Reproductive health research at WHO

The success story of the Special Programme of Research, Development and Research Training in Human Reproduction (HRP)

Paul F.A. Van Look, MD PhD FRCOG
“Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.”

7 April 1948
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)
Growth of total world population

Years

Billions

0 1 2 3 4 5 6 7

1600 1700 1800 1900 2000 2100


1900s-2000s population growth
The Programme’s history

“REQUESTS the Director-General to develop further the programme proposed:

(a) in the fields of reference services, studies on medical aspects of sterility and fertility control methods and health aspects of population dynamics; …”

(WHA Resolution 18.49; 1965)
The Programme’s history

1965: WHA18.49
   Human Reproduction Unit within existing Division of Family Health

1971: Feasibility study
      Expanded (Special) Programme of Research, Development and Research Training in Human Reproduction (HRP)
The Programme’s history

1972-1988: WHO Special Programme

1988-present: UNDP/UNFPA/WHO/World Bank cosponsored Special Programme
(WHA Resolution 41.9; 1988)
“To coordinate, promote, conduct and evaluate international research in human reproduction.”
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

**Mesigyna®**
- 50 mg norethisterone enantate
- + 5 mg estradiol valerate

**Cyclofem®**
- 25 mg medroxyprogesterone acetate
- + 5 mg estradiol cypionate
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
What is emergency contraception?

Methods which women can use AFTER intercourse to PREVENT pregnancy

(Consensus Statement, Bellagio, 1995)
Methods of emergency contraception in early 1990s

- Ethinylestradiol/levonorgestrel (Yuzpe regimen) (1974)
  - nausea 50%, vomiting 20%
  - efficacy approx. 75%

- Copper-T intrauterine device (1970s)
  - often unsuitable, requires trained providers
  - painful at insertion, risk of PID
  - efficacy of greater than 90%
Emergency contraception is indicated to prevent pregnancy after intercourse

- When no contraceptive was used
- When there is a contraceptive failure or misuse, including:
  - condom breakage, slippage or misuse
  - 2 or more consecutive missed oral contraceptive pills
  - late for contraceptive injection
  - failed coitus interruptus, etc.
- In cases of sexual assault
Lower pregnancy rate after levonorgestrel

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

The difference in pregnancy rate was statistically significant.

Less side-effects after levonorgestrel

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

Emergency contraception is more effective the sooner it is started

Availability of levonorgestrel preparations for emergency contraception (as of November 2002)
Levonorgestrel and mifepristone do not differ in efficacy.

<table>
<thead>
<tr>
<th>Group</th>
<th>Observed pregnancies /total</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>LNG 0.75 mg x 2</td>
<td>24/1356</td>
<td>1.77%</td>
</tr>
<tr>
<td>LNG 1.5 mg x 1</td>
<td>20/1356</td>
<td>1.47%</td>
</tr>
<tr>
<td>Mifepristone 10 mg</td>
<td>21/1359</td>
<td>1.55%</td>
</tr>
<tr>
<td><strong>All LNG</strong></td>
<td><strong>44/2712</strong></td>
<td><strong>1.62%</strong></td>
</tr>
</tbody>
</table>

(Source: WHO, Lancet, 2002)
Mifepristone research

- pregnancy termination (first and second trimester)
- cervical ripening
- menses induction
- ovulation blocking
- luteal contraception
- emergency contraception
Faith Versus Facts

WE HAVE TWO OPTIONS. EITHER AN EVIDENCE-BASED TREATMENT OR AN EXCITING, RISKY ALTERNATIVE.
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®
Countries (number of clinics) participating in Post-marketing surveillance of Norplant®

- Bangladesh: 22 clinics
- Indonesia: 55 clinics
- Colombia: 3 clinics
- China: 10 clinics
- Sri Lanka: 1 clinic
- Thailand: 4 clinics
- Egypt: 5 clinics
- Pakistan: 2 clinics
### 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>Rate Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>- excessive /irregular, hospitalised</td>
<td>Norplant</td>
<td>1.14</td>
<td>(0.39, 3.31)</td>
</tr>
<tr>
<td></td>
<td>IUD</td>
<td>1.14</td>
<td>(0.39, 3.31)</td>
</tr>
<tr>
<td></td>
<td>Sterilization</td>
<td>2.33</td>
<td>(0.28, 19.7)</td>
</tr>
</tbody>
</table>

| - excessive/irregular                  | Norplant   | 2.72       | (2.49, 2.97) | P<0.001 |
|                                        | IUD        | 2.72       | (2.49, 2.97) | P<0.001 |
|                                        | Sterilization | 11.39 | (8.49, 15.3) | P<0.001 |

| - amenorrhoea                          | Norplant   | 4.80       | (3.88, 5.95) | P<0.001 |
|                                        | IUD        | 4.80       | (3.88, 5.95) | P<0.001 |
|                                        | Sterilization | 6.69 | (4.07, 11.0) | P<0.001 |

#### Anaemia

| Haemoglobin <10g/dl                    | Norplant   | 0.78       | (0.53, 1.13) | 0.19 |
|                                        | IUD        | 0.78       | (0.53, 1.13) | 0.19 |
|                                        | Sterilization | 1.10   | (0.40, 3.02) | 0.85 |
TCu 380A IUD: US FDA APPROVALS

Cumulative pregnancy rate (per 100 woman-years)

<table>
<thead>
<tr>
<th>Years of use</th>
<th>Cumulative pregnancy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984</td>
<td>4 yrs,NDA</td>
</tr>
<tr>
<td>1989</td>
<td>4 yrs-6 yrs</td>
</tr>
<tr>
<td>1991</td>
<td>6 yrs-8 yrs</td>
</tr>
<tr>
<td>1993</td>
<td>8 yrs-9 yrs</td>
</tr>
<tr>
<td>1994</td>
<td>9 yrs-10 yrs</td>
</tr>
</tbody>
</table>
PID INCIDENCE RATE
(95% confidence interval)

Time since insertion

PID rate (per 1000 years)

Months (first year)

Year
Trends in use of contraception

Emphasis on research capability strengthening

US$ 2
Research and development

US$ 1
Research capability strengthening
Countries collaborating with the Department in the year 2001 (n = 99 countries)
The ICPD paradigm shift

Demographic Transitions

Women's Health Movement

HIV/AIDS

ICPD Programme of Action
The ICPD Programme of Action - A radical departure

- a new language
- a broader agenda to be addressed in a holistic, comprehensive,"horizontal", integrated way
- a new way of working: client-centred, rights-based, gender-sensitive
- a place for neglected groups: young people, men, refugees
- a concern for neglected issues: violence against women, female genital mutilation
“All countries should strive to make accessible through the primary health-care systems, reproductive health to all individuals of appropriate ages as soon as possible and no later than the year 2015.”

*(ICPD Programme of Action, para. 7.6)*
Reproductive ill-health accounts for substantial portions of global burden of disease

## Risks to sexual and reproductive health

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Rank</th>
<th>Attributable deaths (% of total)</th>
<th>Attributable DALYs</th>
<th>Measured adverse outcomes of exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsafe sex</td>
<td>2</td>
<td>2.9 million (5.2%)</td>
<td>91.9 million (6.3%)</td>
<td>HIV/AIDS, STIs, cervical cancer</td>
</tr>
<tr>
<td>Lack of contraception</td>
<td>19</td>
<td>149,000 (0.3%)</td>
<td>8.8 million (0.6%)</td>
<td>maternal mortality and morbidity</td>
</tr>
</tbody>
</table>

“Investments in reproductive health, including family planning and access to contraceptives, are crucial accompaniments of investments in disease control. The combination of disease control and reproductive health is likely to translate into reduced fertility, greater investments in the health and education of each child, and reduced population growth.”

(Commission on Macroeconomics and Health, 2001)
## Maternal health intervention research during 1995-2002 with leading/active participation of the Programme

<table>
<thead>
<tr>
<th>Countries</th>
<th>Women</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antenatal care</td>
<td>4</td>
<td>24,678</td>
</tr>
<tr>
<td>Postpartum haemorrhage</td>
<td>9</td>
<td>18,530</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>5</td>
<td>149,276</td>
</tr>
<tr>
<td>Treatment of pre-eclampsia (MAGPIE trial)</td>
<td>31</td>
<td>10,141</td>
</tr>
<tr>
<td>The WHO Reproductive Health Library</td>
<td>2</td>
<td>76,053</td>
</tr>
<tr>
<td>Primary prevention of pre-eclampsia</td>
<td>6</td>
<td>8,500</td>
</tr>
<tr>
<td>Calcium supplementation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening and treatment of urinary tract infection</td>
<td>4</td>
<td>18,000</td>
</tr>
<tr>
<td>Treatment of postpartum haemorrhage</td>
<td>4</td>
<td>1,000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>25</strong></td>
<td><strong>306,178</strong></td>
</tr>
</tbody>
</table>

*Some countries have been involved in more than one study*
### WHO Antenatal Care Trial

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>New model</th>
<th>Standard model</th>
<th>Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<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 &gt; 1000 ml</td>
<td>4.0 %</td>
<td>2.9 %</td>
<td>1.39 (1.19-1.63)</td>
</tr>
<tr>
<td>Use of additional uterotonics</td>
<td>15.2 %</td>
<td>10.9 %</td>
<td>1.40 (1.29-1.51)</td>
</tr>
</tbody>
</table>

(Gülmezoglu et al., *The Lancet, 2001*)
Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate?

The Magpie Trial: a randomized placebo-controlled trial.

## The Magpie Trial

<table>
<thead>
<tr>
<th></th>
<th>Magnesium sulphate (n=5055)</th>
<th>Placebo (n=5055)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eclampsia</td>
<td>40 (0.8%)</td>
<td>96 (1.9%)</td>
<td>0.42 (0.29 to 0.60)</td>
</tr>
<tr>
<td>Maternal death</td>
<td>11 (0.2%)</td>
<td>20 (0.4%)</td>
<td>0.55 (0.26 to 1.14)</td>
</tr>
<tr>
<td>Baby death (total)</td>
<td>576 (12.7%)*</td>
<td>558 (12.4%)†</td>
<td>1.02 (0.92 to 1.14)</td>
</tr>
</tbody>
</table>

* n=4538; † n=4486

*(Lancet 2002; 359: 1877-90)*
Activities in STI and HIV during 2001-2002

- Cellulose sulphate as microbicide
- Male and female condoms (pregnancy and STI prevention)
- HAART during breastfeeding
- Infant feeding and MTCT of HIV
- COL-1492 (nonoxynol-9)
Getting research into practice

Evidence-based technical and policy guidance
- family planning (global consensus guidelines)
**Medical Eligibility Criteria for Contraceptive Use**

**Selected Practice Recommendations for Contraceptive Use**

**Guidance for guides**

**Guidance for providers and clients**

**Decision-Making Tool for Family Planning Clients and Providers**

**Handbook for Family Planning Providers**

**Process for keeping the guidance up-to-date**
Getting research into practice

Evidence-based technical and policy guidance

- family planning (global consensus guidelines)

- *WHO Reproductive Health Library Issue No.5*
Broadening choice and improving quality of care of reproductive health services
Main areas of ongoing/planned research

- **Family planning**
  - male hormonal contraception
  - emergency contraception
  - long-term safety (IUDs; bone mineral density)

- **Making pregnancy safer**
  - prevention of pre-eclampsia
  - asymptomatic urinary tract infections
Main areas of ongoing/planned research

- **Controlling RTIs/STIs**
  - dual protection methods (microbicides, female condom)
  - contraceptives and HIV
  - HAART for breastfeeding women

- **Preventing unsafe abortion**
  - non-surgical termination of pregnancy
  - provision of abortion by mid-level providers
  - post-abortion care
Main areas of ongoing/planned research

• Technical cooperation with countries
  – enhancing operations research capability
  – improved utilization of research findings
  – strengthening of regional research networks
  – widening scope and use of the Strategic Approach
  – health sector reform and reproductive health
“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