Reproductive health research at WHO

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Department of Reproductive Health and Research
World Health Organization
Geneva, 21 September 2001
“Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.”

7 April 1948
Mission

“The objective of the World Health Organization shall be the attainment by all peoples of the highest possible level of health.”

(WHO Constitution, Article 1)
Functions

“In order to achieve its objective, the functions of the Organization shall be:

(a) to act as the directing and co-ordinating authority on international health work;

... 

(n) to promote and conduct research in the field of health;

…”

(WHO Constitution, Article 2)
“To coordinate, promote, conduct and evaluate international research in human reproduction.”
Growth of total world population

Years

Billions

1804
1927
1960
1974
1987
1999

1600 1700 1800 1900 2000 2100

1800-1900: Linear growth
1900-1927: More rapid growth
1927-1999: Extremely rapid growth

1999 population: 6.1 billion
The Programme’s history

1971: Feasibility study

1972-1988: WHO Special Programme

1988-present: UNDP/UNFPA/WHO/World Bank cosponsored Special Programme
Factors contributing to fertility decline

- Higher age at marriage
- Reduced breastfeeding
- More use of contraception
- More induced abortion
- All other factors

Percentage of reduction by contributing factor

(Source: World Bank, 1984)
Trends in use of contraception

Once-a-month injectables developed by the Programme

<table>
<thead>
<tr>
<th>Product</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesigyna®</td>
<td>50 mg norethisterone enantate + 5 mg estradiol valerate</td>
</tr>
<tr>
<td>Cyclofem®</td>
<td>25 mg medroxyprogesterone acetate + 5 mg estradiol cypionate</td>
</tr>
</tbody>
</table>
Bleeding patterns experienced by injectable users at 1 year of use

**Depo-provera**

- Regular pattern
- Irregular pattern
- Amenorrhoea

**Cyclofem**

- Regular pattern
- Irregular pattern
- Amenorrhoea
Once-a-month injectables for women

Mesigyna

- licensed to Schering
  (low public sector price)
- currently registered in
  - Caribbean and Latin America (44 countries)
  - Egypt
  - Kenya
  - Tanzania
  - Turkey
CYCLOFEM

25 mg medroxyprogesterone acetate + 5 mg estradiol cypionate

Registered

Registration pending

Manufacture
Levonorgestrel for emergency contraception: efficacy

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of women</th>
<th>Observed pregnancies</th>
<th>Pregnancy rate (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yuzpe</td>
<td>979</td>
<td>31</td>
<td>3.2</td>
<td>(2.2, 4.5)</td>
</tr>
<tr>
<td>LNG</td>
<td>976</td>
<td>11</td>
<td>1.1</td>
<td>(0.6, 2.0)</td>
</tr>
</tbody>
</table>

Relative risk (RR) of pregnancy for LNG compared with Yuzpe:

<table>
<thead>
<tr>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.36</td>
<td>(0.18, 0.70)</td>
</tr>
</tbody>
</table>

(Source: WHO, 1998)
## Levonorgestrel for emergency contraception: side-effects

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Yuzpe No. (%) of cases</th>
<th>LNG No. (%) of cases</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>494 (50.5)</td>
<td>226 (23.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Vomiting</td>
<td>184 (18.8)</td>
<td>55 (5.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Headache</td>
<td>198 (20.2)</td>
<td>164 (16.8)</td>
<td>0.06</td>
</tr>
<tr>
<td>Dizziness</td>
<td>163 (16.7)</td>
<td>109 (11.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fatigue</td>
<td>279 (28.5)</td>
<td>165 (16.9)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

(Source: WHO, 1998)
Effect of delay on pregnancy rates

- 0-12 hours: 0.5%
- 13-24 hours: 1.5%
- 25-36 hours: 1.8%
- 37-48 hours: 2.6%
- 49-60 hours: 3.1%
- 61-72 hours: 4.1%

(Source: WHO, 1999)
Availability of levonorgestrel preparations for emergency contraception (as of end March 2001)
Mifepristone research

- pregnancy termination (first and second trimester)
- cervical ripening
- menses induction
- ovulation blocking
- luteal contraception
- emergency contraception
### Mifepristone for emergency contraception

<table>
<thead>
<tr>
<th></th>
<th>Mifepristone</th>
<th>Yuzpe regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of women</strong></td>
<td>597</td>
<td>589</td>
</tr>
<tr>
<td><strong>treated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Expected number of</strong></td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td><strong>pregnancies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Observed number of</strong></td>
<td>0 (3)</td>
<td>9</td>
</tr>
<tr>
<td><strong>pregnancies</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(after Glasier et al., 1992 and Webb et al., 1992)
Efficacy of three doses of mifepristone in emergency contraception

<table>
<thead>
<tr>
<th>Dose</th>
<th>Number of women</th>
<th>Number of observed pregnancies</th>
<th>Pregnancy rate</th>
<th>Number of expected pregnancies*</th>
<th>Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>565</td>
<td>7</td>
<td>1.2</td>
<td>48</td>
<td>85</td>
</tr>
<tr>
<td>50 mg</td>
<td>560</td>
<td>6</td>
<td>1.1</td>
<td>43</td>
<td>86</td>
</tr>
<tr>
<td>600 mg</td>
<td>559</td>
<td>7</td>
<td>1.3</td>
<td>45</td>
<td>84</td>
</tr>
<tr>
<td>ALL</td>
<td>1684</td>
<td>20</td>
<td>1.2</td>
<td>136</td>
<td>85%</td>
</tr>
</tbody>
</table>

* according to Trussell et al., Contraception 1998; 57:363-69
TCu 380A IUD: US FDA APPROVALS

Years of use:
- 1978-1982 start of WHO trials
- 1984 NDA 4 yrs
- 1988 Supplemental NDA 4 yrs
- 1989 4 yrs-6 yrs
- 1991 6 yrs-8 yrs
- 1993 8 yrs-9 yrs
- 1994 9 yrs-10 yrs

Cumulative pregnancy rate (per 100 woman-years):
- 1984 NDA 4 yrs
- 1988 Supplemental NDA 4 yrs
- 1989 4 yrs-6 yrs
- 1991 6 yrs-8 yrs
- 1993 8 yrs-9 yrs
- 1994 9 yrs-10 yrs
PID INCIDENCE RATE
(95% confidence interval)

PID rate
(per 1000 years)

Time since insertion

Months (first year)

Year

0 1 2 3 4 5 6 7 8+
Important new knowledge about safety/efficacy of hormonal fertility-regulating methods

- Oral contraceptives and cancer (benefits and risks)
- Oral contraceptives and cardiovascular disease
- Oral contraceptives and breast cancer
- DMPA and breast cancer
- Safety and efficacy of mifepristone
- Third-generation oral contraceptives and venous thromboembolism
- Long-term safety and efficacy of Norplant®
## Post-marketing surveillance of Norplant®

### Cumulative pregnancy rate at five years

<table>
<thead>
<tr>
<th></th>
<th>Norplant®</th>
<th>Copper IUD</th>
<th>Non-Copper IUD</th>
<th>Sterilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woman-years</td>
<td>32,977</td>
<td>24,289</td>
<td>2619</td>
<td>6905</td>
</tr>
<tr>
<td>Events</td>
<td>88</td>
<td>215</td>
<td>77</td>
<td>10</td>
</tr>
<tr>
<td>Rate (SE)</td>
<td>1.46 (0.16)</td>
<td>4.19 (0.28)</td>
<td>13.00 (1.39)</td>
<td>0.72 (0.23)</td>
</tr>
</tbody>
</table>

(Source: WHO, 2001)
Post-marketing surveillance of Norplant®

Selected side-effects
(Rate ratios Norplant® /controls adjusted for clinic and age)

<table>
<thead>
<tr>
<th>Bleeding disturbances</th>
<th>Norplant®</th>
<th>Rate ratios</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>hospitalised</td>
<td>Norplant®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- excessive /irregular</td>
<td>IUD</td>
<td>1.14 (0.39, 3.31)</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>Sterilisation</td>
<td>2.33 (0.28, 19.7)</td>
<td>0.44</td>
</tr>
<tr>
<td>- excessive/irregular</td>
<td>Norplant®</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IUD</td>
<td>2.72 (2.49, 2.97)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Sterilisation</td>
<td>11.39 (8.49, 15.3)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>- amenorrhoea</td>
<td>Norplant®</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IUD</td>
<td>4.80 (3.88, 5.95)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Sterilisation</td>
<td>6.69 (4.07, 11.0)</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Anaemia

<table>
<thead>
<tr>
<th>Haemoglobin &lt;10g/dl</th>
<th>Norplant®</th>
<th>Rate ratios</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Norplant®</td>
<td>IUD</td>
<td>0.78 (0.53, 1.13)</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>Sterilisation</td>
<td>1.10 (0.40, 3.02)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

(Source: WHO, 2001)
Main areas of ongoing research in fertility regulation

Method development

1. Male hormonal contraception
2. Improved progestogen-only injectable for women
3. Dual protection methods (non-latex male condom; female condom; microbicides/spermicides)
4. Immunocontraception

Surveillance

1. Long-term IUD safety and efficacy
2. Hormonal contraceptives and bone mineral density
3. Hormonal contraceptives and HIV
4. Contraceptive use and cervico-vaginal HIV shedding
5. Male condom efficacy against STIs
6. Female condom efficacy against pregnancy and STIs
Estimated maternal mortality ratios, by region, 1995

Total = 515,000 deaths

(MMR (maternal deaths per 100,000 live births))

- World Average: 400
- Africa: 1000
- Asia: 280
- Oceania: 260
- LAC: 190
- Europe: 28
- North America: 12

(WHO/UNICEF/UNFPA, 2001)
Interventions evaluated during 1999-2000 with leading/active role of the Programme

<table>
<thead>
<tr>
<th>Intervention</th>
<th>CENTRES</th>
<th>WOMEN</th>
<th>STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antenatal care</td>
<td>5</td>
<td>24,678</td>
<td>Published (2001)</td>
</tr>
<tr>
<td>Postpartum haemorrhage</td>
<td>9</td>
<td>18,530</td>
<td>Published (2001)</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>5</td>
<td>149,206</td>
<td>For publication</td>
</tr>
<tr>
<td>Treatment of pre-eclampsia</td>
<td>28</td>
<td>10,000</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Prevention of pre-eclampsia</td>
<td>6</td>
<td>8,500</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>New model</td>
<td>Standard model</td>
<td>Adjusted odds ratio (95% CI)</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>------------</td>
<td>----------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Low birthweight (&lt;2500g)</td>
<td>7.68 %</td>
<td>7.14 %</td>
<td>1.06 (0.97-1.15)</td>
</tr>
<tr>
<td>Pre-eclampsia/eclampsia</td>
<td>1.69 %</td>
<td>1.38 %</td>
<td>1.26 (1.02-1.56)</td>
</tr>
<tr>
<td>Postpartum anaemia</td>
<td>7.59 %</td>
<td>8.67 %</td>
<td>1.01&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Treated urinary tract infection</td>
<td>5.95 %</td>
<td>7.41 %</td>
<td>0.93 (0.79-1.10)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Confidence interval not computed because of heterogeneity between sites and strata
### WHO Misoprostol Trial

**Primary outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Misoprostol</th>
<th>Oxytocin</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood loss ≥ 1000 ml</td>
<td>4.0 %</td>
<td>2.9 %</td>
<td>1.39 (1.19-1.63)</td>
</tr>
<tr>
<td>Need for additional uterotonics</td>
<td>15.2 %</td>
<td>10.9 %</td>
<td>1.40 (1.29-1.51)</td>
</tr>
</tbody>
</table>
## WHO Misoprostol Trial
### Side-effects

<table>
<thead>
<tr>
<th>Side-effect</th>
<th>Misoprostol</th>
<th>Oxytocin</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any shivering</td>
<td>17.6 %</td>
<td>5.0 %</td>
<td>3.48 (3.15-3.84)</td>
</tr>
<tr>
<td>Severe shivering</td>
<td>1.3 %</td>
<td>0.2 %</td>
<td>8.58 (4.93-14.91)</td>
</tr>
<tr>
<td>Body temperature &gt;38°C</td>
<td>6.1 %</td>
<td>0.8 %</td>
<td>7.17 (5.67-9.07)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.8 %</td>
<td>0.4 %</td>
<td>2.27 (1.52-3.39)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.7 %</td>
<td>0.3 %</td>
<td>2.64 (1.67-4.18)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0.4 %</td>
<td>0.1 %</td>
<td>4.38 (2.03-9.43)</td>
</tr>
</tbody>
</table>
Acceptability of Male Condom: Key Findings

Countries: Kenya, Nigeria, Tanzania, Uganda, Zambia

Key findings:

• use of condom within marriage is constrained by lack of interspousal communication and misperceptions about safety of condom

• men report loss of pleasure, inconvenience and embarrassment as reasons for not using it

• potential for increased condom use, especially outside marriage and for prevention of STD/HIV
Non-latex Male Condom
Female Condom

PUBLIC SECTOR PRICE
UK£0.38
Activities in HIV during 2000

- male and female condoms
- dual protection
- COL-1492 (nonoxynol-9)
- cellulose sulphate as microbicide
- nevirapine and prevention of MTCT of HIV
- infant feeding and MTCT of HIV
- male circumcision and HIV transmission
- post-exposure prophylaxis
Global research initiatives in social sciences

1. Attitudes towards male condom use
2. Determinants and consequences of induced abortion
3. Role of men in reproductive health
4. Fertility regulation in the era of HIV/AIDS
5. Adolescent sexual and reproductive health
6. Quality of care in reproductive health
Broadening choices and improving quality of care of reproductive health services

- Brazil: RH service model, Vasectomy, Adolescent services
- Bolivia: DMPA
- Chile: DMPA, EC
- Burkina Faso: DMPA, EC
- South Africa: Barrier methods, EC
- Zambia: DMPA, EC
- Myanmar: Hormonal methods, RTIs
- Vietnam: DMPA, Abortion
- Ethiopia: National RH strategy, Youth, Implants
- Lao PDR: Maternal health
- China (Chongqing): Maternal health
- Zambia: Stage I
- South Africa: Stage II
- Bolivia: Stage III
- Brazil: Stage III
- China: Stage I
- Myanmar: Stage II
Emphasis on Research Capability Strengthening

US$ 2
Research and Development

US$ 1
Research Capability Strengthening
Countries Collaborating with the Programme in the year 2000 (N = 81 countries)
Trends in use of contraception

World population size according to the main fertility scenarios, 1950-2150

- **Medium fertility scenario**: TFR (2050) 2.05-2.09
- **High fertility scenario**: TFR (2050) 2.50-2.60
- **Low fertility scenario**: TFR (2050) 1.50-1.60

(Source: United Nations, 2000)
Increasing contraceptive prevalence

1. Better access to family planning services
2. Improved quality of care in service provision
3. Wider choice of acceptable and affordable methods
4. Availability of new and improved methods
Estimated new cases of curable STI* among adults, 1999

Western Europe: 17 million
Eastern Europe and Central Asia: 22 million
North Africa & Middle East: 10 million
South & South-East Asia: 151 million
North America: 14 million
East Asia & Pacific: 18 million
Latin America & The Caribbean: 38 million
Sub-Saharan Africa: 69 million
Australasia: 1 million

Global total: 340 million

* gonorrhoea, chlamydial infection, syphilis and trichomoniasis
About 15 000 new HIV infections a day in 2000

• More than 95% are in developing countries
• About 1700 are in children under 15 years of age
• About 13 000 are in persons aged 15 to 49 years, of whom:
  – 47% are women
  – over 50% are 15-24 year olds
Life expectancy at birth in 29 African countries with and without AIDS

(Source: UNAIDS, 2000)
Estimated maternal mortality ratios
(per 100 000 live births)

1990
(n= 585,000)

1995
(n= 515,000)

AFRICA

ASIA

EUROPE

L.A MERICA
AND
CARIBBEAN

N.A MERICA

OCEANIA

WORLD

(n= 585,000)

(n= 515,000)
“Eradicating polio, curbing the tobacco epidemic, stimulating research in the developing world — this is our corporate strategy in practice.”

Dr Gro Harlem Brundtland, Statement to the Executive Board at its 105th session, 29 January 2000