Future methods of fertility regulation

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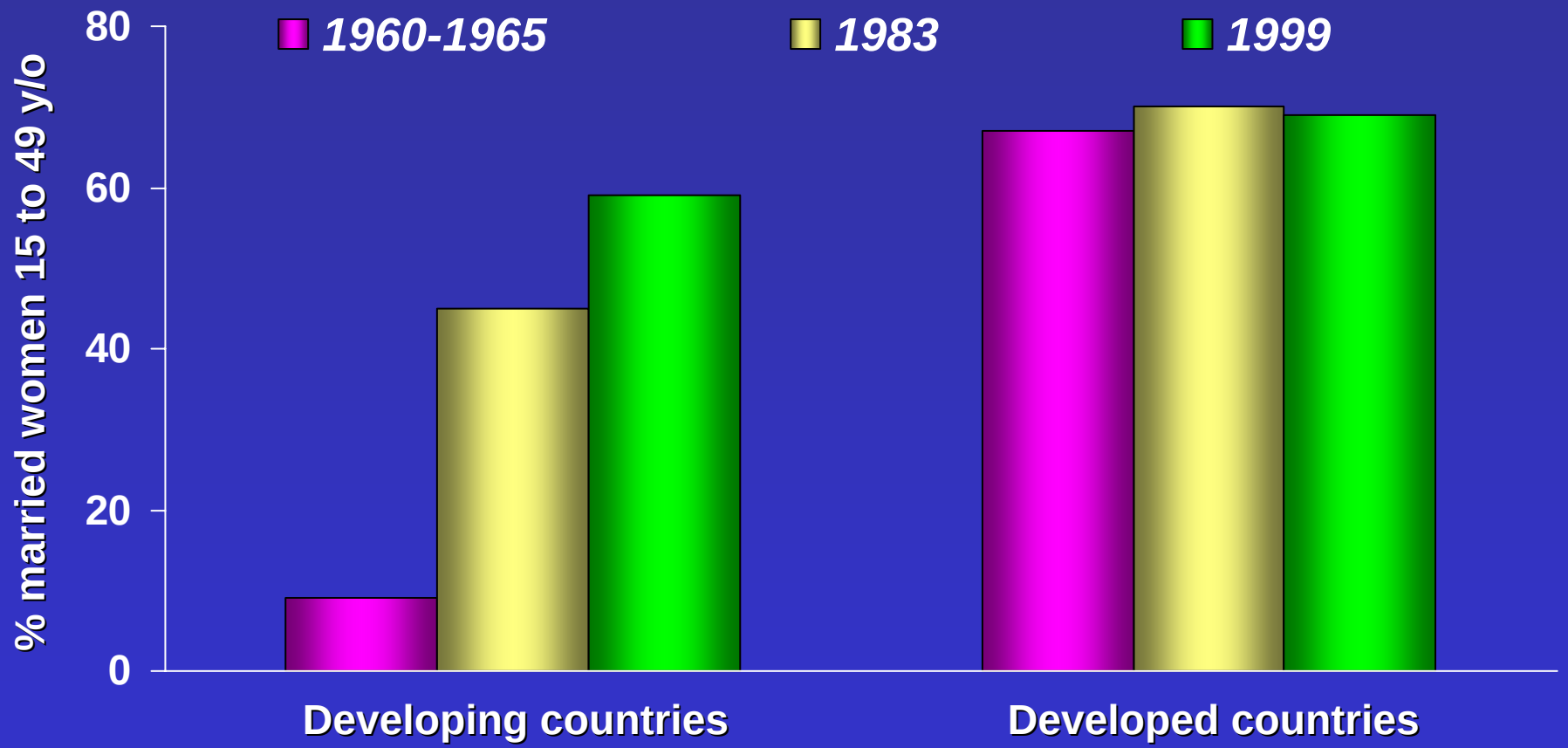
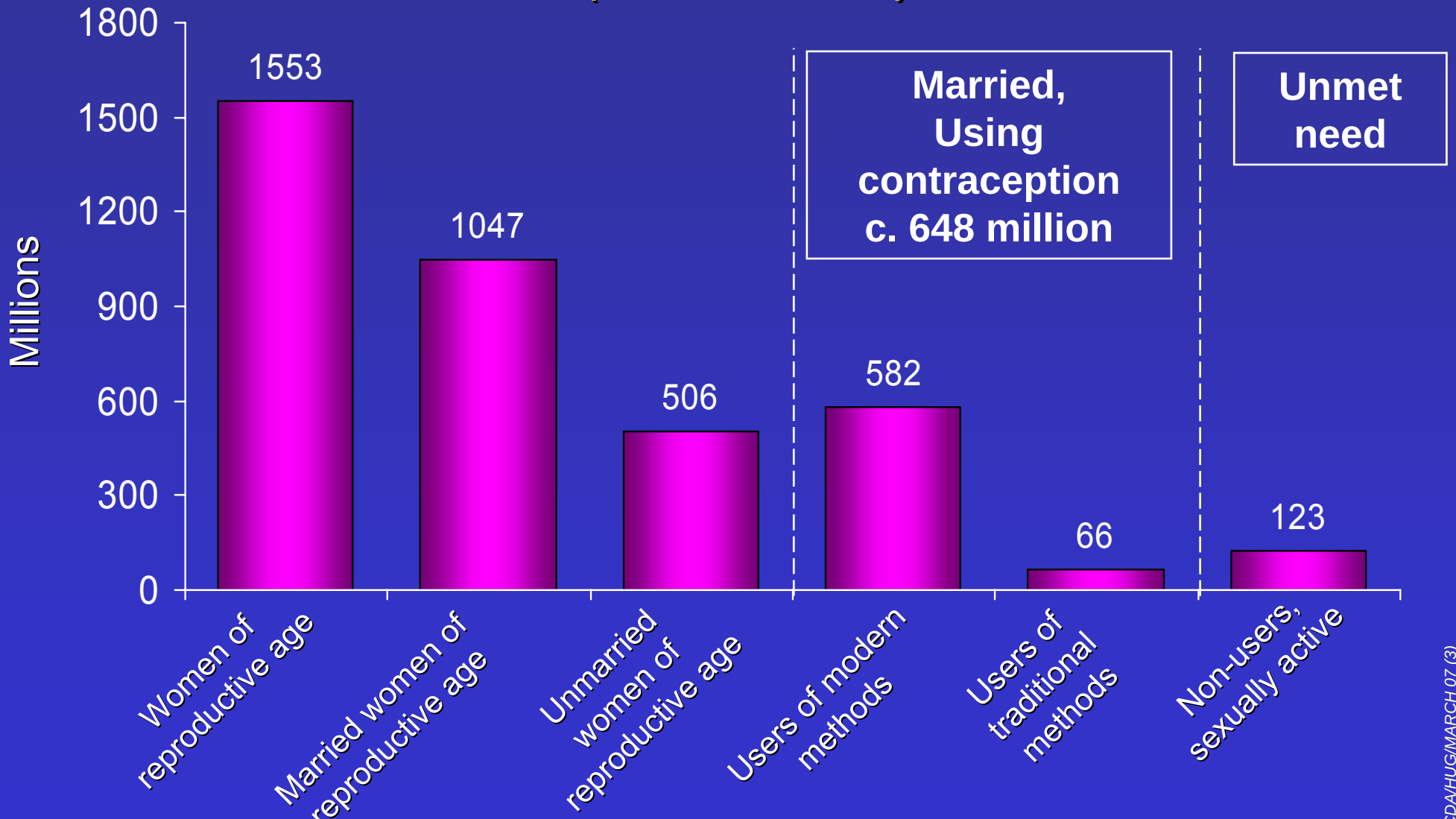
Contraceptive use

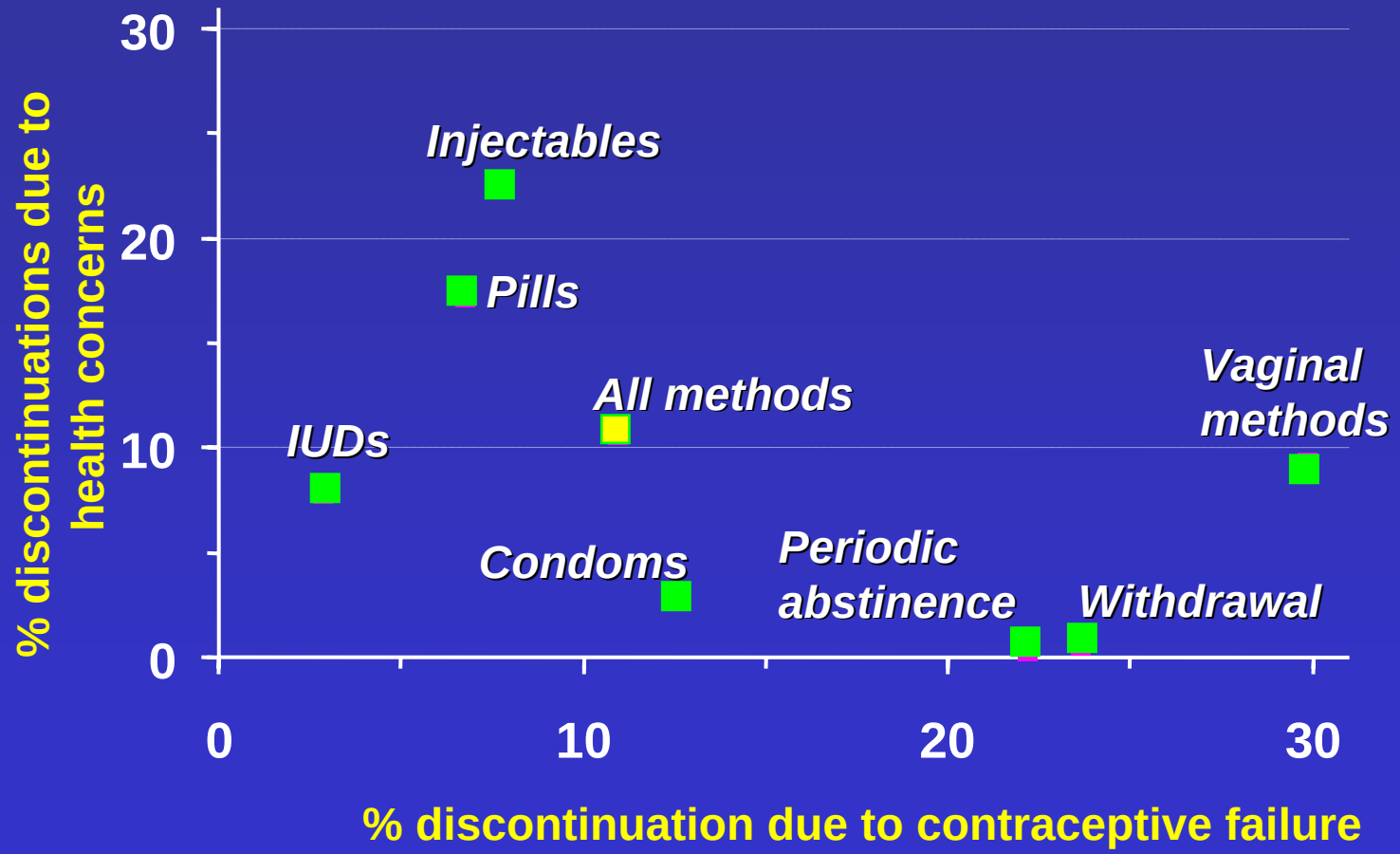


(From: United Nations, 1984, 2001, 2005)

Contraceptive use and unmet need (Year 2000)



Contraceptive discontinuation rates at 12 months

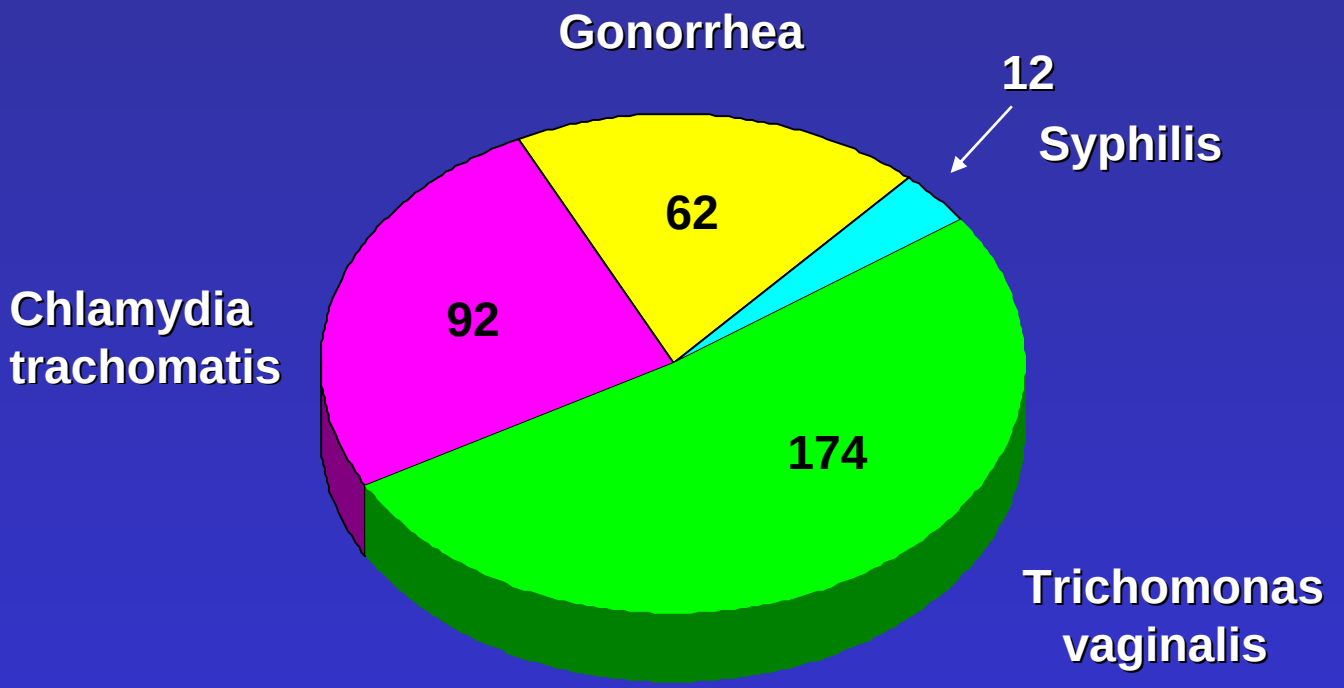


Accidental Pregnancies Resulting from Contraceptive Failure Worldwide

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 2006

- **New HIV infections in 2006: 4.3 (3.6 – 6.6) millions**
- **Adults and children living with HIV/AIDS: 39.5 (34.1 – 47.1) millions**
- **Estimated adult and child deaths due to HIV/AIDS during 2006: 2.9 (2.5 - 3.5) millions**

Major lines of research for the development of new contraceptive methods

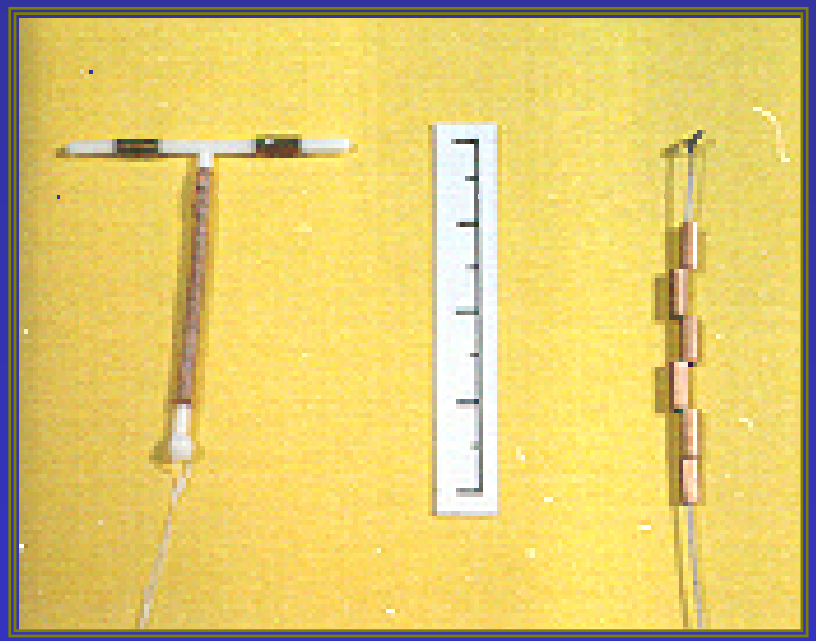
I Improvements of existing methods
- reduced side-effects
- increased duration of action
- decreased cost

II New approaches

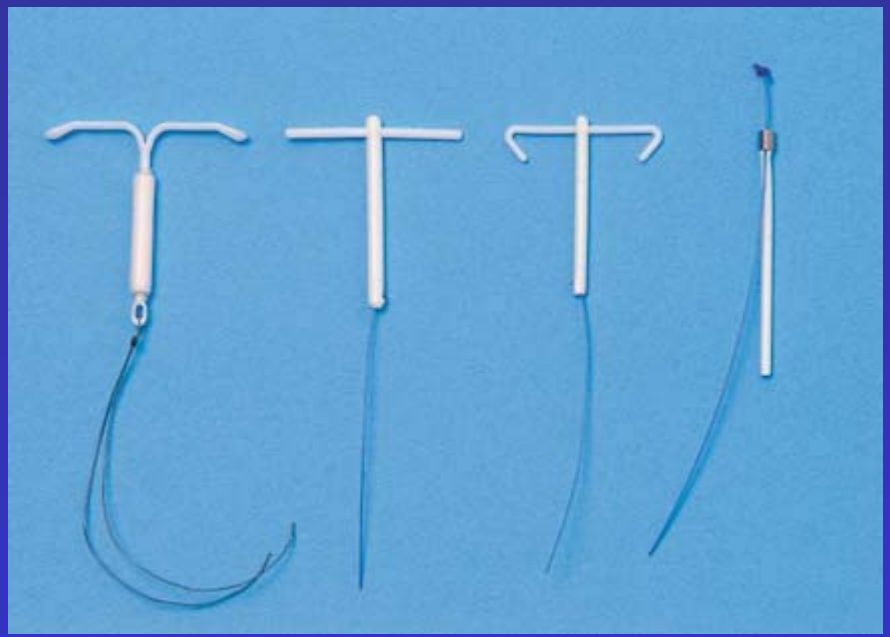
III New targets for contraception

I - IMPROVEMENTS OF EXISTING METHODS

Intra-uterine systems

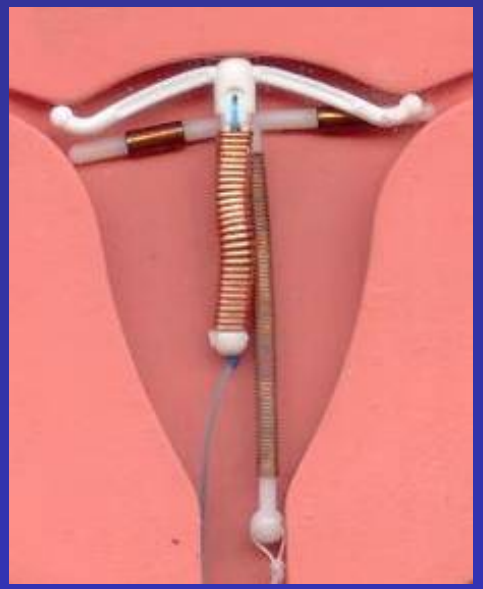


Copper-releasing



Levonorgestrel-releasing

Intra-uterine devices



Also under development:

- Swing: copper IUD with a spiral flexible stem
- IUD releasing a progesterone receptor modulator (CDB-2914)
- Copper IUD releasing indomethacin

Contraceptive implants

- Jadelle:

  levonorgestrel, 2 rods, 5 years

- Implanon:

  etonogestrel, 1 rod, 3 years

- Nestorone:

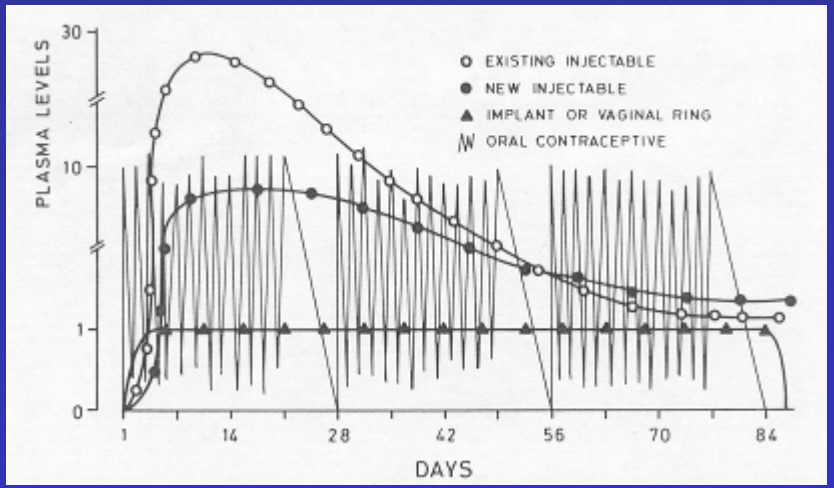
  pure progestin, inactive orally, 1-2 rods, 2 years

New injectable contraceptives

- Improved pharmacokinetic profile

  Progestogen esters:

  levonorgestrel butanoate

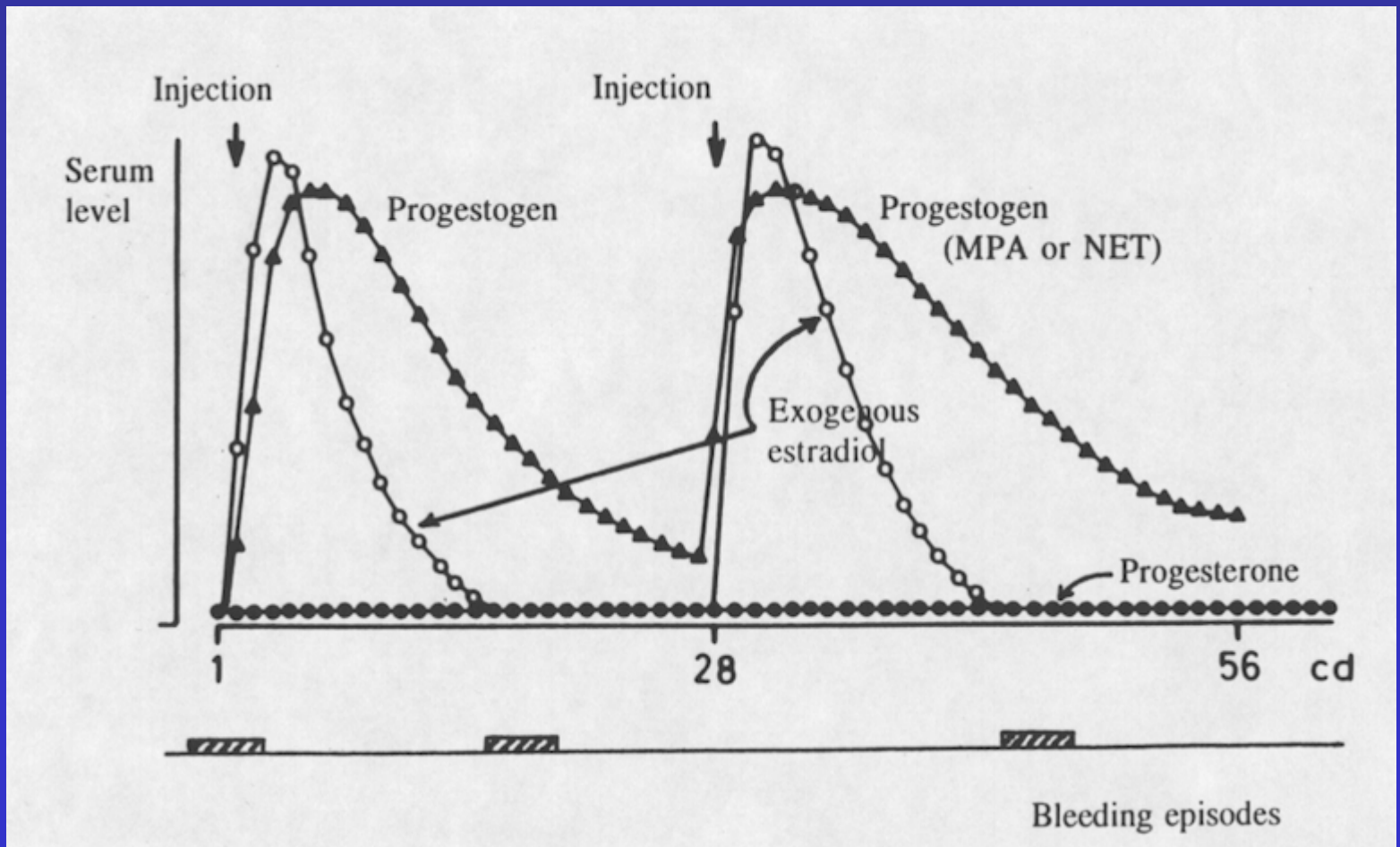


- Decreased metabolic effects

  Monolithic microspheres of natural hormones:

  progesterone, estradiol, testosterone

Idealized pharmacokinetic/pharmacodynamic profile of a typical combined monthly injectable contraceptive

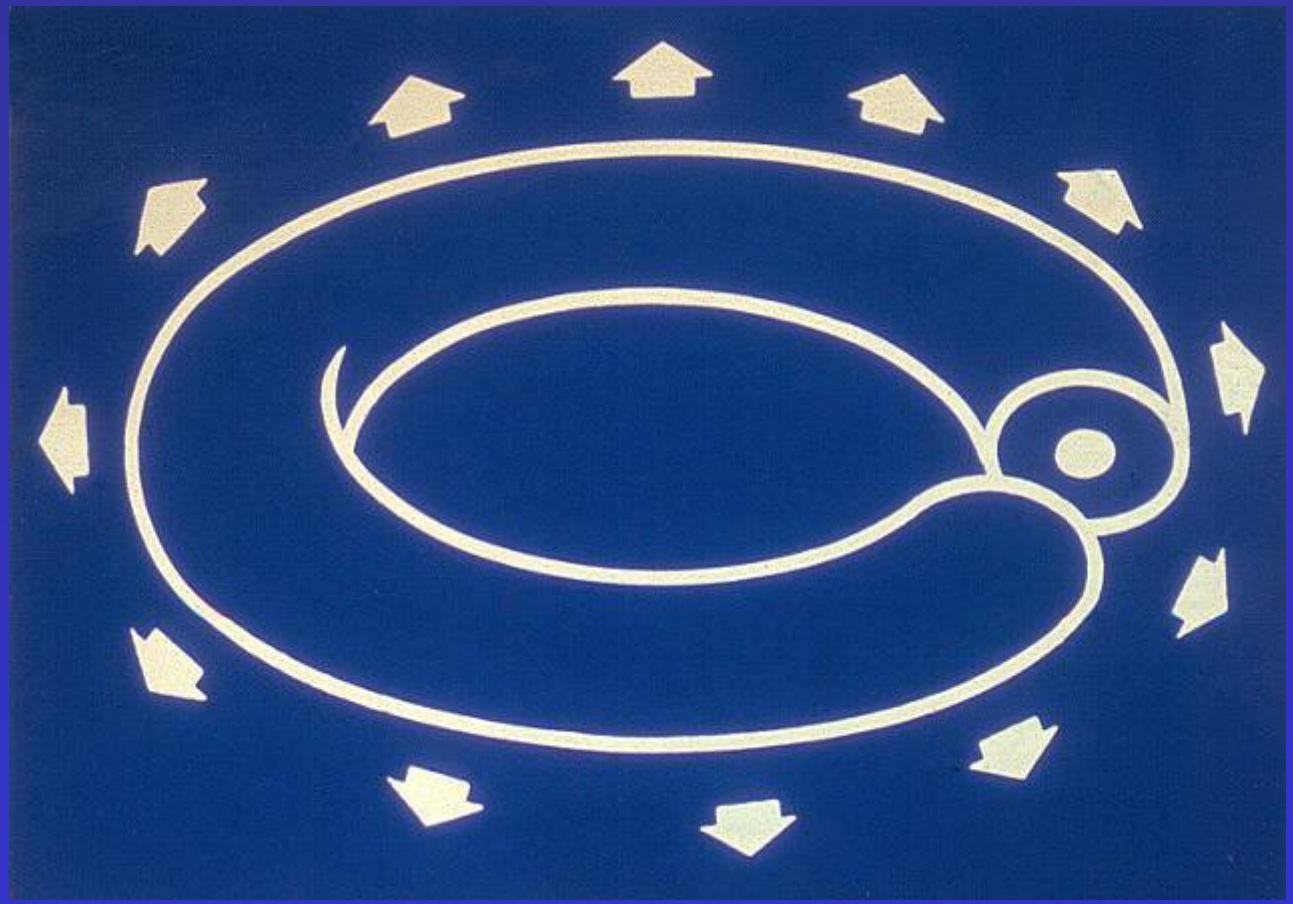


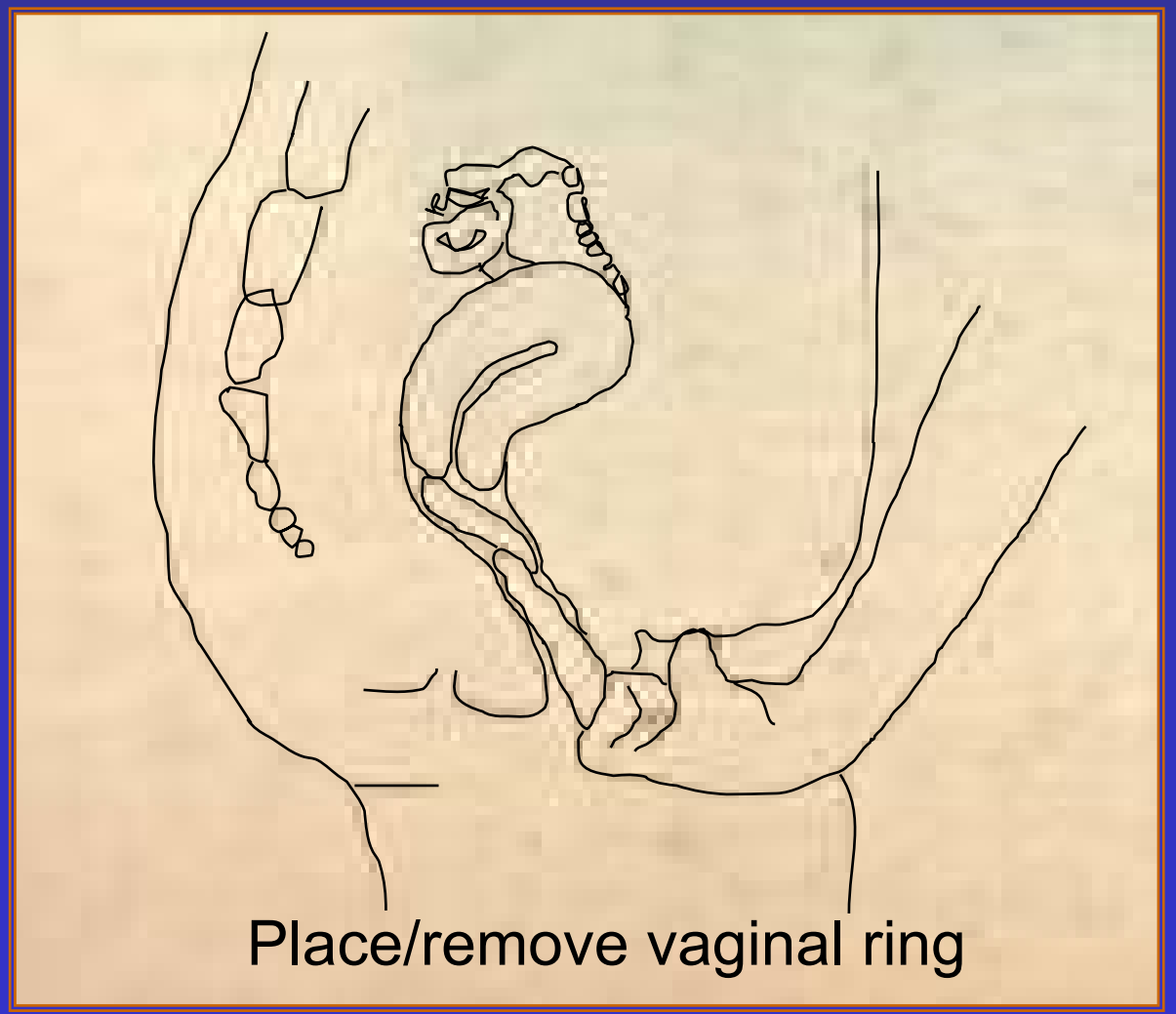
Adapté de: Fraser et Diczfalusy, 1980

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

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)

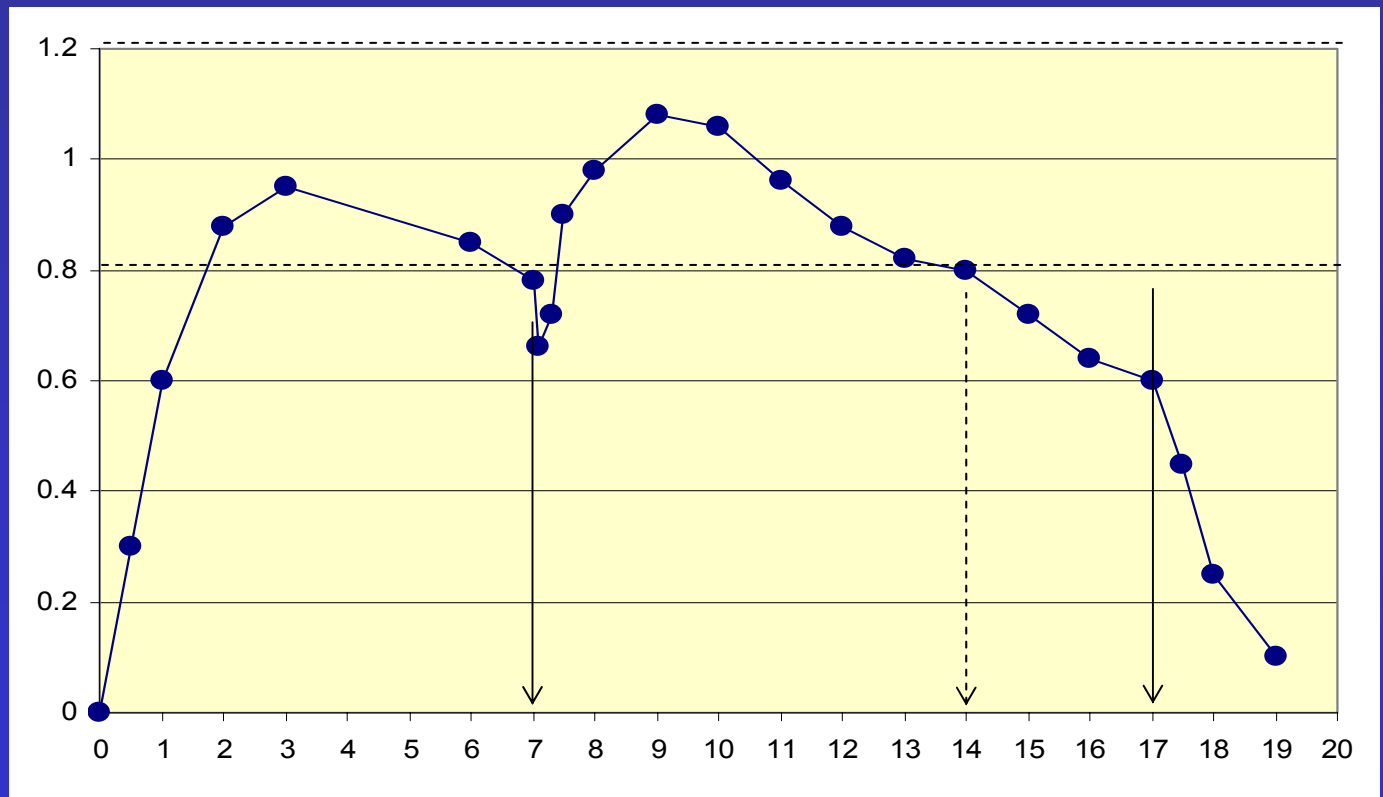
  - Nuvaring - Organon (1 mo.)
  - nestorone/EE - Pop. C. (12 mo.)

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

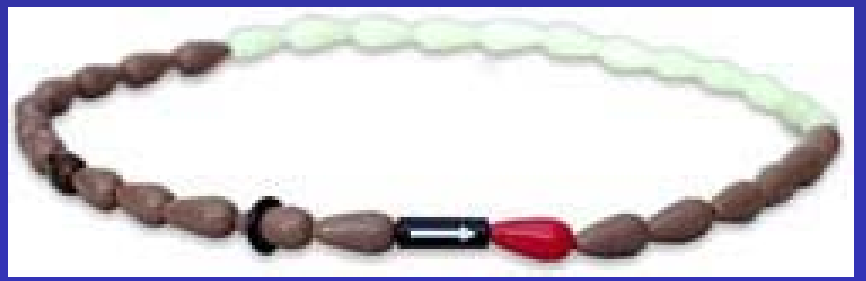
- Systems releasing a progestogen only:
  - nestorone (patch or gel)
  - norgestimate

Mean norelgestromin serum levels (ng/ml) following application of EVRA for 7 and 10 days



Fertility-awareness based methods

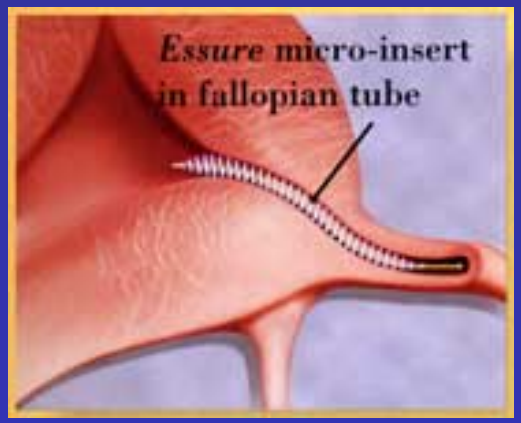
- Standard days method, based on abstinence/protection from day 8 to 19 of the cycle.



- "Two days" method, based on the observation of cervical mucus

Female sterilisation

- Essure



- Adiana
- Ovabloc

- Quinacrine

New male condoms

Polyutherane: Avanti, eZ.on

Styrene-based plastic: Tactylon, Unique, Unisex

Female condoms

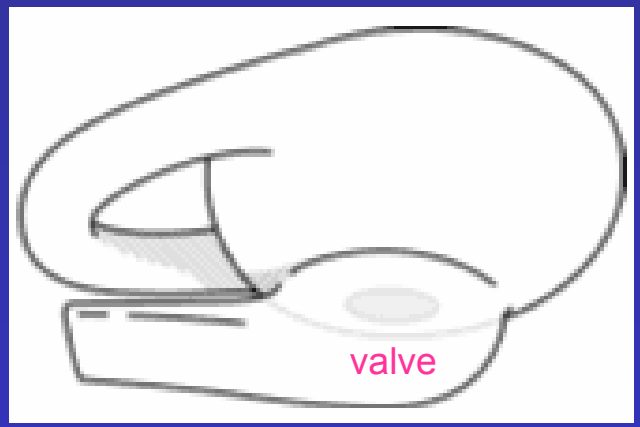
Femidom

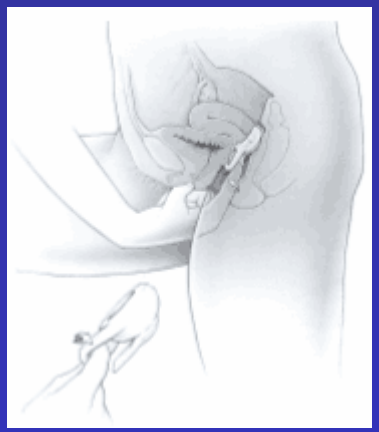
Under development:

- polyurethane (PATH)
- natural latex (Reddy, other)
- synthetic latex (FC2)
- plastic (Panty condom)

V-Amour

New diaphragms



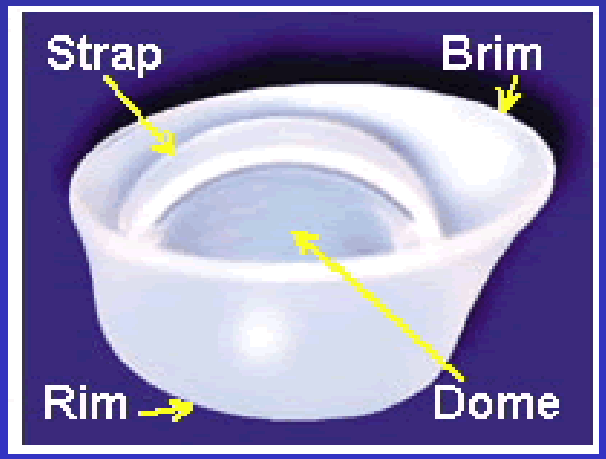


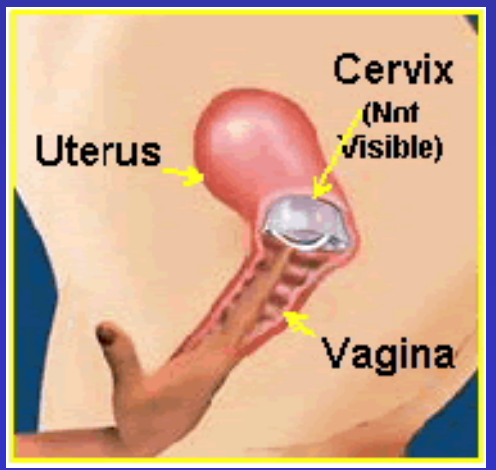
Lea's Shield®

SILCS

New cervical caps

Ovès





FemCap™

II - NEW APPROACHES

- Immunocontraceptives
- Microbicides with spermicidal activity
- Anti-progestins
- (Hormonal methods for men)

WHAT IS IMMUNOCONTRACEPTION?

- The use of the body's natural immune defence mechanisms to provide protection against an unplanned pregnancy.

- It requires the production of a controlled, time-limited and non-pathogenic immune response to components of the reproductive process.

POTENTIAL ADVANTAGES OF IMMUNOCONTRACEPTIVES

- lack of endocrine or metabolic side-effects
- do not require insertion of an implant or device
- provide long term but not permanent protection
- do not require storage or disposal by the user
- use is independent of coitus
- permit confidentiality of use
- low annual cost to users and services

DISADVANTAGES OF IMMUNOCONTRACEPTIVES

- delay between administration and attainment of effective immunity
- individual variations in immune responses and therefore, in level and duration of effectiveness
- cannot be ‘turned off’ on demand
- not a barrier to sexually-transmitted infections
- alleged abuse potential

IMPORTANT AND FUNDAMENTAL DIFFERENCES BETWEEN ANTI-DISEASE VACCINES AND IMMUNOCONTRACEPTIVES

ANTI-DISEASE VACCINES	IMMUNOCONTRACEPTIVES
• designed to provide long-term, ideally life-long, protection against life-threatening or debilitating diseases	• designed to provide long-term but not permanent protection against unplanned pregnancy
• often the only method of protection against such diseases	• other methods of birth control available
• directed against an immunologically foreign pathogen	• directed against a non-pathogenic cell or hormone
• vaccine-induced immunity often boosted by sub-clinical infection or exposure to the pathogen.	• vaccine-induced immunity not boosted by re-exposure to the target antigen or by pregnancy.

IMMUNOCONTRACEPTION

Possible points of intervention

Hypothalamus - GnRH

Pituitary - FSH and LH

Gonads - progesterone, estrogen and testosterone

Gametes - ovum (zona pellucida) and sperm surface

Pre-embryo - structural and endocrine components

*** This is the only target currently being pursued**

HCG IMMUNOCONTRACEPTIVE

World Health Organization
CG Therapeutics, Seattle, Washington, USA

Composition:

βhCG-specific peptides, diphtheria toxoid (carrier), muramyl dipeptide (adjuvant), slow-release copolymer matrix, water-in-oil emulsion vehicle

Current status:

Phase I clinical trial to be launched in mid-2007.

Microbicides with contraceptive effect

- Agents that create a protective physical barrier in the vagina: e.g. sulfated and sulfonated polymers, such as cellulose sulfate, polysterene 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

Anti-progestins for contraception

- Sequential regimen
  - Mifepristone + Norethisterone
  - Mifepristone + Medroxyprogesterone acetate
  - Mifepristone (days 1-15) + nomegestrol acetate (days 16-28)
- Continuous regimen: mifepristone 0,1 - 10 mg/day
- Weekly use: mifepristone 2,5 - 50 mg
- Monthly use: mifepristone 200 mg 2 days after the LH peak
- Emergency use: mifepristone 10 mg, CDB-2914

III. 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; ebaf.
- 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.