

Future methods of fertility regulation

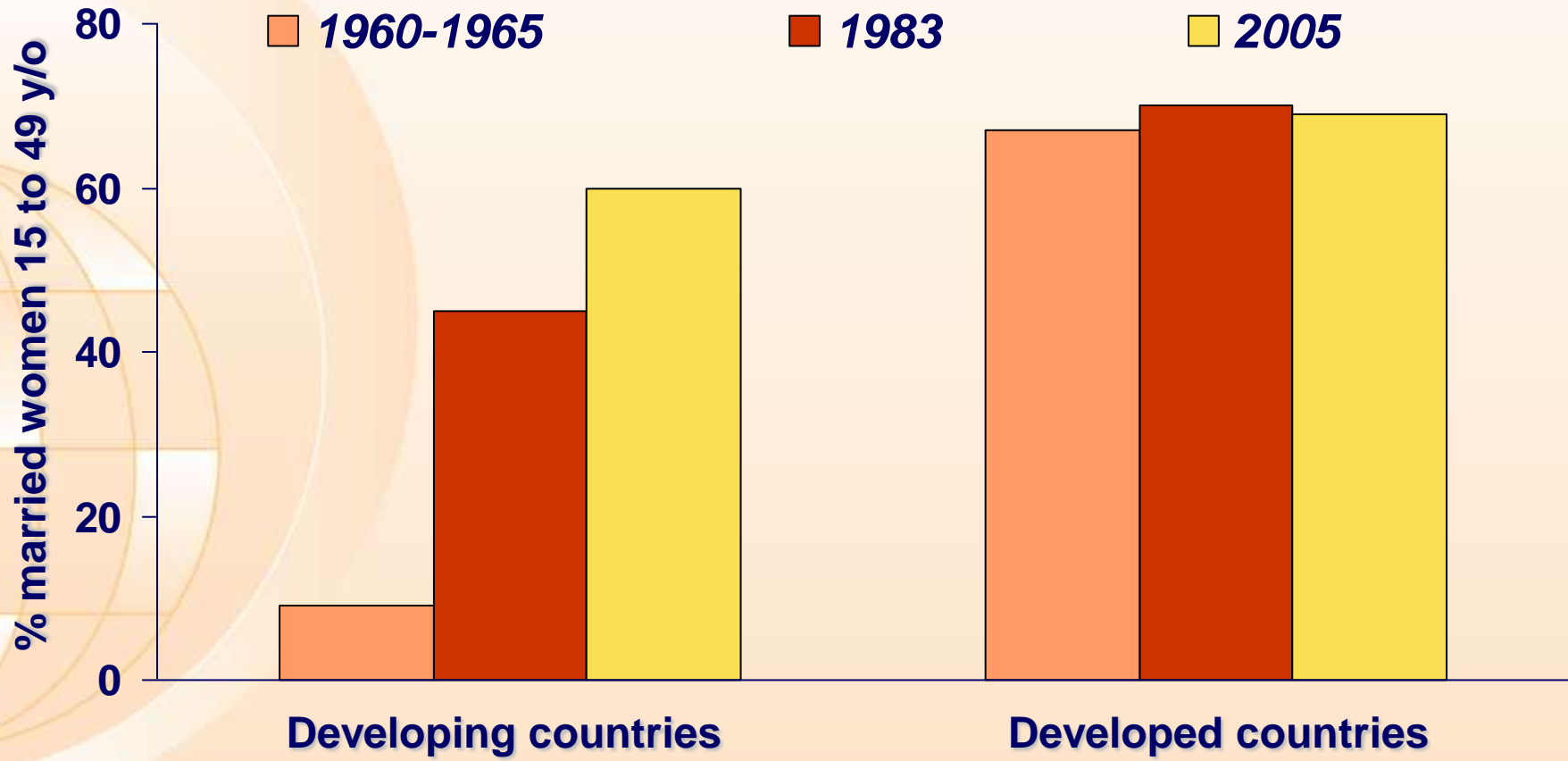
Catherine d'Arcangues, PhD, MD
Kirsten Vogelsong, PhD

Department of Reproductive Health and Research
World Health Organization

Training Course in Sexual and Reproductive Health Research
Geneva, February 2009

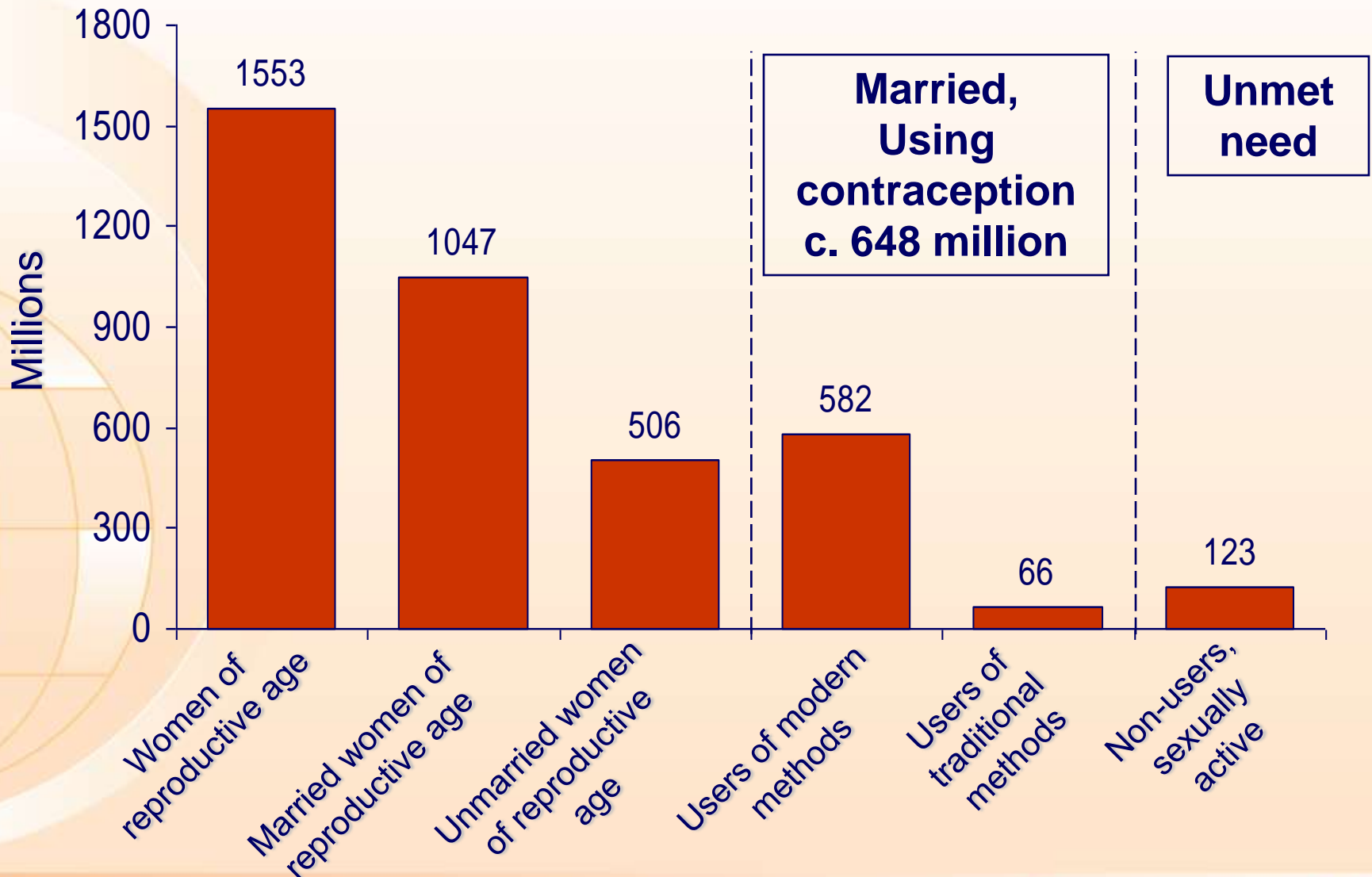
Insert file name 1

Contraceptive use

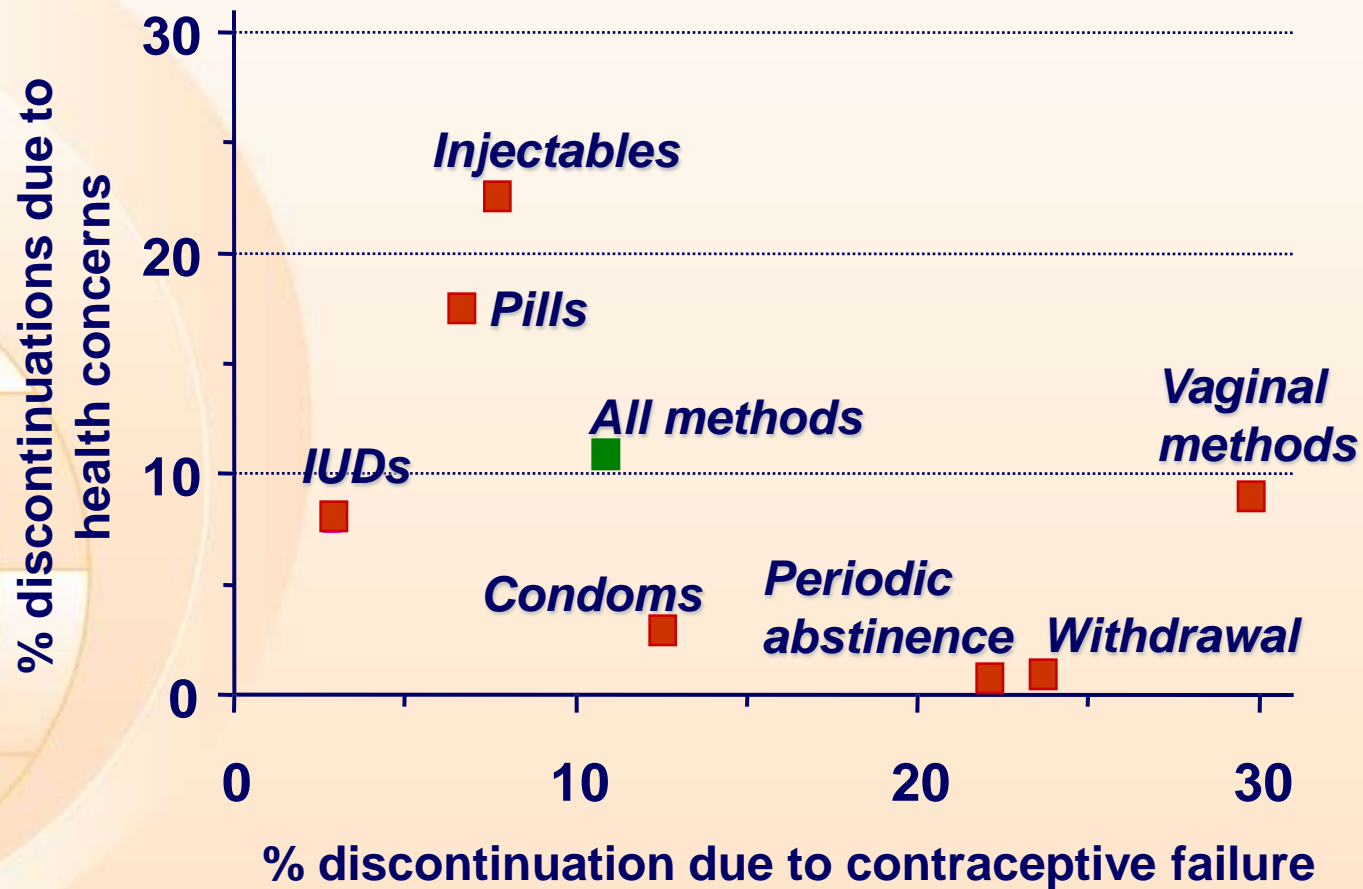


Insert file name 2

Contraceptive use and unmet need (Year 2000)



Contraceptive discontinuation rates at 12 months



Insert file name 4

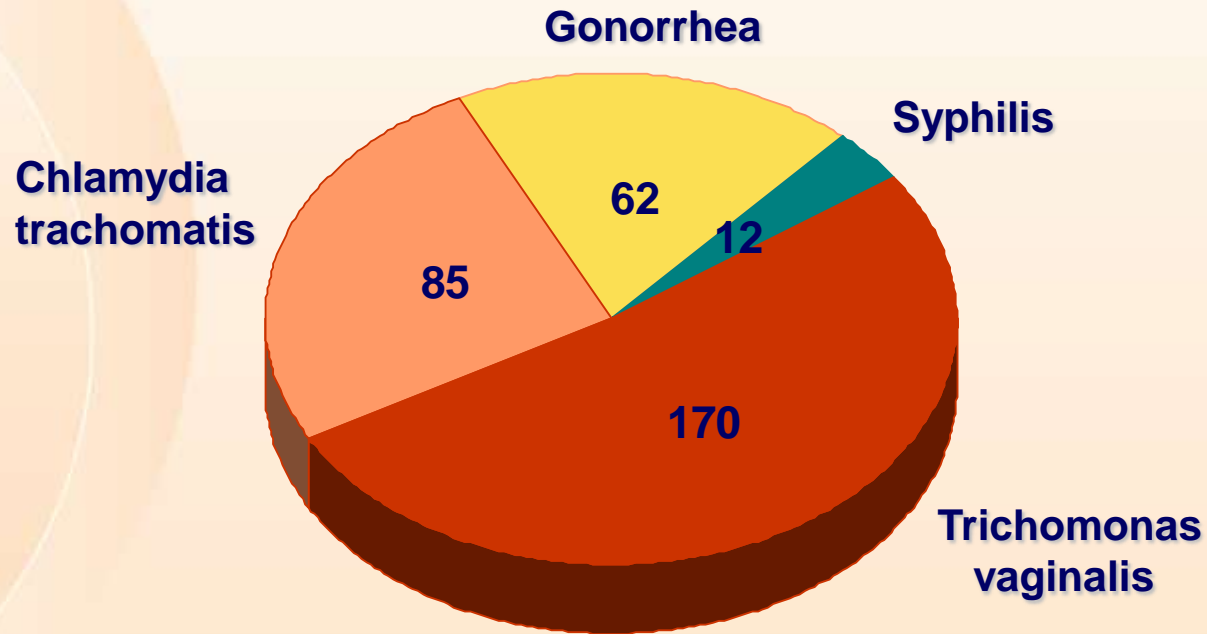
Accidental Pregnancies Resulting from Contraceptive Failure Worldwide

Method	Estimated failure rate %	Number of users (millions)	Number of accidental pregnancies (thousands)
Sterilization	0.2-1.0	155	310-1,550
Injectable	0.3-1.0	6	20-60
Intrauterine device	1-5	80	800-4,000
Oral contraceptive	1-8	55	550-4,400
Vaginal	4-24	6	240-1,400
Rhythm	10-30	16	1,600-4,800
Other traditional	10-20	42	4,200-8,400
Total		398	8,860-30,310

(Source: Segal and LaGuardia, 1990)

Insert file name 5

New cases of curable STDs in 1999 (millions)



Total : 340 millions

(From : WHO, 2001)

HIV/AIDS Epidemic

December 2008

- New HIV infections in 2007: 2.7 million
- Adults and children living with HIV/AIDS: 33 million
- Estimated adult and child deaths due to HIV/AIDS during 2007: 2.0 million

Major lines of research for the development of new contraceptive methods

- Methods with reduced side-effects
- Methods with increased duration of action
- Dual protection (pregnancy and STIs/HIV)
- Contraceptive methods for men
- New targets for contraception

Methods with reduced side-effects

- Injectables
- Implants
- Intra-uterine devices / systems
- Immunocontraceptives
- Estrogen-free pills
- Natural methods

New injectable contraceptives

- Improved pharmacokinetic profile

Progestogen esters:

Levonorgestrel butanoate

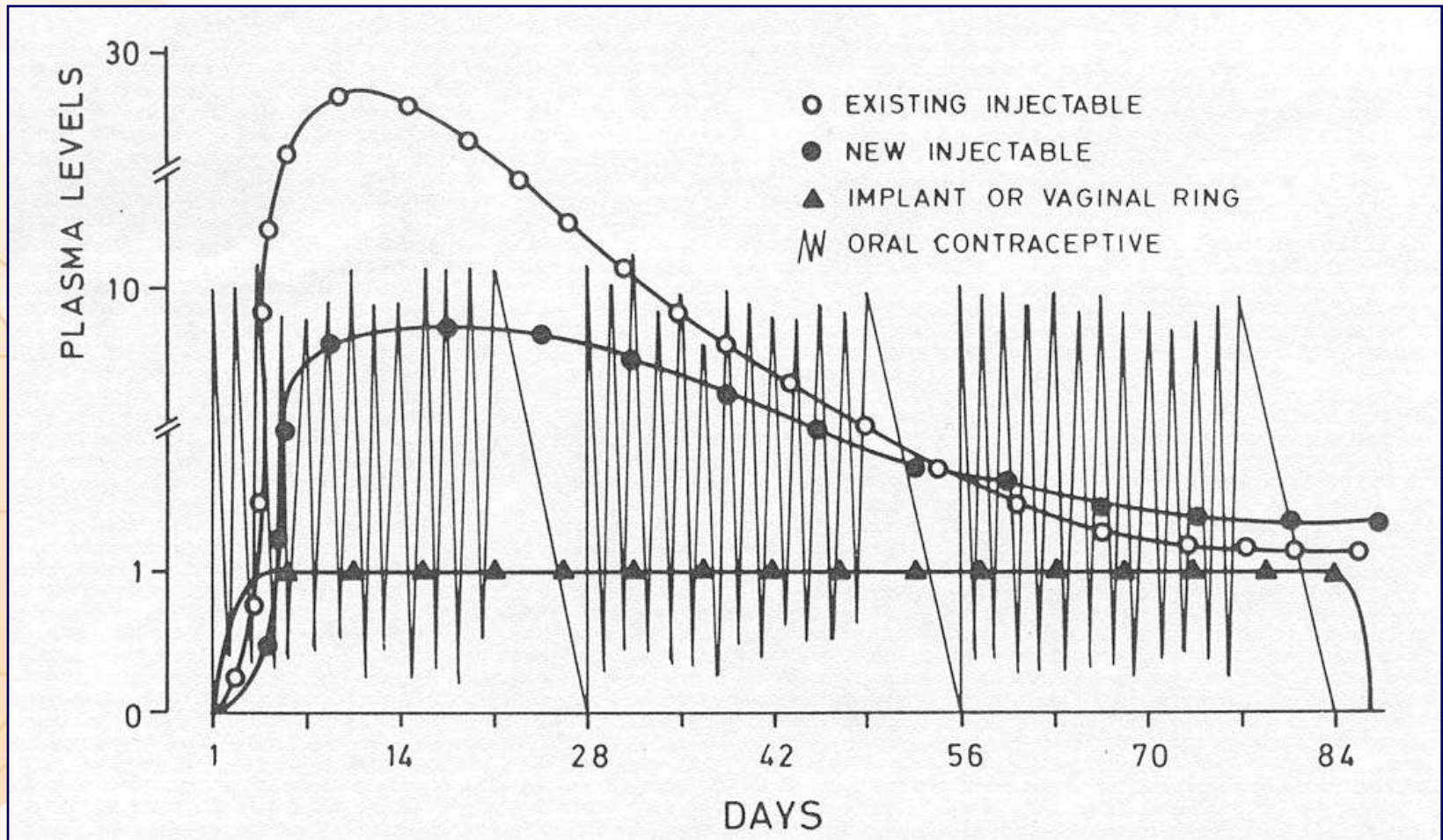
- Decreased metabolic effects:

Monolithic microspheres:

progesterone, estradiol, testosterone

Insert file name 10

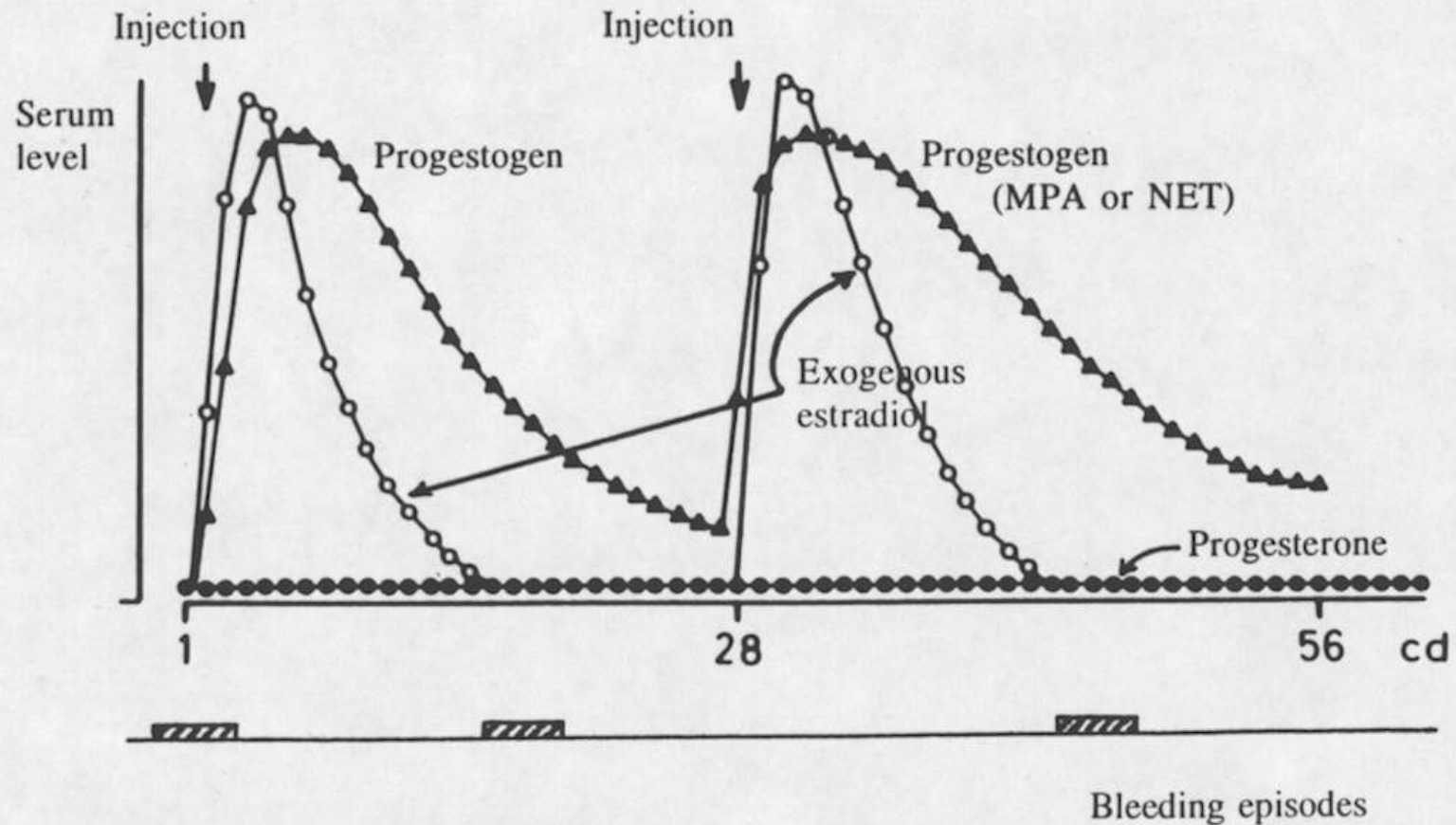
Schematic representation of pharmacokinetic profiles of progestogens administered by different routes



Insert file name 11

Monthly injectable contraceptives

Schematic representation of pharmacokinetic and pharmacodynamic profile



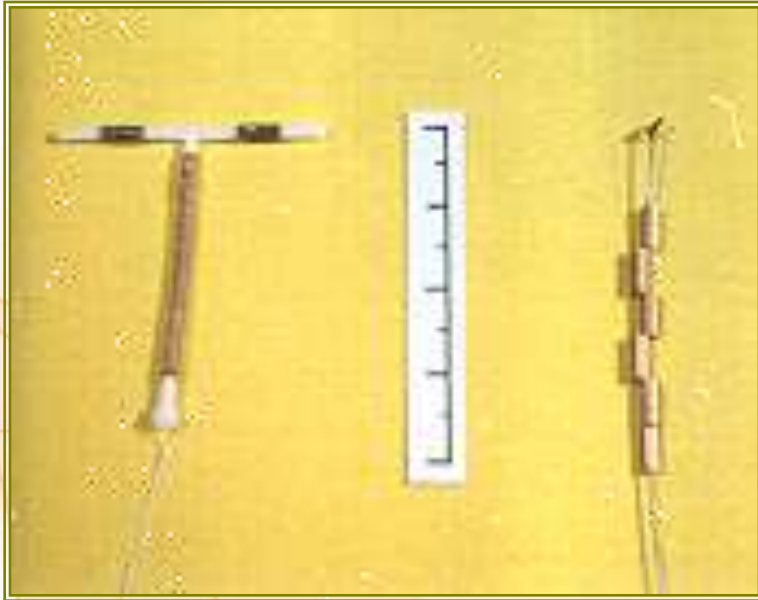
Combined injectable contraceptives

Name	Composition	Availability
Perlutal Topasel	Acétophénide de dihydroxyprogestérone 150 mg + Enanthate d'E ₂ 10 mg	Latin America Spain
Injectable No1	Caproate de 17 α -hydroxyprogestérone 250 mg + Valérianate d'E ₂ 5 mg	China
Mego-E	Acétate de Megestrol 25 mg + 17 β E ₂ 3.5 mg	China
Cyclofem (Lunelle)	AMPR 25 mg + Cypionate d'E ₂ 5 mg	25 c.: Latin America, Indonésie, Thaïland
Mesigyna Norigynon	NET-EN 50 mg + Valérianate d'E ₂ 5 mg	40 c.: Africa, Latin America, Turkey, China

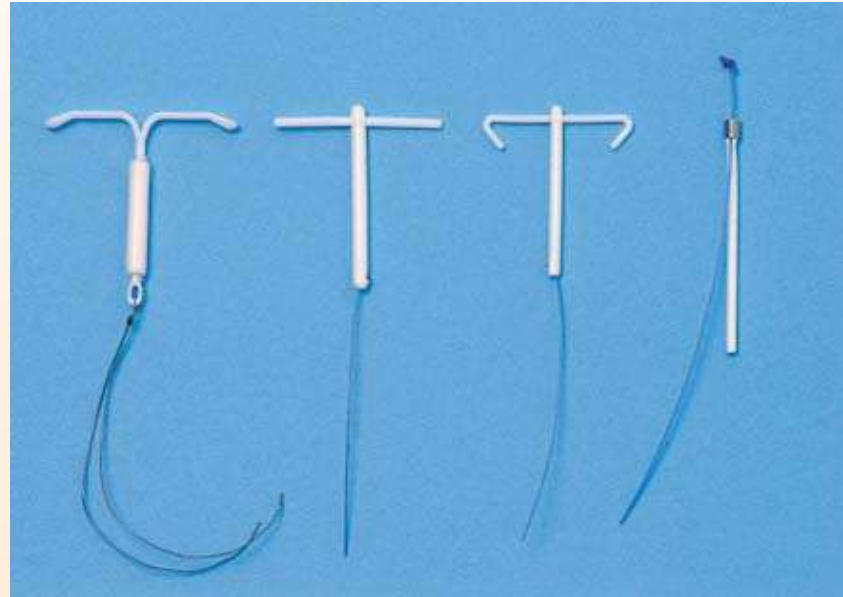
Contraceptive implants

- **Jadelle:**
levonorgestrel, 2 rods, 5 years
- **Implanon:**
etonogestrel, 1 rod, 3 years
- **Nestorone:**
inactive orally, 1-2 rods, 2 years

Intra-uterine systems



Copper-releasing



Levonorgestrel-releasing

Also under development: Anti-progestin-releasing IUD (CDB-2914)

Insert file name 15

Immunocontraceptive

To elicit antibodies to hCG secreted by the trophoblastic cells of the embryo and necessary for maintenance of the corpus luteum and continued progesterone production:

- aa sequence 109-145 of the C terminus of β -hCG
- + diphtheria toxoid as carrier
- + muramyl dipeptide as water-soluble adjuvant
- + squalene/mannide monooleate (4:1) as an emulsifying agent

Estrogen-free pills

- Mifepristone 5 mg daily
- Mifepristone (days 1-15) + nomegestrol acetate (days 16-28)

Insert file name 17

Natural methods

- Standard days methods, based on abstinence/protection from cycle day 8 to cycle day 19.



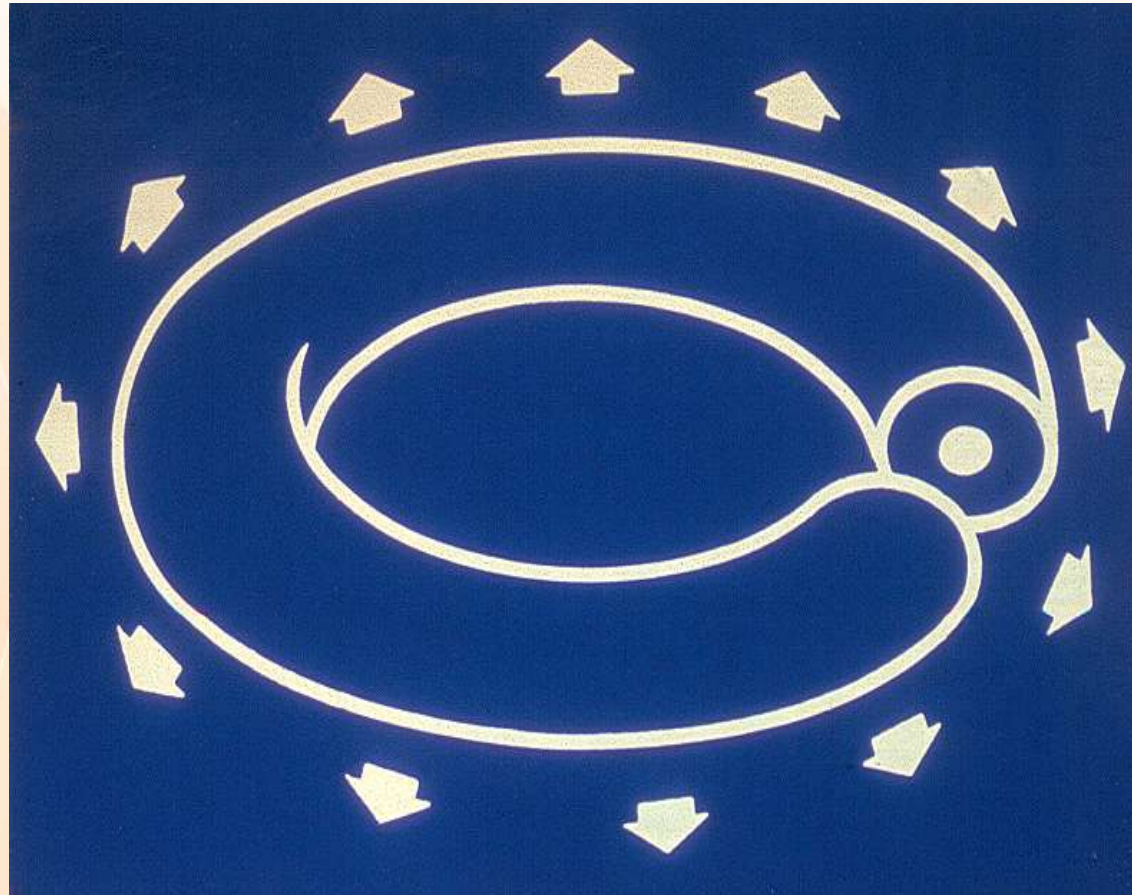
- Two-day method based on the observation of cervical secretions

Methods with prolonged duration of action

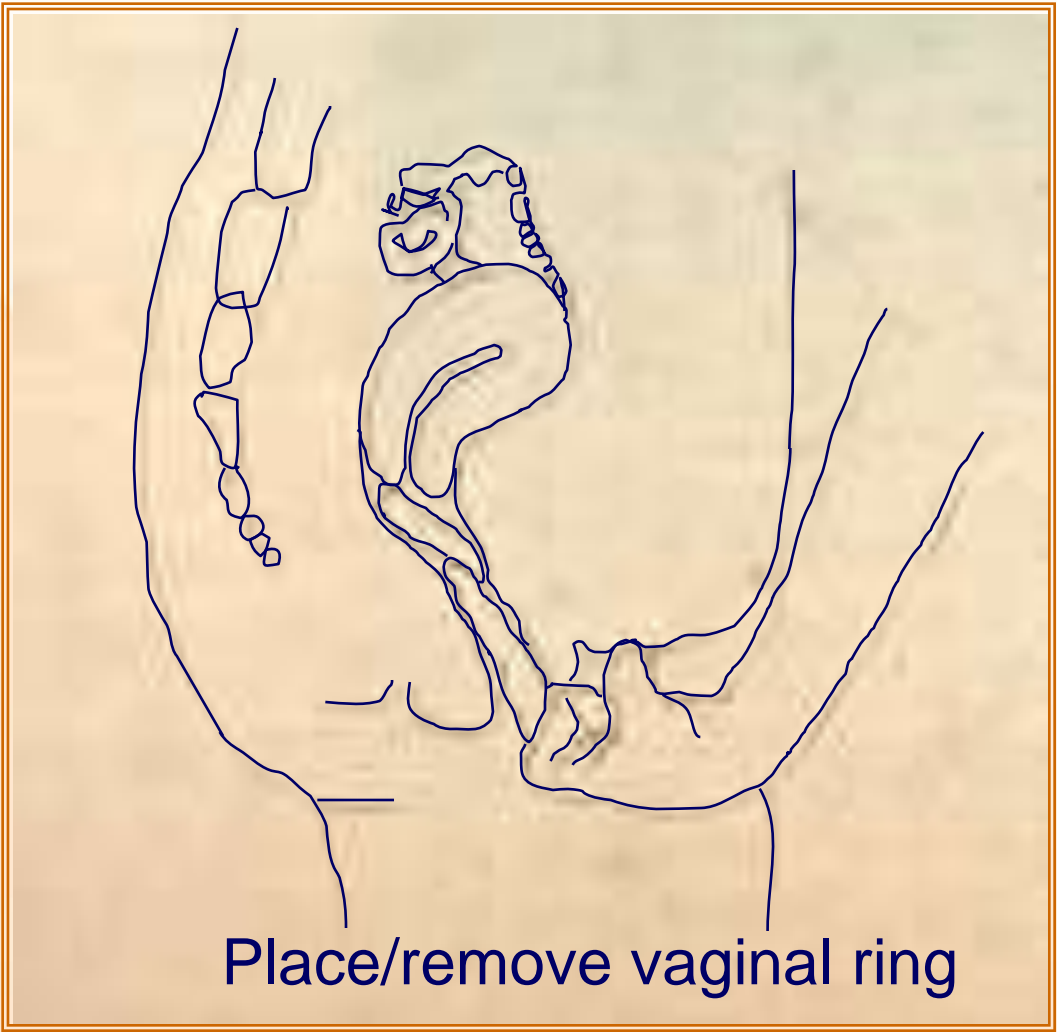
- Under the user's control:
 - Vaginal rings
 - Transdermal delivery systems
- Not under the user's control
 - Female sterilization



Vaginal ring



Insert file name 20



Contraceptive vaginal rings

- Progestogen alone
(used continuously)
 - Progering - Silesia (3 mo.)
 - nesorone - Pop Council (12 mo.)
- Estrogen-progestogen
(3 weeks in /1 week out)
 - Nuvaring - Organon (1 mo.)
 - nesorone/EE - Pop. Council (12 mo.)



Transdermal systems

- Systems releasing an estrogen and a progestogen:
 - norelgestromin 150 μg + ethinyl estradiol 20 μg (Evra - Ortho-McNeil)
 - levonorgestrel + ethinyl estradiol
 - gestodene + ethinyl estradiol
- Systems releasing a progestogen only:
 - nesterone (patch, spray or gel)
 - norgestimate

Insert file name 23

Methods for female sterilization

Essure



Adiana

Ovabloc

Quinacrine



Dual protection

- New male condoms
- Female condoms
- Microbicides/spermicides

Insert file name 25

New male condoms



Polyetherane: Avanti, eZ.on

Styrene-based plastic: Tactylon, Unique, Unisex

Female condoms



Femidom

Under development:

1. polyurethane
(PATH)
2. natural latex
(Reddy)
3. plastic
(Panty condom)



V-Amour

Insert file name 27

Microbicides with contraceptive effect

- Agents that create a **protective physical barrier** in the vagina: e.g. sulfated and sulfonated polymers, such as cellulose sulfate, polystyrene sulfonate
- Agents that enhance vaginal defence mechanisms by maintaining **natural levels of acidity** (which immobilizes sperm): e.g. BufferGel and Acidform
- **Surfactant** agents: e.g. acylcarnitine analogs, C31G
- Agents that **block HIV binding to target cell and sperm-zona pellucida binding**: e.g. naphthyl urea derivatives

See www.microbicide.org

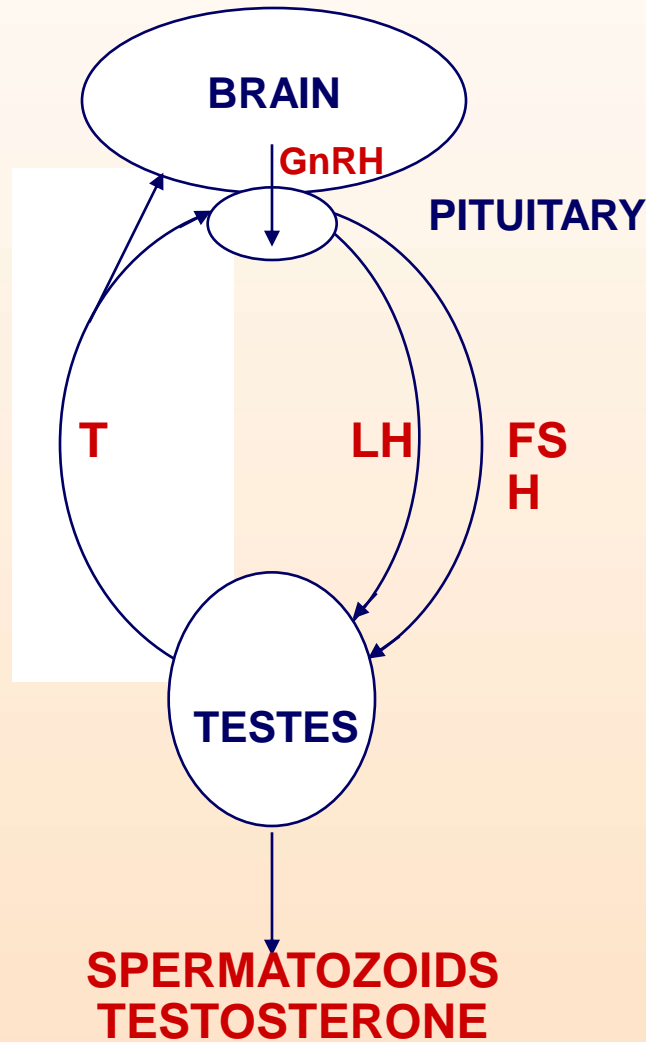
Insert file name 28

Methods for male contraception

- Prevent sperm production
- Prevent sperm transport
- Prevent sperm deposition
- Modify sperm function
- Prevent fertilization

Insert file name 29

Hormonal control of sperm production



Insert file name 30

Methods to suppress sperm production

- **Hormonal**
 - Testosterone esters
 - progestogen or GnRH analogue + testosterone
- **Immunological, based on antibodies against**
 - GnRH, LH, FSH, their receptors

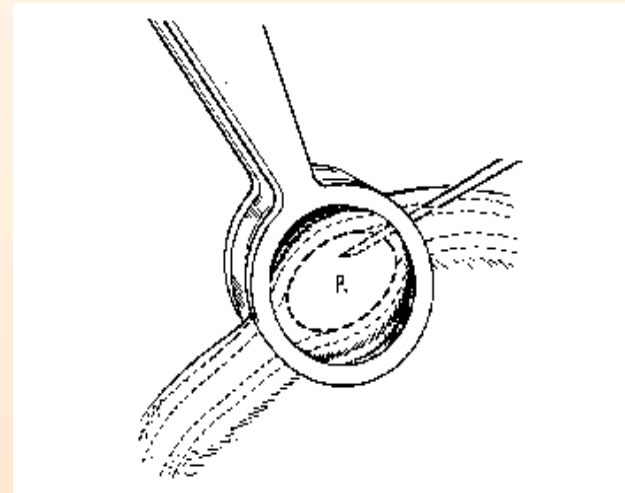
Methods for male sterilization

No scalpel vasectomy

Fascial interposition

Percutaneous vas occlusion

- Permanent, with **sclerosing agents**:
e.g. methylcyanoacrylate,
polyurethane
- Reversible, with **non-sclerosing agents**:
e.g. silicone plugs
or **resins**: e.g. styrene maleic anhydride



New targets for contraception

- Gametogenesis
- Sperm motility
- Sperm capacitation
- Acrosomal reaction
- Follicular development
- Implantation

Some of these research leads

- **Triptolide**: derived from a Chinese plant, *Tripterygium wilfordii*, which induces a complete loss of sperm motility.
- **Lonidamine analogues**: deplete immature germ cells from seminiferous epithelium.
- Inhibitors of **epididymal proteins**: eppin and cystatin-11
- Inhibitors of **testis-specific enzymes** (GST, SAC)
- Inhibitors of **fusion of sperm with zona pellucida**: GnRH antagonists.
- Change in **endometrial receptivity**: LIF antagonists; antibodies against LIF, IL-11, or the IL-11 receptor; eba1.
- **Anti-angiogenic agents** (magainin analogues, fumagillin).

Insert file name 34

Challenges

for the development of new technologies

- Cost and time (10-15+ years, US\$ 200-300 million)
- (Lack of) Industry involvement
- Perspectives of users and potential users, of different religious and socio-cultural backgrounds, and of new generations of women and men
- Access in resource-poor settings (cost, technology)

For the full benefit of these new technologies to be realized, women need better access to education and income and to have greater decision-making power.