Future methods of fertility regulation

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Training in Reproductive Health Research
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1. Improvement of existing methods
   Efficacy, side-effects, duration of action, manufacturing process, cost

2. New approaches
   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
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 gel and spray)
  - norgestimate
Natural methods

- **Standard days method**, based on abstinence/protecti on 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

Under development:

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

Femidom
FC2
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 maintenance 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

- BRAIN
  - GnRH
  - PITUITARY
    - T
    - LH
    - FSH
  - TESTES
    - SPERMATOZOIDS
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
3. New targets
Possible targets

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