Long-acting contraceptive methods for women

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Rationale for the development of long-acting methods of contraception

• Methods that do not require daily use or interfere with sexual intercourse
  [Duration of action: 7 days → 7 years]
  ▶ greater use-effectiveness

• Methods with improved pharmacokinetic profile
  ▶ reduced side-effects

Note: ▶ dependance on health care provider
Schematic representation of expected PK profiles of progestogens administered by different routes and in different formulations.
Long-acting methods

- Injectables
- Implants
- Vaginal rings
- Transdermal systems
Injectable contraceptive preparations

- Two-to-three monthly: progestogen-only
- Once-a-month: progestogen-estrogen combinations
Two-to-three monthly injectables

- Depot-medroxyprogesterone acetate (DMPA)
- Norethisterone enanthate (NET-EN)

Mechanism of action:
- ovulation inhibition
- additional effects on endometrium, tubal function and cervical mucus
Rationale for the development of combined injectable contraceptives

Offer to women an alternative to progestogen-only injectable contraceptives, which ensures:

- a more regular vaginal bleeding pattern:
  - by adding an estrogen
- faster return to baseline fertility upon discontinuation:
  - through improved pharmacokinetic profile
Idealized pharmacokinetic/pharmacodynamic profile of a typical combined monthly injectable contraceptive

Adapted from: Fraser and Diczfalusy, 1980
## Once-a-month combined injectable contraceptives

### Main preparations currently available

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Composition</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perlutal, Topasel</td>
<td>Dihydroxyprogesterone acetophenide 150 mg + E₂ enanthate 10 mg</td>
<td>Latin America, Spain</td>
</tr>
<tr>
<td>Cyclofem, Lunelle</td>
<td>DMPA 25 mg + E₂ cypionate 5 mg</td>
<td>22 c., Latin America, Indonesia, Thailand</td>
</tr>
<tr>
<td>Mesigyna, Norigynon</td>
<td>NET-EN 50 mg + E₂ valerate 5 mg</td>
<td>Latin America, Turkey, 7 African c., China</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>
### Percentage of ovulatory cycles after administration of various monthly injectables

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Dose (mg)</th>
<th>3(^{rd}) treatment month</th>
<th>1(^{st}) follow-up month</th>
<th>2(^{nd}) follow-up month</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMPA</td>
<td>25</td>
<td>0</td>
<td>24</td>
<td>48</td>
</tr>
<tr>
<td>DMPA</td>
<td>25</td>
<td>0</td>
<td>60</td>
<td>71</td>
</tr>
<tr>
<td>E(_2) Cyp</td>
<td>25 5</td>
<td>0</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>DMPA</td>
<td>12.5 2.5</td>
<td>0</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>E(_2) Cyp</td>
<td>12.5 5</td>
<td>42</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

*From: Garza-Flores, 1991*
WHO phase III clinical trials of Cyclofem, Mesigyna and DMPA. Cumulative life table discontinuation rates per 100 women at 12 months

<table>
<thead>
<tr>
<th>Event</th>
<th>Cyclofem</th>
<th>Mesigyna</th>
<th>DMPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>0</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding-related reasons</td>
<td>6.3</td>
<td>7.5</td>
<td>15.5</td>
</tr>
<tr>
<td>Amenorrhoea</td>
<td>2.1</td>
<td>1.6</td>
<td>12.5</td>
</tr>
<tr>
<td>Other medical reasons</td>
<td>6.3</td>
<td>6.6</td>
<td>4.3</td>
</tr>
<tr>
<td>Non-medical reasons</td>
<td>15.1</td>
<td>16.6</td>
<td>10.1</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>11.4</td>
<td>10.5</td>
<td>8.6</td>
</tr>
<tr>
<td>Total discontinuations</td>
<td>35.5</td>
<td>36.8</td>
<td>41.2</td>
</tr>
</tbody>
</table>

Woman-months: 10 969, 10 608, 5 429

Proportions (%) of women experiencing different types of bleeding patterns. Months 6-9 of a one year diary

<table>
<thead>
<tr>
<th>Group</th>
<th>(n)</th>
<th>Amenorrhea</th>
<th>Infrequent bleeding</th>
<th>Frequent bleeding</th>
<th>Irregular bleeding</th>
<th>Prolonged bleeding</th>
<th>Regular pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>3,893</td>
<td>1.3</td>
<td>2.8</td>
<td>0.1</td>
<td>5.4</td>
<td>9.9</td>
<td>90.1</td>
</tr>
<tr>
<td>Cyclofem</td>
<td>802</td>
<td>1.1</td>
<td>5.4</td>
<td>2.8</td>
<td>25.4</td>
<td>9.4</td>
<td>61.3</td>
</tr>
<tr>
<td>Mesigyna</td>
<td>766</td>
<td>1.3</td>
<td>2.9</td>
<td>4.9</td>
<td>24.8</td>
<td>12.6</td>
<td>63.3</td>
</tr>
<tr>
<td>DMPA</td>
<td>311</td>
<td>37.0</td>
<td>24.8</td>
<td>8.3</td>
<td>27.7</td>
<td>17.3</td>
<td>6.4</td>
</tr>
</tbody>
</table>

From: Fraser, 1994; Sang et al, 1995; Coutinho et al, 1997
Mechanisms of progestin-induced endometrial bleeding

- Abnormal angiogenesis → neovascular formations, increased microvascular density, reduced smooth muscle α-actin, deficient microvascular basement membrane, dilated surface vessels.

- Infiltration, proliferation and activation of leukocytes and mast cells → expression and activation of growth factors, cytokines and proteases (MMPs), degradation of extracellular matrix.

- Abnormal epithelium with reduced cytokeratin formation or deposition → less likely to contain micro-hemorrhages.
### 12-months life-table d/c rates for medical reasons in multicentre trials of DMPA, NET-EN and Cyclofem

<table>
<thead>
<tr>
<th>Side Effect</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>
Metabolic effects of DMPA and NET-EN

• Small degree of insulin resistance

• Moderate unfavourable lipid changes.

In epidemiological studies: no increased risk of stroke, VTE or AMI in healthy women BUT increased risk of stroke in those with hypertension

• No quantitative effect on milk production, some changes in milk composition

• No measurable effect on breast-fed infants (growth, hypothalamic-pituitary gonadal axis)

• Delayed return of fertility after use discontinuation
Metabolic effects of Cyclofem and Mesigyna

- Minor lipid changes, which revert promptly at discontinuation
- Minor hemostatic changes, which revert promptly at discontinuation
- No significant change in glucose metabolism
- No studies on their effect on lactation
- Delay in the return to fertility during 3 months after d/c
## Return of ovulation and fertility after prolonged use of different methods

<table>
<thead>
<tr>
<th>Method</th>
<th>n</th>
<th>Median time to conception (months)</th>
<th>Cumulative conception rate at one year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclofem</td>
<td>70</td>
<td>5.5</td>
<td>82.9</td>
</tr>
<tr>
<td>DMPA</td>
<td>796</td>
<td>5.5</td>
<td>76.2</td>
</tr>
<tr>
<td>IUD</td>
<td>125</td>
<td>4.5</td>
<td>75.8</td>
</tr>
<tr>
<td>OC</td>
<td>437</td>
<td>3.0</td>
<td>84.9</td>
</tr>
</tbody>
</table>
DMPA and HIV

- HIV transmission may be promoted through:
  - vaginal thinning, immunosuppression,
  - prolonged vaginal bleeding, unsterilised needles
- or may be hindered through:
  - cervical mucus thickening

- To date, one study suggests a 3-fold increase in the number of HIV-infected cells in the vaginal secretions of HIV+ DMPA users. More research needed
DMPA and bone metabolism

- Between the ages of 25 and 45, slight acceleration of bone metabolism with bone resorption that is not fully compensated by bone formation, reversible upon discontinuation and without any apparent long-term effect.

- In adolescents, slow down of the normal bone mass accumulation. Current research focuses on the effects on adult bone mass and long-term risks.

- Few data on the peri-menopause.
DMPA

- First registered for this indication in 1967
- Currently registered in over 70 countries, including 10 EC countries and the USA
- Currently used by over 10 million women worldwide
- Approved by the US Food and Drug Administration (USFDA) in 1982
Relative risks of 5 neoplasms in women who have ever used DMPA
WHO Collaborative Study

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Number of Subjects</th>
<th>Adjusted Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls*</td>
</tr>
<tr>
<td>Endometrium</td>
<td>122</td>
<td>939</td>
</tr>
<tr>
<td>Ovary</td>
<td>224</td>
<td>1,781</td>
</tr>
<tr>
<td>Liver</td>
<td>57</td>
<td>290</td>
</tr>
<tr>
<td>Breast</td>
<td>869</td>
<td>11,890</td>
</tr>
<tr>
<td>Cervix</td>
<td>2,009</td>
<td>9,583</td>
</tr>
</tbody>
</table>

* Controls matched with cases by age, centre and year of entry into study
DMPA and Breast Cancer (1)

**Setting:** New Zealand (entire country)
- Thailand (3 centres)
- Kenya (1 centre)
- Mexico (1 centre)

1,768 cases and 13,905 controls

DMPA used by 14.1% cases and 14.2% controls
DMPA and Breast Cancer (2)

RR (95% CI) in ever users of DMPA = 1.1 (0.97 - 1.4)

Risk increased during first 4 years after initial exposure, in women < 35 years at diagnosis; small n

Risk did not increase with duration of use and was not increased in women who began use > 5 years previously

Maximum increase in risk attributable to DMPA:

3.2 - 4.5 cases per 100 000 women-years
### DMPA and Invasive Squamous Cell Cervical Cancer

**WHO Collaborative Study**

<table>
<thead>
<tr>
<th>Months of use</th>
<th>Number of Subjects</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td>0</td>
<td>782</td>
<td>5,184</td>
</tr>
<tr>
<td>1-12</td>
<td>58</td>
<td>216</td>
</tr>
<tr>
<td>13-24</td>
<td>50</td>
<td>92</td>
</tr>
<tr>
<td>25-60</td>
<td>17</td>
<td>127</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>26</td>
<td>86</td>
</tr>
</tbody>
</table>
DMPA and Cervical Carcinoma in situ (1)

Setting: Mexico, Thailand
1,217 cases and 8,956 controls

23.3% cases and 15.4% controls had ever used DMPA

RR (CI 95%) = 1.43 (1.22 - 1.67) adjusted for age, number of pregnancies, use of OC, Pap smear frequency
DMPA and Cervical Carcinoma \textit{in situ} (2)

The risk increased with duration of use but decreased with time since first and last use.

Since no relationship was established between invasive cervical cancer and DMPA in this same study, the findings suggest that if DMPA increases the risk of cervical CA \textit{in situ}:

- this is a reversible effect, or
- cervical lesions induced by DMPA do not progress to invasive disease
Injectables - Developments (1)

Improved pharmacokinetic profile:

- **Biodegradable microspheres:**
  - norethisterone, norgestimate, progesterone

- **Monolithic macrocrystals:**
  - progesterone, 17-beta-estradiol,
  - combined for once-a-month administration

- **Controlled particle size distribution:**
  - DMPA, levonorgestrel butanoate
Injectables - Developments (2)

Safer delivery system:

• Provision of Cyclofem in non-reusable disposable syringes (Uniject, Soloshot)
Implantable contraceptives
## Implantable contraceptives for women

<table>
<thead>
<tr>
<th>Progestin</th>
<th>Tradename</th>
<th>Units</th>
<th>Duration of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levonorgestrel</td>
<td>Norplant*</td>
<td>Six capsules</td>
<td>7 y</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>Jadelle*</td>
<td>Two rods</td>
<td>5 y</td>
</tr>
<tr>
<td>Etonogestrel</td>
<td>Implanon</td>
<td>Single rod</td>
<td>3 y</td>
</tr>
<tr>
<td>Nestorone**</td>
<td>Nestorone</td>
<td>Single rod</td>
<td>2 y</td>
</tr>
<tr>
<td>Elcometrine**</td>
<td>Elcometrine</td>
<td>Single capsule</td>
<td>6 mo</td>
</tr>
<tr>
<td>Nomegestrol ac.</td>
<td>Uniplant</td>
<td>Single capsule</td>
<td>1 y</td>
</tr>
</tbody>
</table>

*Sino-implants Domestic No. I and II not shown are generic versions of Norplant and Jadelle respectively, available in China.

**Same progestin with a different name.

From: Croxatto 2001
Norplant

- Silastic medical adhesive
- Silastic tubing
- 36 mg free crystals
- 2.4 mm

Jadelle

- 75 mg crystals embedded in copolymer
- 4.3 mm

From: Croxatto 2001
Serum level of levonorgestrel in women using Norplant for 8 years

From: Diaz et al 1987
Serum levels of levonorgestrel in women using Norplant or Jadelle

- **Serum LNG pg/mL**
  - 0
  - 200
  - 400
  - 600
  - 800

- **Contraceptive threshold**

- **Duration of Treatment**
  - **WEEKS**: 2 3 4 1 2 3 4 5 6 7 8 9 10 11 12
  - **MONTHS**: 2 3 4 1 2 3 4 5 6 7 8 9 10 11 12

From: Croxatto et al 1991
Norplant and Jadelle

- Mechanism of action:
  - mostly ovulation inhibition
  - luteal phase abnormalities
  - cervical mucus thickening

- Efficacy:
  - 5 year cumulative pregnancy rate: 1.1 per 100
  - highest rates in women < 25 y/o or > 70 kg
  - For Norplant:
    - 7 year cumulative pregnancy rate: 1.9 per 100
## Cumulative gross pregnancy rates per 100 Norplant\textsuperscript{R} users through 5 years

<table>
<thead>
<tr>
<th>Weight</th>
<th>Rate</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 kg</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>50-59 kg</td>
<td>3.4</td>
<td>0.9</td>
</tr>
<tr>
<td>60-69 kg</td>
<td>5.0</td>
<td>1.4</td>
</tr>
<tr>
<td>&gt; 70 kg</td>
<td>8.5</td>
<td>2.3</td>
</tr>
</tbody>
</table>

From Population Council, 1990
Discontinuation resulting from adverse experiences:
Gross annual rate per 100 Norplant\textsuperscript{R} users

<table>
<thead>
<tr>
<th>Year</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstrual</td>
<td>9.1</td>
<td>7.9</td>
<td>4.9</td>
<td>3.3</td>
<td>2.9</td>
</tr>
<tr>
<td>Other medical</td>
<td>6.0</td>
<td>5.6</td>
<td>4.1</td>
<td>4.0</td>
<td>5.1</td>
</tr>
<tr>
<td>Total adverse</td>
<td>15.1</td>
<td>13.5</td>
<td>9.0</td>
<td>7.3</td>
<td>8.0</td>
</tr>
<tr>
<td>Total discontinuation</td>
<td>19.0</td>
<td>22.6</td>
<td>20.8</td>
<td>23.3</td>
<td>22.4</td>
</tr>
</tbody>
</table>

From Sivin, 1990
Bleeding patterns (%) of Norplant\textsuperscript{R} users during 5 years of use, assigned to most frequent category for each year

<table>
<thead>
<tr>
<th>Year</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular</td>
<td>26.6</td>
<td>54.7</td>
<td>53.5</td>
<td>66.8</td>
<td>62.5</td>
</tr>
<tr>
<td>Irregular</td>
<td>66.3</td>
<td>40.0</td>
<td>39.9</td>
<td>28.1</td>
<td>37.5</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>7.1</td>
<td>5.3</td>
<td>6.6</td>
<td>5.1</td>
<td>0</td>
</tr>
</tbody>
</table>

Women-years | 198.0 | 127.9 | 101.9 | 68.8  | 34.9  |
No. of women  | 215   | 138   | 115   | 77    | 46    |

Adapted from Shoupe et al., 1991
### Adverse effects with Norplant use (other than menstrual disorders)

<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>Hair loss / hirsutism</td>
<td>2 - 5</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 - 11</td>
</tr>
<tr>
<td>Mood changes</td>
<td>1 - 9</td>
</tr>
</tbody>
</table>
Implanon

- EVA rod releasing etonogestrel
- More consistent ovulation inhibition
- No pregnancies observed in 5629 years of exposure (women > 70kg were excluded)
- Vaginal bleeding patterns:
  - 30-40% amenorrhea throughout 3 years
  - 30% infrequent bleeding
  - 10-20% prolonged bleeding
Metabolic effects of implants
(Norplant, Jadelle, Implanon)

- Lipid effects: small or none.
- Carbohydrate metabolism: mild insulin resistance in some users
- Clotting and fibrinolytic systems: minor changes
- Liver function: elevated bilirubin in some women, within normal range

Note: Predictive value questionable
No studies in women at risk
Safety of Norplant (1)

- Potential beneficial effects:
  - decreased risk of ectopic pregnancy
  - decreased risk of pelvic inflammatory disease
  - and lower genital tract infection

- No effect on:
  - bone density
  - anemia
  - ovarian cyst enlargement
  - reovery of fertility
  - connective tissue disorders
Safety of Norplant (2)

- Potential adverse effects that need further evaluation:
  - increased risk of hypertension
  - increased risk of gallbladder disease
  - hormonal side-effects

- No studies large enough to assess effect on:
  - cardio-vascular disease
  - cancer
  - HIV/AIDS
  - diabetes
Contraceptive implants and lactation

• Breast-feeding women using Norplant:
  - experience longer periods of amenorrhea
  - after weaning, bleeding pattern same as in non-nursing users
  - no effect on bone metabolism

• Infants breast-fed by women using Norplant or Implanon:
  - absorb about 100 ng/day of progestogen
  - no effect on infant growth and development
  - with Norplant: slight ↑ in mild respiratory diseases, eye infections and skin conditions during the first year (?)
## Percentage of women with insertion site complications during the first year of Norplant use

2674 women in 19 centres in 7 countries

<table>
<thead>
<tr>
<th>Complication</th>
<th>All Centres</th>
<th>%</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>INFECTION</td>
<td>0.8</td>
<td>%</td>
<td>0 – 3.0</td>
</tr>
<tr>
<td>EXPLUSION</td>
<td>0.4</td>
<td>%</td>
<td>0 – 3.0</td>
</tr>
<tr>
<td>LOCAL REACTION</td>
<td>4.7</td>
<td>%</td>
<td>0 – 18.0</td>
</tr>
<tr>
<td>- Pain</td>
<td>2.2</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>- Itching</td>
<td>1.9</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>- Rashing</td>
<td>0.3</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>- Other</td>
<td>0.3</td>
<td>%</td>
<td></td>
</tr>
</tbody>
</table>

From: Klavon and Grubb, 1990
Occurrences of Insertion Site Infection and Implant Expulsion, by Follow-up Interval

* Follow-up interval and the inclusive days post-insertion were: 1-month (days 1-60), 3-month days (61-136), 6-month (days 137-273), and 12-month (days 274-456).

From: Klavon and Grubb, 1990
Lessons learnt from Norplant as a delivery system

Positive attributes

- long duration of action; no action required from user for 5 y.
- near-zero order release of minimal dose required: minimal metabolic changes, good reversibility but reduced efficacy in heavier women

Specific requirements

- provider training for careful insertion and removal, and for careful counselling
- adaptation of health services; planning of removals
Lessons learnt from Norplant as a delivery system

Controversies

- coercive use by providers/target-driven national family planning programmes
- financing, including free insertion and payment for early removal
- misuse by judiciary system and politicians
- class action suits in the USA and the UK
Implantable contraceptives for women under development

- Nestorone-releasing single implant, suitable for breast-feeding women. Infants are not exposed to steroids as nestorone is not absorbed orally.
Contraceptive vaginal rings
Contraceptive vaginal rings

Placing/removing the vaginal ring
CONTRACEPTIVE VAGINAL RINGS

- releasing estrogen + progestogen
  (3 weeks in/1 week out)
  **NUVARING**

- releasing a progestogen
  (continuous use over 3 months)
  **PROGERING**
NUVARING
(120 µg/day etonogestrel + 15 µg/day EE)
Serum concentration-time curves

NUVARING
Maximum estradiol concentration and follicular diameter during normal and extended use

Source: Mulders & Dieben, 2001
NUVARING - Phase III clinical trials

- Pearl index of 0.77 (CI: 0.37-1.41) with perfect use, 1.18 with actual use in clinical trial setting.
- Withdrawal bleeding when expected (2-4 days after ring removal) in 98.5 % cycles, lasting 4-5 days.
- Breakthrough bleeding/spotting in 5.5 % of all cycles.
- Complaints of hormonal side-effects: 3-6 %
- Device-related events (foreign body sensation, coital pb, expulsion): 4.4 %
- No adverse effect on cervical or vaginal cytology during one year of use.
- Minimal effects on lipid, CHO and hemostatic variables.
PROGERING

(15→ 5 mg/day progesterone, over 3 months)

Pre-registration study

- 285 ring users vs 262 CuT380A IUD users, all nursing women
- one year follow-up: no pregnancy in either group
- breast-feeding and infant growth similar in both groups
- mean duration or amenorrhea: 12 months in ring users vs 6 months in IUD users
- some early discontinuations among ring users because of discomfort or ring expulsion
Transdermal systems
Transdermal systems
ORTHO-EVRA

- 20 cm² (4.5 cm side), three-layered patch:
  - outer polyethylene+polyester protective layer
  - middle layer that contains an adhesive and the two contraceptive steroids
  - inner, clear polyester liner, peeled off before use

- releasing 150 µg/day norelgestromin (active metabolite of norgestimate)+ 20 µg/day EE

- blood levels reach steady state in < 48 hours and are maintained over 7 days (+2 days as safety window)
Mean norelgestromin serum levels (ng/ml) following application of EVRA for 7 and 10 days

Time (days)

17d-NGM Conc. (ng/mL)

Therapeutic range
ORTHO-EVRA

• Same mechanism of action as the combined OC.

• Differences with OC in randomized clinical trials:
  – better compliance (88% vs 77%)
  – application site reaction in 20% users (2.6% d/c for this reason)
  – patch partial or complete detachment needing replacement patch: 5%
  – breast discomfort (19% vs 6%). 1% d/c for this reason.
  – dysmenorrhea (14% vs 10%)