Future methods of fertility regulation

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Contraceptive use and unmet need
(Year 2000)

- Women of reproductive age: 1553 million
- Married women of reproductive age: 1047 million
- Unmarried women of reproductive age: 506 million
- Users of modern methods: 582 million
- Users of traditional methods: 66 million
- Non-users sexually active: 123 million

Married, Using contraception c. 648 million

Unmet need
Contraceptive discontinuation rates at 12 months

- % discontinuations due to health concerns
  - Injectables
  - Pills
  - IUDs
  - All methods
  - Condoms
  - Periodic abstinence
  - Withdrawal
  - Vaginal methods

- % discontinuation due to contraceptive failure

Department of reproductive health and research
Accidental Pregnancies Resulting from Contraceptive Failure Worldwide

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

(Source: Segal and LaGuardia, 1990)
New cases of curable STDs in 1999 (millions)

- Gonorrhea: 174
- Chlamydia trachomatis: 92
- Syphilis: 12
- Trichomonas vaginalis: 62

Total: 340 millions

(From: WHO, 2001)
HIV/AIDS Epidemic
December 2003

• New HIV infections in 2003: 5 (4.2 - 5.8) millions

• Adults and children living with HIV/AIDS: 40 (34 - 46) millions

• Estimated adult and child deaths due to HIV/AIDS during 2003: 3 (2.5 - 3.5) 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-EFFECTS

- Injectables
- Implants
- Intra-uterine devices / systems
- Immunocontraceptives
- Estrogen-free pills
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.
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 βhCG
  - + diphtheria toxoid as carrier
  - + muramyl dipeptide as water-soluble adjuvant
  - + squalene/mannide monooleate (4:1) as an emulsifying agent

**Estrogen-free pills**

- Mifepristone (days 1-15) + nomegestrol acetate (days 16-28)
II. METHODS WITH PROLONGED DURATION OF ACTION

- under the user’s control

• Vaginal rings
• Transdermal systems
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
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

Alternative:

natural latex
Reddy female condom
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

1. BRAIN
   - GnRH

2. PITUITARY
   - T
   - LH
   - FSH

3. TESTES
   - SPERMATOZOIDES
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

- 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.