



Long-acting Contraceptive Methods for Women

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Today's Presentation

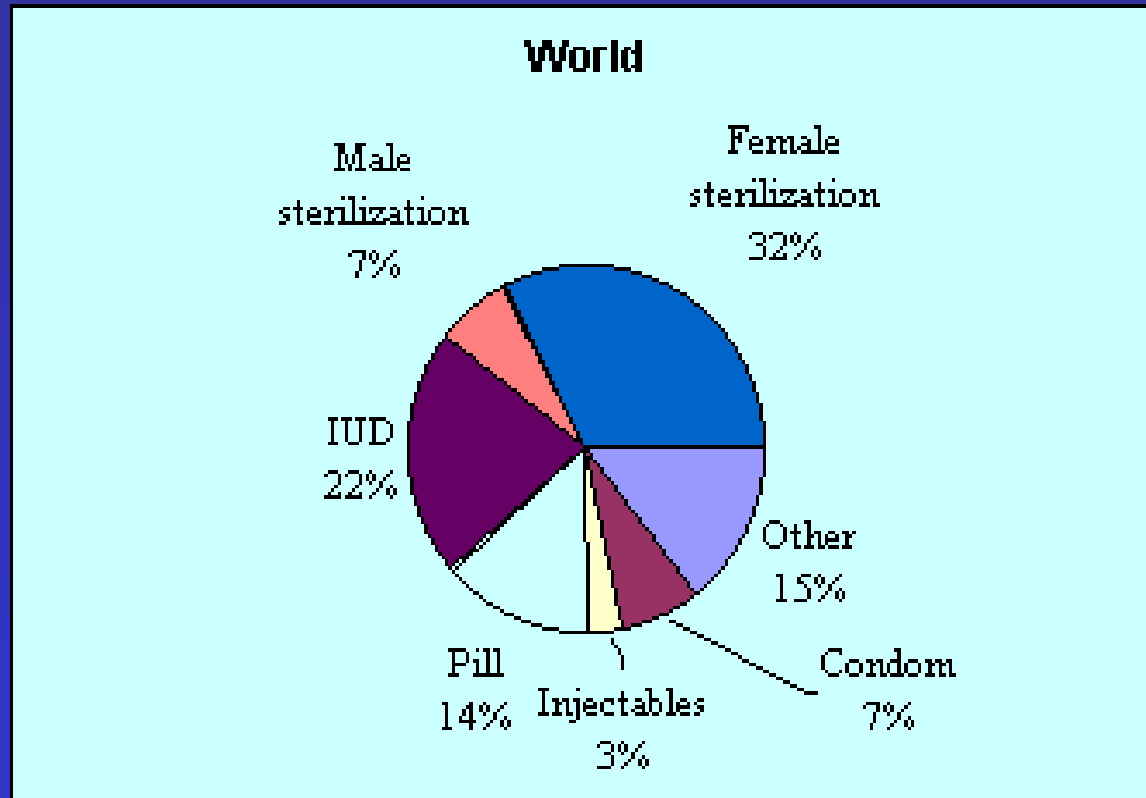
Part I Contraceptive use worldwide

Part II Overview of long-acting contraceptives

Part III Current and future challenges



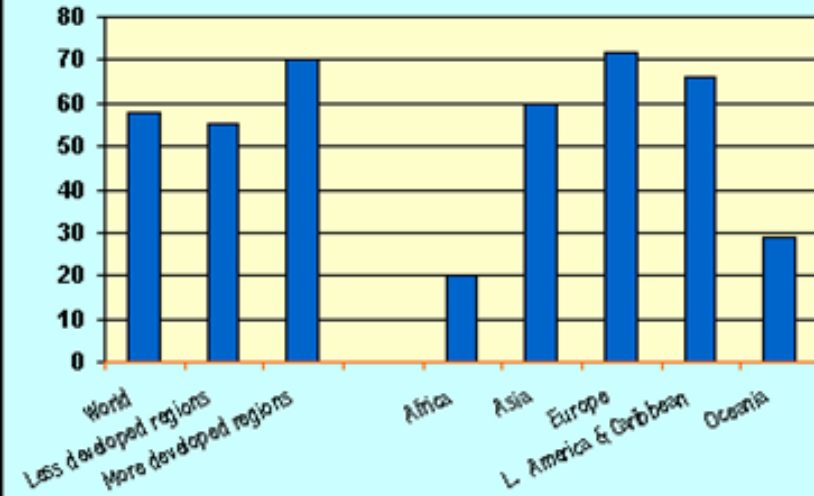
Most contraceptive users worldwide rely on modern methods



Source: UN Population Division 2001. World Contraceptive Use.

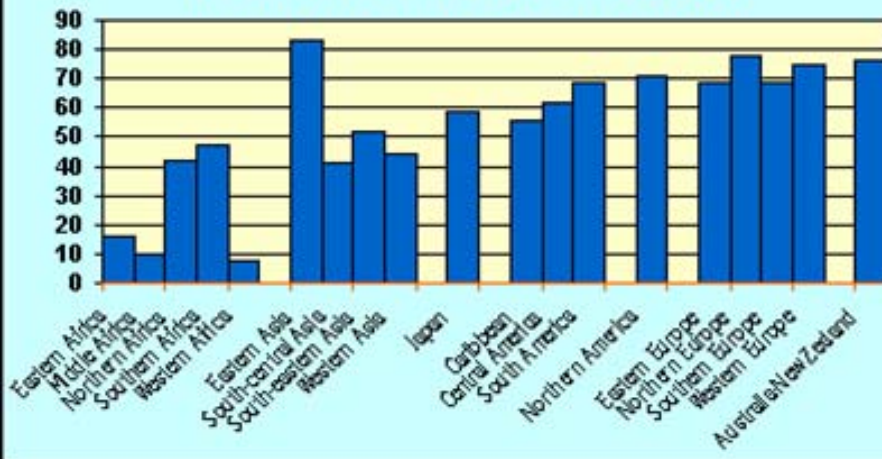


Level of current contraceptive use by major areas



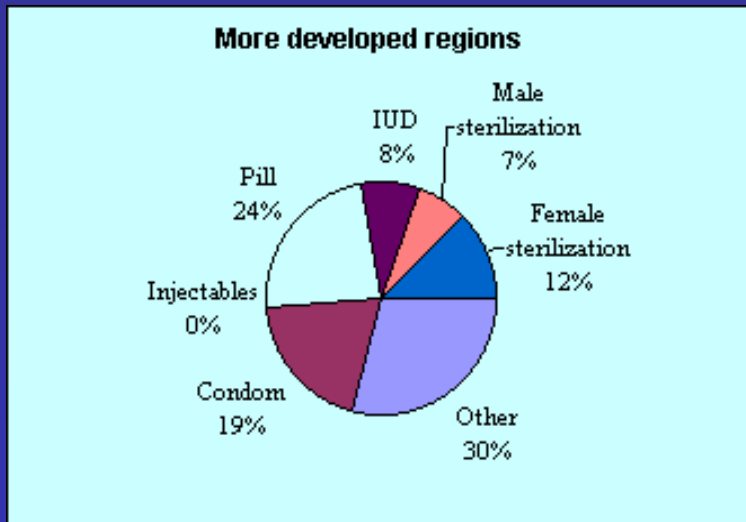
Large proportion of the world's couples are using contraception

Level of current contraceptive use by region

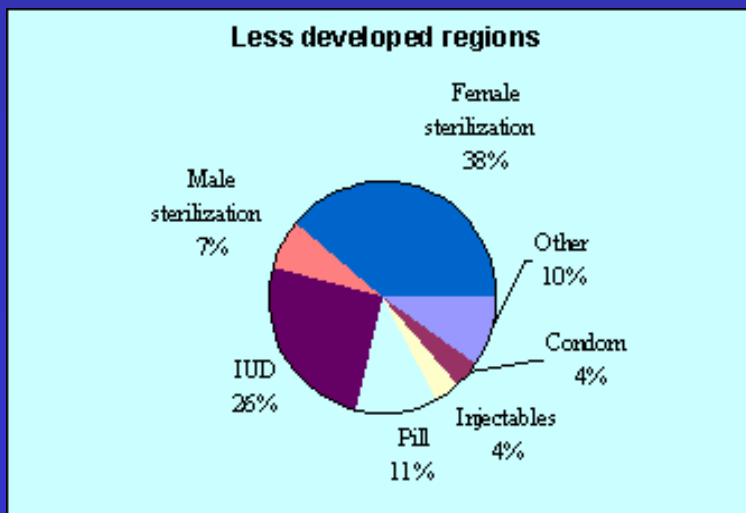


Level of contraceptive use is higher in developed regions, highest in Europe and lowest in Africa.

Source: UN Population Division 2001. World Contraceptive Use.



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

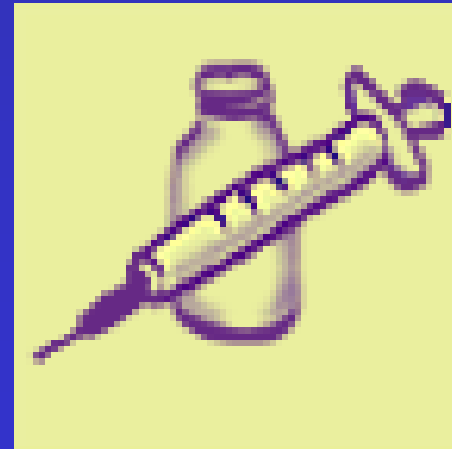


4 long term contraceptives as effective as female sterilization

METHOD	TRADE NAME	USE TIME	USERS (in million)
TCu380A IUD	Paragard^R	10-12 years	30-40
6 Silastic capsules implant	Norplant^R	7 years	8
LNG releasing IUS	Mirena^R	5 years	2
DMPA	Depo Provera^R	3 months	12



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^R
- DMPA Examples: Depo-Provera^R, Megestron^R

2. Once-a-month: combined progestogen-estrogen

- Examples: Cyclophem^R, Cycloprovera^R, Mesigyna^R



Mechanism of action

- **Mainly: ovulation inhibition**
- **Effects on morphology and function of endometrium, Fallopian tubes, cervix**

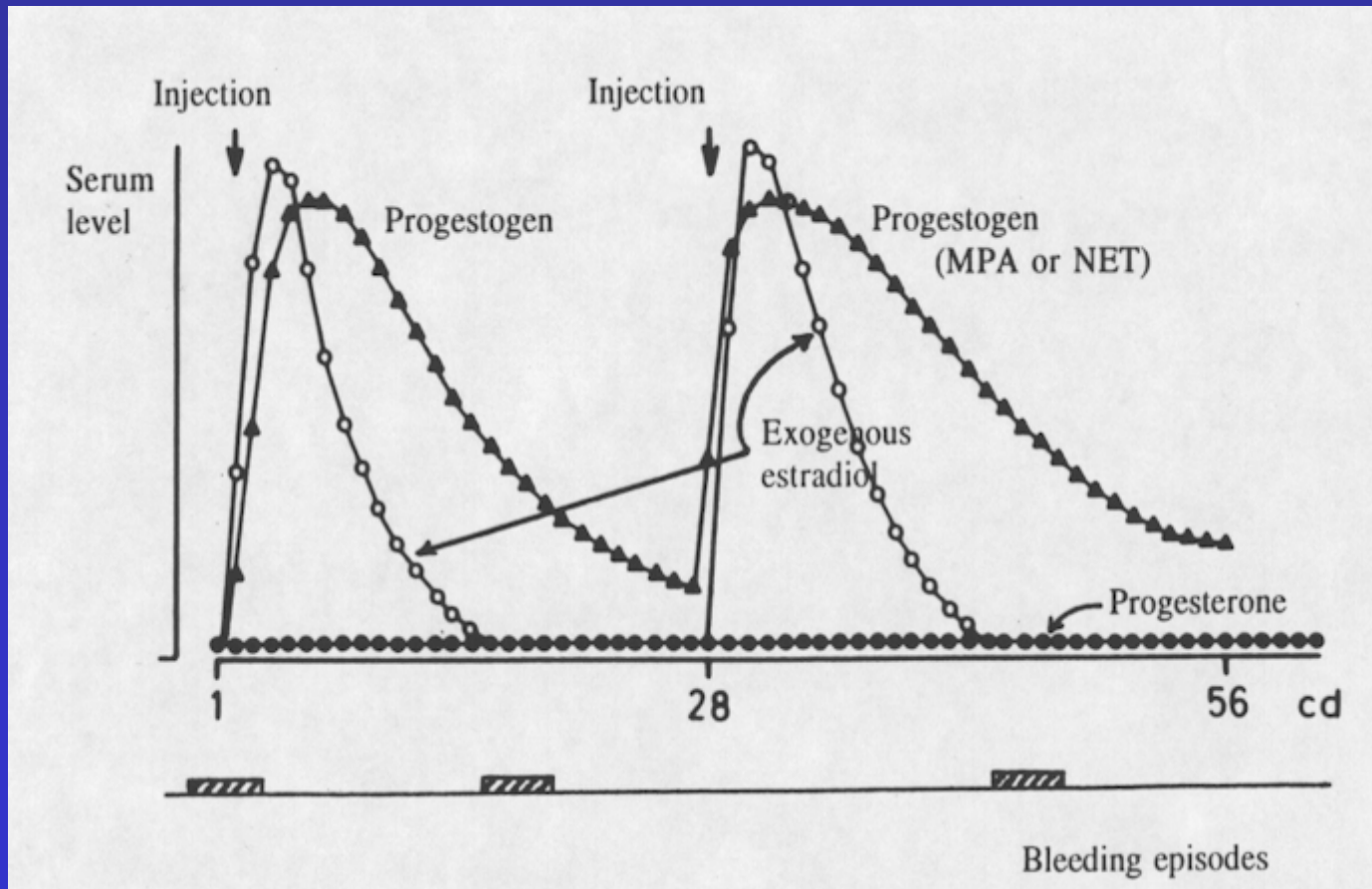


Combined monthly injectables

Trade name	Composition	Availability
Perluta 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	17 α -hydroxyprogesterone caproate 250 mg + E ₂ valerate 5 mg	China
Mego-E	Megestrol acetate 25 mg + 17 β E ₂ 3.5 mg	China



Combined monthly injectables: Typical pharmacokinetic profile

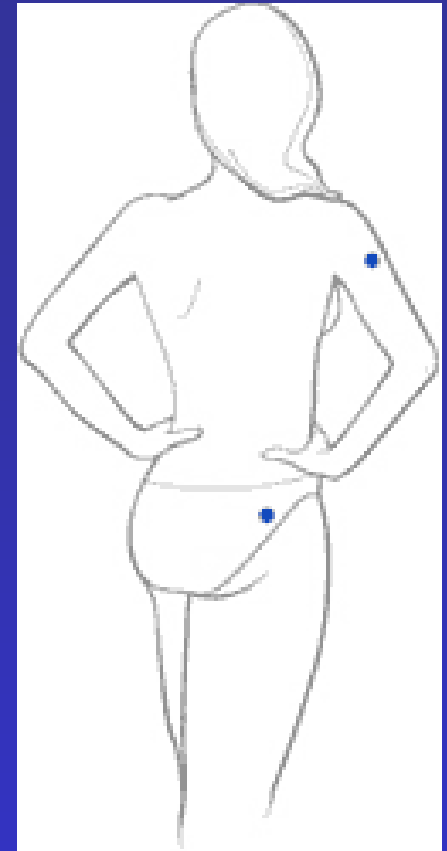


Adapted from: Fraser & Diczfalusy, 1980



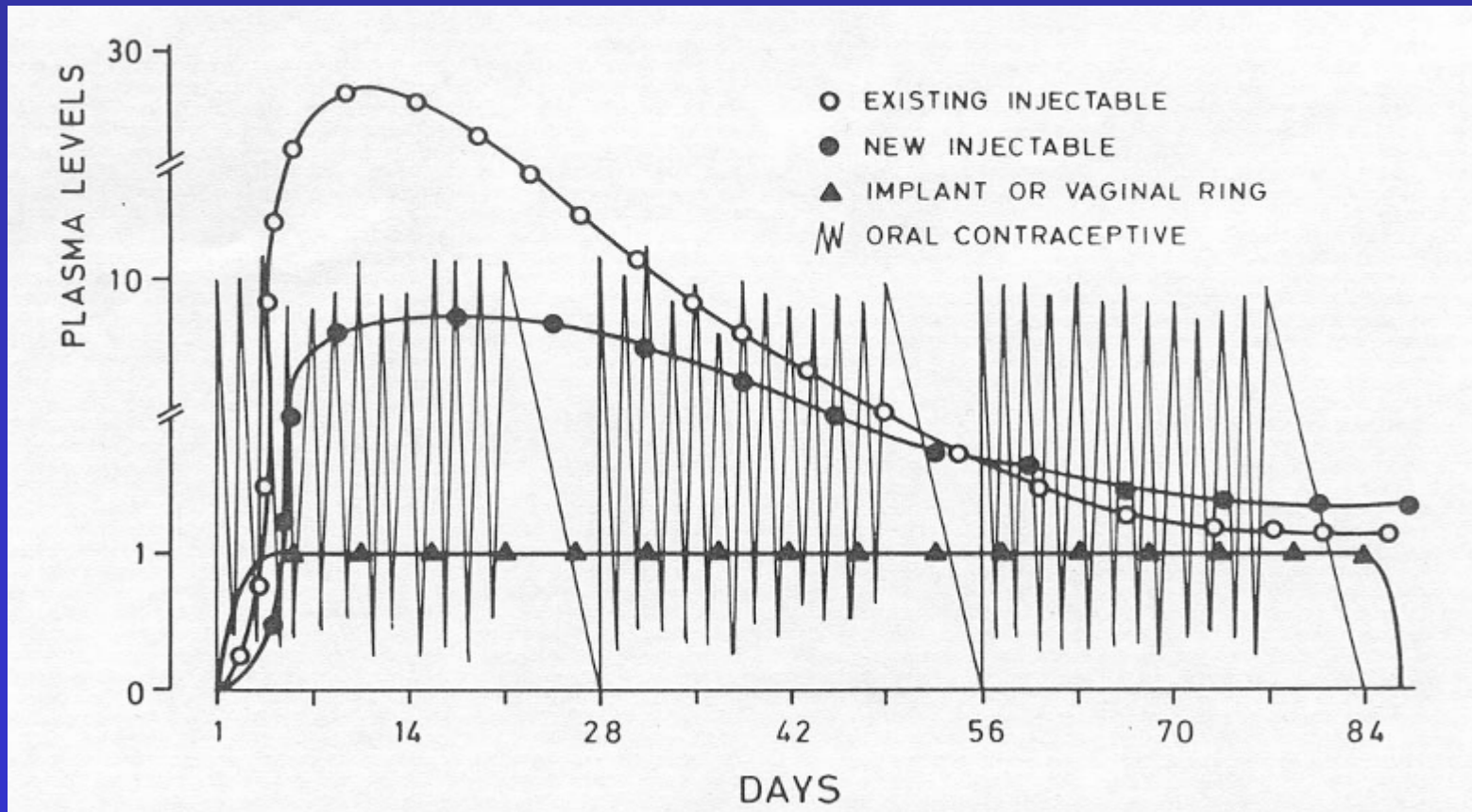
DMPA: Background

- 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





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 %)

	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
TOTAL	8.7	9.3	6.3
Woman-months	20,550	10,361	10,969



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

Scholes D et al. Contraception (2004) 69: 99 and: Epidemiology (2002) 13:581.



Implantable contraceptives

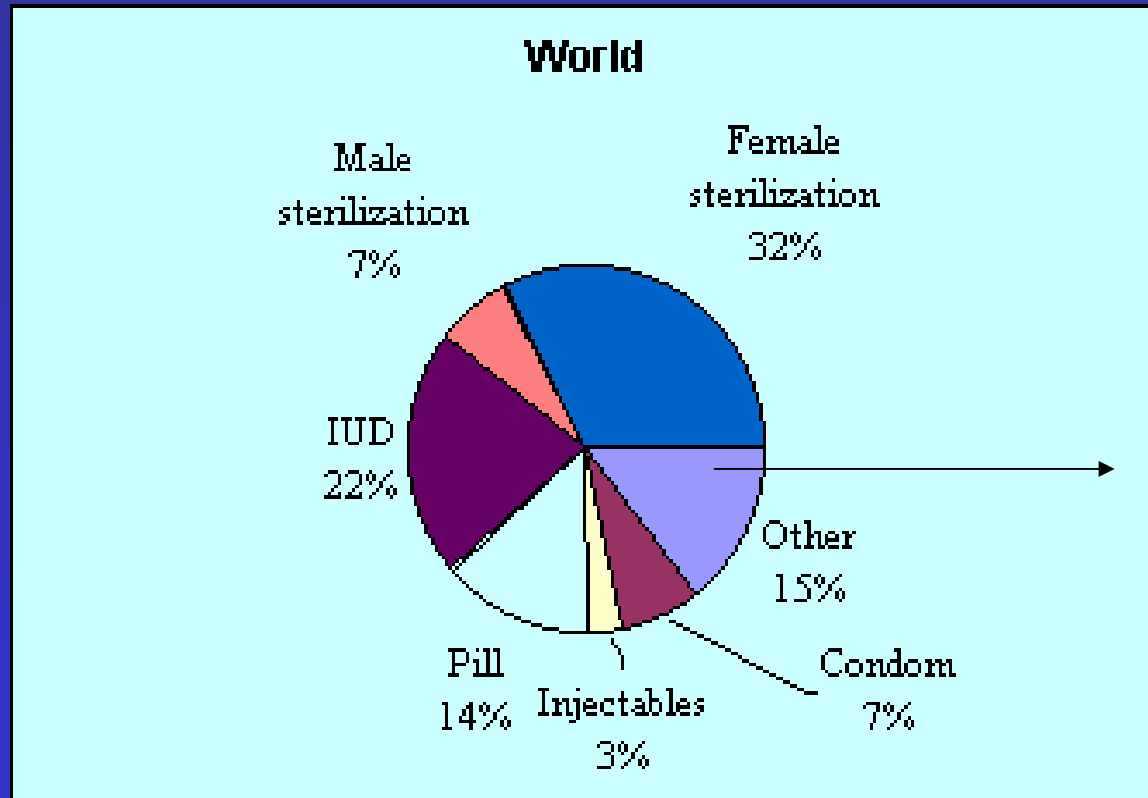


Which role do
implants

play in the
worldwide
method mix ?



World Contraceptive Use 2001: Share of Implants in the method mix



**Includes
Implants**

Source: UN Population Division 2001. World Contraceptive Use.



Implants: Numbers on Current Use

	World	No. of countries where licensed
Norplant	4 million	62
Jadelle	15,000	11
Implanon	1 million	25



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**



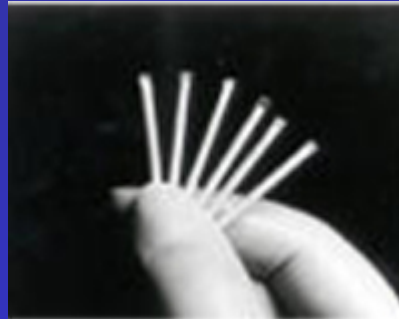
Implant Contraceptives for Women

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

Source: Croxatto HB, et al. Contraception 2002; 65:15-9.

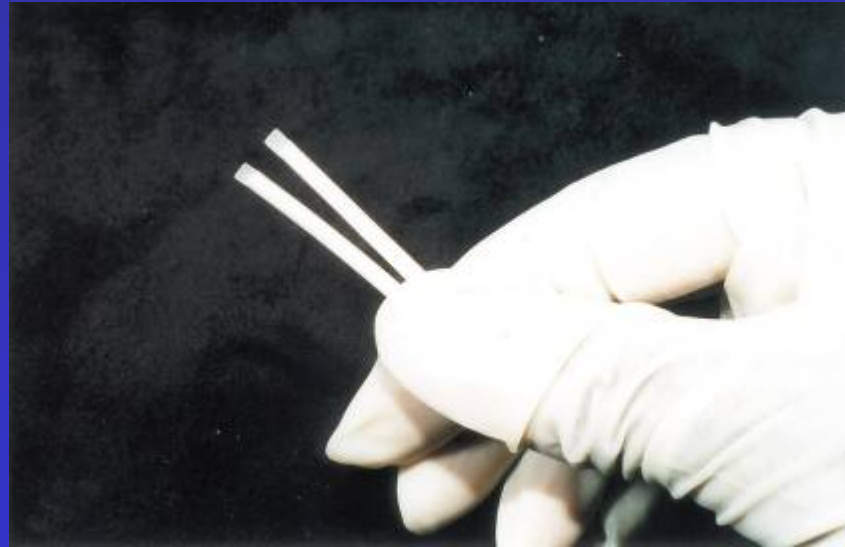


Norplant



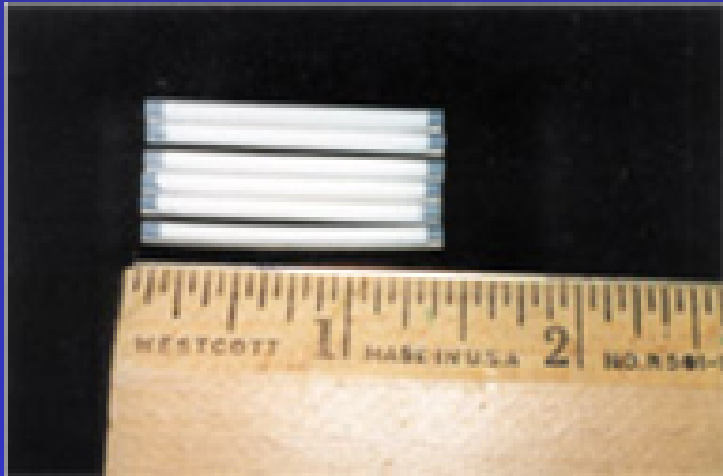


Jadelle





Norplant & Jadelle

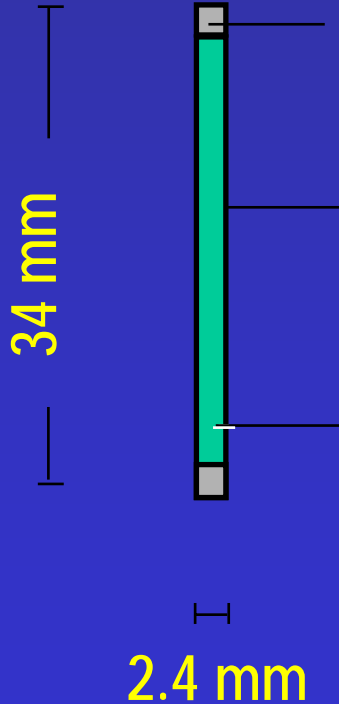




Norplant & Jadelle

Norplant (6 capsules)

216 mg LNG



Silastic medical adhesive

Silastic tubing

Levonorgestrel

36 mg
free
crystals

Jadelle (2 rods)

150 mg LNG



75 mg
crystals
in silicone
copolymer

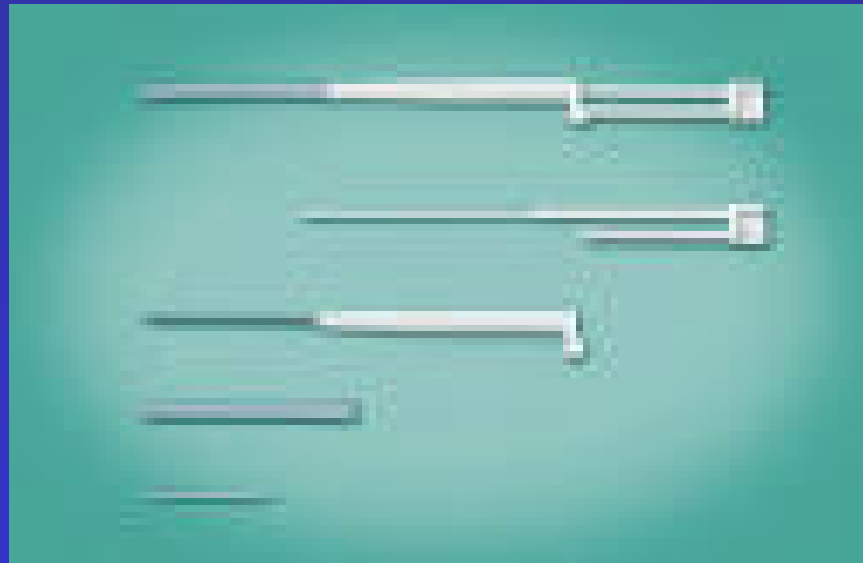


Implanon





Implanon



**Sterile
disposable
applicator**

Obturator

Cannula with needle

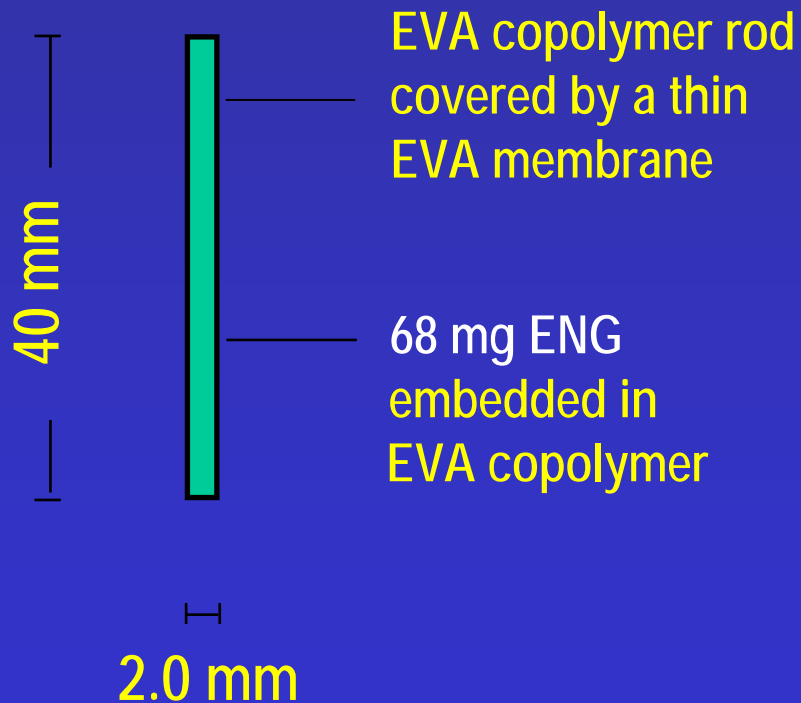
Needle shield

Rod



Implanon

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





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)

	Insertion	Removal
Norplant	4.3 (0.8 - 18.0)	10.2 (1.3 - 50.0)
Jadelle	2.0	4.8
Implanon	1.1 (0.03 - 5.0)	2.6 (0.2 - 20.0)

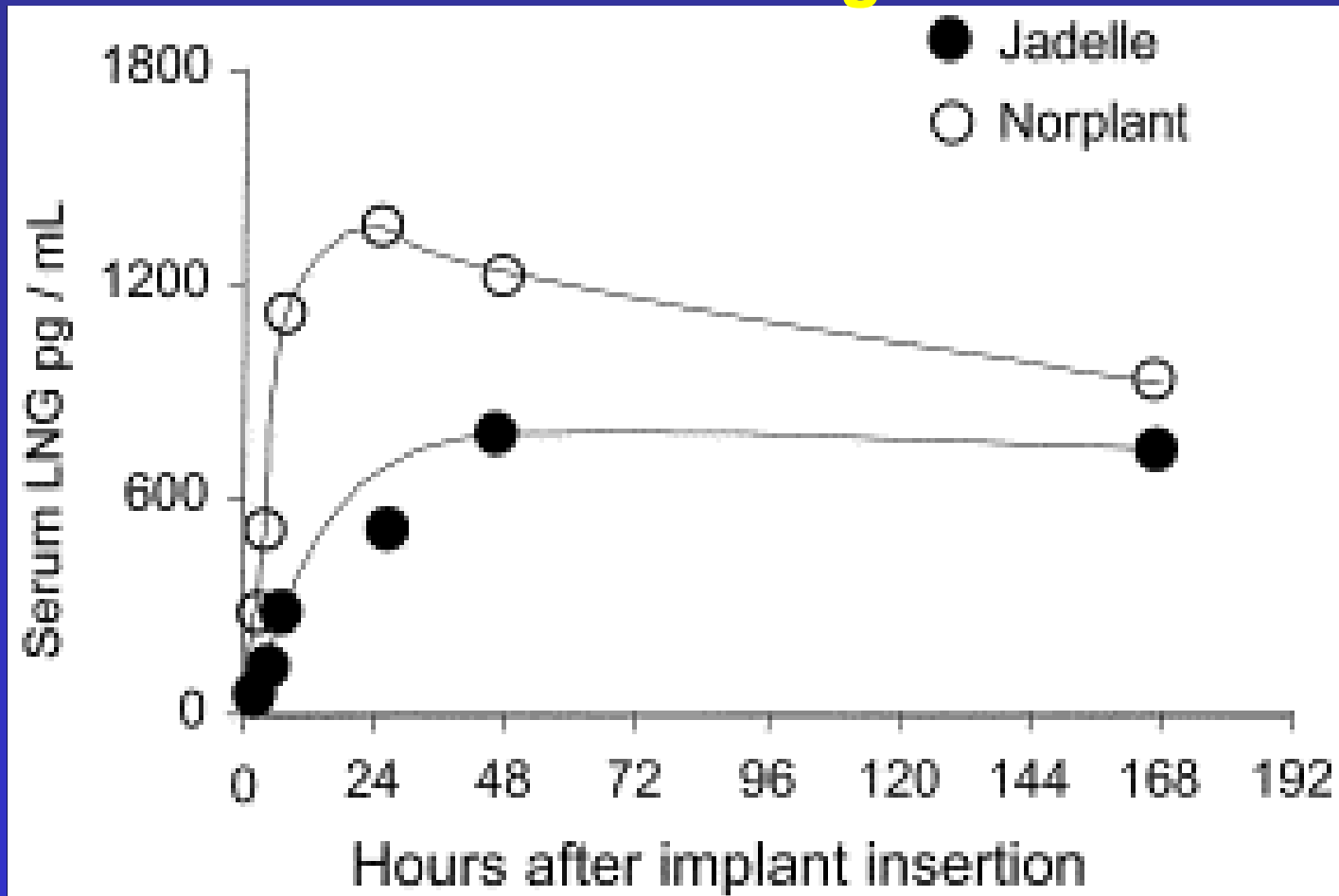
Source: Mascarenhas L. Contraception 1998;58:79S.
Sivin I et al. Human Reproduction 1998;13:3371







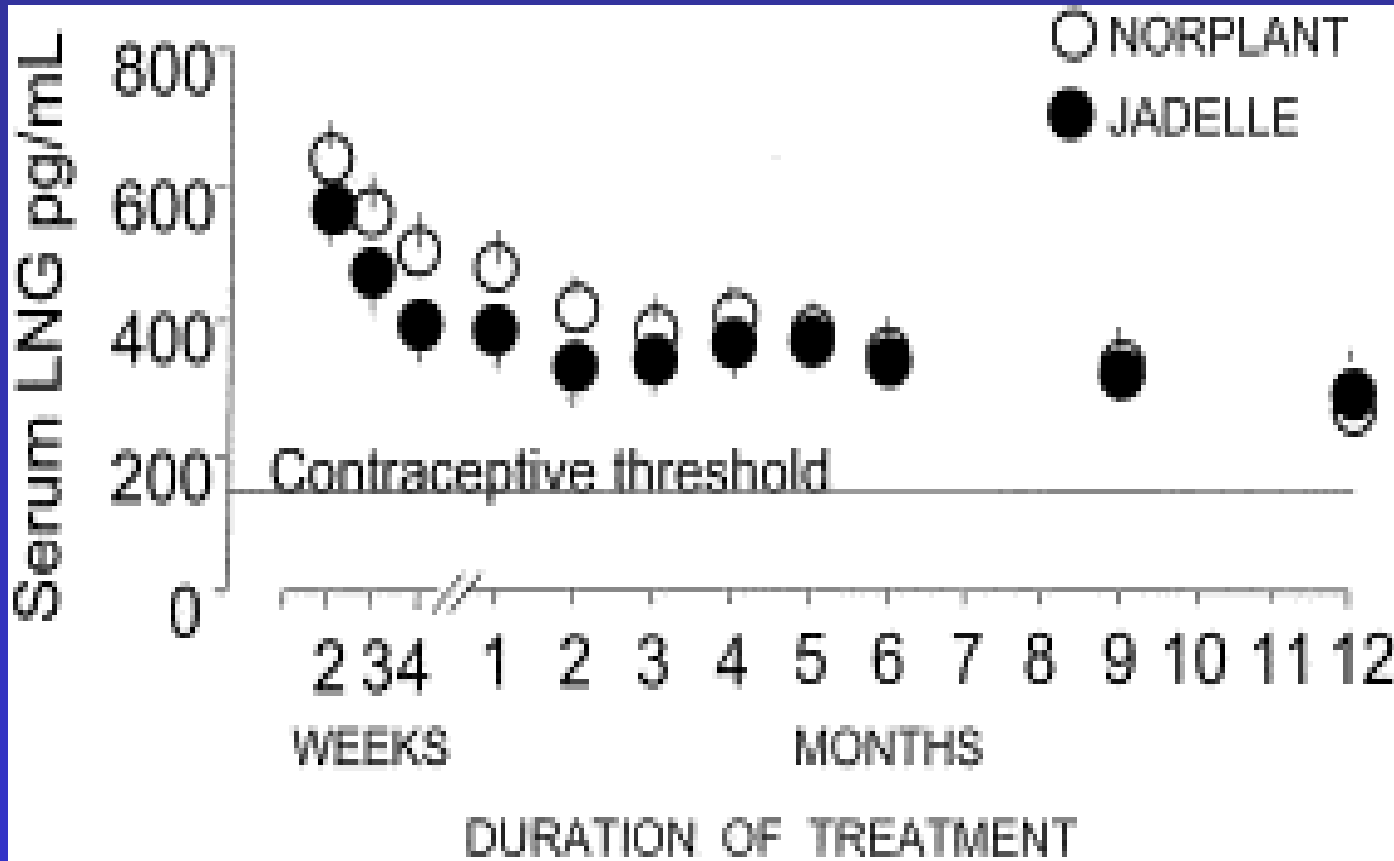
Serum Levels of Levonorgestrel (LNG) One Week following insertion



Source: Croxatto HB et al. Contraception 2002; 65:15.



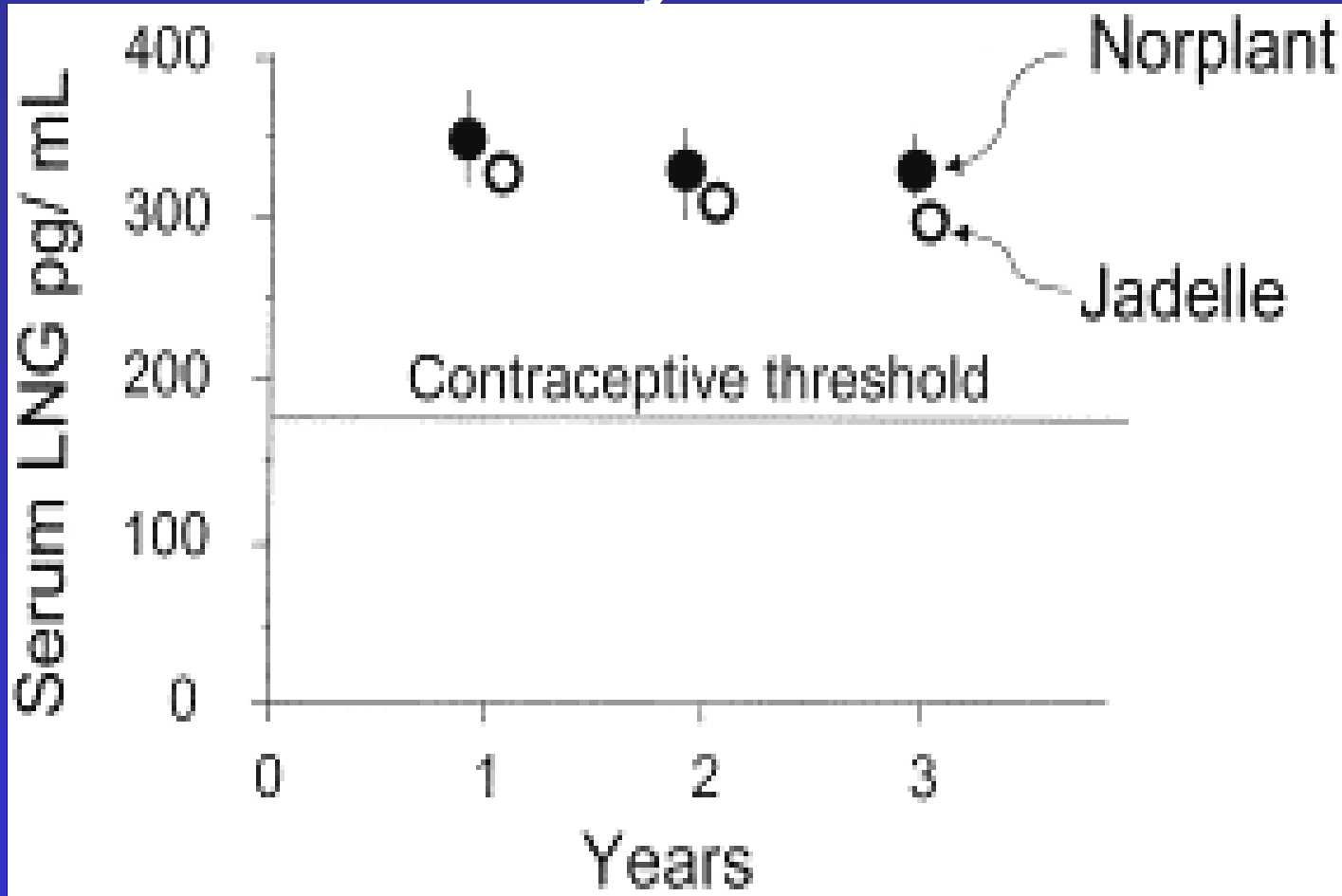
Serum Levels of Levonorgestrel (LNG) *One Year after insertion*



Source: Croxatto HB et al. Contraception 2002; 65:15.



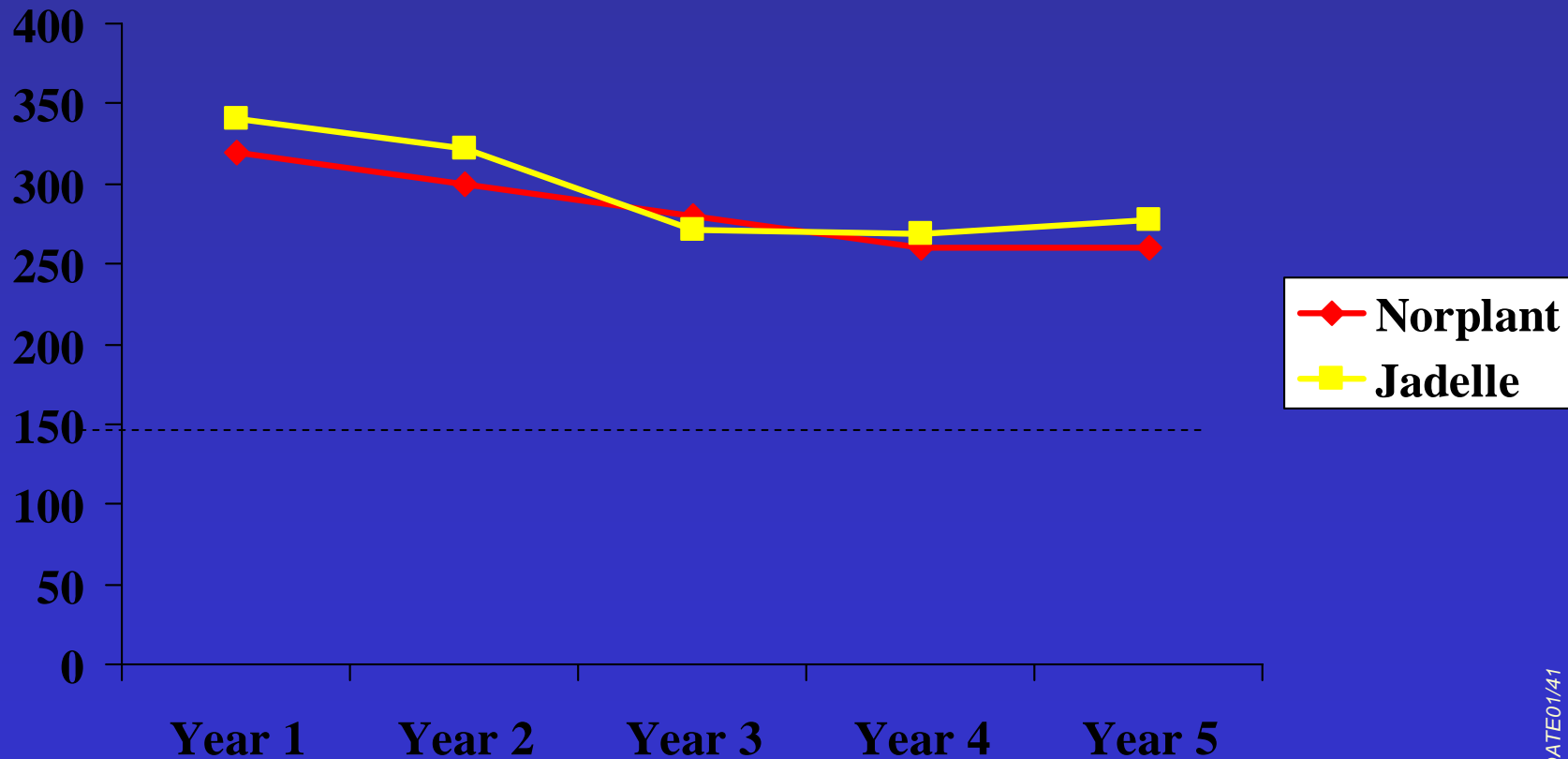
Serum Levels of Levonorgestrel (LNG) First 3 years of use



Source: Croxatto HB et al. Contraception 2002; 65:15.



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

Source: Sivin I, et al. Contraception 2000;61:187.



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

Sources: Sivin I, et al. Contraception 2000;61:187.
Gu S, et al. Contraception 1995;52:99.



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

Source: Zheng et al. Contraception 1999;60:1.

Affandi et al. Contraception 1999;59:167.



Menstrual Bleeding Disturbances

Norplant and Jadelle

- prolonged or irregular bleeding
- spotting between periods
- amenorrhoea

Implanon

- prolonged or irregular bleeding
- amenorrhoea

Source: Hickey M, d'Arcangues C. Contraception 2002;65:75.



Non-menstrual Adverse Events

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

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



Title

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^R, LevoNova^R
- Now registered in > 100 countries
- Number of current users > 2 million

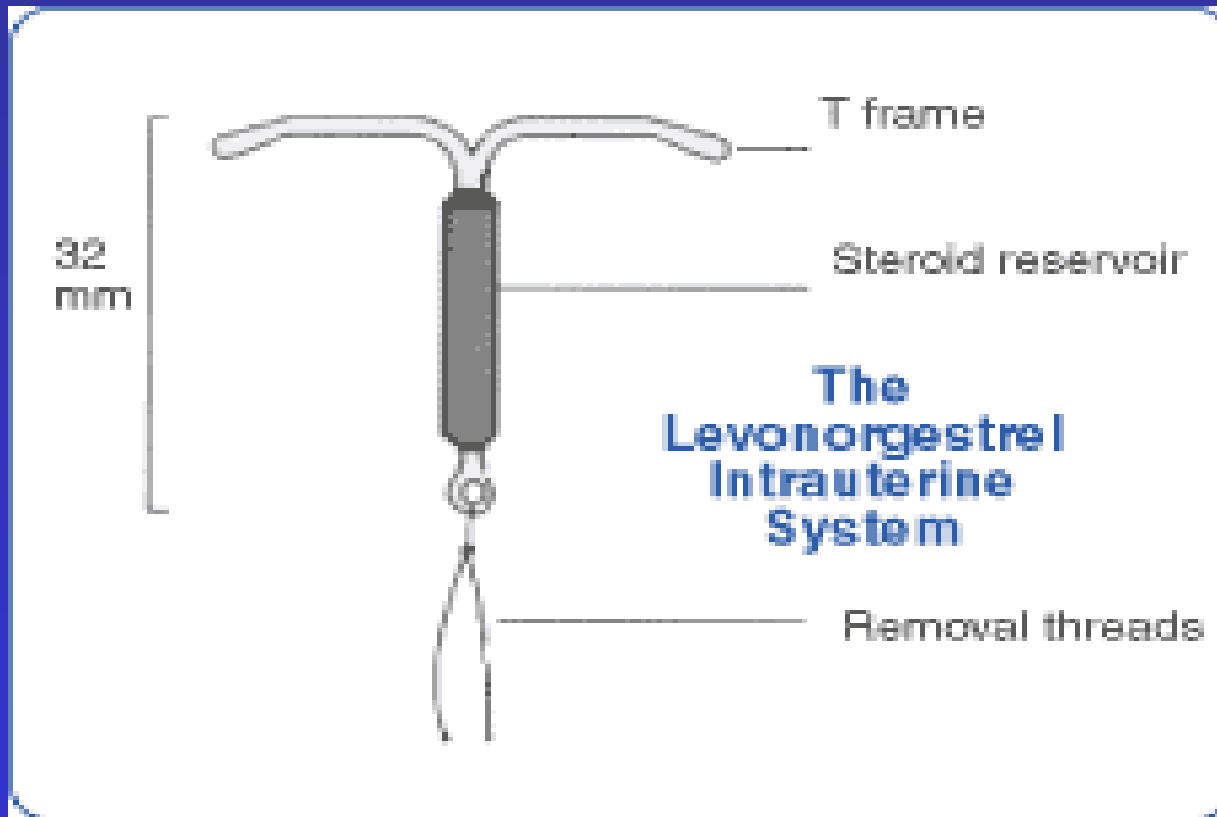


Background: LNG-IUS (2)

- 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

Glasier A et al: Contraception (2003) 67:1-3.



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

	TCu 380A	20 µg LNG device
Total pregnancy	2.0 (0.5)	0.5 (0.2) ←
- Ectopic pregnancy	0.1 (0.1)	-
- Intrauterine pregnancy	1.9 (0.4)	0.5 (0.2)
Expulsions	8.2 (0.8)	7.5(08)
Pelvic inflammatory disease	0.1 (0.1)	0.3 (0.1)
- Menstrual reasons	10.9 (0.9)	35.9 (1.4) ←
- Amenorrhoea	0.5 (0.3)	23.6 (1.3) ←
- Reduced bleeding	3.1 (0.5)	10.9 (1.0) ←
- Increased bleeding	7.1 (0.7)	5.9 (0.7)
Total device-related removals	25.5 (1.1)	47.8 (1.3)
Loss to follow-up	7.9 (0.7)	5.8. (0.7)
Woman-years	7420.7	6381.6

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%**



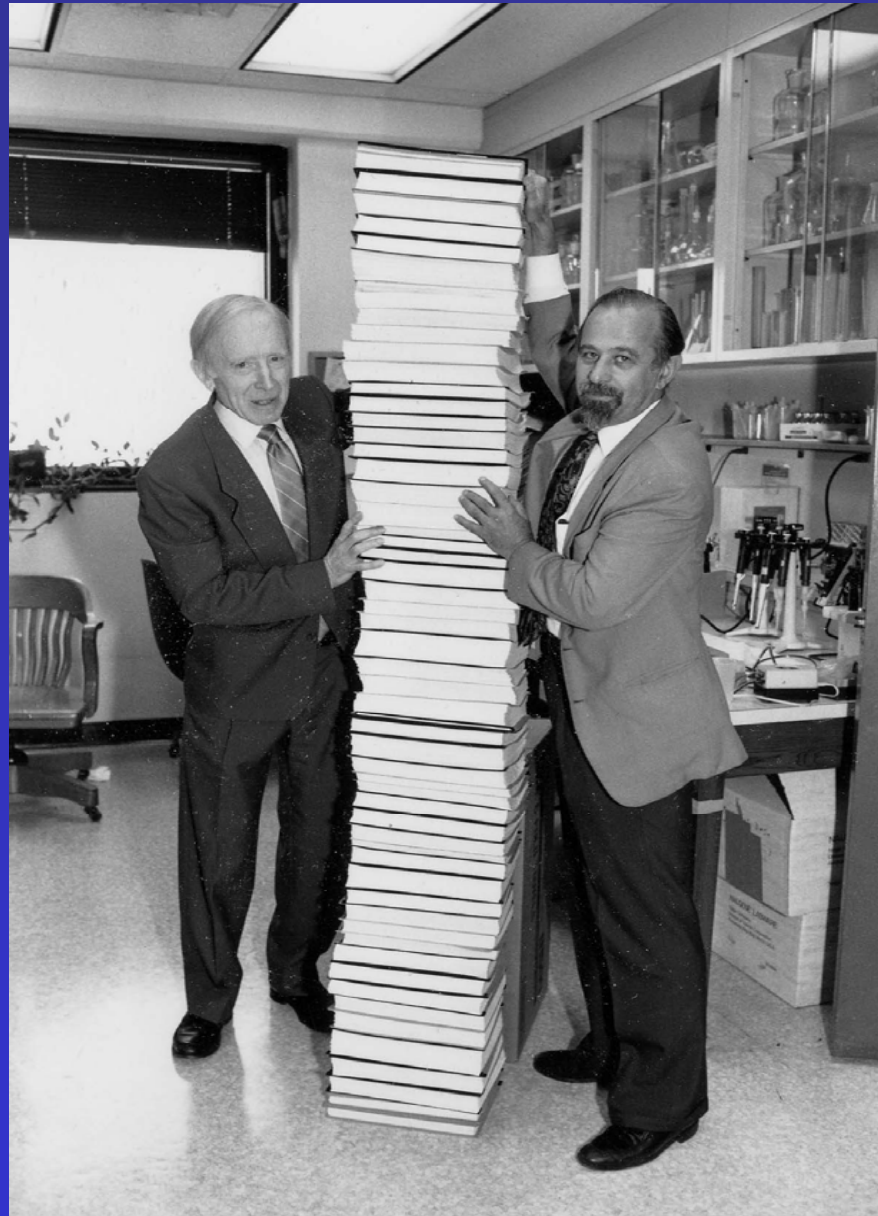
Progress towards reducing the unmet needs requires ...

- 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^R)
- 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

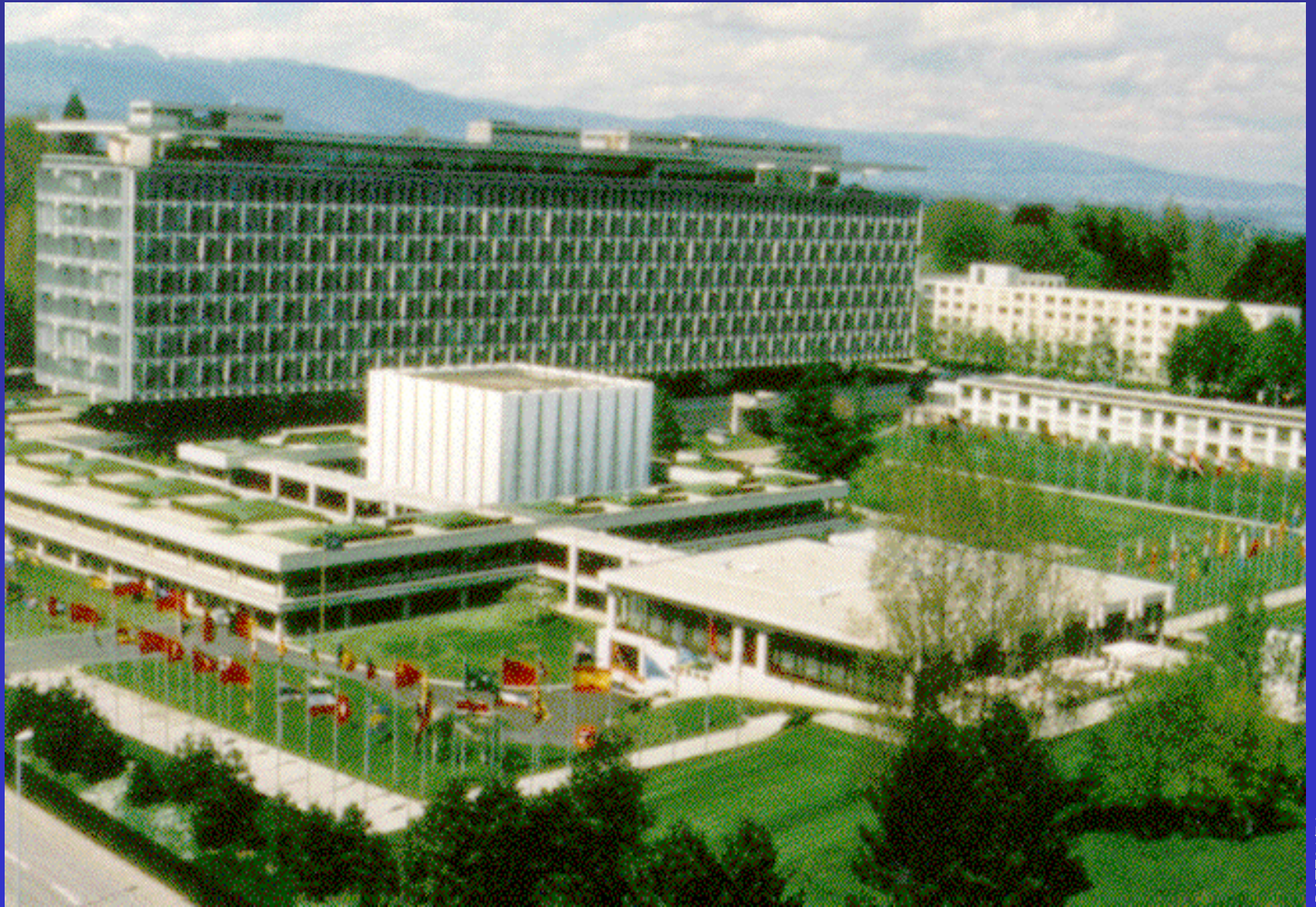
Requires an integrated approach of:

- 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.



DEPARTMENT OF REPRODUCTIVE HEALTH AND RESEARCH



DÉPARTEMENT SANTÉ ET RECHERCHE GÉNÉSIQUES