Long-acting hormonal 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: dependence on health care provider

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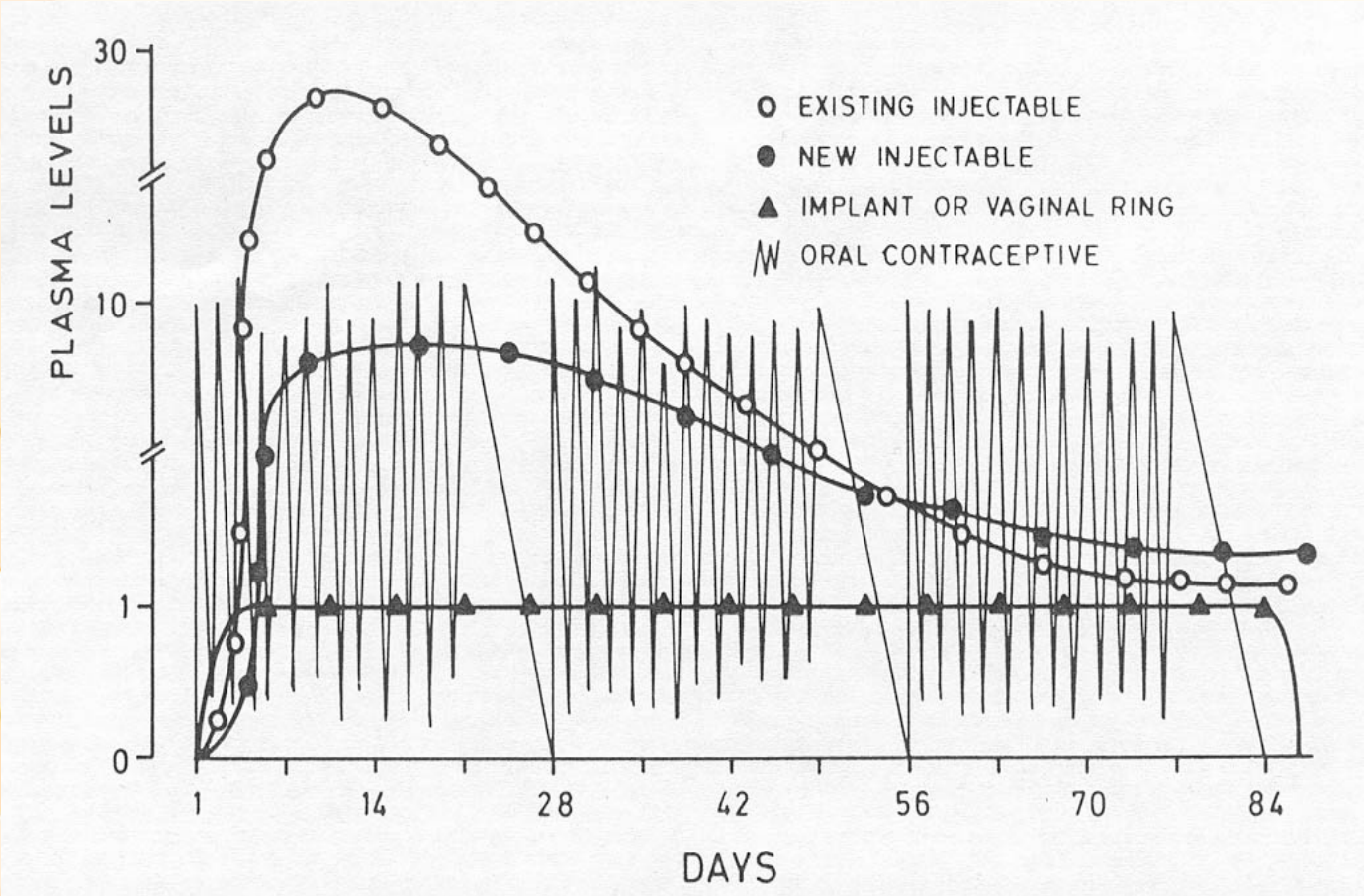
Schematic representation of expected PK profiles of progestogens administered by different routes and in different formulations



Long-acting methods

- Injectables
- Implants
- Vaginal rings
- Transdermal systems

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Injectable contraceptive preparations

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

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Two-to-three monthly injectables

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

Mechanism of action:

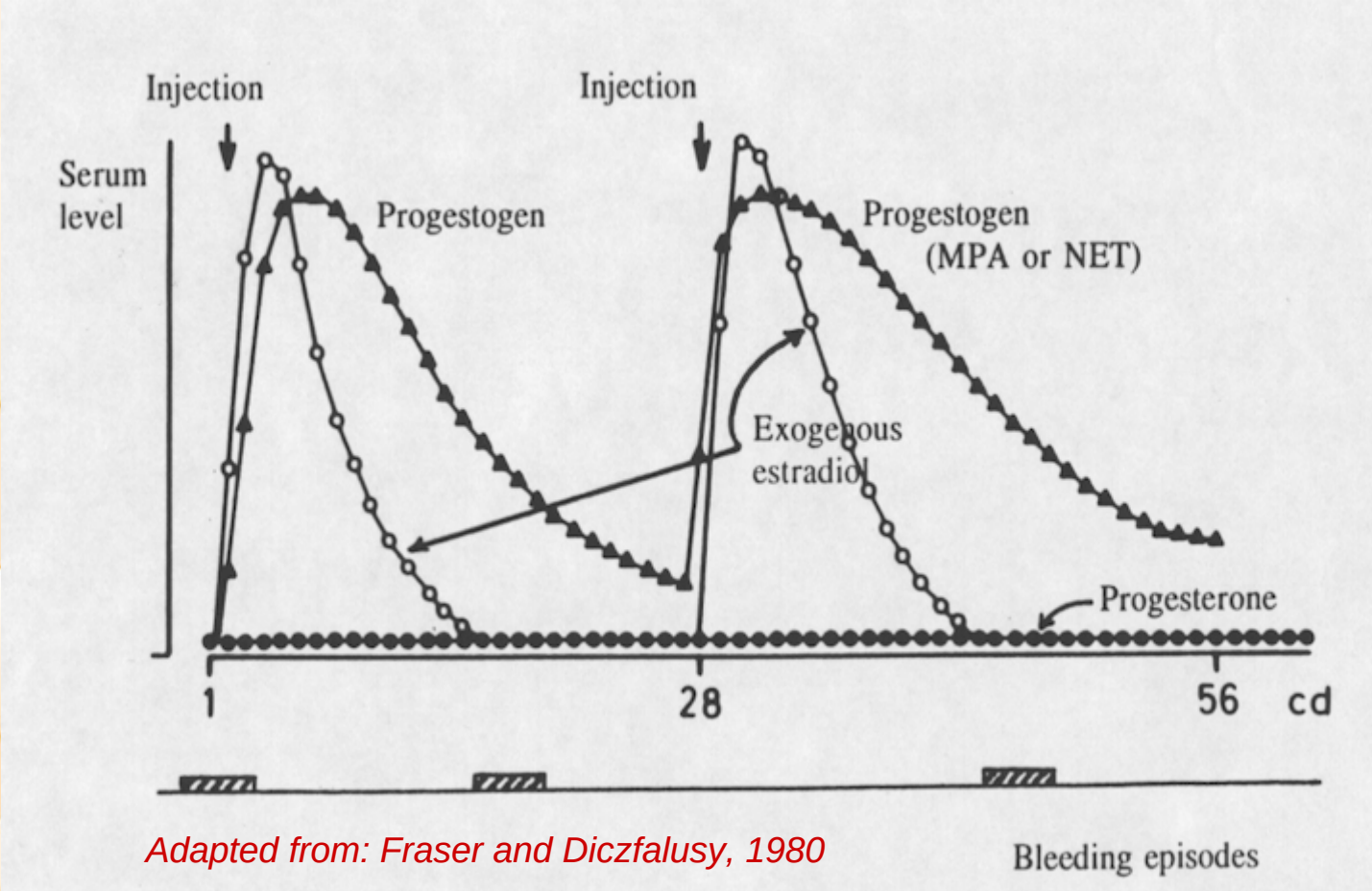
  - ovulation inhibition
  - additional effects on endometrium, tubal function and cervical mucus

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

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Once-a-month combined injectable contraceptives
Main preparations currently available

Trade name	Composition	Availability
Perlutal Topasel	Dihydroxyprogesterone acetophenide 150 mg + E_2 enanthate 10 mg	Latin America, Spain
Cyclofem Lunelle	DMPA 25 mg + E_2 cypionate 5 mg	22 c., Latin America, Indonesia, Thailand
Mesigyna Norigynon	NET-EN 50 mg + E_2 valerate 5 mg	Latin America, Turkey, 7 African c., China
Chinese injectable No1	17α-hydroxyprogesterone caproate 250 mg + E_2 valerate 5 mg	China
Mego-E	Megestrol acetate 25 mg + 17β E_2 3.5 mg	China

Percentage of ovulatory cycles after administration of various monthly injectables

Formulation	Dose (mg)	3rd treatment month	1st follow-up month	2nd follow-up month
DMPA	25	0	24	48
DMPA E_2 Cyp	25 5	0	60	71
DMPA E_2 Cyp	12.5 2.5	0	60	90
DMPA E_2 Cyp	12.5 5	42	100	100

From: Garza-Flores, 1991

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WHO phase III clinical trials of Cyclofem, Mesigyna and DMPA. Cumulative life table discontinuation rates per 100 women at 12 months

Event	Cyclofem	Mesigyna	DMPA
Pregnancy	0	0.2	0
Bleeding-related reasons	6.3	7.5	15.5
Amenorrhoea	2.1	1.6	12.5
Other medical reasons	6.3	6.6	4.3
Non-medical reasons	15.1	16.6	10.1
Lost to follow up	11.4	10.5	8.6
Total discontinuations	35.5	36.8	41.2
Woman-months	10 969	10 608	5 429

From : WHO, 1986,1988

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

Group	(n)	Ameno-rrhoea	Infrequent bleeding	Frequent bleeding	Irregular bleeding	Prolonged bleeding	Regular pattern
Untreated	3 893	1.3	2.8	0.1	5.4	9.9	90.1
Cyclofem	802	1.1	5.4	2.8	25.4	9.4	61.3
Mesigyna	766	1.3	2.9	4.9	24.8	12.6	63.3
DMPA	311	37.0	24.8	8.3	27.7	17.3	6.4

From: Fraser,1994; Sang et al, 1995; Coutinho et al, 1997

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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 extra-cellular 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

	DMPA	NET-EN	Cyclofem
Abdominal discomfort	1.1	0.6	0.1
Weight gain	2.1	1.6	1.5
Anxiety/depression	0.7	0.9	0.3
Fatigue	0.9	0.9	0.4
Dizziness	1.2	1.6	1.2
Headaches	2.3	2.0	1.2
Decreased libido	0.9	0.6	-
Hypertension	0.5	0.7	0.8
T O T A L	8.7	9.3	6.3
Woman-months	20,550	10,361	10,969

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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**

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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

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Return of ovulation and fertility after prolonged use of different methods

Method	n	Median time to conception (months)	Cumulative conception rate at one year (%)
Cyclofem	70	5.5	82.9
DMPA	796	5.5	76.2
IUD	125	4.5	75.8
OC	437	3.0	84.9

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DMPA use and risk of STIs

- 5 cross-sectional studies and 3 prospective studies
- No increased risk of infection with gonorrhoea, trichomoniasis, syphilis, herpes or HPV.
- Two studies found an increased risk of chlamydial infection with DMPA use (hazard ratios of 4.3 and 1.6, respectively) but this could be due to differential STI exposure among the study groups.

DMPA use and HIV acquisition

- 4 cohort studies and 14 cross-sectional studies give inconsistent results:
  - 15 find no association
  - 3 find a positive association

DMPA used by HIV+ women

- No evidence that DMPA use affects HIV disease progression (one study)
- Three studies gave inconsistent results re. a possible association between DMPA use and HIV and HSV shedding
- Few data on possible interaction between DMPA and anti-retroviral drugs

Pharmacokinetic COC-ARV drug interactions

ARV	Contraceptive steroid levels	ARV levels
Protease inhibitors		
Nelfinavir	↓	No data
Ritonavir	↓	No data
Lopinavir/ritonavir	↓	No data
Atazanavir	↑	No data
Amprenavir	↑	↓
Indinavir	↑	No data
Saquinavir	No data	No change
Non-nucleoside reverse transcriptase inhibitors		
Nevirapine	↓	No change
Efavirenz	↑	No change
Delavirdine	?↑	No data

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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 impact on adult bone mass and long-term risks.
- Few data on the peri-menopause.

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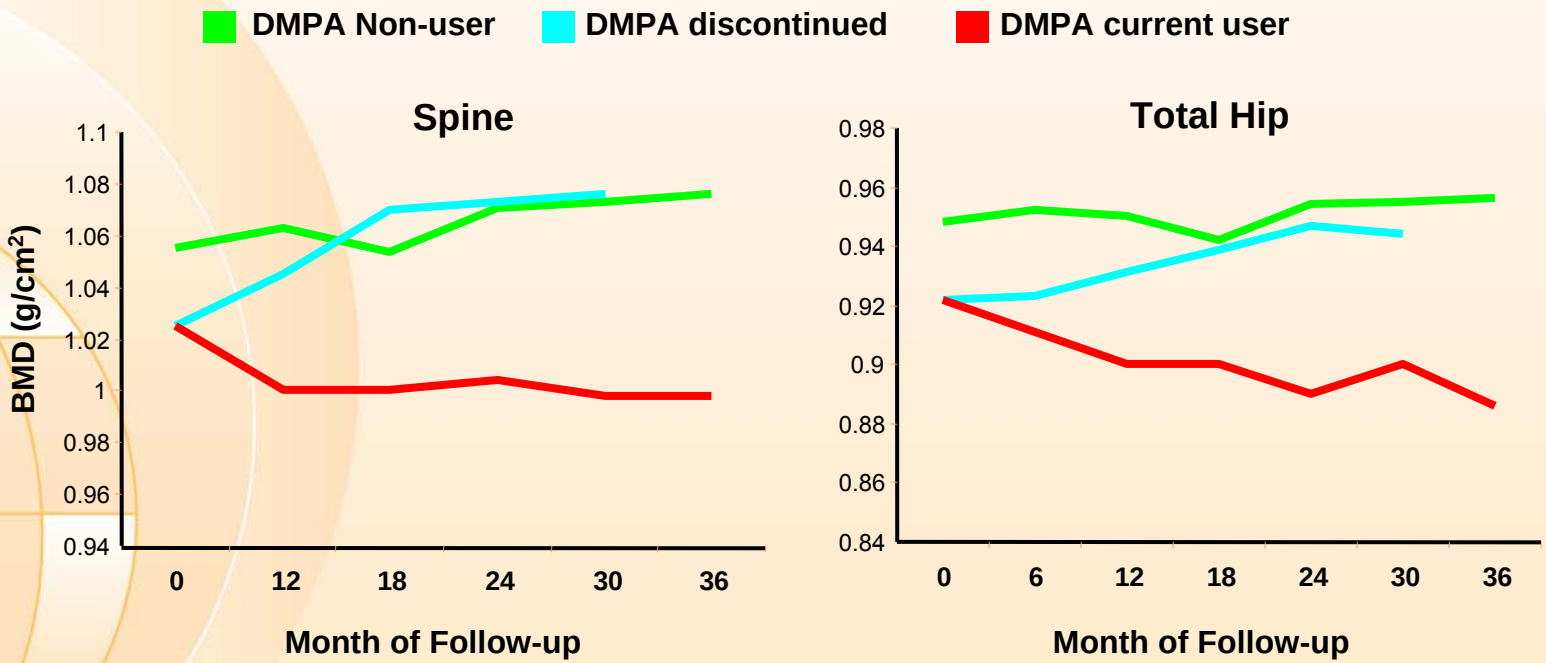
Changes in bone mineral density among 182 DMPA users and 258 non-users, 18-39 years old



Source: Scholes et al, 2002

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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

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Relative risks of 5 neoplasms in women who have ever used DMPA WHO Collaborative Study

Cancer Site	Number of Subjects Cases	Controls*	Adjusted Relative Risk (95% CI)	
Endometrium	122	939	0.21	(0.06-0.79)
Ovary	224	1,781	1.07	(0.6-1.8)
Liver	57	290	1.0	(0.4-2.8)
Breast	869	11,890	1.21	(0.96-1.52)
Cervix	2,009	9,583	1.1	(0.96-1.29)

* Controls matched with cases by age, centre and year of entry into study

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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

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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

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DMPA and Invasive Squamous Cell Cervical Cancer WHO Collaborative Study

Months of use	Number of Subjects Cases	Controls	Relative Risk (95% CI)
0	782	5,184	1.0
1-12	58	216	1.4 (1.0 - 2.0)
13-24	50	92	1.2 (0.7 – 2.0)
25-60	17	127	0.6 (0.4 – 1.1)
> 60	26	86	1.4 (0.9 – 2.2)

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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

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DMPA and Cervical Carcinoma *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 *in situ*:

- this is a reversible effect, or
- cervical lesions induced by DMPA do not progress to invasive disease

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Implantable contraceptives

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Implantable contraceptives for women

Progestin	Tradename	Units	Duration of action
Levonorgestrel	Norplant*	Six capsules	7 y
Levonorgestrel	Jadelle*	Two rods	5 y
Etonogestrel	Implanon	Single rod	3 y

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

From: Croxatto 2001

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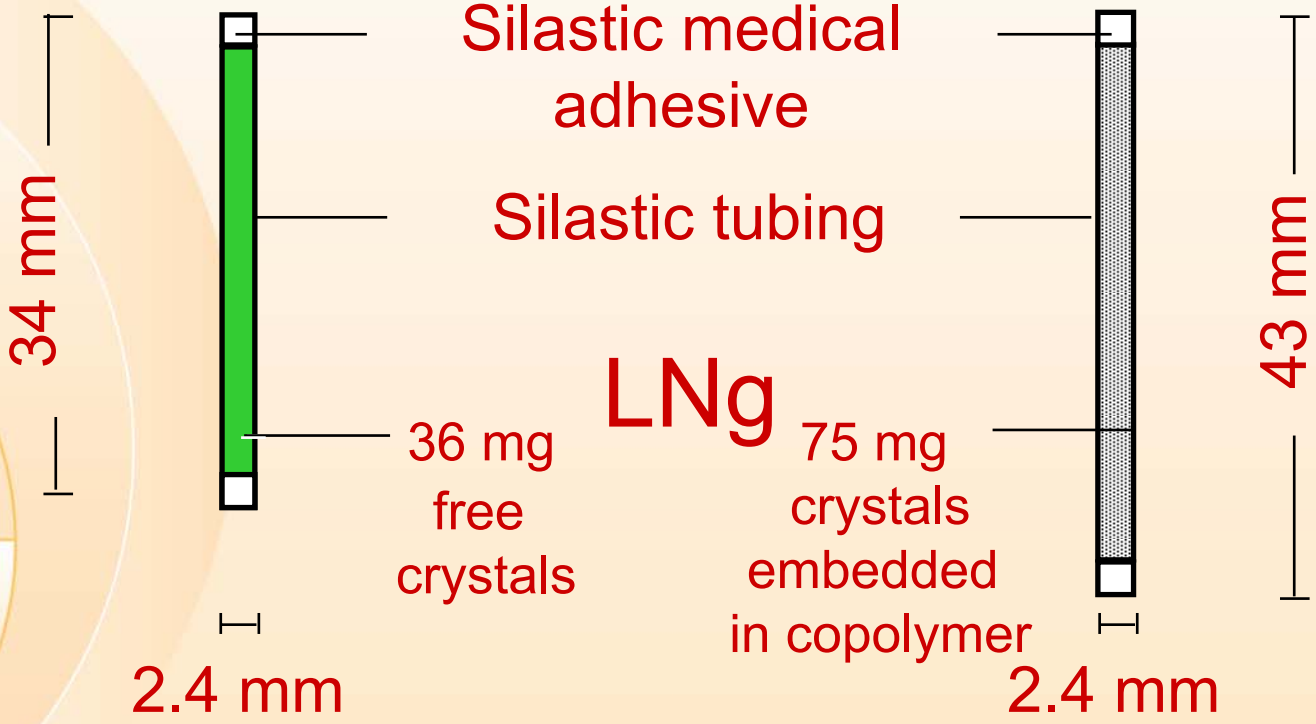
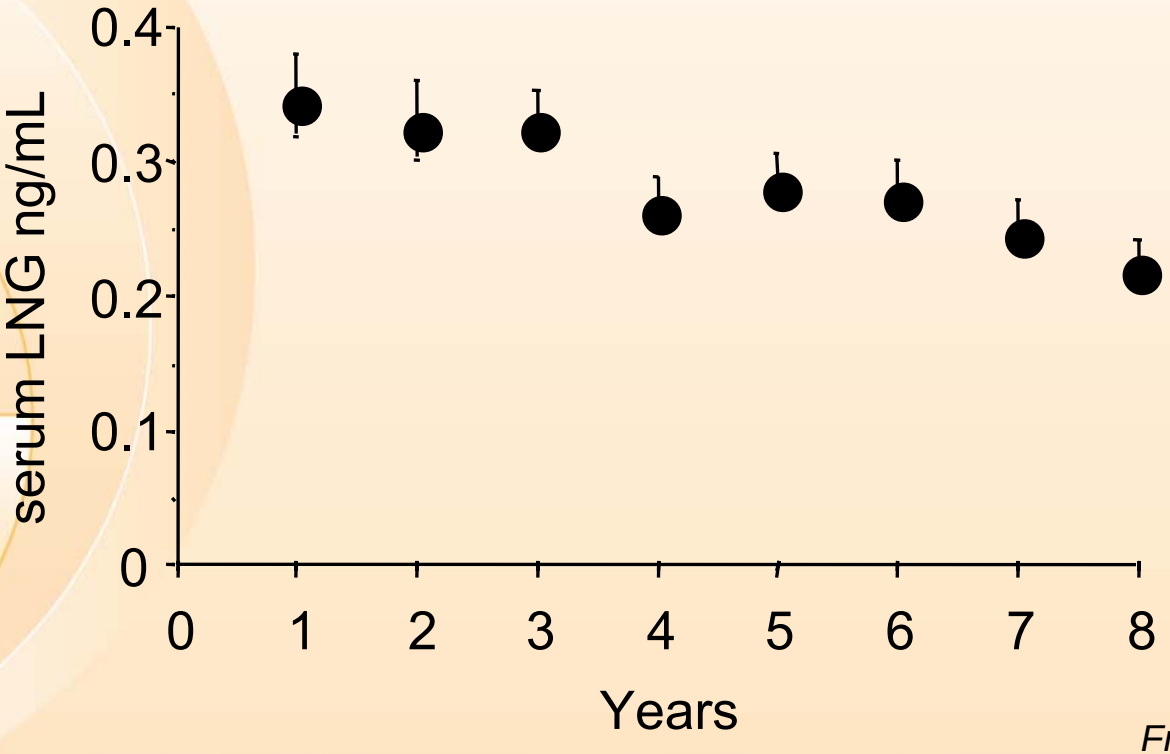
Norplant

Jadelle



From: Croxatto 2001

Serum level of levonorgestrel in women using Norplant for 8 years



From: Diaz et al 1987

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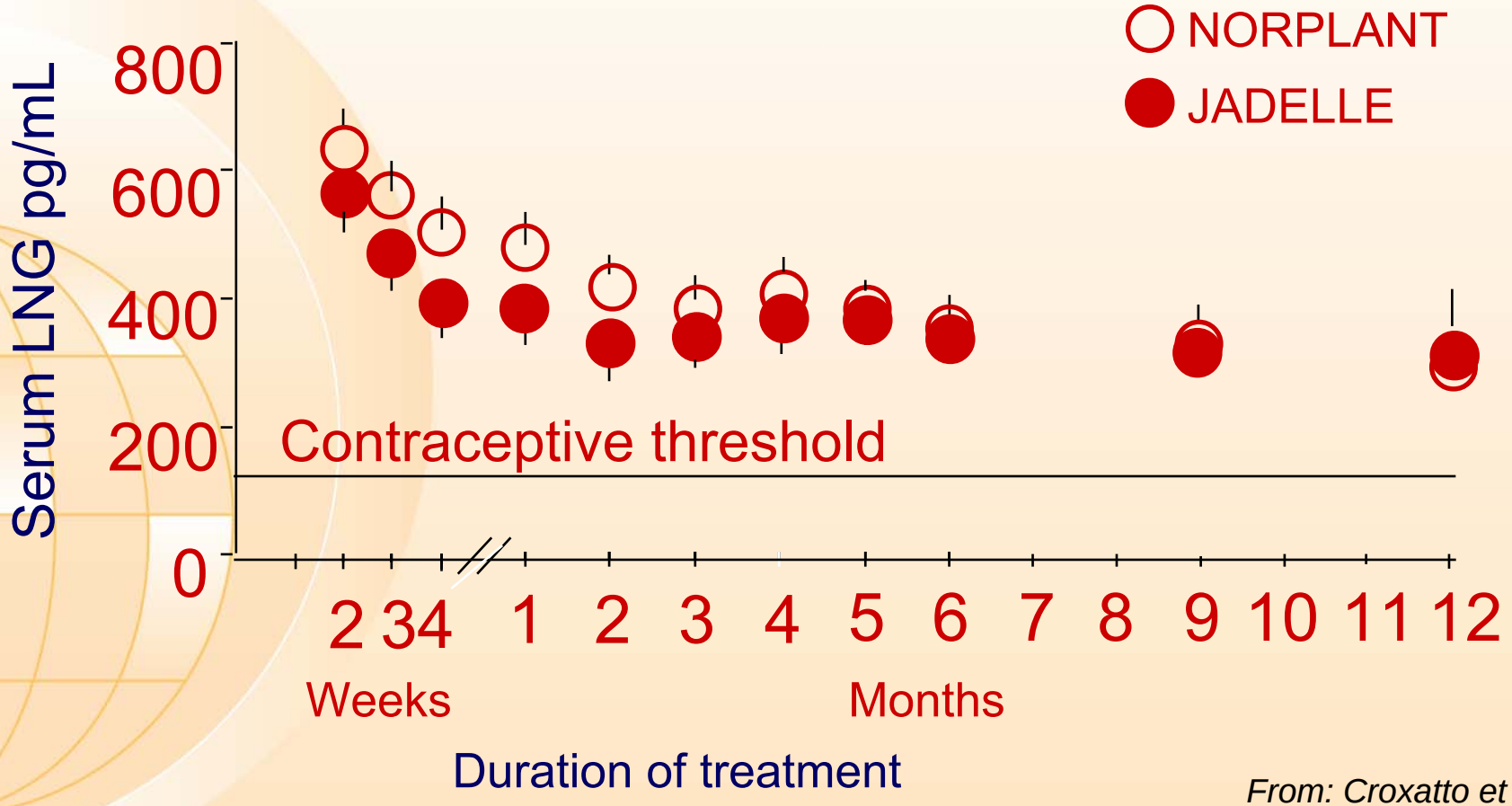
Serum levels of levonorgestrel in women using Norplant or Jadelle



From: Croxatto et al 1991

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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

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Cumulative gross pregnancy rates per 100 Norplant^{R} users through 5 years

Weight	Rate	SE
< 50 kg	0.2	0.2
50-59 kg	3.4	0.9
60-69 kg	5.0	1.4
> 70 kg	8.5	2.3

From Population Council, 1990

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Discontinuation resulting from adverse experiences: Gross annual rate per 100 Norplant^{R} users

	Year 1	2	3	4	5
Menstrual	9.1	7.9	4.9	3.3	2.9
Other medical	6.0	5.6	4.1	4.0	5.1
Total adverse	15.1	13.5	9.0	7.3	8.0
Total discontinuation	19.0	22.6	20.8	23.3	22.4

From Sivin, 1990

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

	Year 1	2	3	4	5
Regular	26.6	54.7	53.5	66.8	62.5
Irregular	66.3	40.0	39.9	28.1	37.5
Amenorrhea	7.1	5.3	6.6	5.1	0
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

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Adverse effects with Norplant use (other than menstrual disorders)

Symptom	% users
Headache	10 - 30
Weight gain	4 - 22
Acne	3 - 22
Hair loss / hirsutism	2 - 5
Dizziness	4 - 11
Mood changes	1 - 9

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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

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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
  - anaemia
  - ovarian cyst enlargement
  - recovery of fertility
  - connective tissue disorders

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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 (?)

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Percentage of women with insertion site complications during the first year of Norplant use

2674 women in 19 centres in 7 countries

	% All Centres	% Range Individual Centres
INFECTION	0.8	0 – 3.0
EXPLUSION	0.4	0 – 3.0
LOCAL REACTION	4.7	0 – 18.0
- Pain	2.2	
- Itching	1.9	
- Rashing	0.3	
- Other	0.3	

From: Klavon and Grubb, 1990

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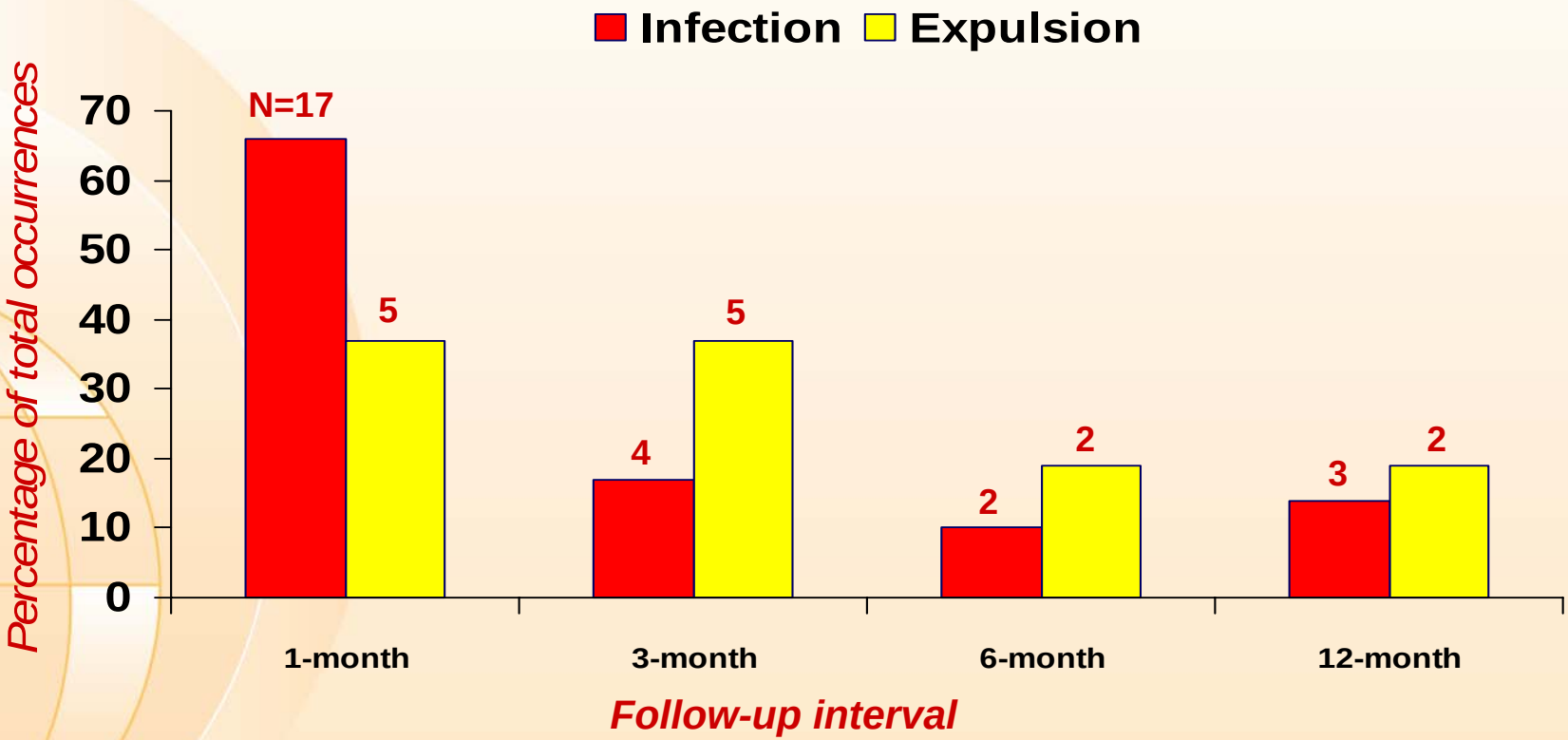
Occurences of Insertion Site Infection and Implant Expulsion, by Follow-up Interval



* 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

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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

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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

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Contraceptive vaginal rings

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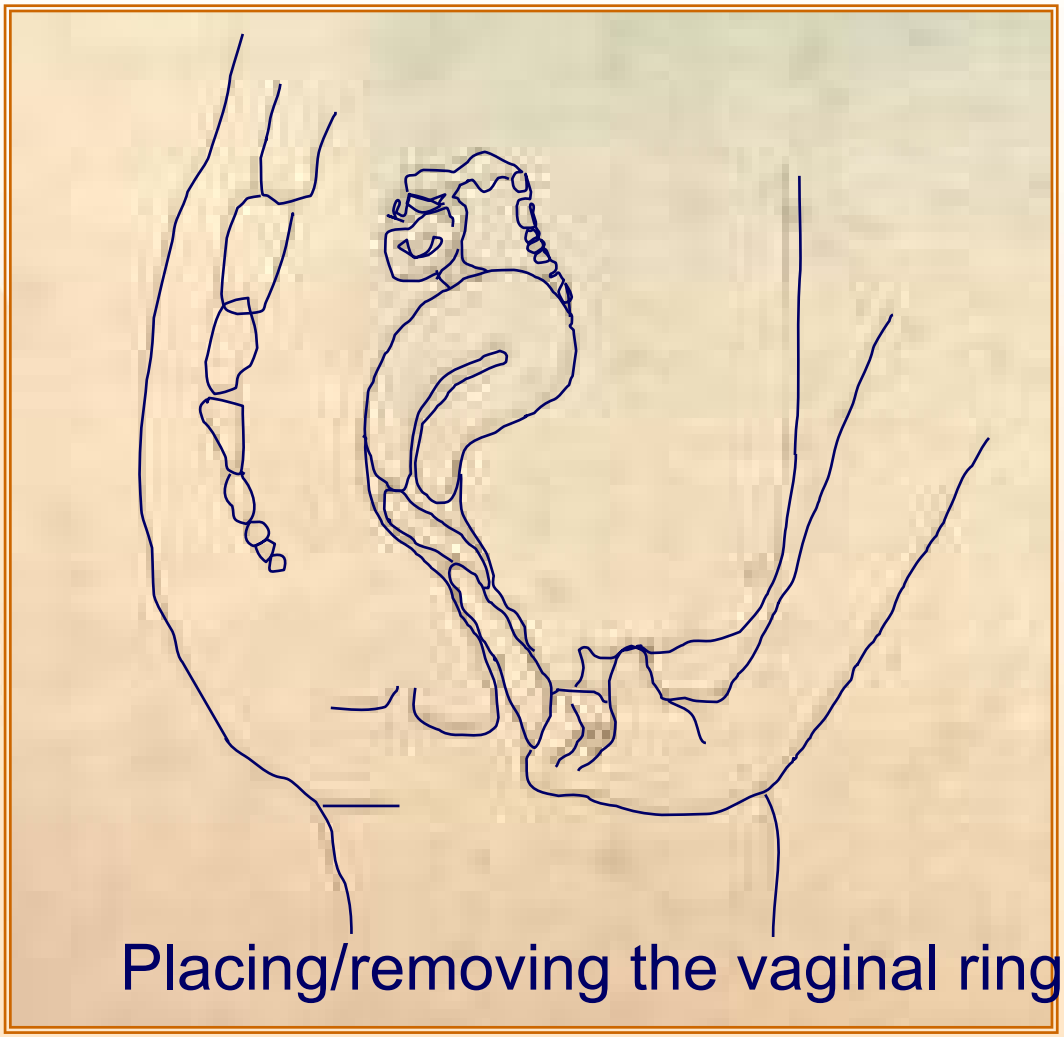
Contraceptive vaginal rings



Placing/removing the vaginal ring

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CONTRACEPTIVE VAGINAL RINGS

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

NUVARING

- releasing progesterone (continuous use over 3 months)

PROGERING

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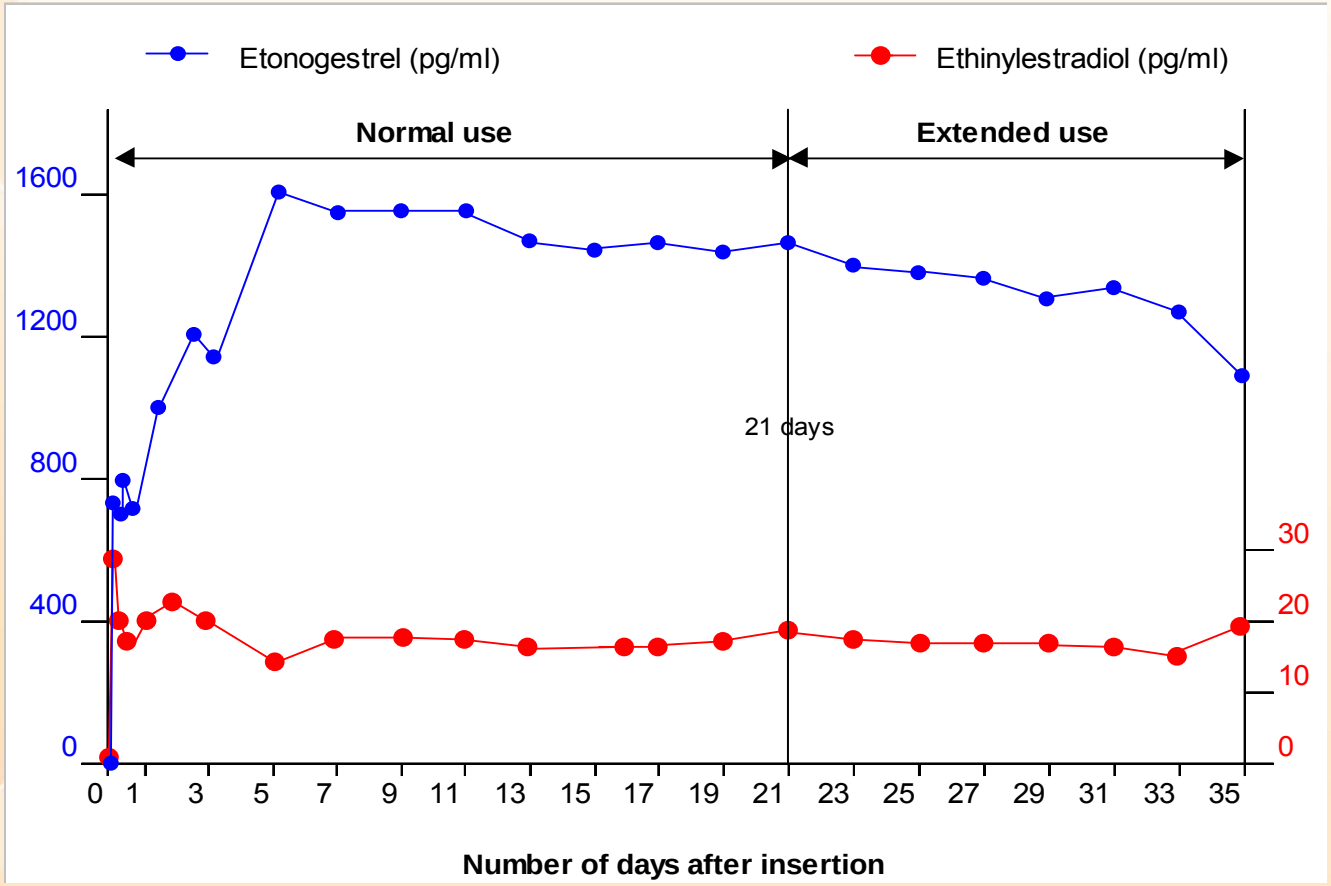
NUVARING

(120 μg/day etonogestrel + 15 μg/day EE)

Serum concentration-time curves



Timmer & Mulders, 2000.

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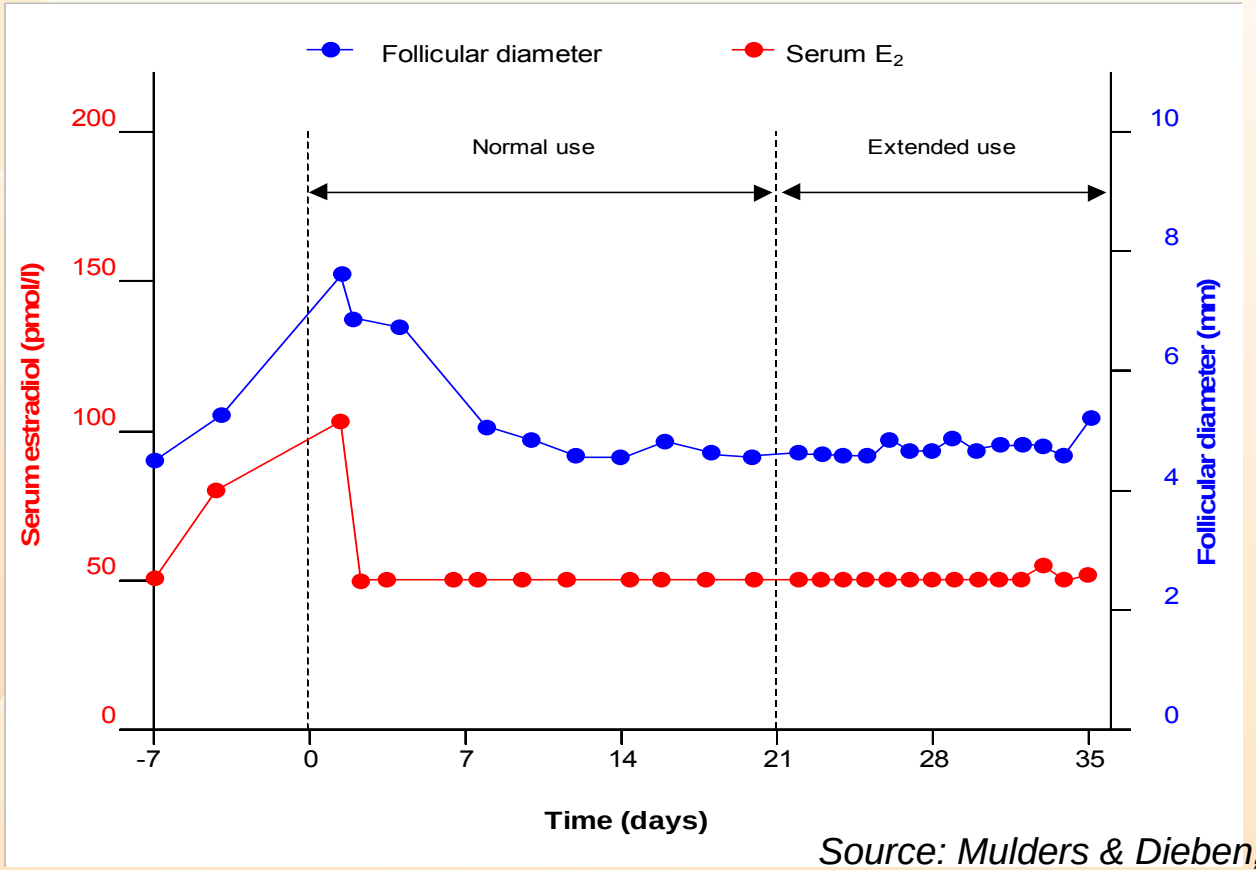
NUVARING

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

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Transdermal systems

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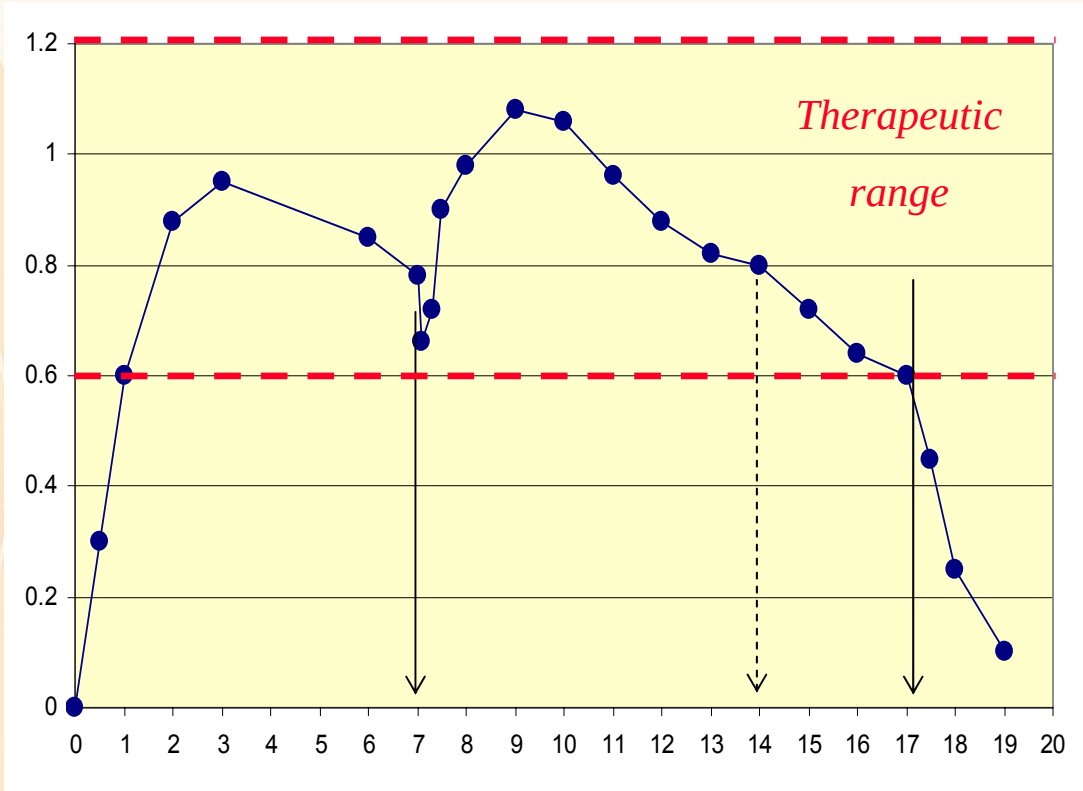
Transdermal systems ORTHO-EVRA

- 20 cm^2 (4.5 cm side), three-layered patch:
  - **outer polyethelene+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



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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%)**