# GLOBAL SITUATION OF EMERGENCY CONTRACEPTION


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# EMERGENCY CONTRACEPTIVES

ARE METHODS WHICH WOMEN CAN USE AFTER INTERCOURSE TO PREVENT PREGNANCY

(from Consensus Statement on Emergency Contraception, Bellagio 1995)

- not for regular use but for emergency

# METHODS USED FOR EMERGENCY CONTRACEPTION

- HIGH-DOSE ESTROGENS (1963)
- ETHINYLESTRADIOL/LEVONORGESTREL (1974)
- COPPER T (1970's)
- LEVONORGESTREL 0.75mg x 2 (1993)

# PILOT STUDY ON THE COMBINED REGIMEN IN 1974

- 100 µg ethinylestradiol
- I.0 mg dl-norgestrel

} In one dose

  - 148 cycles
  - treatment up to 5 days
  - 3 pregnancies

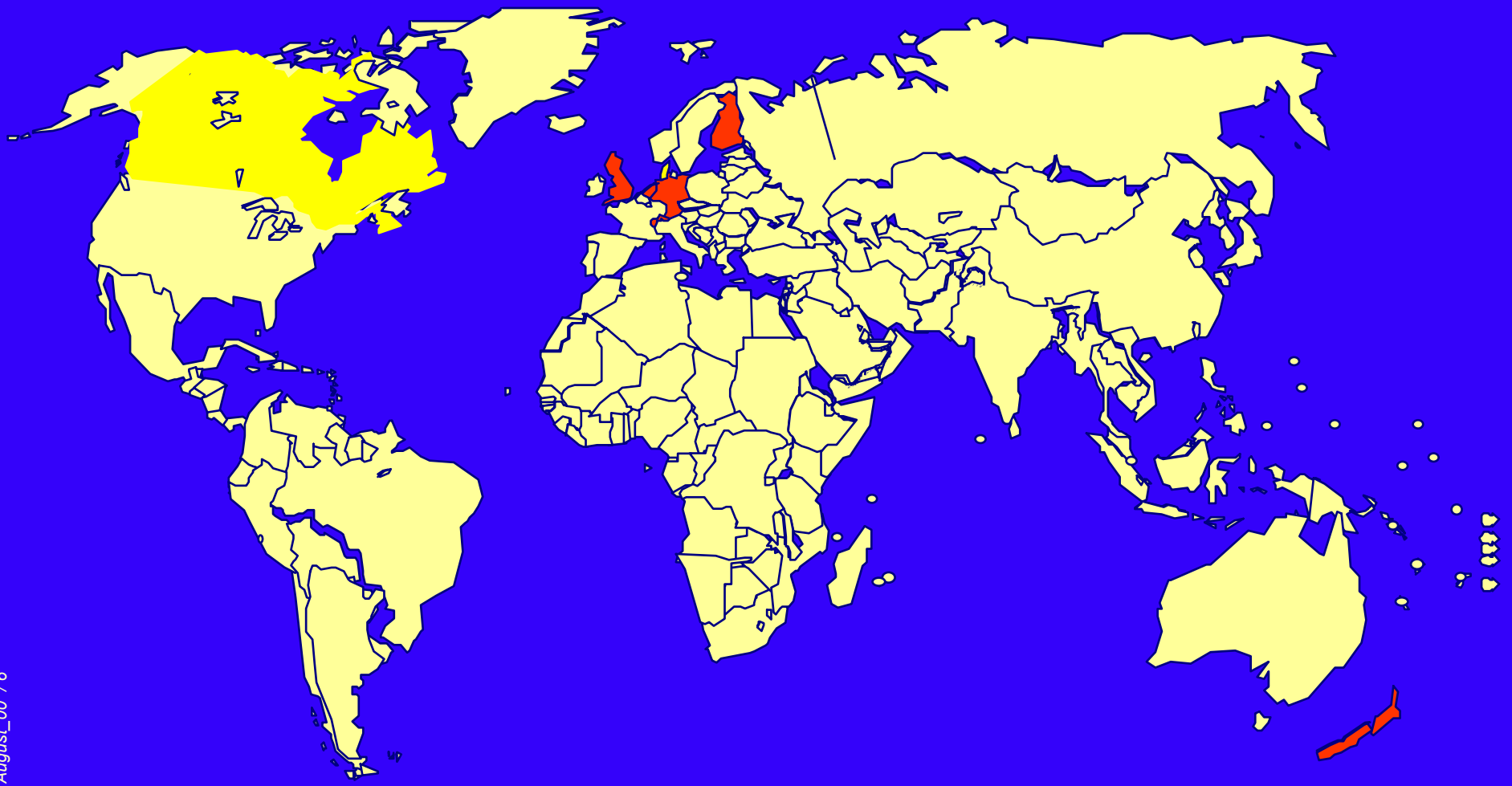
(Yuzpe A.A. et al. Contraception 1974)

# EFFECTIVENESS OF THE YUZPE REGIMEN*

| Study | Cycles | Pregnancies | Prevented Pregnancies |
|---|---|---|---|
| 1. Yuzpe et al. 1982 | 451 | 5 | 86.8% |
| 2. Glasier et al. 1992 | 359 | 4 | 83.1% |
| 3. Van Santen et al. 1985 | 461 | 5 | 80.7% |
| 4. Percival-Smith et al. 1987 | 648 | 12 | 75.4% |
| 5. Zuliani et al. 1990 | 407 | 9 | 75.1% |
| 6. WHO 1998 | 976 | 28 | 67.4% |
| 7. Webb et al. 1992 | 191 | 5 | 65.9% |
| 8. Ho et al. 1993 | 341 | 9 | 63.7% |
| Total | 3834 | 77 | 74.1% |

*100 µg ethinylestradiol and 0.5 mg levonorgestrel taken twice at 12-hr interval (Trussel et al, 1999)

# YUZPE REGIMEN BEFORE 1990's



# DISADVANTAGES OF YUZPE REGIMEN

1. HIGH INCIDENCE OF NAUSEA (50%) AND VOMITING (up to 20%)

2. EFFICACY DECLINES WITH TREATMENT DELAY

3. 12-HOUR INTERVAL BETWEEN DOSES INCONVENIENT

# Disadvantages of IUD for Emergency Contraception

1. May be difficult and painful to insert
   - timing not ideal
   - women seeking EC often nulligravida

2. Risk of infection
   - new sexual partner, rape

# TWO NEW APPROACHES FOR EMERGENCY CONTRACEPTION

- LEVONORGESTREL (0.75 mg tablets)
  - research on repeated postcoital use
  - tablets available in several countries
- MIFEPRISTONE
  - influence on ovulation and endometrium

# LEVONORGESTREL IN EMERGENCY CONTRACEPTION

| | number of cycles | dose/time | pregnancies |
|---|---|---|---|
| Kovacs L et al. (1979) | 150 | 0.75 mg/immediately | 0 |
| Hoffmann K (1984) | 205 | 0.6 mg/<12 hours | 6 (2.9%) |
| Ho PC and Kwan MSW (1993) | 410 | 0.75 mg x2/<48hours | 12 (2.9%) |

# Levonorgestrel versus the Yuzpe regimen

## Objectives

1) To confirm that two doses of 0.75 mg of levonorgestrel given 12 hours apart for emergency contraception have
   - the same effectiveness but
   - fewer side-effects than the Yuzpe regimen.

2) To assess whether the same effectiveness can be achieved if the delay between intercourse and the start of the treatment is extended (from 48 hours) to 72 hours.

# Levonorgestrel versus the Yuzpe regimen

## Design

- Double-blind
- randomized controlled trial
- conducted at 21 centres (14 countries)
- sample size calculation for an equivalence trial



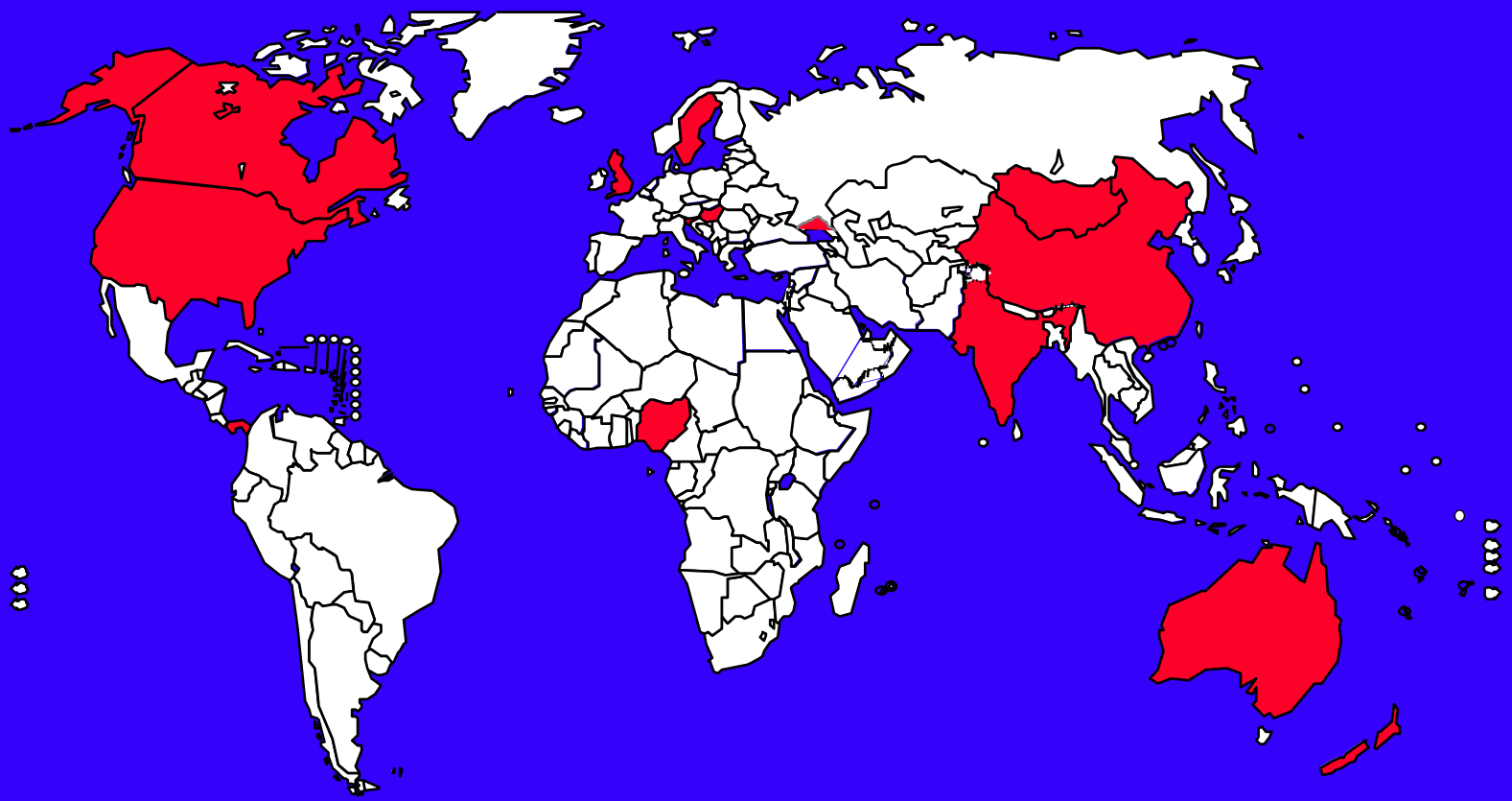




(Lancet, 352:428-33)

# Levonorgestrel versus the Yuzpe regimen

## Participating countries



(Lancet 352:428-33)

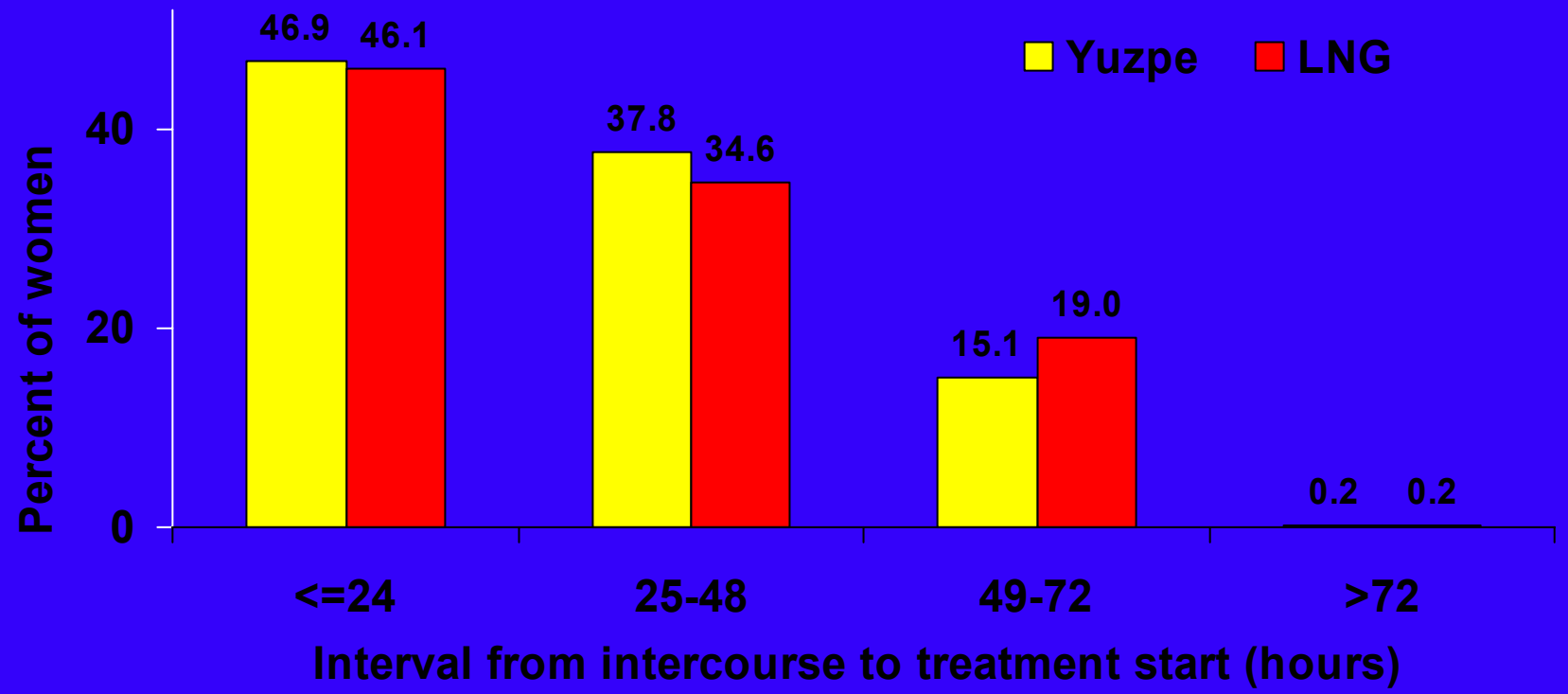
# Levonorgestrel versus the Yuzpe regimen
## Reason for requesting emergency contraception

| | Yuzpe (n=979) % | LNG (n=976) % |
|---|---|---|
| No method used | 55.7 | 56.3 |
| Method failure | 44.0 | 43.5 |
| Other | 0.3 | 0.2 |

(Lancet 352:428-33)

# Levonorgestrel versus the Yuzpe regimen

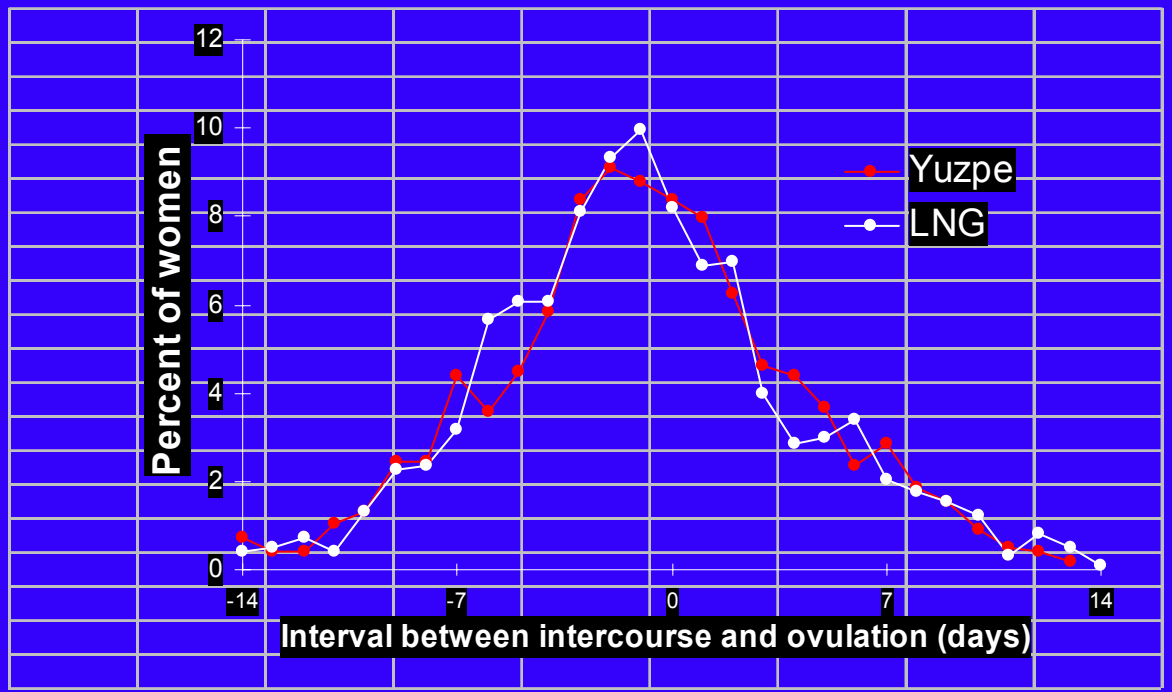
## Delay in taking emergency contraceptive




(Lancet, 352:428-33)

# Levonorgestrel versus the Yuzpe regimen

## Day of intercourse in relation to estimated day of ovulation




(Lancet, 352:428-33)

# Levonorgestrel versus the Yuzpe regimen

## Efficacy: prevented fraction

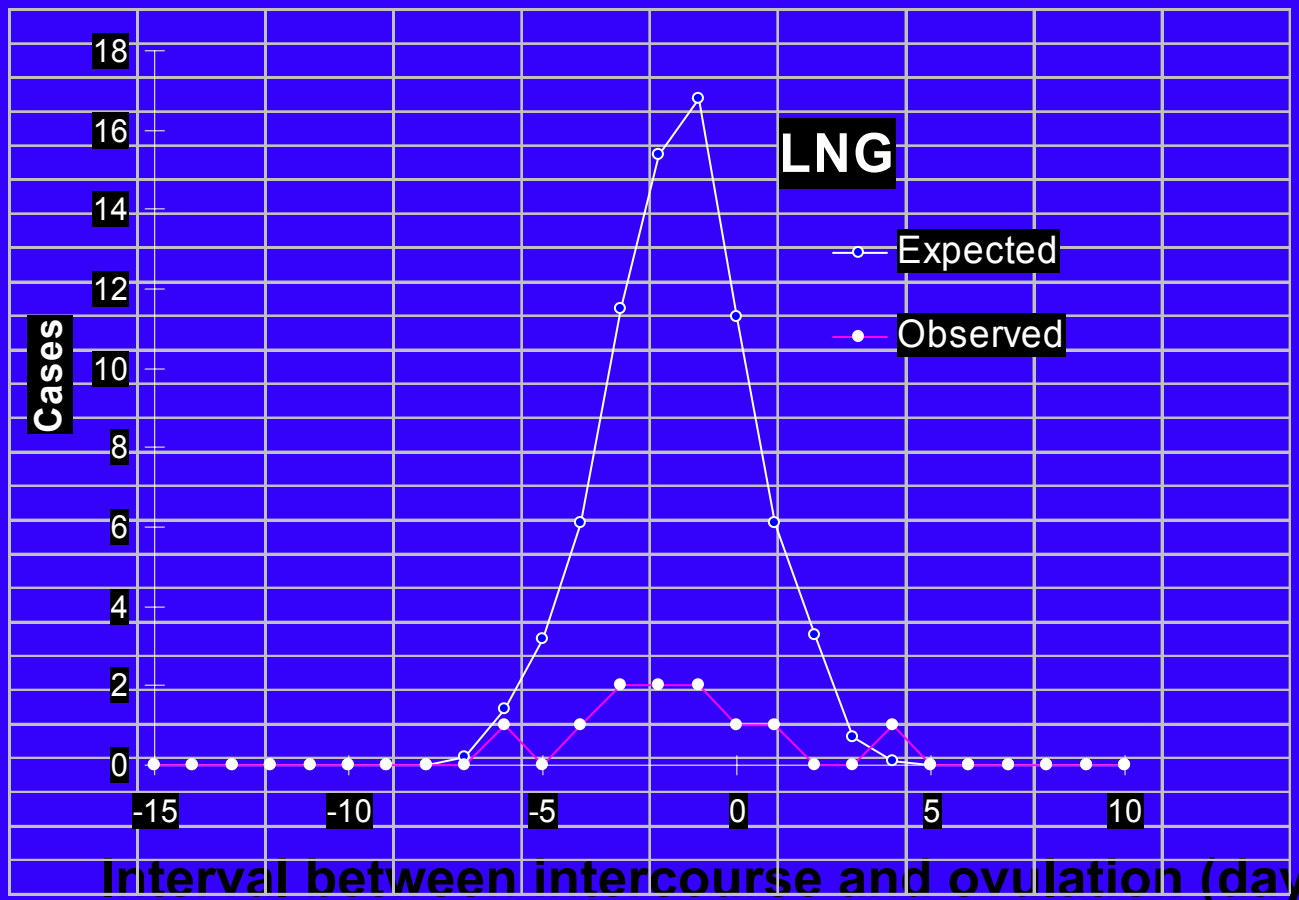
| Group | No. of women | No. of pregnancies | | Efficacy** | |
|---|---|---|---|---|---|
| | | Observed | Expected* | (%) | 95% CI |
| Yuzpe | 979 | 31 | 74.2 | 58 | (41, 72) |
| LNG | 976 | 11 | 76.3 | 86 | (74, 93) |

* Using Dixon's estimates of conception probabilities

** Prevented fraction

(Lancet, 352:428-33)

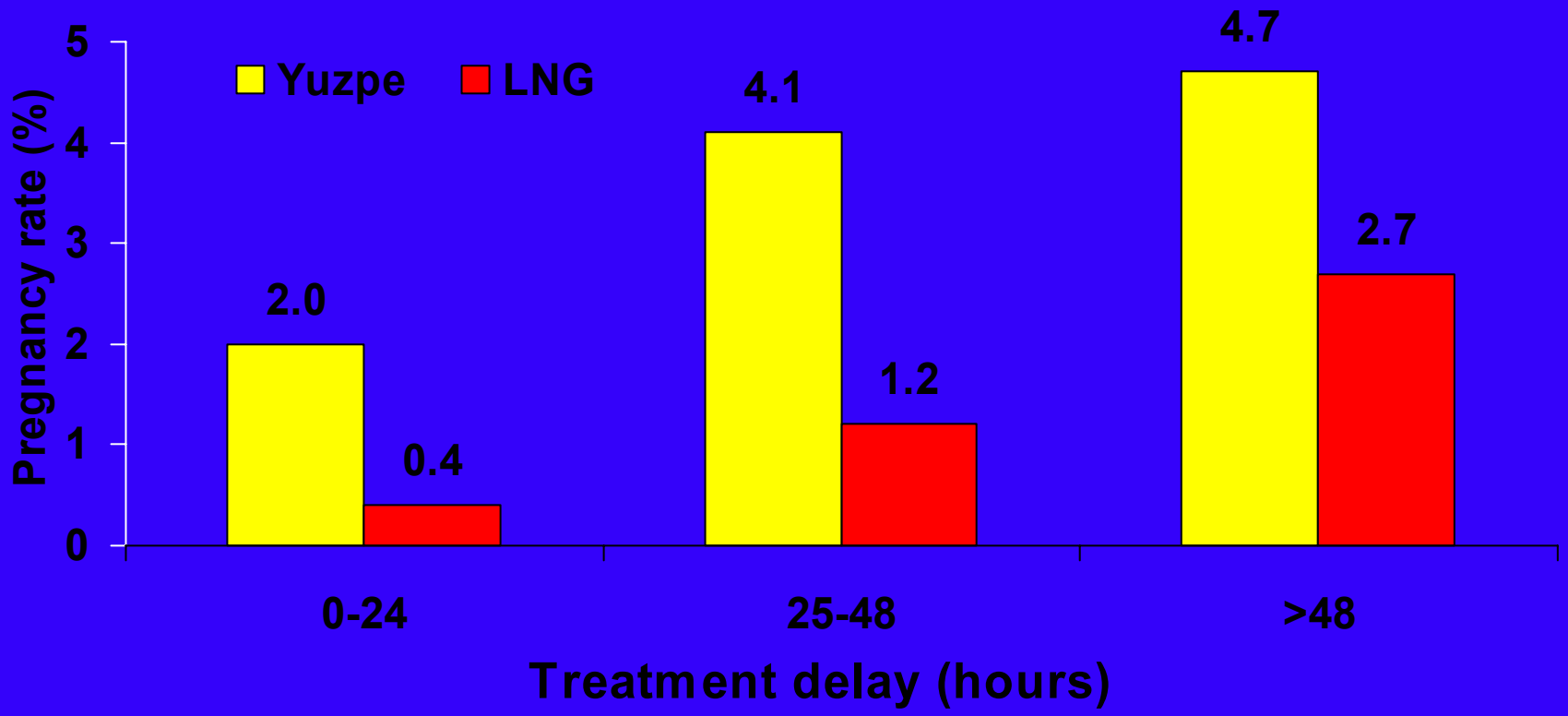
# Observed vs expected pregnancies by day of intercourse




(Lancet, 352:428-33)

# Levonorgestrel versus the Yuzpe regimen

## Efficacy of emergency contraceptives




(Lancet, 352:428-33)

# Levonorgestrel versus the Yuzpe regimen
## Incidence of side-effects

| | Yuzpe | | LNG | | |
|---|---|---|---|---|---|
| | No. of Cases | Rate (%) | No. of Cases | Rate (%) | p-value |
| Nausea | 494 | 50.5 | 226 | 23.1 | <0.01 |
| Vomiting | 184 | 18.8 | 55 | 5.6 | <0.01 |
| Dizziness | 163 | 16.7 | 109 | 11.2 | <0.01 |
| Fatigue | 279 | 28.5 | 165 | 16.9 | <0.01 |
| Headache | 198 | 20.2 | 164 | 16.8 | 0.06 |

(Lancet, 352:428-33)

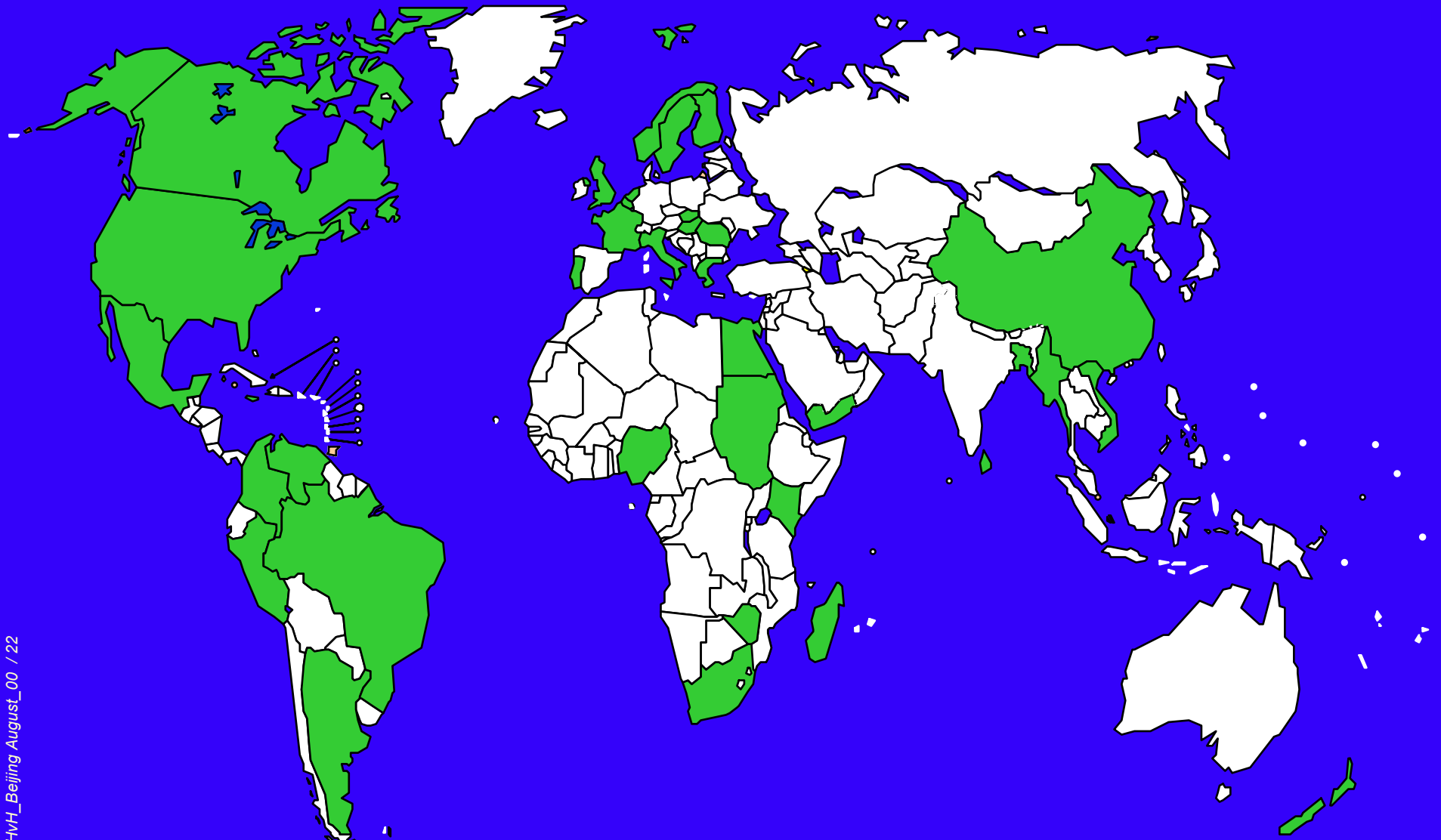
# Levonorgestrel versus the Yuzpe regimen

## Conclusions

- The LNG regimen is more effective than the Yuzpe regimen
- It is better tolerated
- With both regimens, earlier treatment is more effective

(Lancet, 352:428-33)

# Availability of levonorgestrel for emergency contraception (as of November 2000)



# EMERGENCY CONTRACEPTION USING MIFEPRISTONE
# (600 mg, 50 mg, 10 mg - 120 hours)

# Three doses of mifepristone in emergency contraception

## Baseline characteristics of participants

| | 10 mg (n=565) | | 50 mg (n=560) | | 600 mg (n=559) | |
|---|---|---|---|---|---|---|
| | MEAN | SD | MEAN | SD | MEAN | SD |
| Age (years) | 27.7 | 6.5 | 27.9 | 6.4 | 27.7 | 6.4 |
| Weight (kg) | 57.0 | 10.1 | 57.2 | 9.1 | 57.9 | 9.6 |
| Height (cm) | 163.2 | 5.9 | 163.3 | 6.2 | 163.5 | 6.2 |
| BMI (kg/m$^2$) | 21.4 | 3.3 | 21.4 | 2.9 | 21.6 | 3.2 |
| Cycle length (days) | 28.8 | 2.3 | 29.1 | 2.6 | 29.1 | 2.5 |





The Lancet, Vol 353; No. 9154; 697-702

# Three doses of mifepristone in emergency contraception

## Reasons for requesting emergency contraception

| | 10 mg (n=565) | 50 mg (n=560) | 600 mg (n=559) |
|---|---|---|---|
| No method use | 40.9% | 40.5% | 40.8% |
| Condom failure | 56.8% | 58.2% | 55.6% |
| Other contraceptive failure | 2.3% | 1.3% | 3.6% |

The Lancet, Vol 353, No 9154; 697-702

# Three doses of mifepristone in emergency contraception

## Delay in taking mifepristone

| Hours | 10 mg (n=565) | 50 mg (n=560) | 600 mg (n=559) |
|---|---|---|---|
| ≤ 24 | 36.3% | 33.0% | 33.8% |
| 25-48 | 27.3% | 32.3% | 30.9% |
| 49-72 | 20.7% | 16.8% | 21.3% |
| 73-96 | 10.8% | 12.5% | 8.4% |
| >96 | 5.0% | 5.4% | 5.6% |

The Lancet, Vol 353, No 9154; 697-702

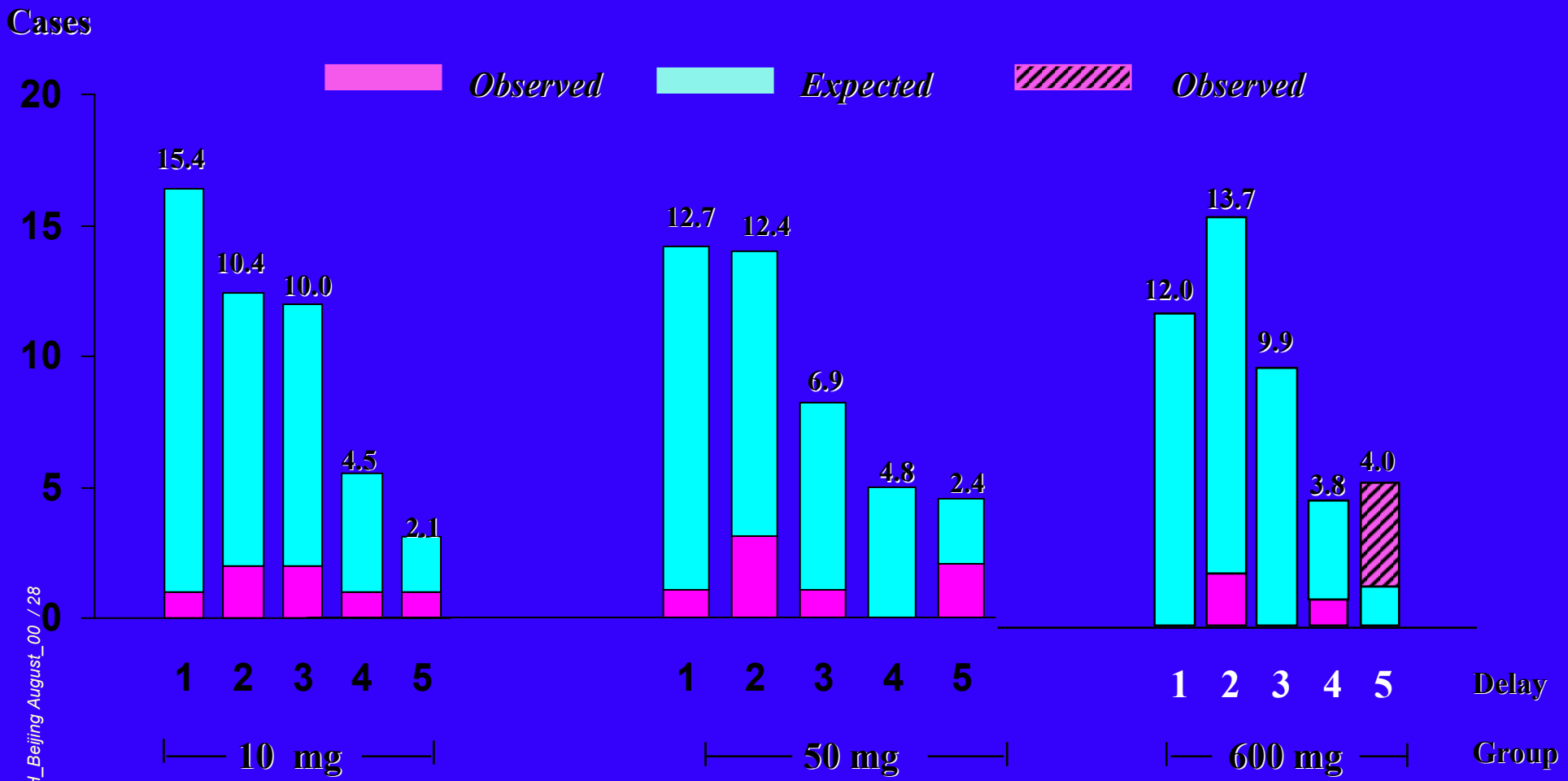
# Pregnancy rates and prevented fractions by treatment group

| | Observed pregnancies total | Proportion pregnant (%) | Relative risk (95% CI) | No. of pregnancies expected | Prevented fraction (%) |
|---|---|---|---|---|---|
| Group | | | | | |
| 600 mg | 7/559 | 1.3 | 1.00 | 45 | 84 |
| 50 mg | 6/560 | 1.1 | 0.85 (0.29-2.51) | 43 | 86 |
| 10 mg | 7/565 | 1.2 | 0.99 (0.35-2.80)† | 48 | 85 |
| All participants | 20/1684 | 1.2 | | 136 | 85 |

† 1.2 (0.4-3.4) when 50 mg is reference category

# Three Doses of Mifepristone in Emergency Contraception

## Observed vs Expected Pregnancies (Dixon)



# Three doses of mifepristone in emergency contraception
## Details of pregnancies

| Pregnancies | Coitus-treatment interval (hours) | Coitus-conception interval (days) | Further acts of coitus | Comment |
|---|---|---|---|---|
| **600 mg group** | | | | |
| 15 | 98 | 30 | protected | user failure |
| 16 | 102 | 27 | protected | user failure |
| 17 | 108 | 15 | protected | user failure |
| 18 | 108 | 22 | protected | user failure |
| 19 | 36 | -6 | none | |
| 20 | 37 | -3 | unprotected | |
| 21 | 82 | -4 | unprotected | |

The Lancet, Vol 353, No. 9154; 697-702

# SIDE EFFECTS* OF THREE DOSES OF MIFEPRISTONE IN EMERGENCY CONTRACEPTION (n = 1677)

| Side effect | 10 mg (n=561) | 50 mg (n=558) | 600 mg (n=558) | p value ** |
|---|---|---|---|---|
| Nausea | 17.5 | 14.9 | 19.7 | 0.324 |
| Vomiting | 1.8 | 1.3 | 2.0 | 0.819 |
| Headache | 12.7 | 13.8 | 11.3 | 0.522 |
| Dizziness | 12.3 | 10.4 | 15.2 | 0.145 |
| Fatigue | 19.6 | 20.6 | 24.2 | 0.055 |
| Bleeding disturbances | 15.7 | 31.0 | 35.8 | 0.001 |

** percentage rates (recorded for 7 days after treatment)*

*** non-zero correlation between mifepristone dose and occurrence of side effects*

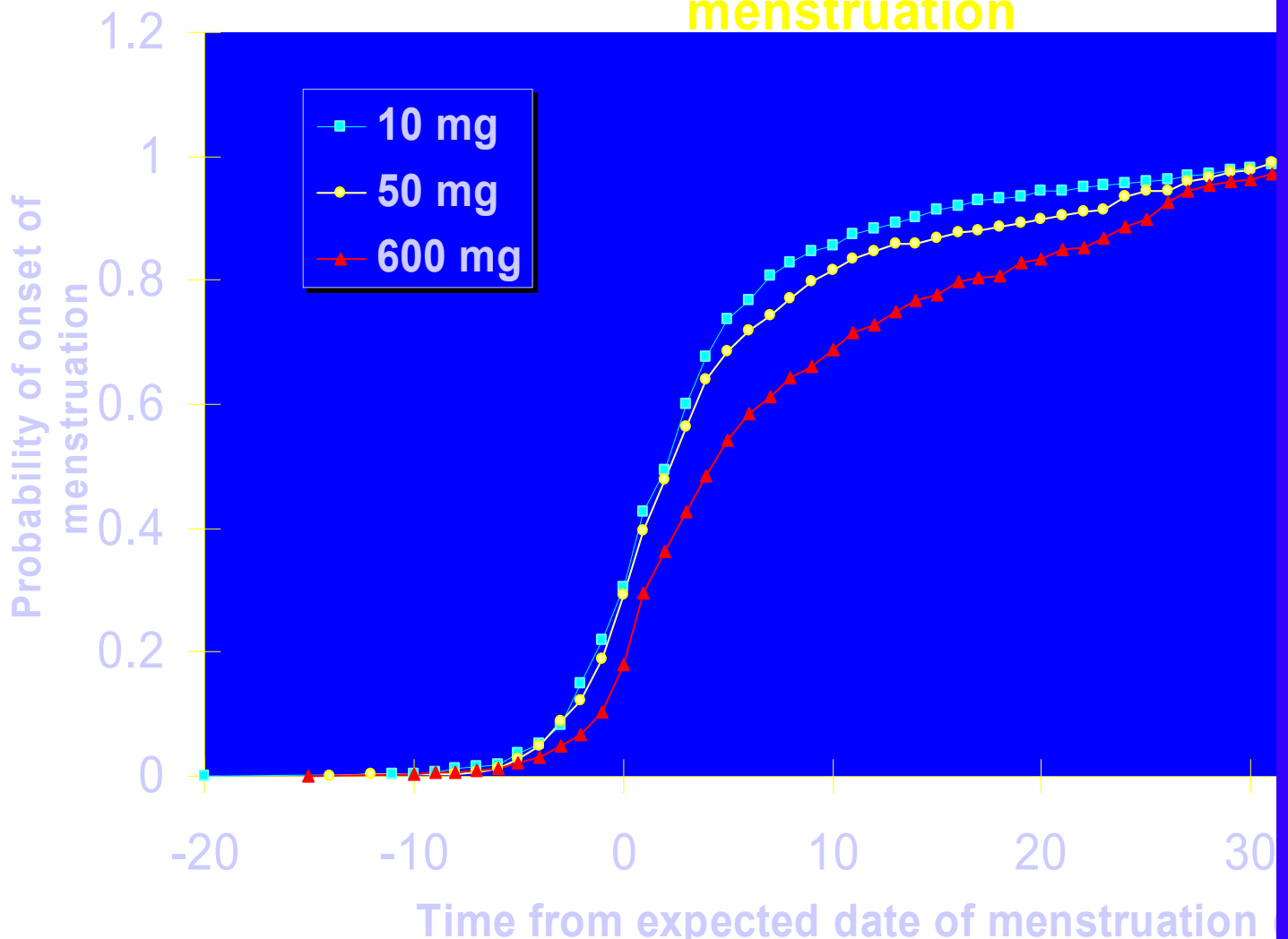




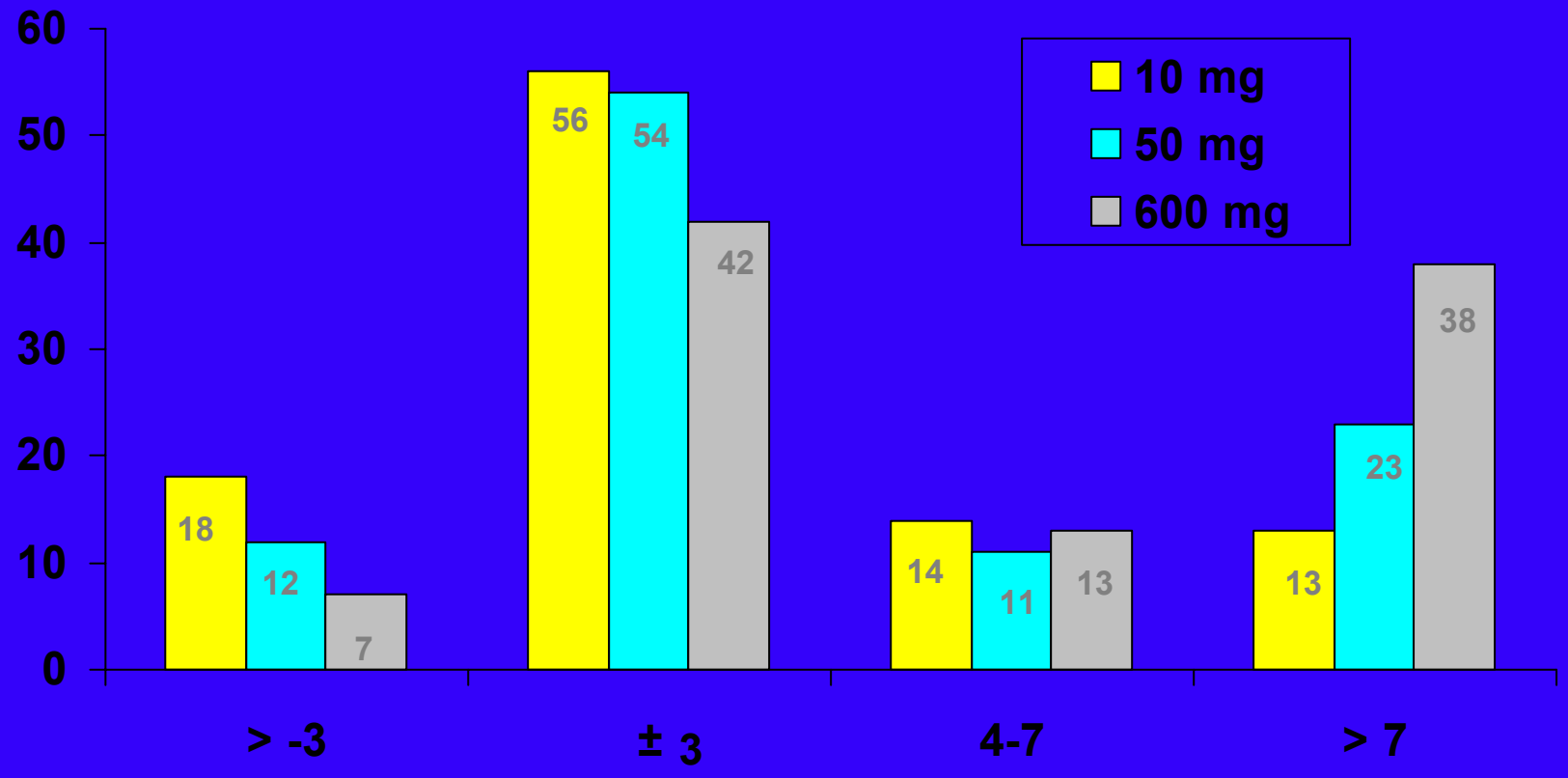


(HRP Project 92903)

# Delay of menses by group: cumulative probabil of menstruation in relation to time from expec menstruation



# TIMING OF MENSES AFTER MIFEPRISTONE AMONG 521 CHINESE WOMEN



# CONCLUSIONS

- The 10mg, 50mg and 600mg groups did not differ in the pregnancy rates (1.2%, 1.1% and 1.3% respectively).
- Delay in menses was associated with higher doses
- Other side-effects were mild and not related to the mifepristone dose

# Comparison of two regimens of levonorgestrel and 10 mg of mifepristone

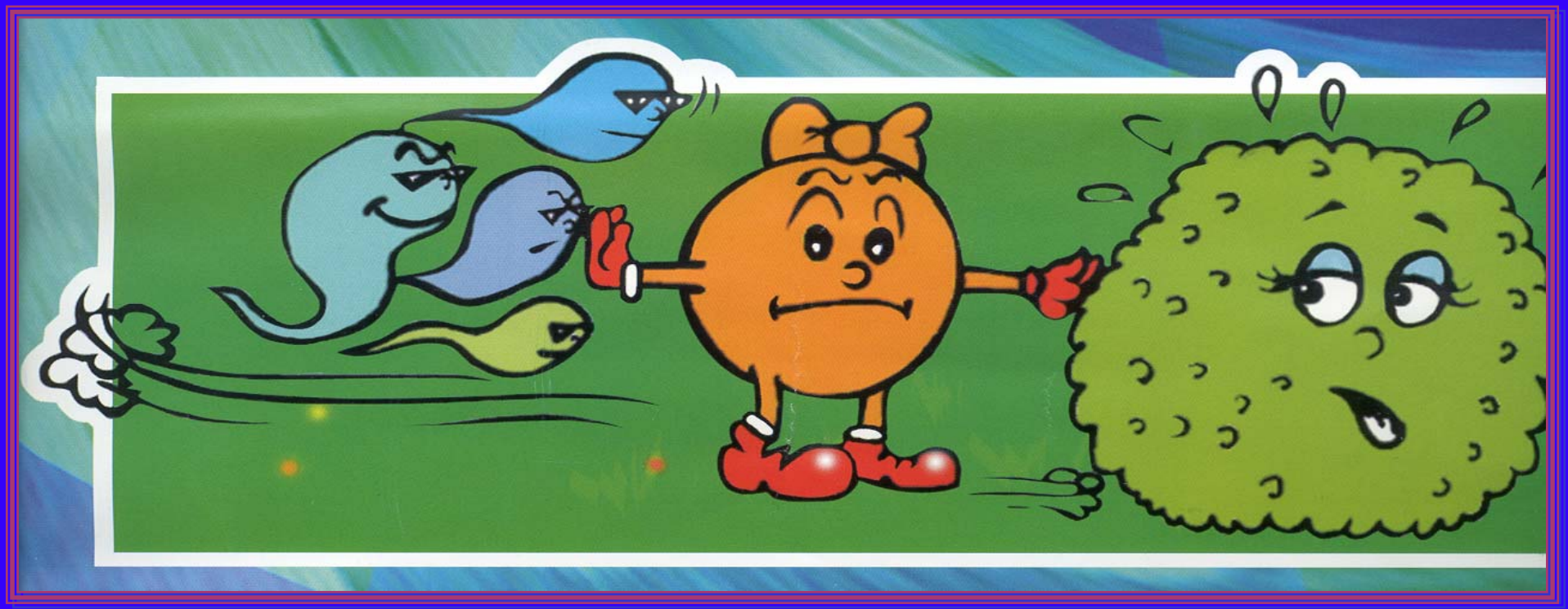
- randomized, double-blind multicentre study
- 15 centres, 4200 women, up to 120 hours

| | | | | | |
|---|---|---|---|---|---|
| **LNG** | 0.75 mg | —— | 12 h | —— | 0.75 mg |
| **LNG** | 1.5 mg | —— | 12 h | —— | placebo |
| **MIFEPRISTONE** | 10 mg | —— | 12 h | —— | placebo |

# EFFICACY OF EMERGENCY CONTRACEPTION

| Method | No. of women | No. of pregnancies | Pregnancy rate | Prevented pregnancies |
|---|---|---|---|---|
| Yuzpe | 3834 | 77 | 2.0% | 74% |
| IUD | > 8400 | 8 | 0.1% | 99% |
| LNG (0.75 x 2) | 1307 | 19 | 1.5% | 84% |
| Mifepristone (10mg) | 2038 | 24 | 1.2% | 84% |

1. Trussel et al. 1999
2. Trussel & Ellertson 1995
3. Ho & Kwan 1992; WHO 1998
4. WHO 1999 & Project 9801, 2000



# LEVONORGESTREL 0.75 mg

## Pharmacokinetics after oral administration:

| | |
|---|---|
| peak concentration | 1.6 ( ± 0.7) hours |
| elimination half-life | 24.4 ( ± 5.3) hours |

# CONSENSUS CONFERENCE ON EMERGENCY CONTRACEPTION*

(Bellagio, Italy, August 1995)

Consensus Statement on Emergency Contraception:

- Definition of emergency contraception
- Call for:
  - more information to women and service providers on ECs
  - collaboration between industry and health care providers

Women everywhere should have access to emergency contraception

(*supported by the Rockefeller Foundation, South to South Cooperation in Reproductive Health, IPPF, FHI, the Population Council and WHO)

# CONSORTIUM ON EMERGENCY CONTRACEPTION

1. Collaborative agreement with Gedeon Richter Ltd. Hungary
   - e.g. preferential public-sector pricing; development of labelling, client information, packaging, etc.

2. Nine steps to assist countries to develop strategies for introducing emergency contraception

# CONSORTIUM FOR EMERGENCY CONTRACEPTION

- Concept  Foundation
- International Planned Parenthood Federation
- Pacific Institute for Women's Health
- Pathfinder International
- Population Council
- Program for Appropriate Technology in Health
- WHO Special Programme of Research, Development and Research Training in Human Reproduction

# THE 9 STEPS

1. Assess user needs and service capabilities
2. Build support for EC introduction at appropriate levels
3. Select a product
4. Develop distribution plans
5. Train providers
6. Identify and meet clients' needs
7. Introduce the product
8. Monitor and evaluate EC services
9. Disseminate evaluation results

Four demonstration countries: Indonesia, Kenya, Mexico, Sri Lanka