Discontinuation rates below 5%**
Return to Fertility

- Implant removal possible at any time
- **Within days:** progestins cleared from circulation
- **Within 3 months:** return of normal ovulation
- **Within 1 year:** high pregnancy rates

No adverse effect on post-removal fertility
Requirements for implant provision

Training of providers

For counseling, insertion, removal, management of side effects and of difficult removals

Adaptation of health services

Access to trained providers for insertion, follow up, removal on demand, facilities, and supplies
WHO Study A15229:

Multi-centre randomized clinical trial of two implantable contraceptives for women:

Jadelle and Implanon.
WHO Project A15229: Study Design & Sample Size

- Randomized clinical trial (RCT)
- Total sample size: 3,000 women
  - 2,000 implant users
  - 1,000 Copper-IUD users
- 10 study centres in 9 countries
- Semi-annual follow-up for up to 3 years
Project A15229: Principal Investigators at Investigator’s Meeting, Geneva, June 2002
Intrauterine methods
Intrauterine methods

1. Levonorgestrel-releasing intrauterine system

2. Copper-releasing intrauterine device
Background: LNG-IUS (1)

- 1990 first regulatory approval (Finland)
- 2000 approved by US FDA
- Brand names: Mirena®, LevoNova®
- Now registered in > 100 countries
- Number of current users > 2 million
Background: LNG-IUS (2)

- T-shaped flexible plastic frame
- Hormone reservoir containing 52 mg LNG
- Daily LNG release rate: 20 µg
- Sustained release into the uterine cavity
- Contraceptive protection for at least 5 years
Background: LNG-IUS (3)
LNG-IUS: Mechanism of action (1)

High local LNG concentration

Suppresses endometrial morphology
Thickens cervical mucus

Inhibits sperm motility & function
Prevents fertilisation
LNG-IUS: Return of fertility

Upon discontinuation:

• Endometrial changes fully reversible
• Prompt return of fertility
• Planned pregnancy rates at 1 year: > 80%
LNG-IUS: Contraceptive effectiveness

• Pregnancy rates (per 100 women):
  Annual 0.1 - 0.2
  Cumulative 0.5

• Single most effective method of reversible contraception, closely followed by the TCu380A

• Nearly equal to female sterilization
LNG-IUS: Menstrual bleeding pattern

Reduction in volume and duration of bleeding

- Lighter + shorter periods: starts at 3 - 6 months
- Spotting: subsides after 6 months
- Amenorrhea: 25% at 1 year, 60% at 10 years
- Potential non-contraceptive health benefits

Single most common reason for discontinuation
Amenorrhea: the issue of acceptability

- Perceptions vary according to culture & religion
- Early surveys: amenorrhea unacceptable
- Recent survey: variable picture
- African women more likely to want monthly bleeds

Non-menstrual adverse events

- Headaches, nausea
- Lower abdominal pain, back pain
- Acne, hair loss
- Breast tenderness
- Mood swings
- Weight gain

Prevalence low, symptoms subside after 3 - 4 months
TCu380A Intrauterine device (IUD)
TCu380A Intrauterine device (IUD)

- 1984 approved by US FDA for 4 years
- 1988 on US market ‘Paragard T380A’
- Registered in >70 countries
- T-shaped flexible plastic frame
- Highly effective in preventing pregnancy
TCu380A IUD [vs LNG IUS]

- 30-40 million current users [2 million]
- Efficacy period at least 10 years [5 years]
- Releases copper [levonorgestrel]
- Heavier & painful periods [lighter & shorter]
- Most cost-effective reversible contraceptive
- Most affordable ever developed
- Differences in clinical performance
## TCu380A versus LNG-IUS: Discontinuation rates per 100 women at 6 years of use

<table>
<thead>
<tr>
<th></th>
<th>TCu 380A</th>
<th>20 µg LNG device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total pregnancy</td>
<td>2.0 (0.5)</td>
<td>0.5 (0.2)</td>
</tr>
<tr>
<td>- Ectopic pregnancy</td>
<td>0.1 (0.1)</td>
<td>-</td>
</tr>
<tr>
<td>- Intrauterine pregnancy</td>
<td>1.9 (0.4)</td>
<td>0.5 (0.2)</td>
</tr>
<tr>
<td>Expulsions</td>
<td>8.2 (0.8)</td>
<td>7.5 (0.8)</td>
</tr>
<tr>
<td>Pelvic inflammatory disease</td>
<td>0.1 (0.1)</td>
<td>0.3 (0.1)</td>
</tr>
<tr>
<td>- Menstrual reasons</td>
<td>10.9 (0.9)</td>
<td>35.9 (1.4)</td>
</tr>
<tr>
<td>- Amenorrhoea</td>
<td>0.5 (0.3)</td>
<td>23.6 (1.3)</td>
</tr>
<tr>
<td>- Reduced bleeding</td>
<td>3.1 (0.5)</td>
<td>10.9 (1.0)</td>
</tr>
<tr>
<td>- Increased bleeding</td>
<td>7.1 (0.7)</td>
<td>5.9 (0.7)</td>
</tr>
<tr>
<td>Total device-related removals</td>
<td>25.5 (1.1)</td>
<td>47.8 (1.3)</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>7.9 (0.7)</td>
<td>5.8 (0.7)</td>
</tr>
<tr>
<td>Woman-years</td>
<td>7420.7</td>
<td>6381.6</td>
</tr>
</tbody>
</table>

Source of data: WHO Study 91908 Randomized trial TCu380A vs LNG-releasing IUD
Long-acting methods: Common features

- Long-acting, convenient & reversible
- Highly effective & generally safe
- Efficacy independent of compliance
- Unpredictable bleeding disturbances
- No dual protection
- Provider dependency
- Requires training of service provider
- Requires adaptation of health services
Part III: Contraception over the past 50 years ...

- Safer, more effective, more widely used
- Broader choice
- Contraceptive and non-contraceptive benefits
- More and more women find some type of hormonal contraceptive acceptable

However ...
Family planning: the “unmet needs”

- Unmet need: 120 million
- Ultimate unmet need: 45 million
- Unsafe induced abortion: 20 million
- Maternal deaths from unsafe abortion: 78,000
- Contribution to maternal mortality: 15%
Progress towards reducing the unmet needs requires ...

• Improved access to good quality services
• Strengthened capacity of health systems
• Improved education & counseling of users
• New & improved methods
Leads in contraceptive R & D

1- Long-acting methods under user’s control
   Vaginal ring, transdermal patch, self-administered injectable (Uniject®)

2- Dual protection methods
   Microbicides, female condom

3- Emergency post-coital methods
   Yuzpe regimen, levonorgestrel, anti-progestins (mifepristone)

4- Male methods
   Hormonal methods, improved (non-surgical) vasectomy

5- Methods with less side effects
   Immunocontraceptives (hCG), frameless IUDs
... Concluding remarks
Reducing the unmet needs

Requires an integrated approach of:
- Contraceptive research & development
- Improvement of the status of women
- Good quality provider services
- Adaptation of health services

Recommended reading:
1) Bongaarts J, Johansson E. 2000, No 141
2) d’Arcangues C. Reproductive BioMedicine Online 2001;3:34.