EMERGENCY CONTRACEPTION

Helena von Hertzen

UNDP/UNFPA/WHO/World Bank Special Programme of Research,Development and Research Training in Human Reproduction (HRP)

World Health Organization
Geneva, Switzerland

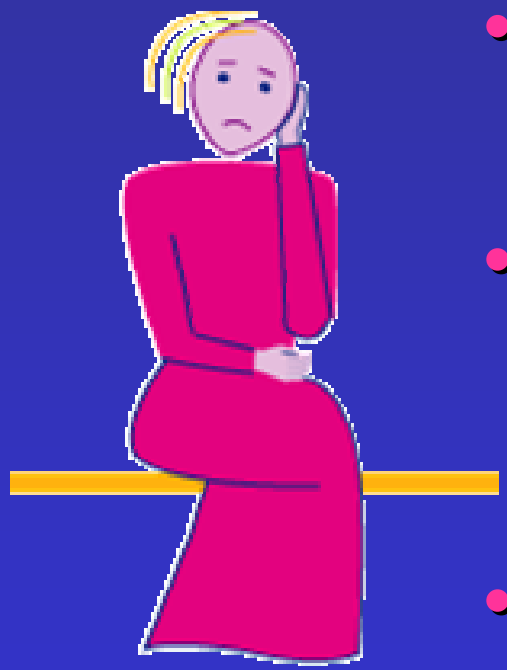
What is emergency contraception?

- Methods which women can use AFTER intercourse to PREVENT pregnancy

  (Consensus Statement, Bellagio, 1995)

- Prevents about 80% of pregnancies
- Does not replace regular contraception
- Does not cause abortion

Unwanted pregnancies result in unnecessary suffering every year

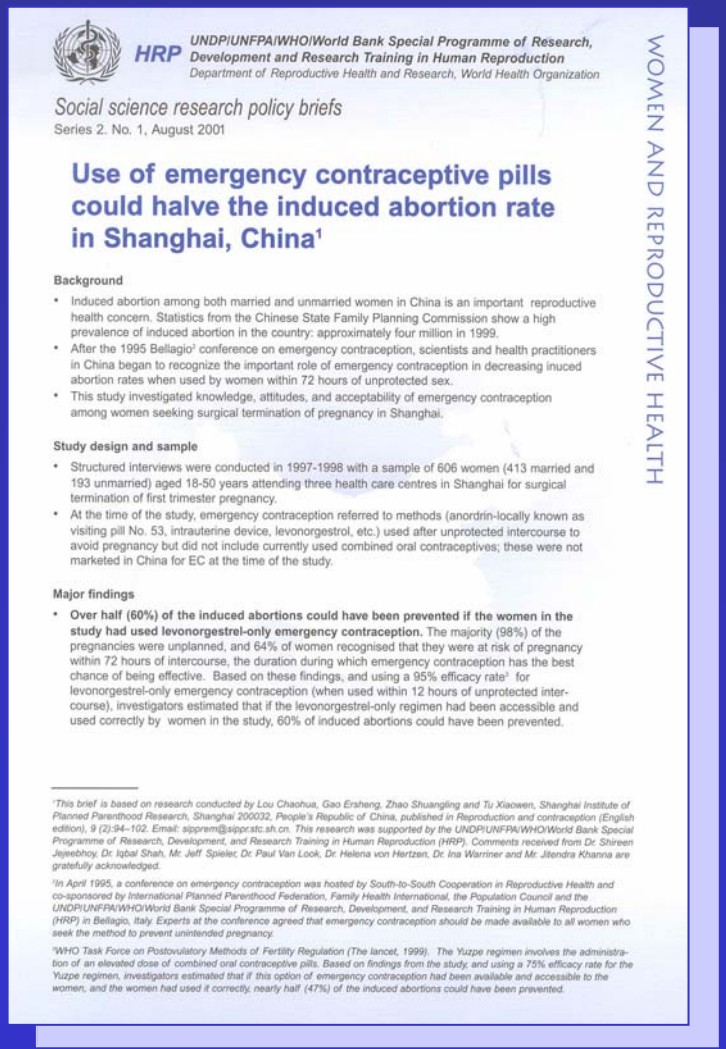


- 84 million unwanted pregnancies occur world-wide
- 46 million abortions take place, out of which 19 million are performed under unsafe conditions
- 70 000 women die as a consequence of unsafe abortion; 5 million suffer temporary or permanent disability

EC 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

Emergency contraception can help ...



HRP UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction
Department of Reproductive Health and Research, World Health Organization

WOMEN AND REPRODUCTIVE HEALTH

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Use of emergency contraceptive pills could halve the induced abortion rate in Shanghai, China[1]

Background

- Induced abortion among both married and unmarried women in China is an important reproductive health concern. Statistics from the Chinese State Family Planning Commission show a high prevalence of induced abortion in the country: approximately four million in 1999.
- After the 1995 Bellagio[2] conference on emergency contraception, scientists and health practitioners in China began to recognize the important role of emergency contraception in decreasing inuced abortion rates when used by women within 72 hours of unprotected sex.
- This study investigated knowledge, attitudes, and acceptability of emergency contraception among women seeking surgical termination of pregnancy in Shanghai.

Study design and sample

- Structured interviews were conducted in 1997-1998 with a sample of 606 women (413 married and 193 unmarried) aged 18-50 years attending three health care centres in Shanghai for surgical termination of first trimester pregnancy.
- At the time of the study, emergency contraception referred to methods (anordrin-locally known as visiting pill No. 53, intrauterine device, levonorgestrol, etc.) used after unprotected intercourse to avoid pregnancy but did not include currently used combined oral contraceptives; these were not marketed in China for EC at the time of the study.

Major findings

- **Over half (60%) of the induced abortions could have been prevented if the women in the study had used levonorgestrel-only emergency contraception.** The majority (98%) of the pregnancies were unplanned, and 64% of women recognised that they were at risk of pregnancy within 72 hours of intercourse, the duration during which emergency contraception has the best chance of being effective. Based on these findings, and using a 95% efficacy rate[3] for levonorgestrel-only emergency contraception (when used within 12 hours of unprotected intercourse), investigators estimated that if the levonorgestrel-only regimen had been accessible and used correctly by women in the study, 60% of induced abortions could have been prevented.

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[1]This brief is based on research conducted by Lou Chaohua, Gao Ersheng, Zhao Shuangling and Tu Xiaowen, Shanghai Institute of Planned Parenthood Research, Shanghai 200032, People's Republic of China, published in Reproduction and contraception (English edition), 9 (2):94–102. Email: siprem@sippr.stc.sh.cn. This research was supported by the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development, and Research Training in Human Reproduction (HRP). Comments received from Dr. Shireen Jejeebhoy, Dr. Iqbal Shah, Mr. Jeff Spieler, Dr. Paul Van Look, Dr. Helena von Hertzen, Dr. Ina Warriner and Mr. Jitendra Khanna are gratefully acknowledged.

[2]In April 1995, a conference on emergency contraception was hosted by South-to-South Cooperation in Reproductive Health and co-sponsored by International Planned Parenthood Federation, Family Health International, the Population Council and the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development, and Research Training in Human Reproduction (HRP) in Bellagio, Italy. Experts at the conference agreed that emergency contraception should be made available to all women who seek the method to prevent unintended pregnancy.

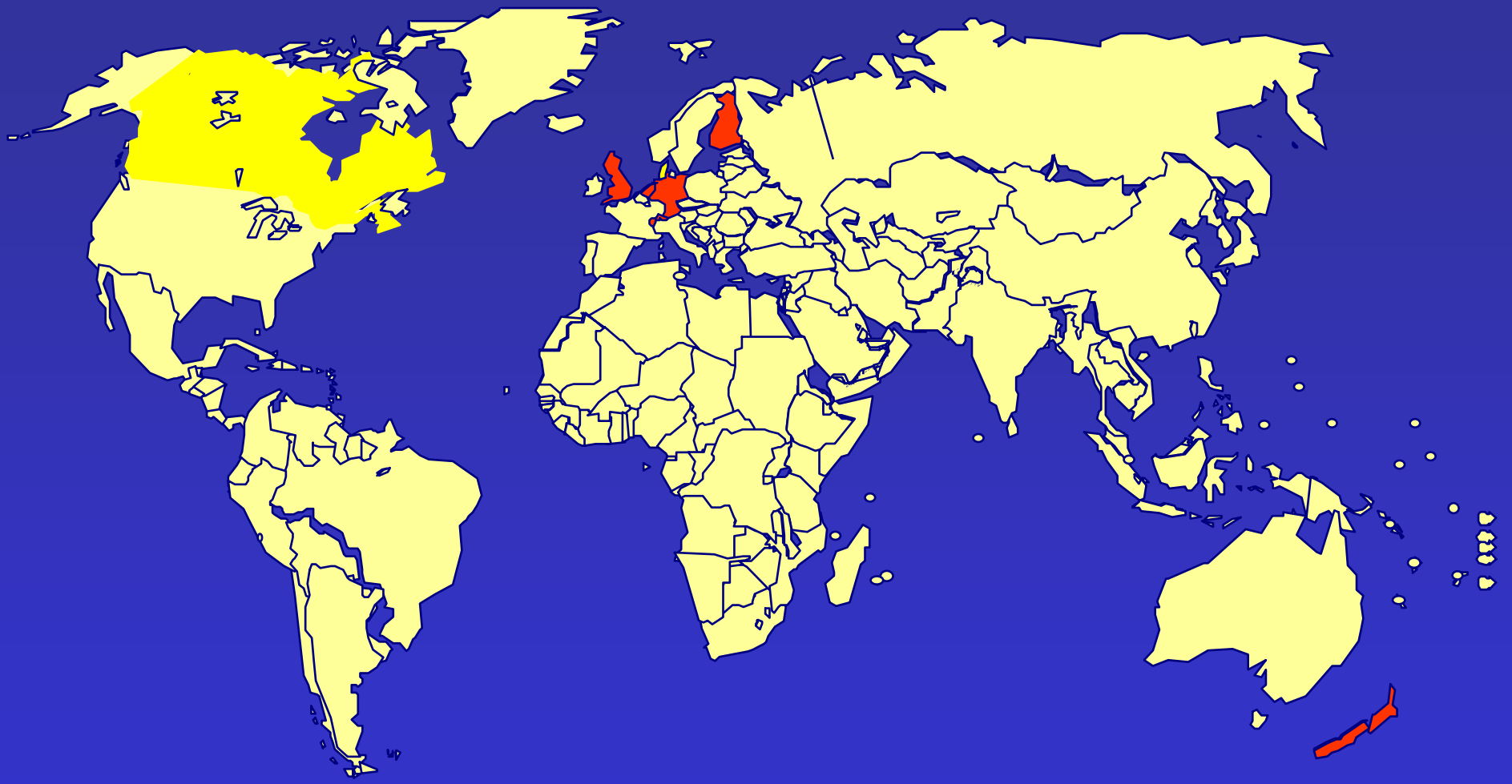
[3]WHO Task Force on Postovulatory Methods of Fertility Regulation (The lancet, 1999). The Yuzpe regimen involves the administration of an elevated dose of combined oral contraceptive pills. Based on findings from the study, and using a 75% efficacy rate for the Yuzpe regimen, investigators estimated that if this option of emergency contraception had been available and accessible to the women, and the women had used it correctly, nearly half (47%) of the induced abortions could have been prevented.

Use of emergency contraception could halve the induced abortion rate in Shanghai, China

Methods of EC until 1998

- Ethinylestradiol/levonorgestrel (Yuzpe regimen) (1974)
  - nausea 50%, vomiting 20%, efficacy approx. 74%
- Copper-T intrauterine device (1970s)
  - often unsuitable, requires trained providers
  - painful at insertion, risk of PID

YUZPE REGIMEN BEFORE 1995



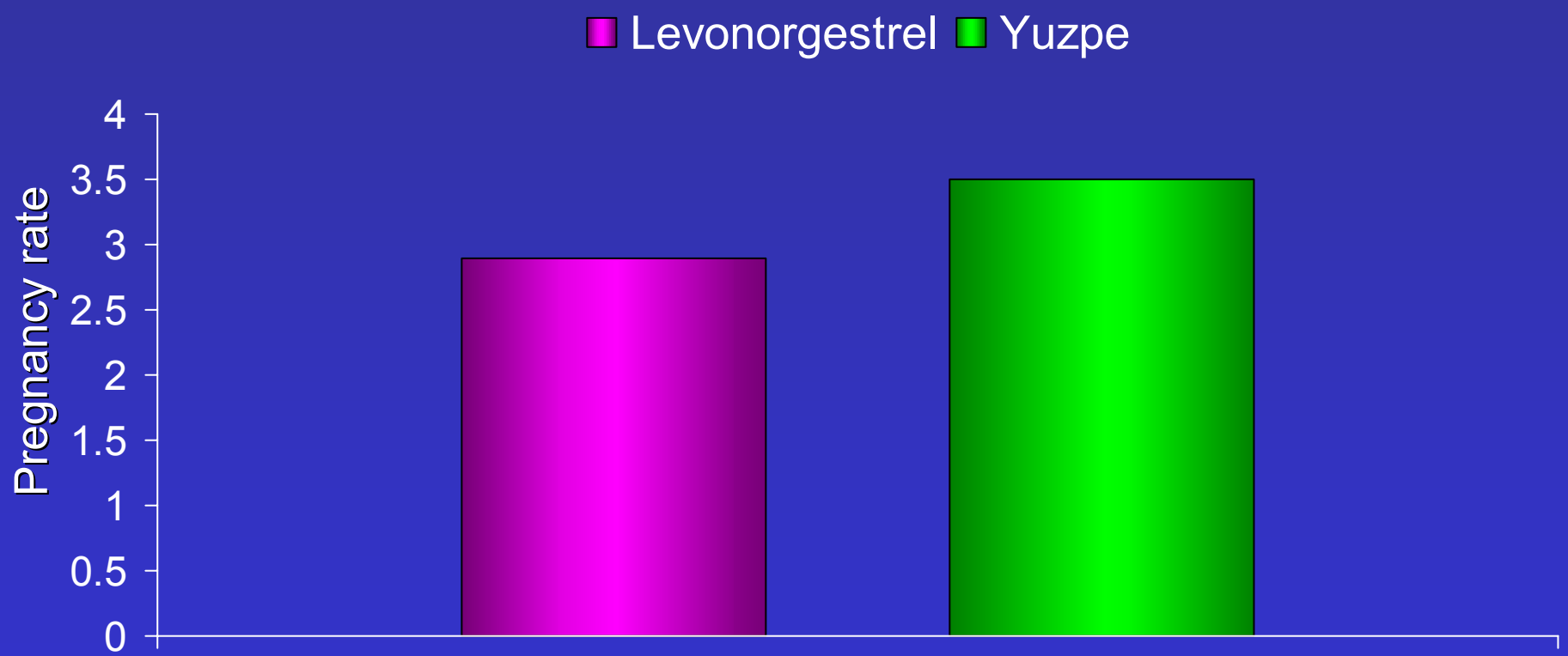
HRP's new approaches for emergency contraception

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

From single centre studies to multinational research

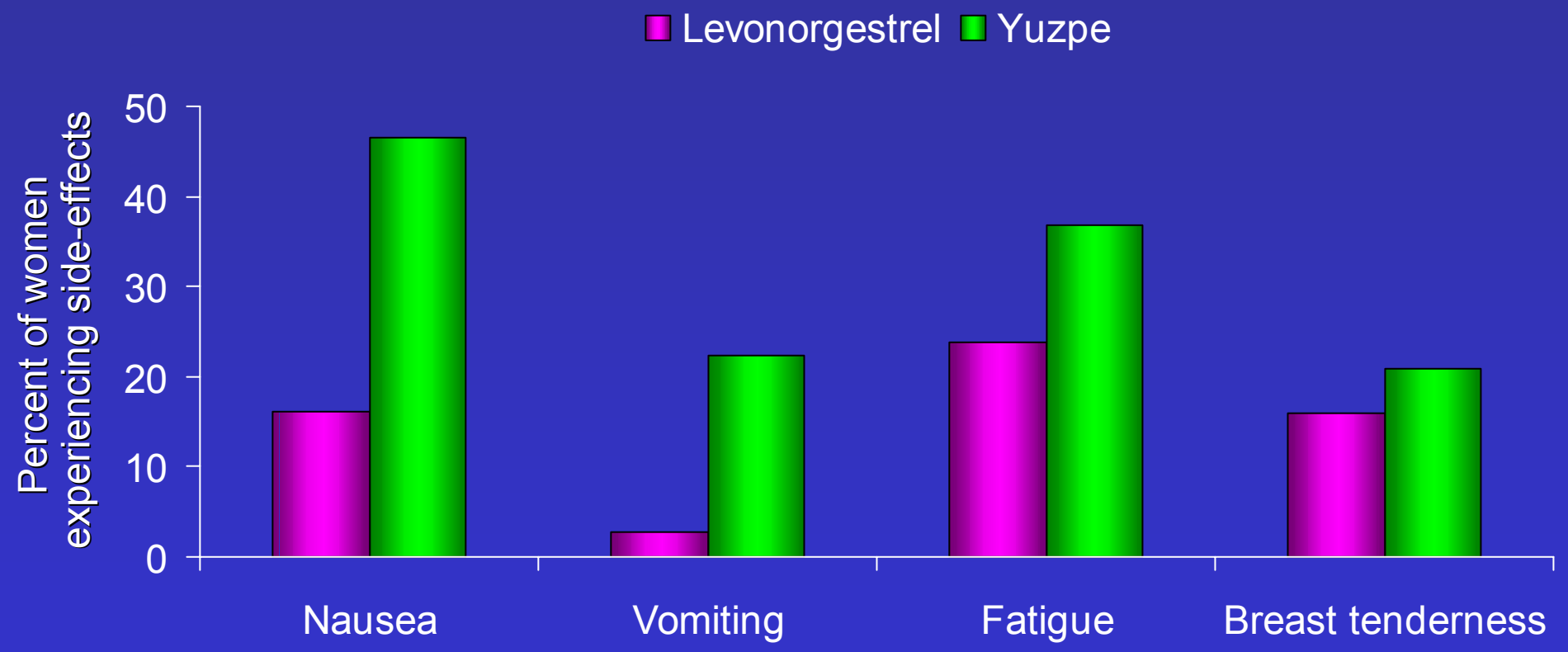
- Randomized comparative trial of levonorgestrel and Yuzpe regimens in Hong Kong
- Randomized comparative trial of mifepristone and Yuzpe regimens in Edinburgh and Manchester
- Multinational studies including 27 centres in 16 countries

No difference in efficacy in Hong Kong study



(Ho and Kwan, 1993)

Significant difference in side-effects!

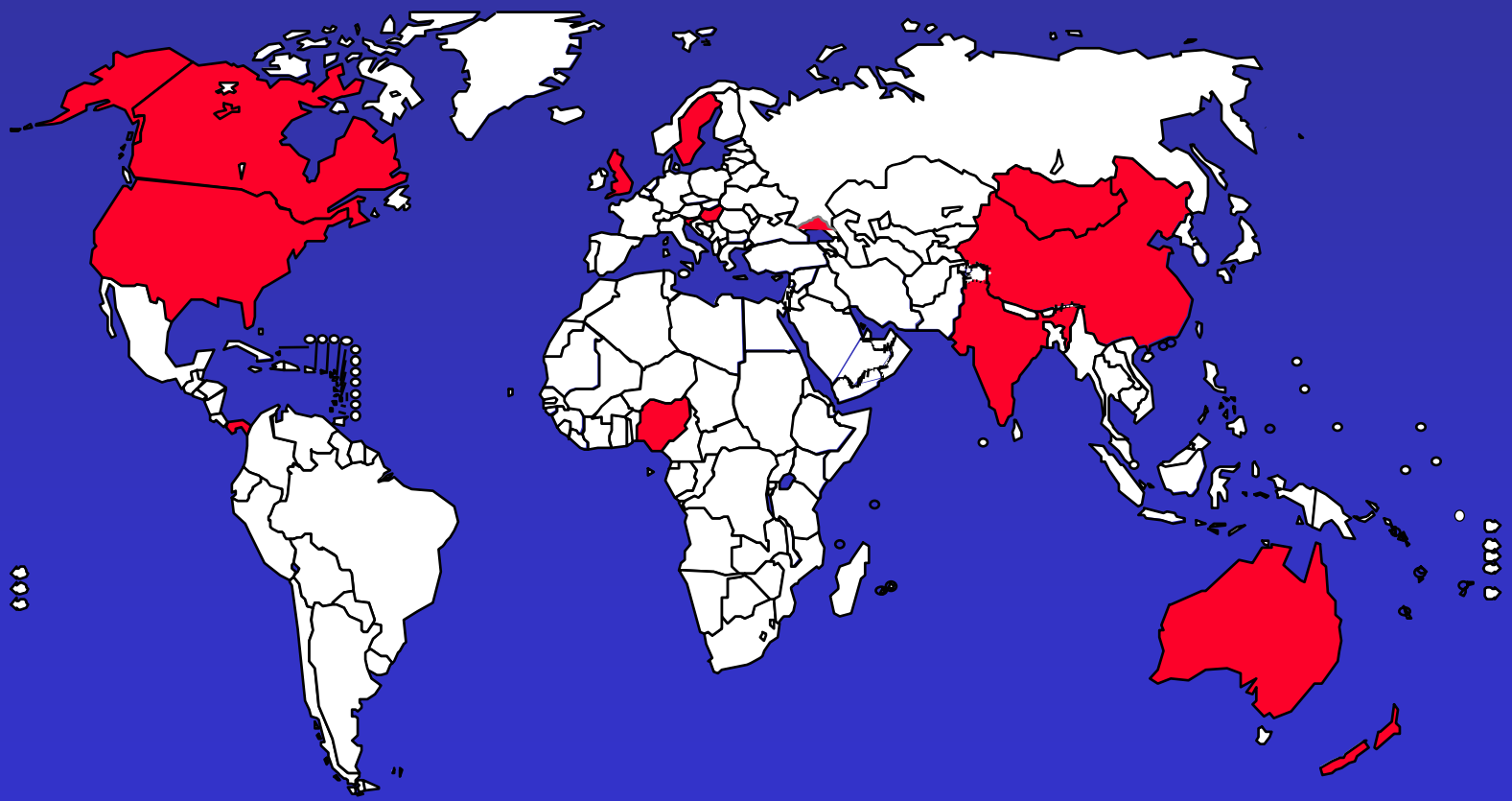


(Ho and Kwan, 1993)

Multicentre confirmation of the findings from Hong Kong study

- Two doses of 0.75 mg of levonorgestrel given 12 hours apart vs. Yuzpe regimen
- But start of treatment up to 72 hours

Double-blind randomized comparison of levonorgestrel vs Yuzpe in 14 countries



(WHO 1998)

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Press Release WHO/58
7 August 1998

EMBARGOED UNTIL 7 AUGUST
1998 AT 00.01 H GMT

LEVONORGESTREL FOR EMERGENCY CONTRACEPTION IS MORE EFFECTIVE AND HAS FEWER SIDE-EFFECTS THAN THE YUZPE REGIMEN

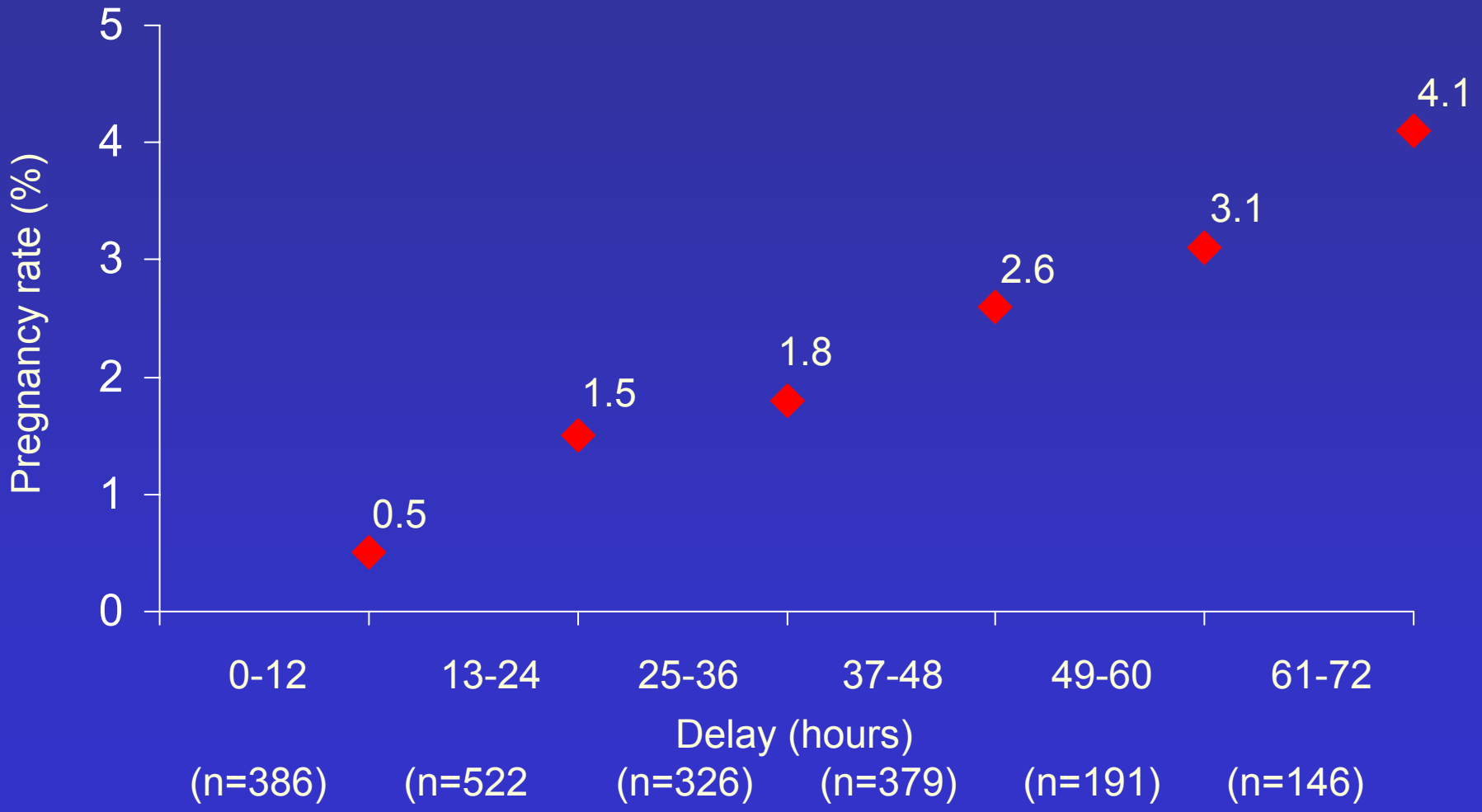
In a paper published in the 8 August issue of the journal *The Lancet*, researchers working with the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) confirm that the use of levonorgestrel alone for emergency contraception is more effective and produces side-effects in considerably fewer users than the Yuzpe regimen – currently the most widely used method for such contraception.

Lower pregnancy rate after LNG

Group	Number of women	Observed pregnancies	Pregnancy rate	95% CI
Yuzpe	979	31	**3.2%**	(2.2, 4.5)
LNG	976	11	**1.1%**	(0.6, 2.0)

The difference in pregnancy rate was statistically significant

Pregnancy rates and treatment delay



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)

HRP's work catalysed global EC activities

- International Consortium of Emergency Contraception, established in 1996
- The registration of levonogrestrel for EC has gone from 4 to >80 countries in four years
- Stimulation of research
- Enhanced funding to the field

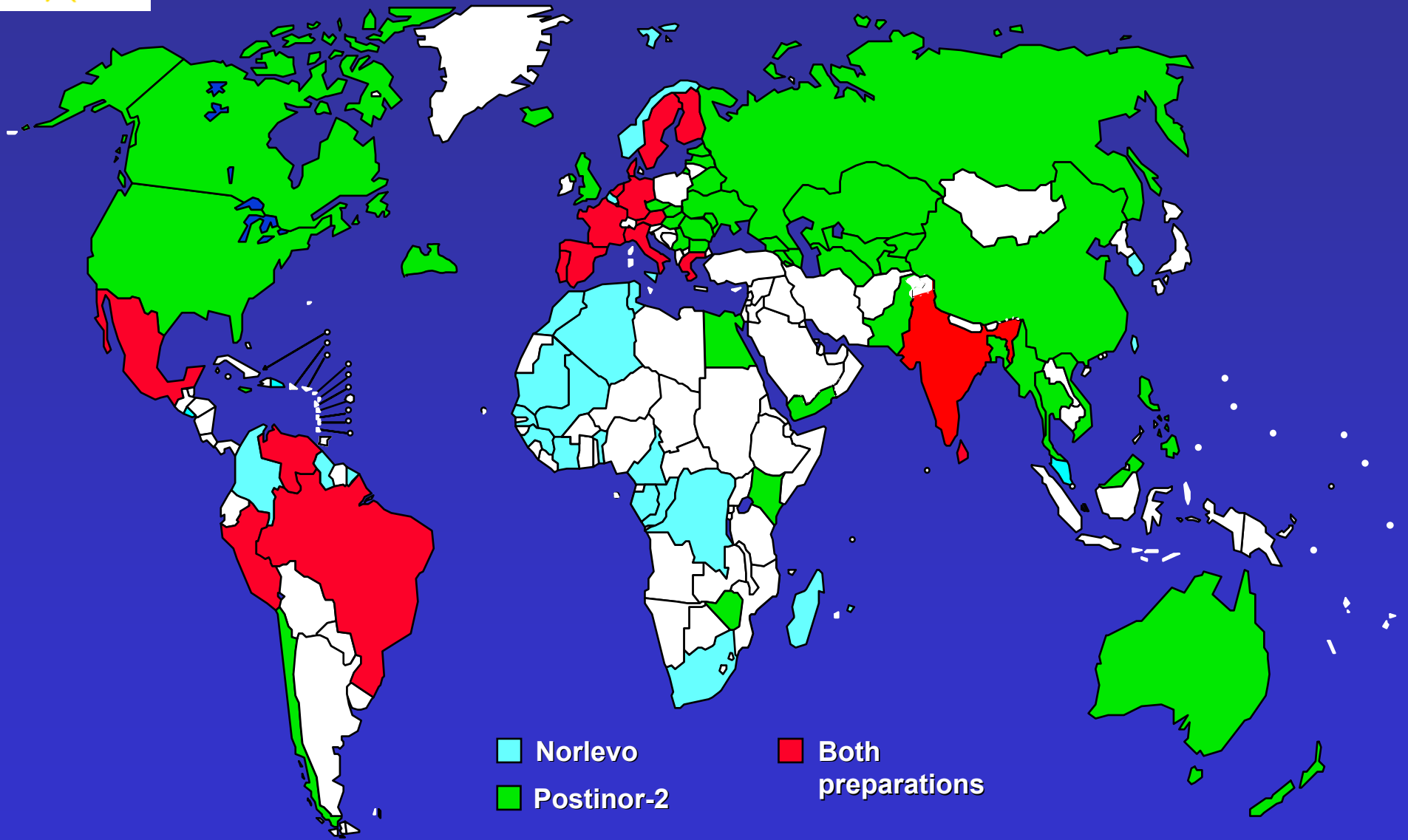
Consortium on emergency contraception

1. Collaborative agreement with pharmaceutical industry
   - e.g. preferential public-sector pricing
2. Development of standard medical and service delivery guidelines for EC
3. Nine steps to assist countries to develop strategies for introducing EC


2 Tabl.
POSTINOR-2™
Levonorgestrel


NORLEVO®
750 microgrammes
Lévonorgestrel
2 Comprimés
Voie Orale

Availability of levonorgestrel preparations for emergency contraception (as of June 2002)

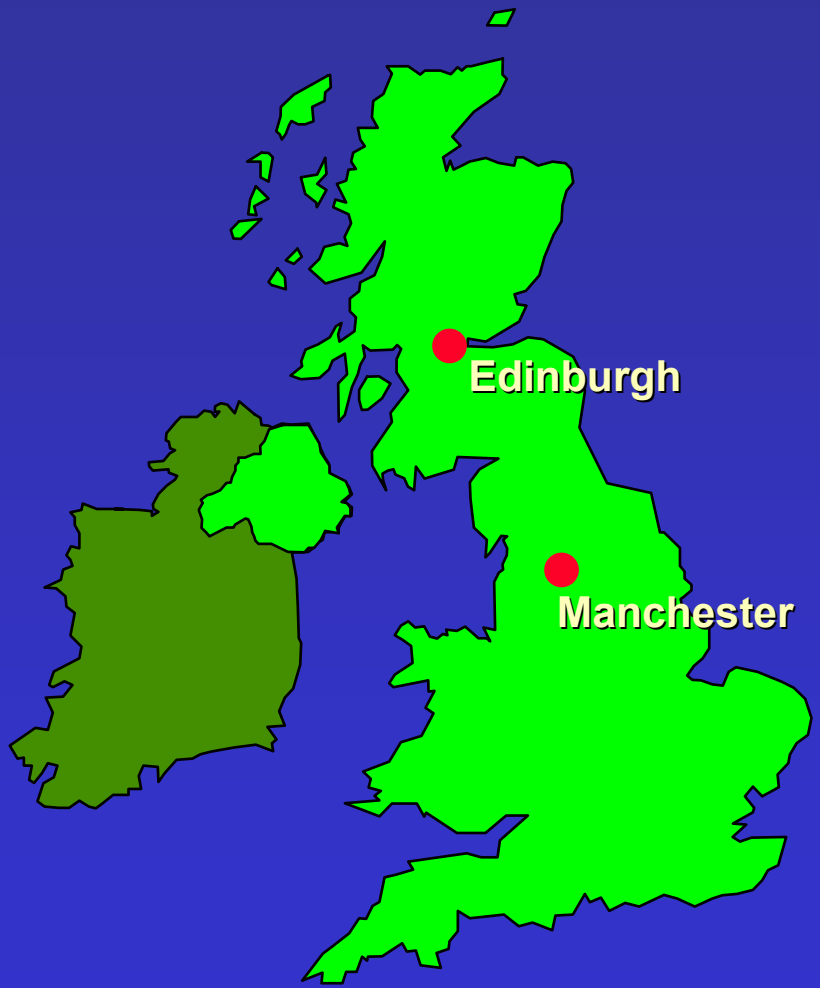


Research highly acknowledged also scientifically

- *The Lancet* 1998; 352: 426-433
- *The Lancet* 1999; 353: 697-702
- *The Lancet* 1999; 353: 721
- *The Lancet* 2002; 360: 1803-1810


TIME
The Pill That Changes Everything

Mifepristone vs Yuzpe regimen compared in the UK (600 mg - 72 hours)



Efficacy of emergency contraception

	Mifepristone	Yuzpe regimen
Number of women treated	597	589
Expected number of pregnancies	35	34
Observed number of pregnancies	0 (3)	9

(after Glasier et al., 1992 and Webb et al., 1992)

Emergency contraception using mifepristone (600 mg, 50 mg, 10 mg - 120 hours)

Efficacy of three doses of mifepristone in emergency contraception

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

* according to Trussell et al., Contraception 1998; 57:363-69

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

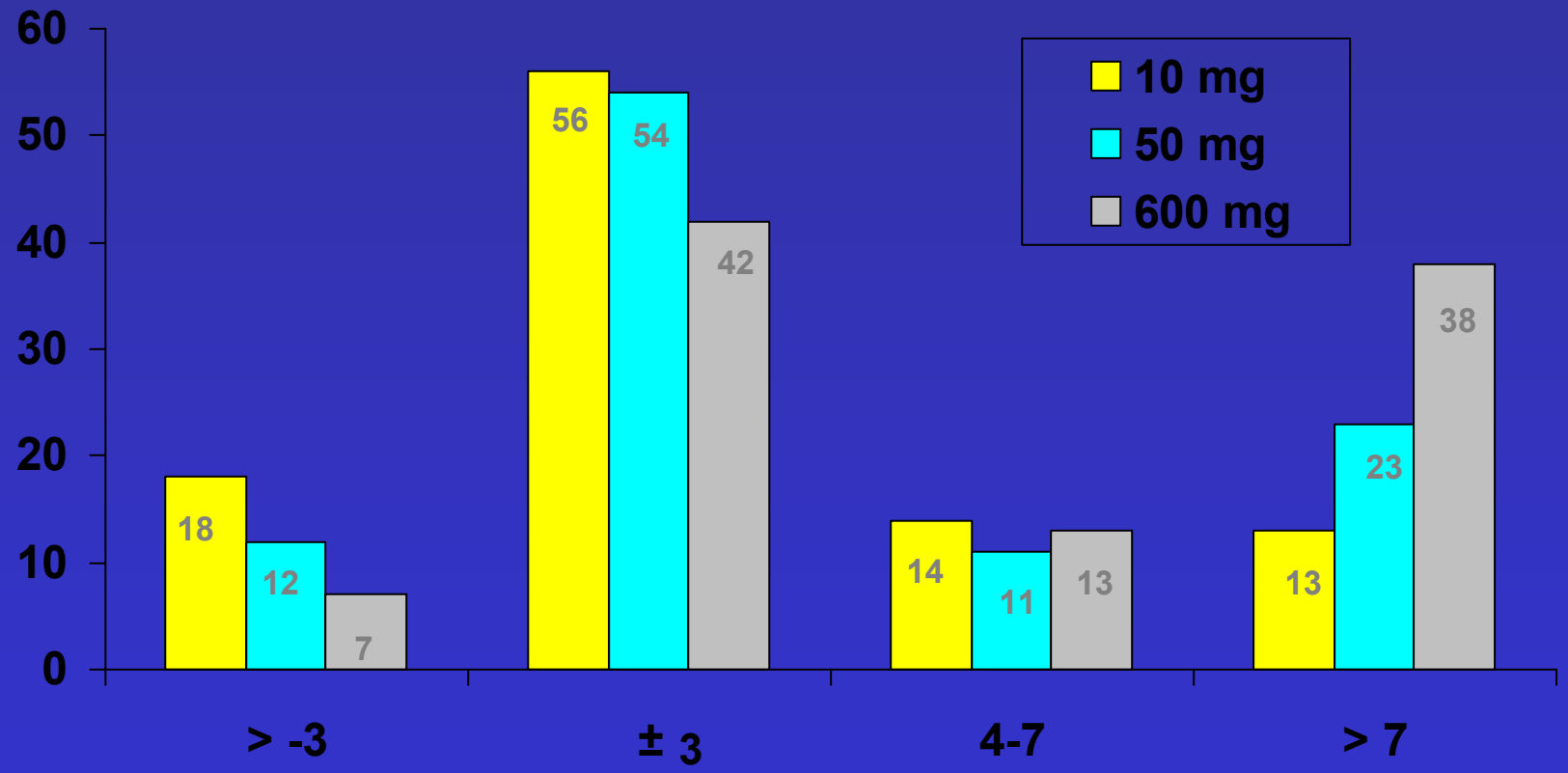
Side-effects* of three doses of Mifepristone in emergency contraception

Side effect	10 mg (n=562)	50 mg (n=557)	600 mg (n=558)	p value **
Nausea	17%	15%	20%	NS
Vomiting	2%	1%	2%	NS
Headache	13%	14%	11%	NS
Dizziness	12%	10%	15%	NS
Fatigue	20%	21%	24%	0.06
Bleeding disturbances	18%	23%	36%	< 0.01

* percentage rates (recorded for 7 days after treatment)

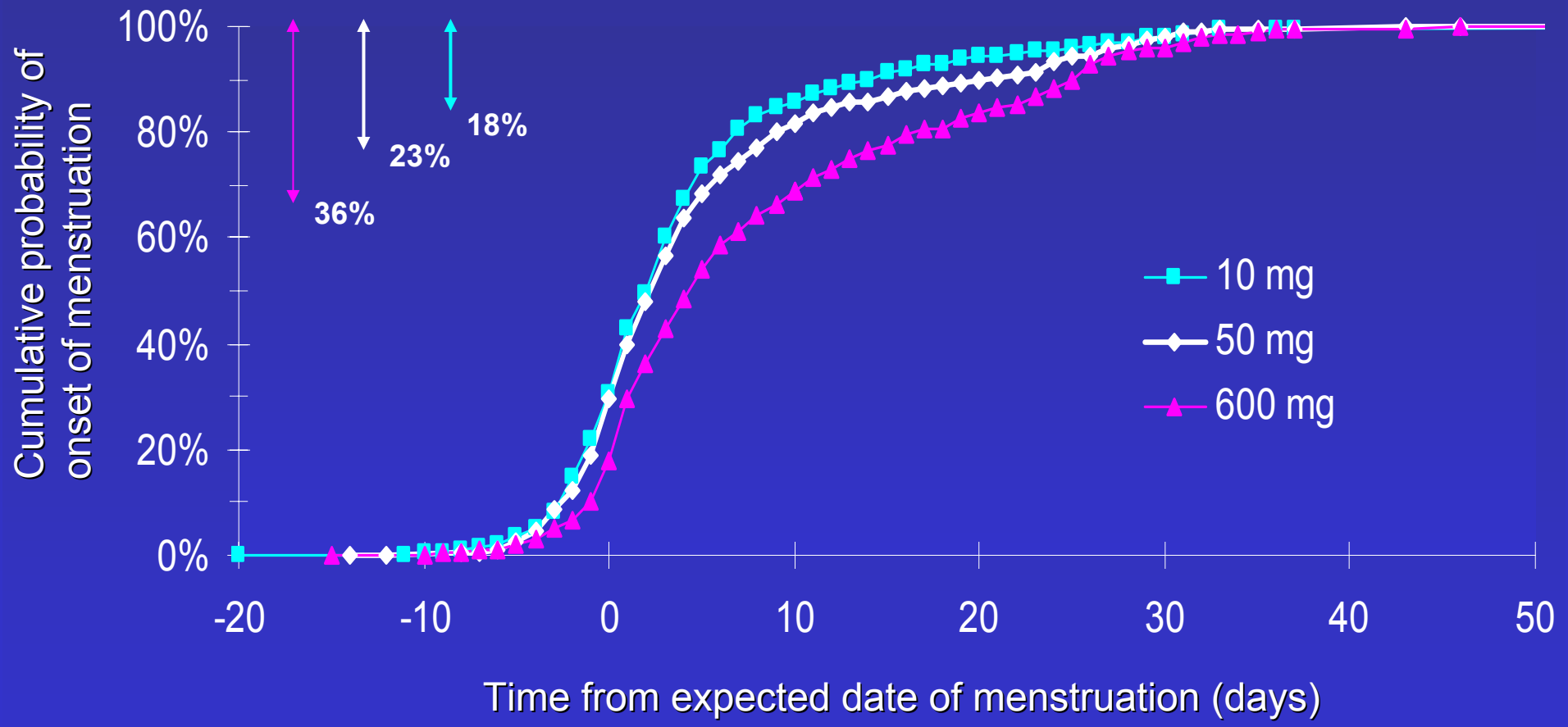
** non-zero correlation between mifepristone dose and occurrence of side-effects

TIMING OF MENSES AFTER MIFEPRISTONE AMONG 521 CHINESE WOMEN



(HRP Project 92903)

Delay of menses by group: cumulative probabilities of onset of menstruation in relation to time from expected date of menstruation



LEVONORGESTREL 0.75 mg

Pharmacokinetics after oral administration:

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

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

Mifepristone and levonorgestrel do not differ in efficacy

Group	Observed pregnancies /total	Rate
Mifepristone	21/1359	1.55%
LNG 1.5 mg x 1	20/1356	1.47%
LNG 0.75 mg x 2	24/1356	1.77%
All LNG	44/2712	1.62%

Side-effects within 7 days after treatment

Side effect	Mifepristone	LNG 1.5 mg x 1	LNG 0.75 mg x 2	p-value
Nausea	14.4%	13.9%	14.6%	NS
Vomiting	0.9%	1.4%	1.4%	NS
Headache	10.3%	10.4%	9.6%	NS
Bleeding	18.9%	31.3%	31.3%	<.0001
Delay of menses >7 days	8.9%	4.6%	4.7%	<.0001

(Mifepristone and two LNG regimens)

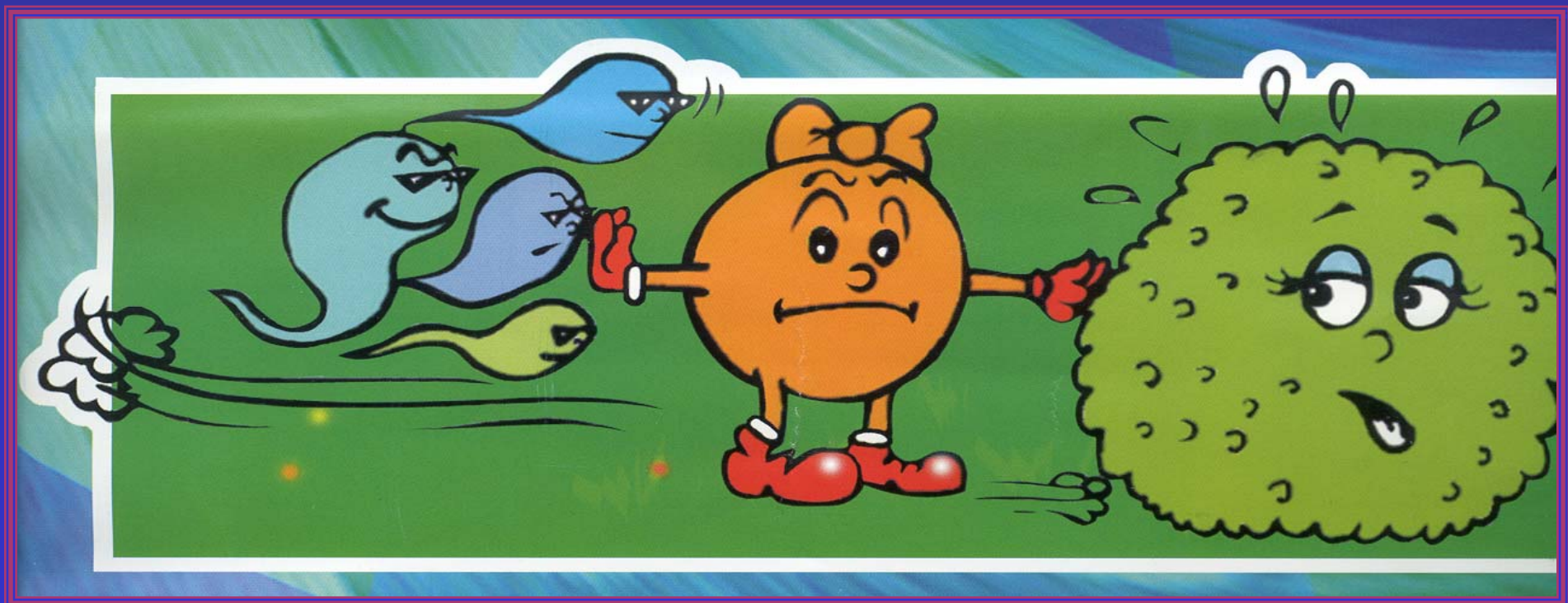
High risk of pregnancy after Mifepristone

Intercourse without contraception after treatment

Group	NO		YES	
	Observed pregnancies /total	Rate	Observed pregnancies /total	Rate
Mifepristone	**12/1318**	**0.9%**	**9/41**	**22.0%**
LNG	**40/2651**	**1.5%**	**4/61**	**6.6%**

Interaction p=0.0226

(Mifepristone and two LNG regimens)



Tremendous advancement in the development of EC in the Past Decade

- Technical developments
- Provision of guidance to policy makers
- Support for introduction activities

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