Future methods of fertility regulation

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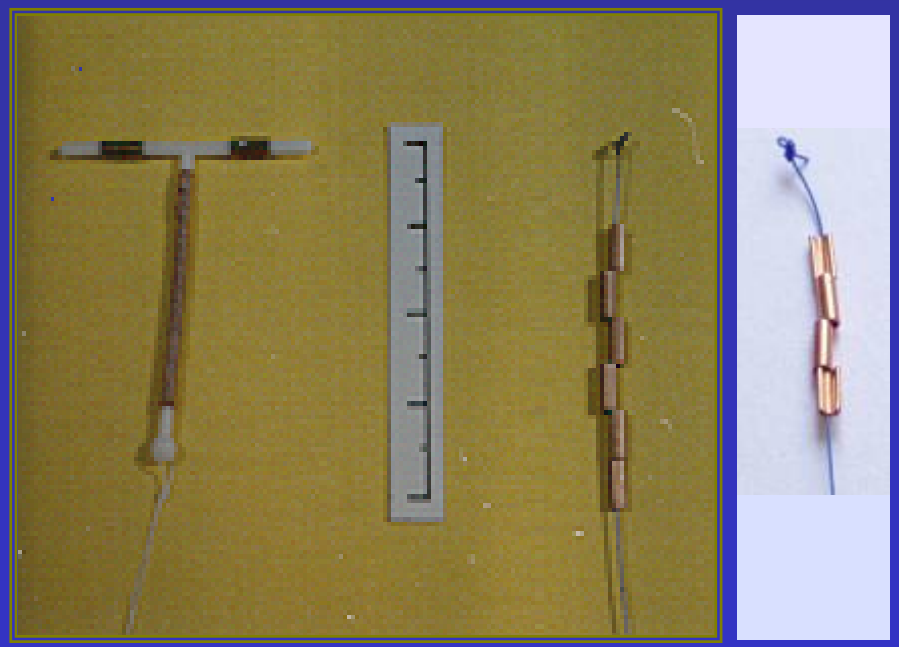
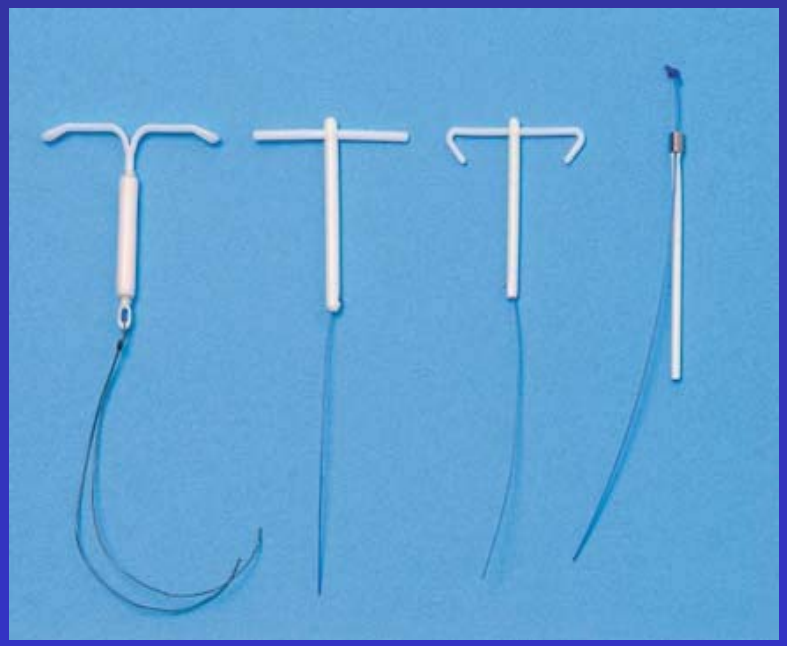
1. Improvement of existing methods
   - Efficacy, side-effects, duration of action, manufacturing process, cost
2. New approches
   - Mode of action
3. New targets for contraception

1. Improvement of existing methods

Intra-uterine devices

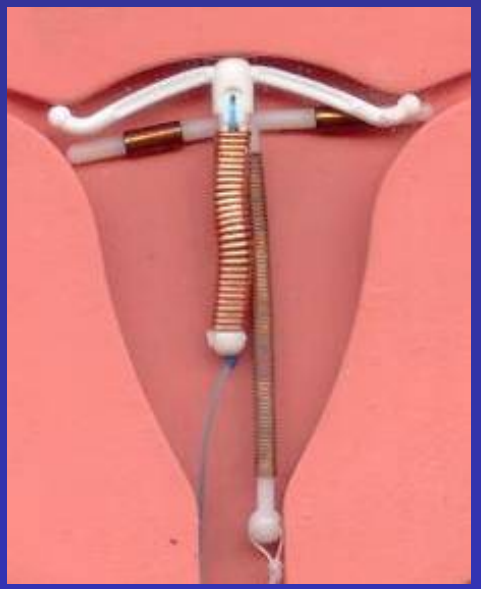


Copper-releasing



Levonorgestrel-releasing

Intra-uterine devices



Also under development:

- Swing: copper-releasing with coil 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 progestogen, 1 rod, 2 years

Injectables (1)

Improved pharmacokinetic profile :

- **Biodegradable microspheres:**

  norethisterone, norgestimate, progesterone

- **Controlled particle size distribution:**

  DMPA, levonorgestrel butanoate

Decreased side-effects :

- **Monolithic macrocrystals:**

  progesterone, 17-beta- estradiol, testosterone combined for once-a-month administration

Injectables (2)

Safer delivery system :

- Provision of Cyclofem in non-reusable disposable syringes (Uniject, Soloshot)

Contraceptive vaginal rings

- Progestogen only

  (for continuous use)

  - Progering - Silesia (3 months)
  - nestorone - Pop.C. (12 months)

- Estrogen-progestogen

  (3 weeks in /1 week out)

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

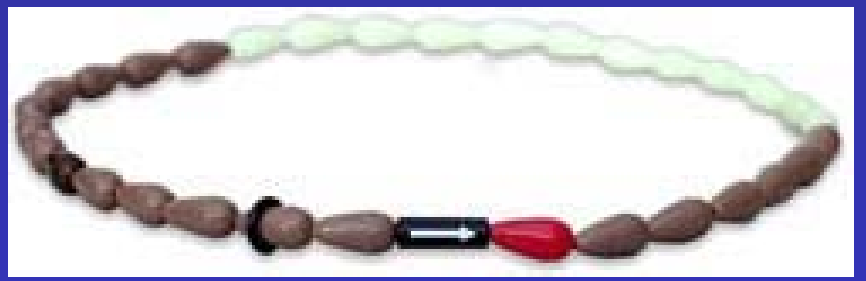
Transdermal systems

- Patch releasing an estrogen and a progestogen:
  - EVRA: norelgestromin 150 μg + ethinyl estradiol 20 μg
  - levonorgestrel + ethinyl estradiol
  - gestodene 50 μg + ethinyl estradiol 18 μg (Angeliq - Schering)

- Patch releasing a progestogen:
  - nestorone (also being developed as a gel and a spray)
  - norgestimate

Natural methods

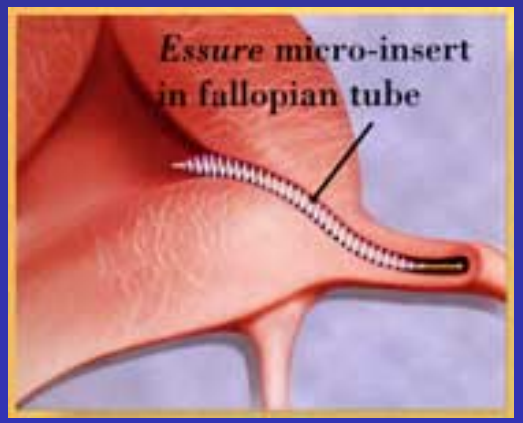
- Standard days method, based on abstinence/protection from cycle day 8 to cycle day 19.



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

Female sterilization

- Essure



- Adiana
- Ovabloc

- Quinacrine

Male condoms

Polyurethane: Avanti, eZ.on, Supra
Styrene-based plastic: Tactylon, Unique, Unisex

Female condoms

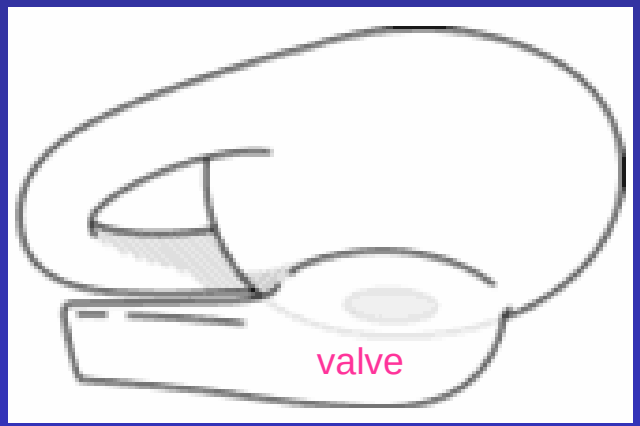
Femidom

Under development:

- polyurethane
  (PATH)
- natural latex
  (Reddy, other)
- plastic

V-Amour

New diaphragms

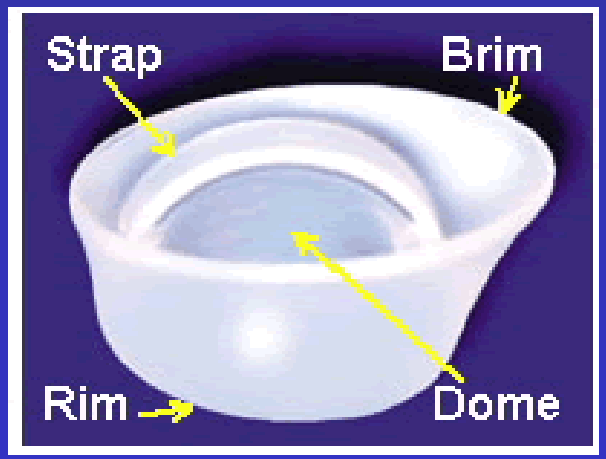


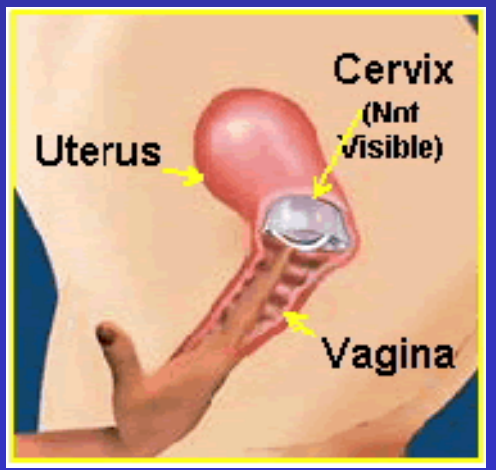
Lea's Shield®

SILCS

New cervical caps

Ovès





FemCap™

2. New approaches

Microbicides with contraceptive action

- Products that create a protective physical barrier in the vagina: e.g. Sulfated and sulfonated polymers, such as cellulose sulfate, polystyrene sulfonate.
- Products which increase vaginal defense mechanisms by maintaining natural acidity (which immobilises sperm): e.g. BufferGel and Acidform.
- Surfactant products: e.g. acylcarnitine analogs, C31G.
- Products which block attachment of HIV to target cells and sperm - zona pellucida fusion: e.g. naphthyl urea derivatives.

Immunocontraceptives

Most advanced immunocontraceptives are based on hCG :

Their goal is to generate antibodies against hCG secreted by embryonic trophoblastic cells, necessary for maintainance of the corpus luteum and the continued production of progesterone:

hCG β Chain: whole or the 109-145 amino acid sequence of the C-terminal portion
+ diphtheria toxoid as carrier
+ muramyl dipeptide as adjuvant
+ squalene/mannide monooleate (4:1) as emulsifying agent

Other targets: - zona pellucida (permanent effect on ovaries)
- molecules on sperm surface, e.g. fertilin (PH-30), fertilisation antigen (FA-1), sperm protein (SP-10), LDH-C4

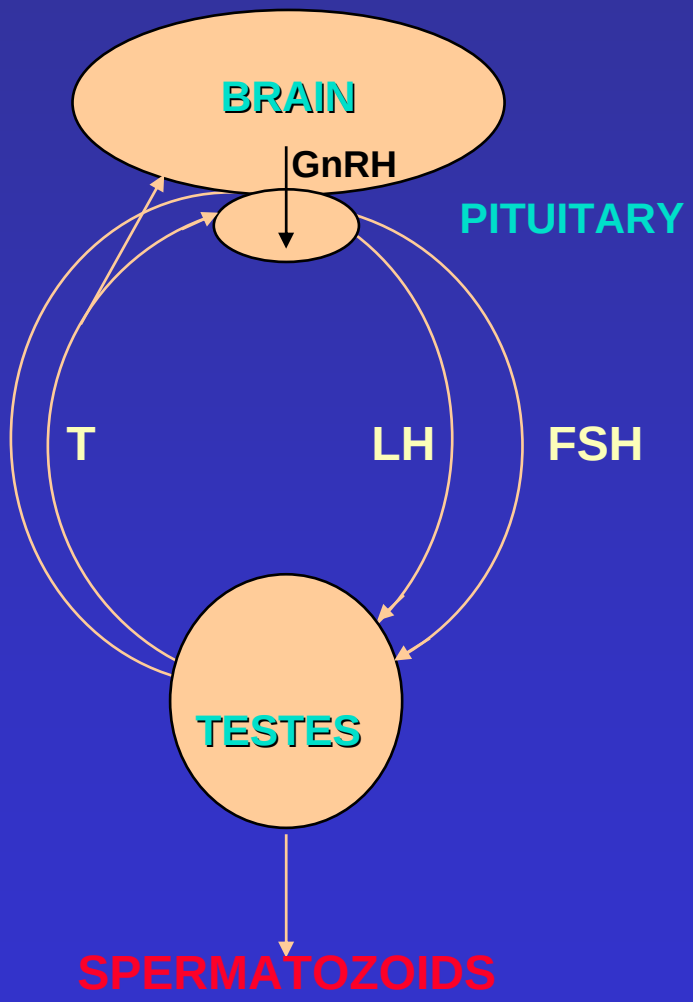
Anti-progestins for contraception

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

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 supress sperm production

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

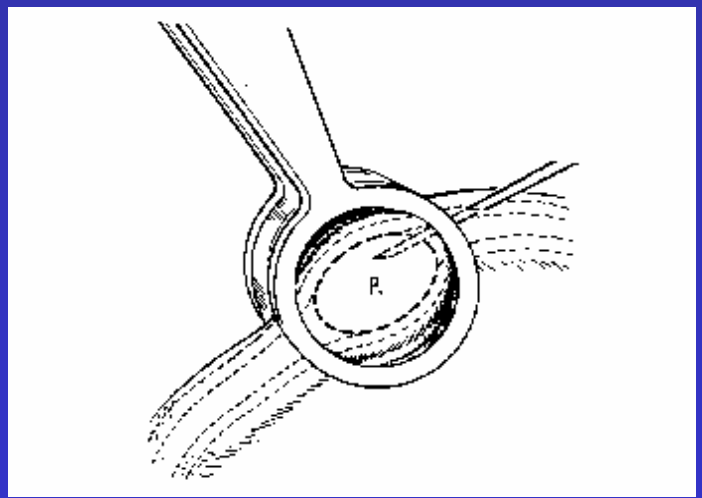
Methods for male sterilization

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



3. New targets

Possible targets

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


NEW FRONTIERS
IN CONTRACEPTIVE
RESEARCH
A
Blueprint
for
Action
INSTITUTE OF MEDICINE
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Some of the more promising leads

- 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.