



Future methods of fertility regulation

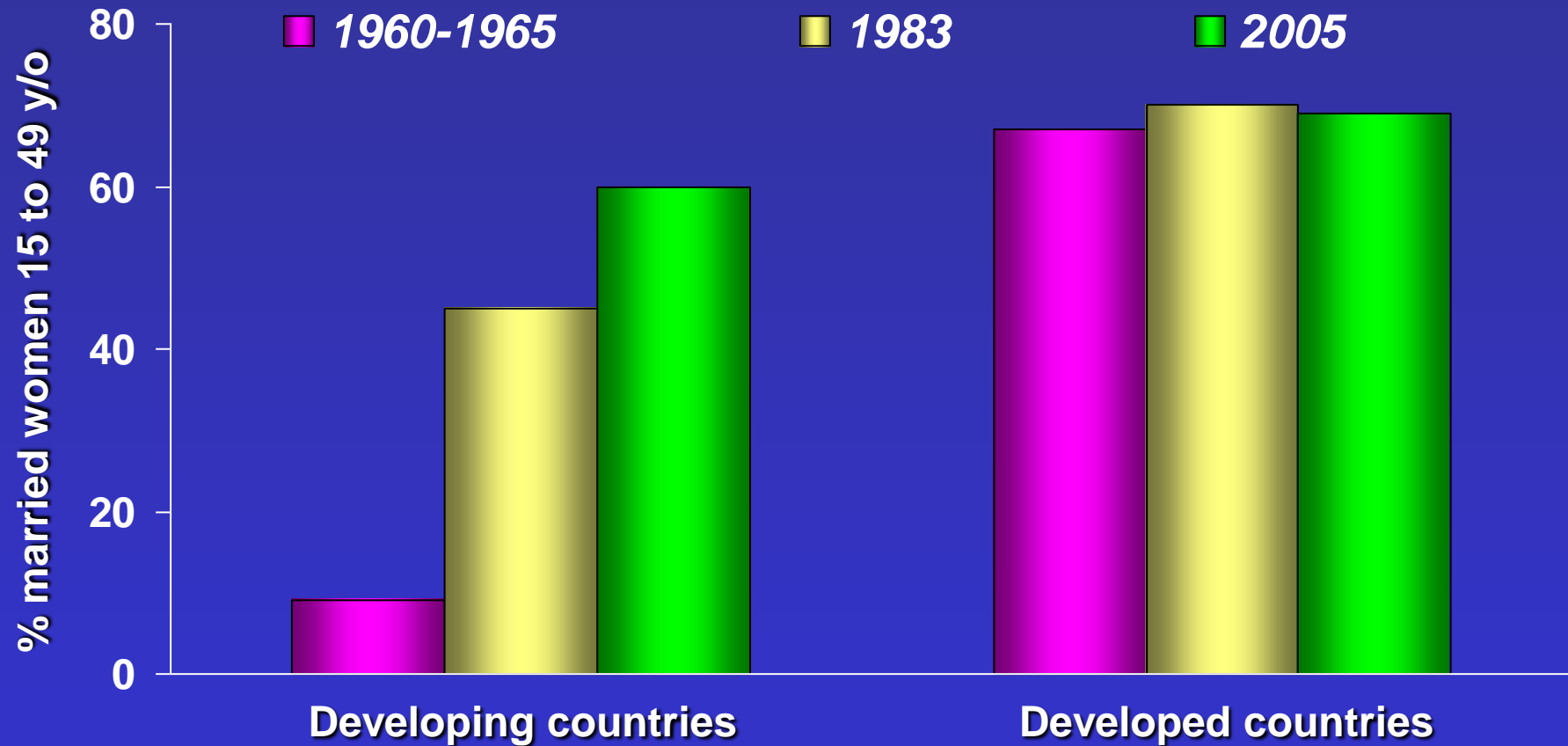
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World Health Organization**

Training Course in Reproductive Health Research 2008



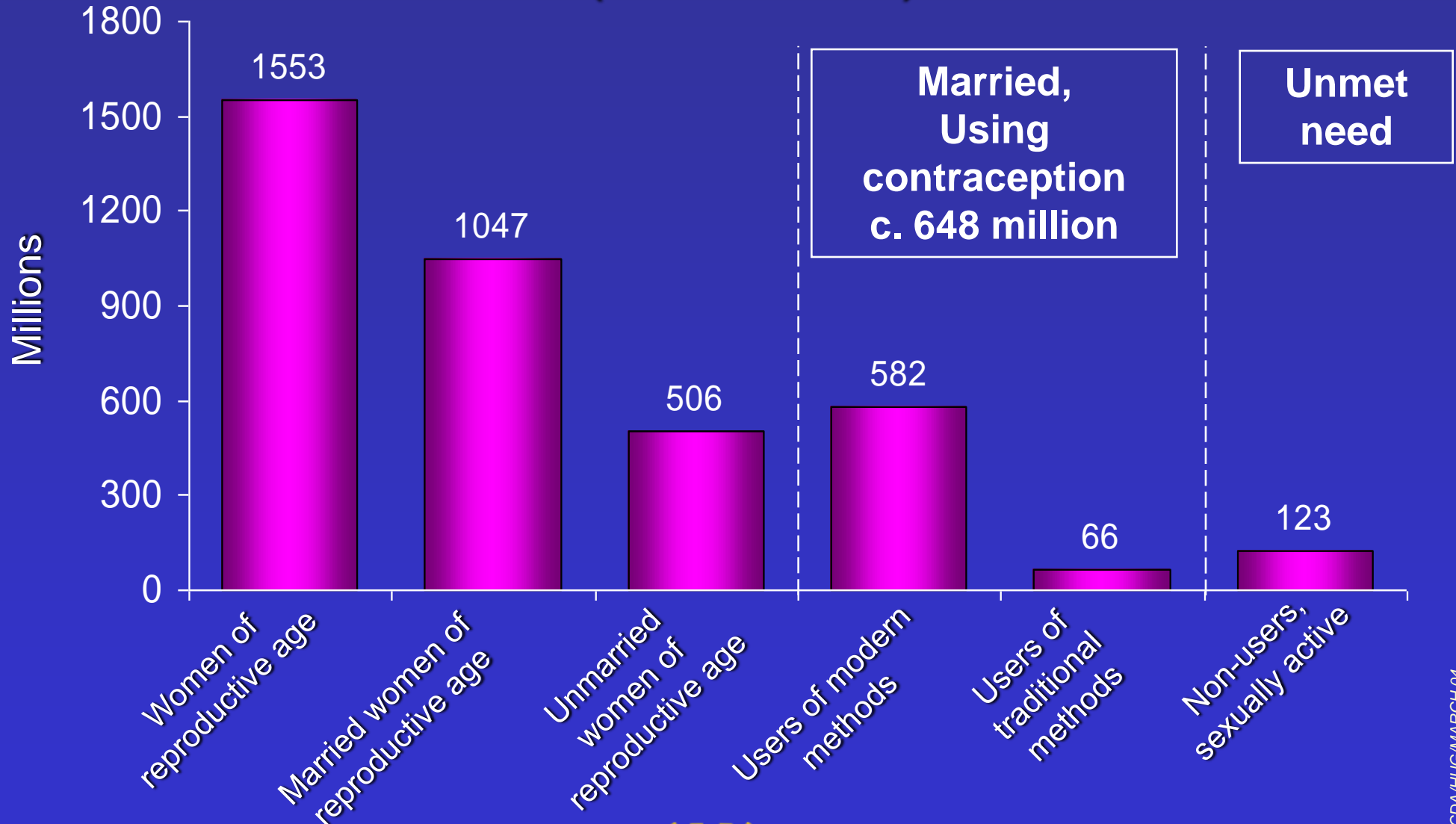
Contraceptive use



(From: United Nations, 1984 et 2005)

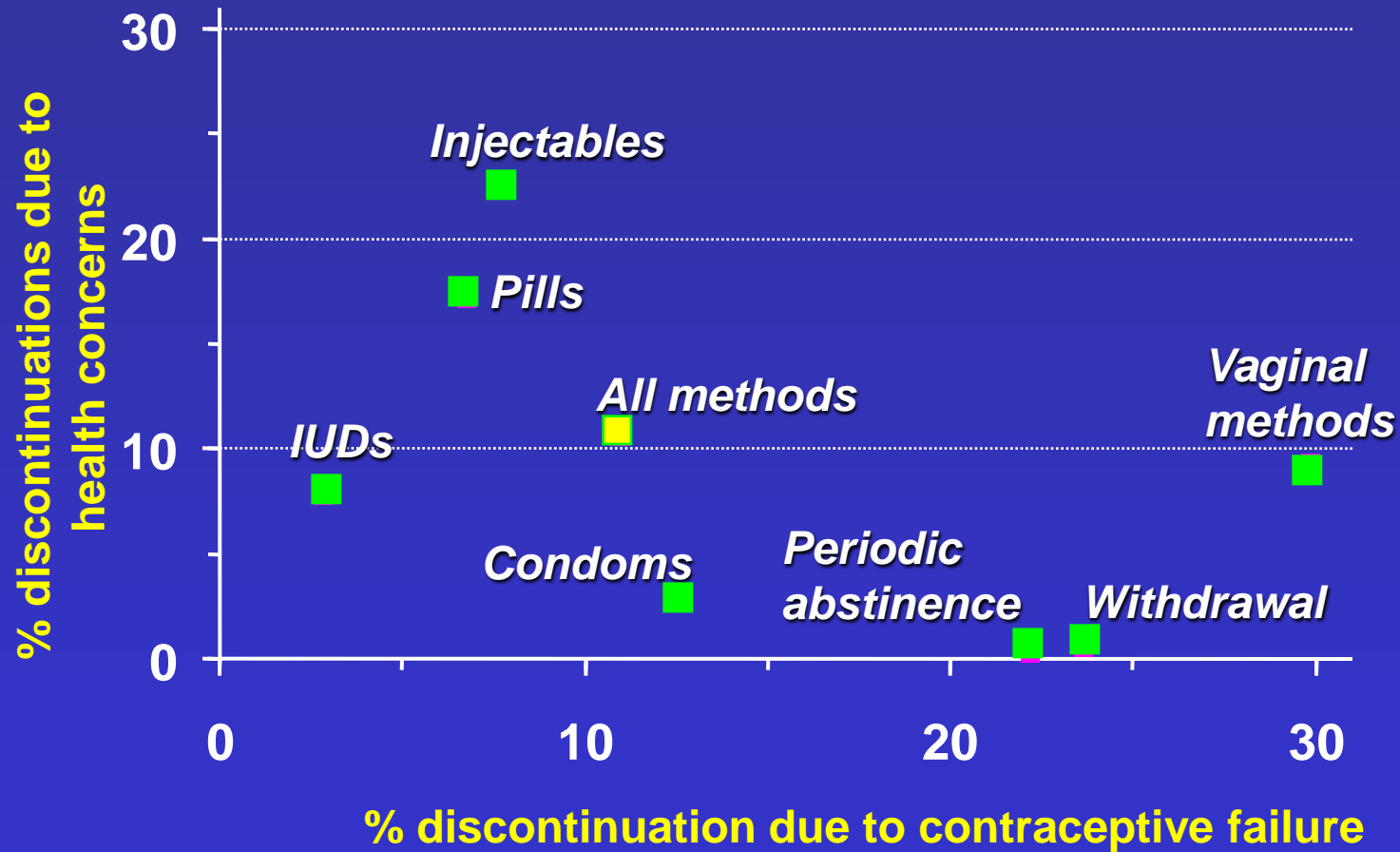


Contraceptive use and unmet need (Year 2000)





Contraceptive discontinuation rates at 12 months





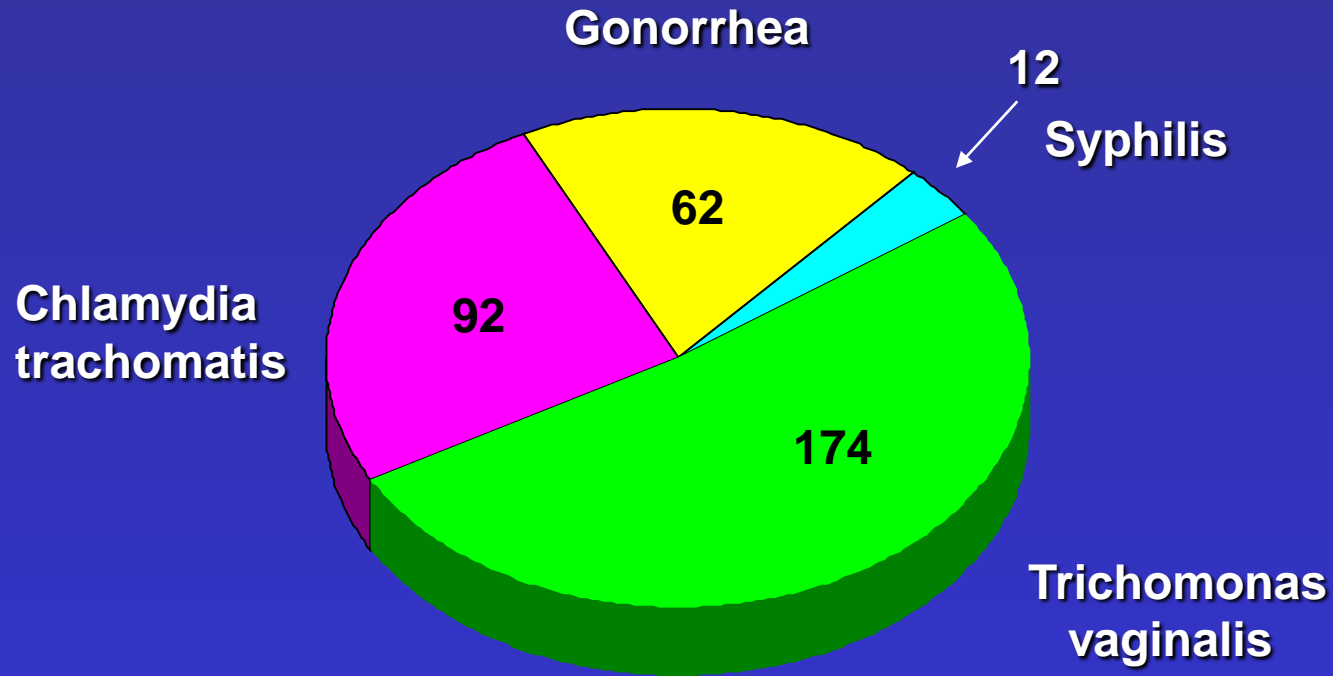
Accidental Pregnancies Resulting from Contraceptive Failure Worldwide

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)



New cases of curable STDs in 1999 (millions)



Total : 340 millions

(From : WHO, 2001)



HIV/AIDS Epidemic December 2007

- **New HIV infections in 2007: 2.5 (1.8 – 4.1) millions**
- **Adults and children living with HIV/AIDS:
33.2 (30.6 – 36.1) millions**
- **Estimated adult and child deaths due to HIV/AIDS
during 2007: 2.1 (1.9 – 2.4) millions**



Major lines of research for the development of new contraceptive methods

- I Methods with reduced side-effects
- II Methods with increased duration of action
- III Dual protection (against pregnancy and STIs)
- IV Contraceptive methods for men
- V New targets for contraception



I - METHODS WITH REDUCED SIDE-EFFETS

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

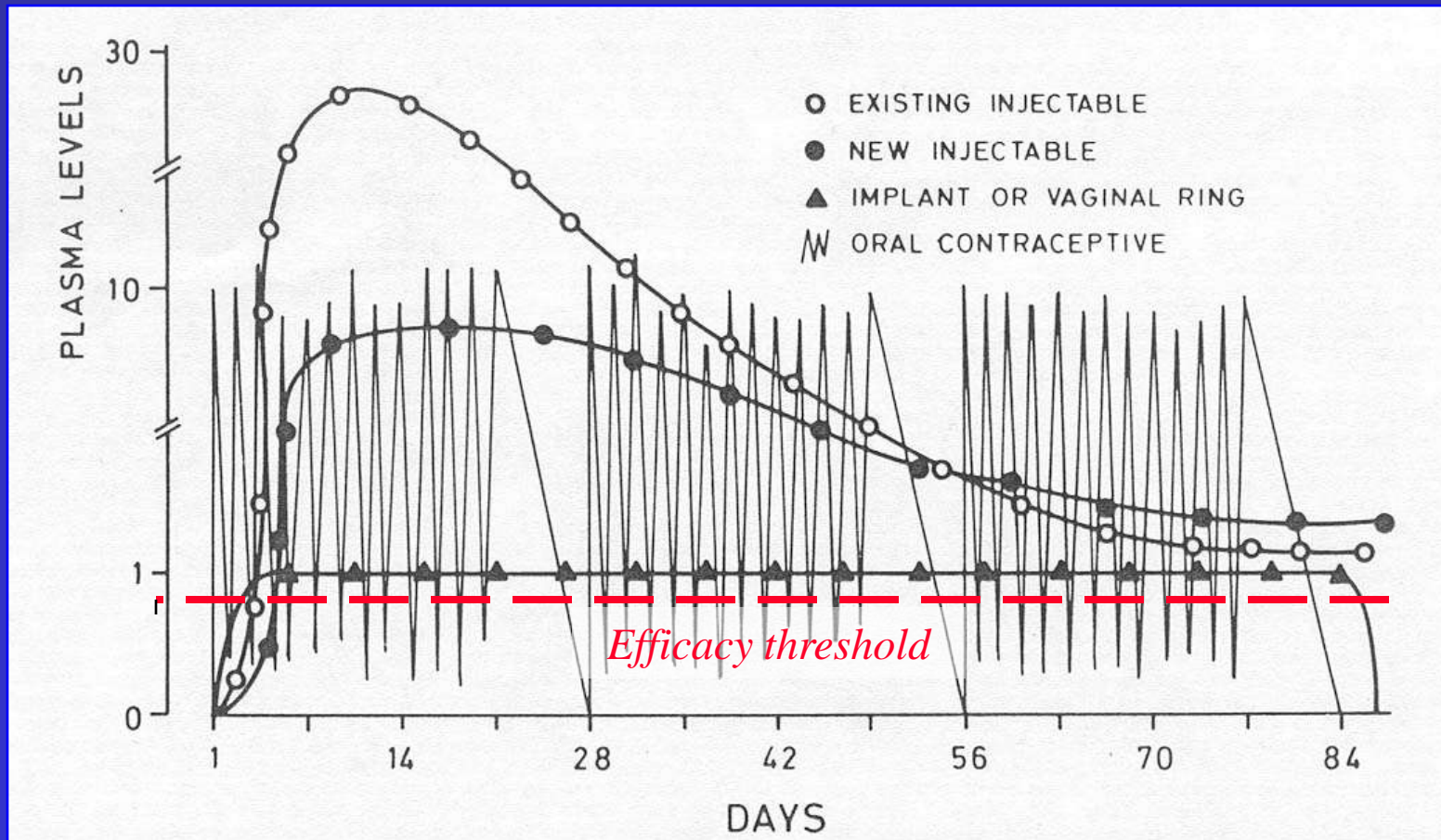


New injectable contraceptives

- Improved pharmacokinetic profile
Progestogen esters:
Levonorgestrel butanoate
- Decreased metabolic effects:
Monolithic microspheres:
progesterone, estradiol, testosterone



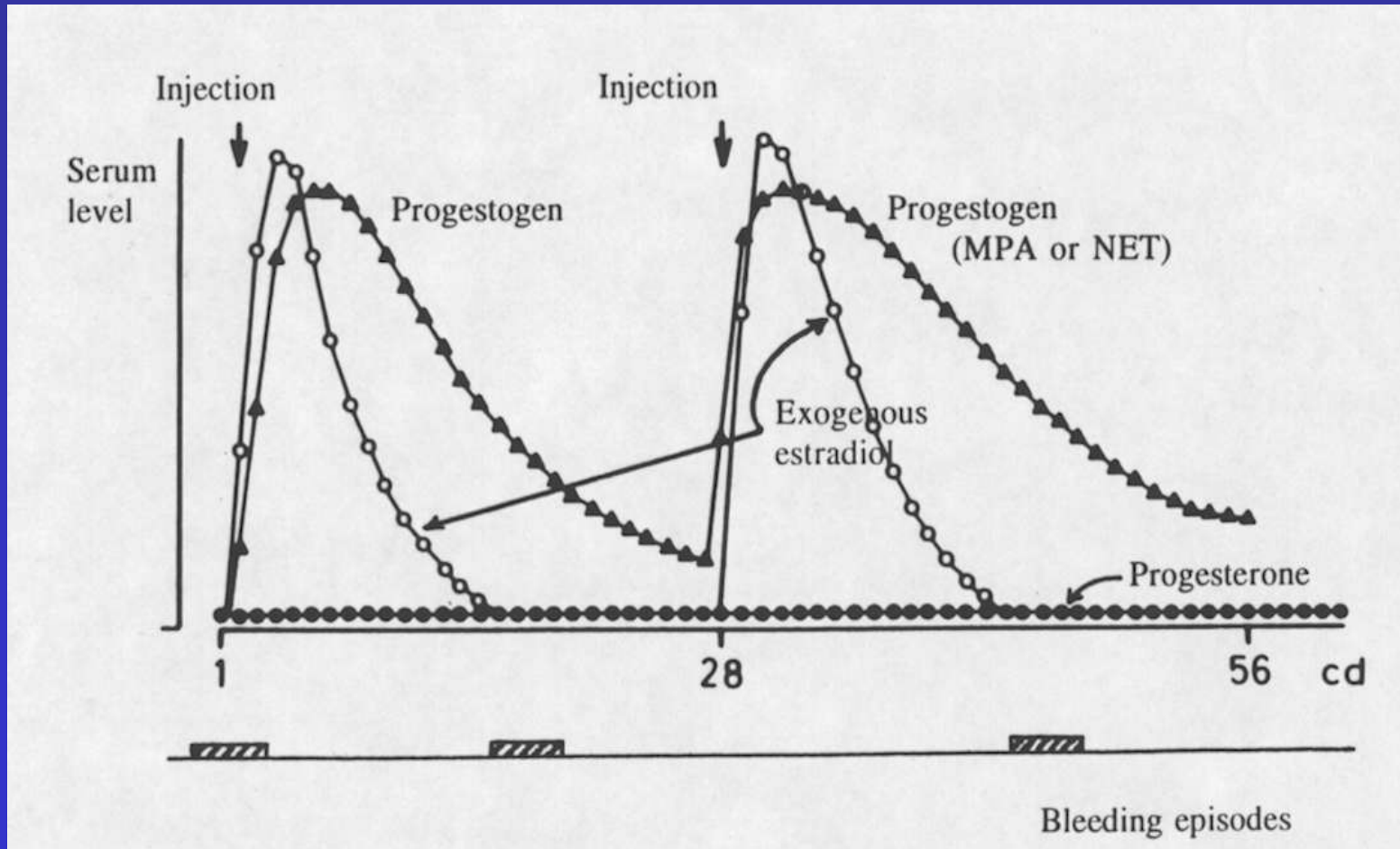
Schematic representation of pharmacokinetic profiles of progestogens administered by different routes





Monthly injectable contraceptives

Schematic representation of pharmacokinetic and pharmacodynamic profile



Adapté de: Fraser et Diczfalusy, 1980



Combined injectable contraceptives

Name

Composition

Availability

Perlutal
Topasel

Acétophenide de
dihydroxyprogestérone 150 mg
+ Enanthate d'E₂ 10 mg

Latin America
Spain

Injectable No1

Caproate de 17 α -
hydroxyprogestérone 250 mg
+ Valérianate d'E₂ 5 mg

China

Mego-E

Acétate de Megestrol 25 mg +
17 β E₂ 3.5 mg

China

Cyclofem
(Lunelle)

AMPR 25 mg +
Cypionate d'E₂ 5 mg

25 c.: Latin America,
Indonésia, Thaïland

Mesigyna
Norigynon

NET-EN 50 mg +
Valérianate d'E₂ 5 mg

40 c.: Africa, Latin
America, Turkey,
China

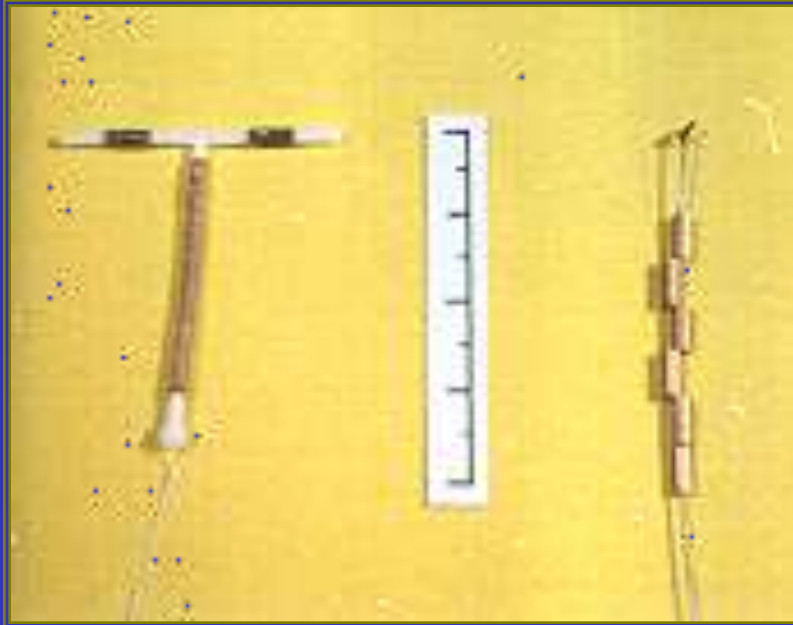


Contraceptive implants

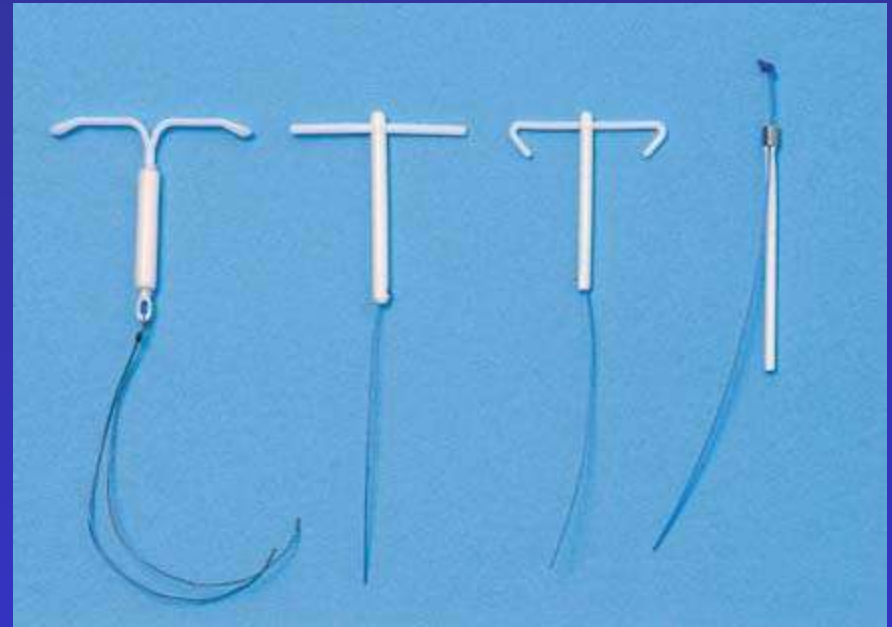
- **Jadelle:**
levonorgestrel, 2 rods, 5 years
- **Implanon:**
etonogestrel, 1 rod, 3 years
- **Nestorone:**
inactive orally, 1-2 rods, 2 years



Intra-uterine systems



Copper-releasing



Levonorgestrel-releasing

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



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 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)



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



II. METHODS WITH PROLONGED DURATION OF ACTION

- under the user's control

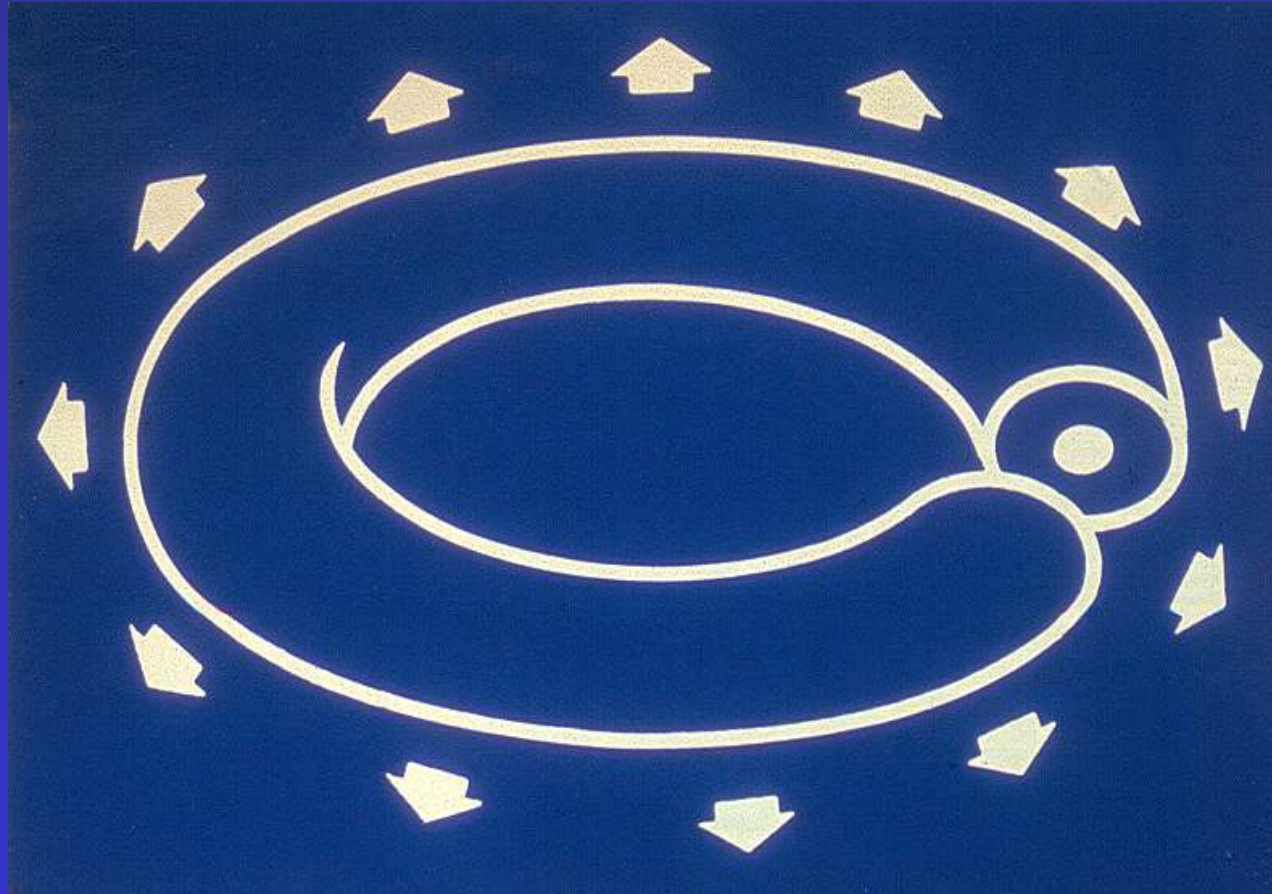
- Vaginal rings
- Transdermal systems

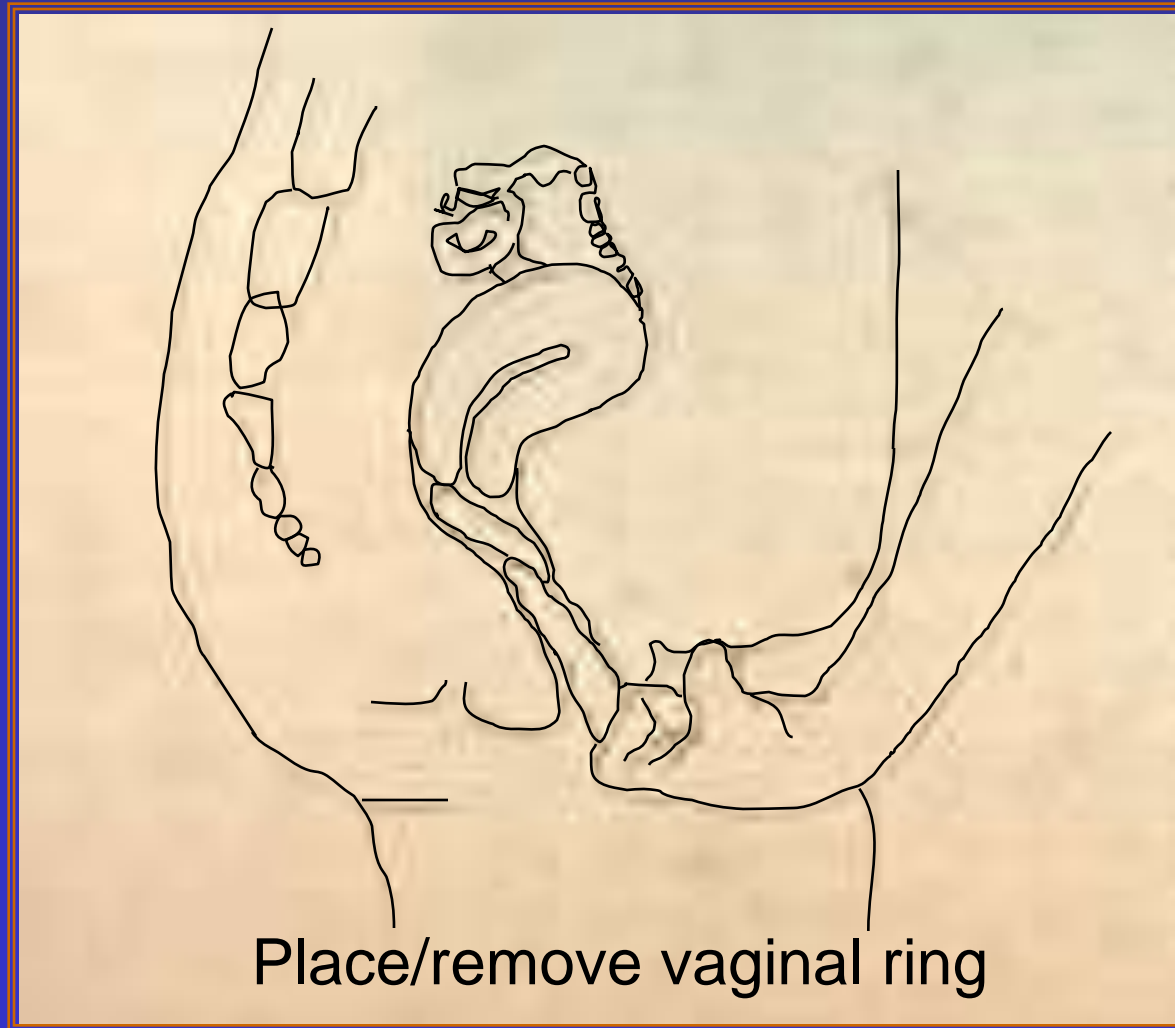
- not under the user's control

- Female sterilisation



Vaginal ring





Place/remove vaginal ring



Contraceptive vaginal rings

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



Methods for female sterilisation

- Essure



- Adiana

- Ovabloc



- Quinacrine



III. DUAL PROTECTION

- New male condoms
- Female condoms
- Microbicides/spermicides



New male condoms



Polyetherane: Avanti, eZ.on

Styrene-based plastic: Tactylon, Unique, Unisex



Female condoms



Femidom

Under development:

- polyurethane (PATH)
- natural latex (Reddy, autre)
- plastic (Panty condom)



V-Amour



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

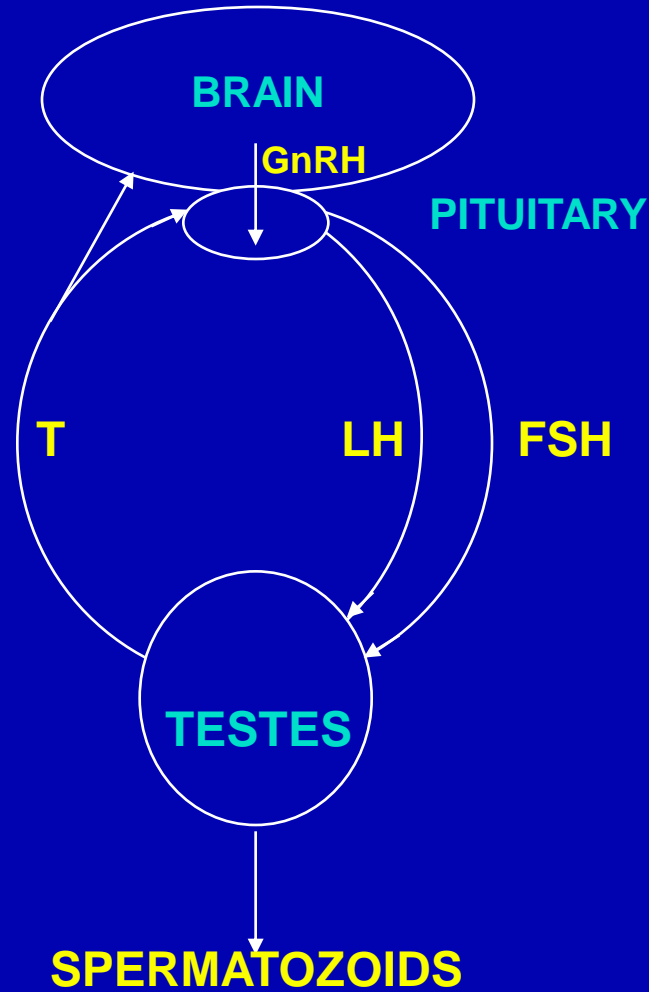


IV. METHODS FOR MALE CONTRACEPTION

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



Hormonal control of sperm production





Methods to suppress sperm production

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



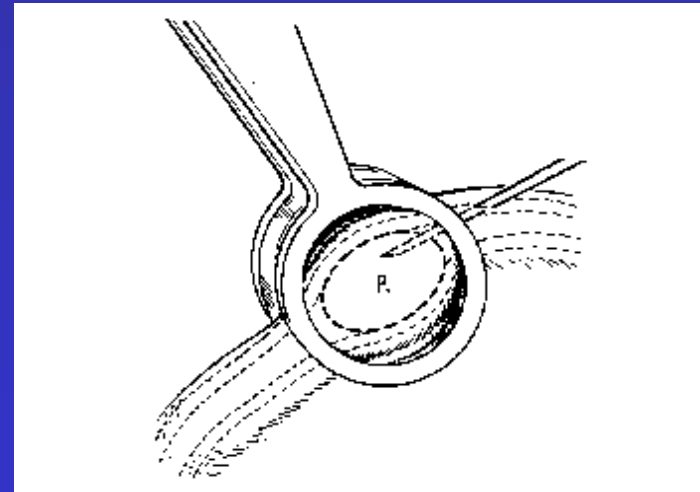
Methods for male sterilization

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. maleic anhydride / styrene





V. 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; ebaif.
- Anti-angiogenic agents (magainin analogues, fumagillin).



Challenges

for the development of new technologies

- Cost and time (10-15 years, US\$ 200-300 million)
- 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 women to benefit from these new technologies, they need better access to education and income and to have greater decision-making power.