EMERGENCY CONTRACEPTION

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What is emergency contraception?

- Methods which women can use AFTER intercourse to PREVENT pregnancy

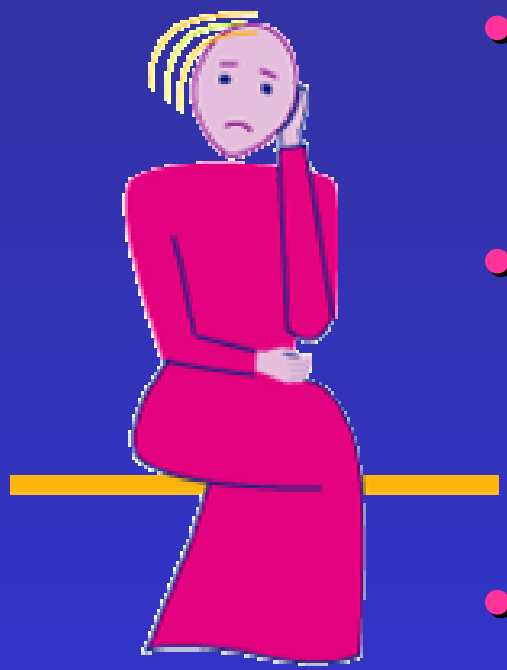
  (Consensus Statement, Bellagio, 1995)

- For occasional / emergency use only!
- Less effective than regular contraception
- Estimated to prevent about 50-99% of pregnancies
- Does not cause abortion

EC - a second chance to prevent pregnancy

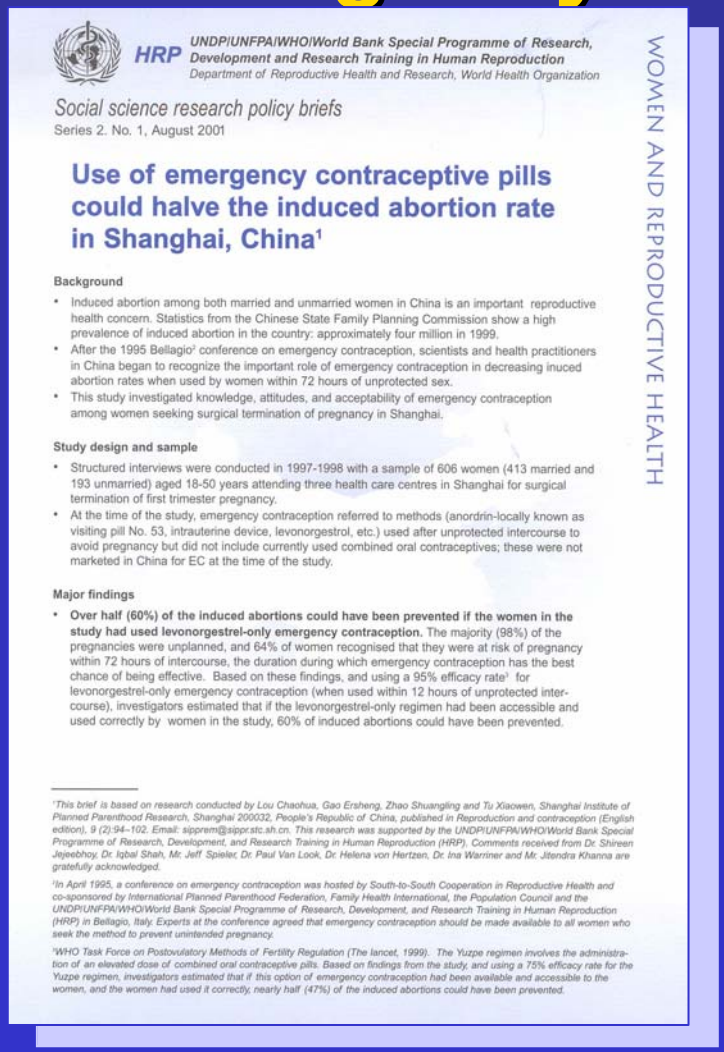
- when no contraceptive was used
- when there is a contraceptive failure or misuse, including:
  - condom breakage, slippage or misuse
  - 2 or more consecutive missed oral contraceptive pills
  - late for contraceptive injection
  - failed coitus interruptus, etc
- in case of sexual assault

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

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@sippor.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.

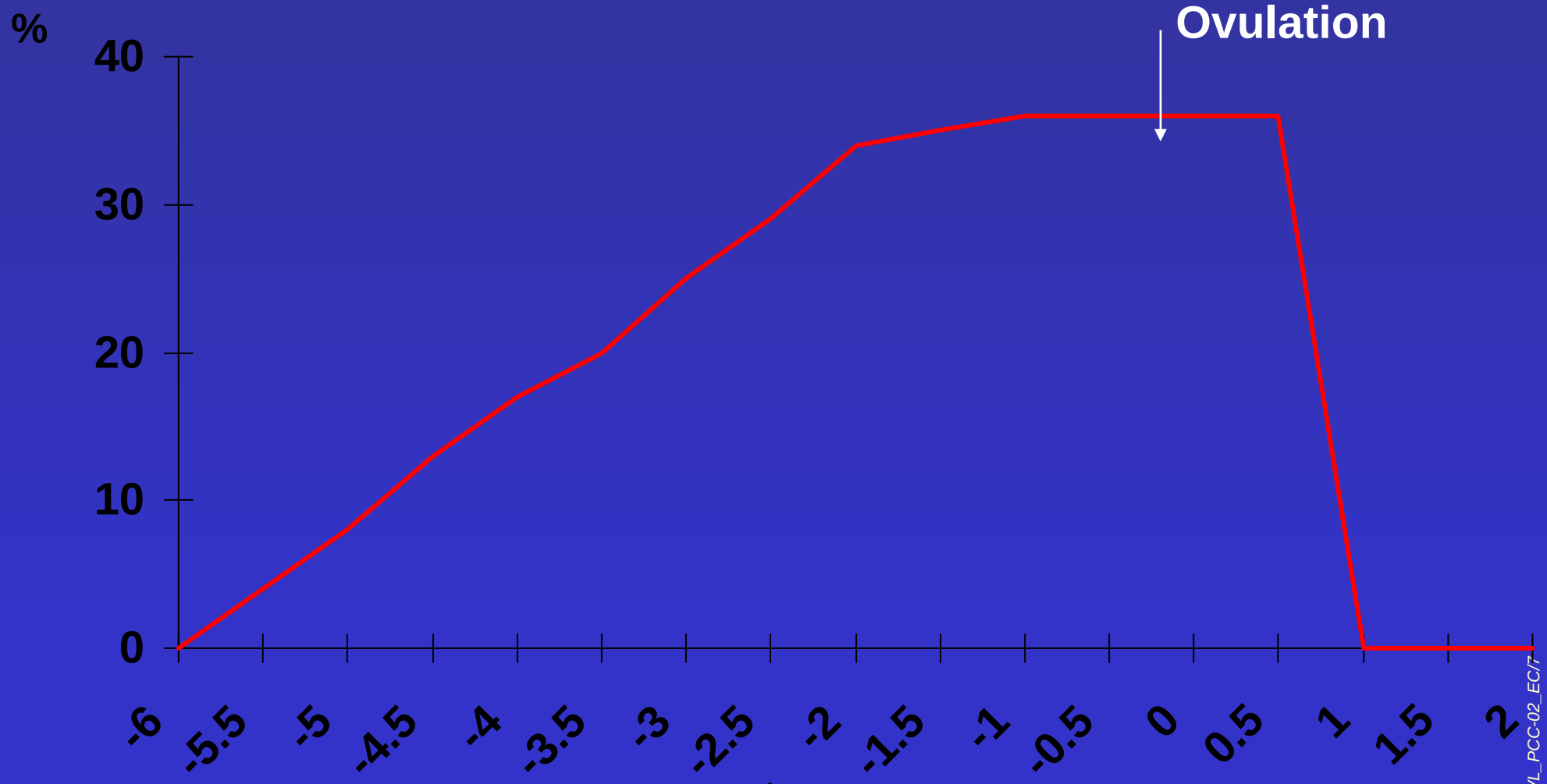
[3]WHO Task Force on Postovulatory Methods of Fertility Regulation (The lancet, 1999). The Yuzpe regimen involves the administration of an elevated dose of combined oral contraceptive pills. Based on findings from the study, and using a 75% efficacy rate for the Yuzpe regimen, investigators estimated 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

PREGNANCY RISK ?

If 100 women each have one act of intercourse without contraception during a cycle it is estimated that 8 of them will become pregnant, i.e. pregnancy risk per act is 8%

Conception probability by day of intercourse in relation to ovulation



(de Wilcox et al., 1995)

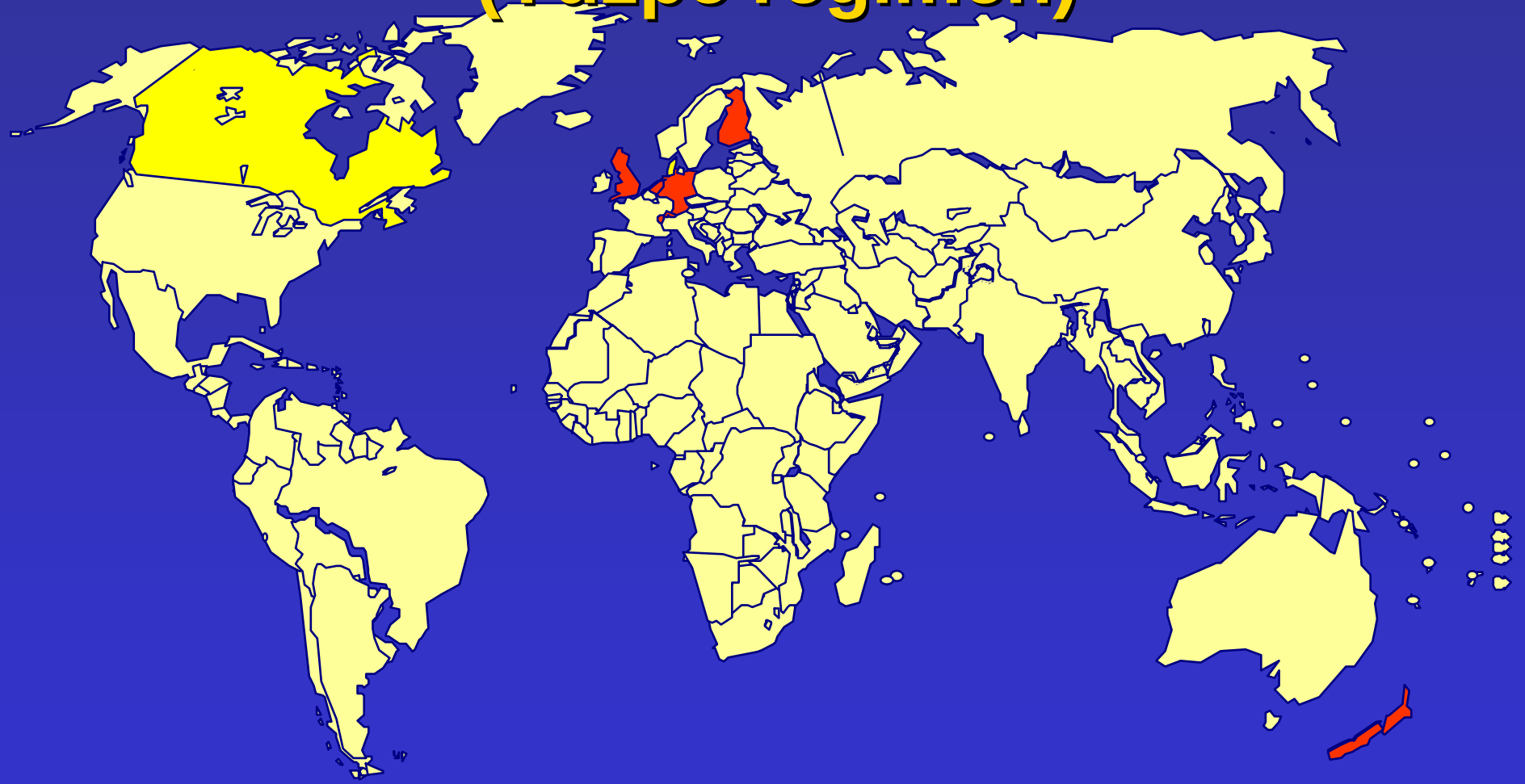
There are six fertile days in which a single coitus can result in pregnancy. 83% of those days precede ovulation by one to five days

Wilcox et al NEJM 333:1517,1995

Methods of EC

- **LEVONORGESTREL 1.5 mg**
  a.s.a.p. up to 72-120 h (85%)
- **ETHINYLESTRADIOL/LEVONORGESTREL**
  a.s.a.p. up to 72-120 h (74%)
- **COPPER-T IUD** up to >120 h (99-100%)
- **MIFEPRISTONE 10 MG** up to 120 h (85%)

Registration of EC until late 1990s (Yuzpe regimen)



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

RESEARCH ON LEVONORGESTREL

- **Ho PC and Kwan MS 1993 (LNG 0.75 mg x2 at 12-hour interval/Yuzpe, up to 48 hours)**
- **WHO 1998 (LNG/Yuzpe up to 72 hours)**
- **WHO 2002 (LNG 0.75 mg x 2 at 12-h interval / one dose of 1.5mg / mifepristone 10 mg up to 120 hours)**

LEVONORGESTREL / 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.

(Lancet, 352:428-33)

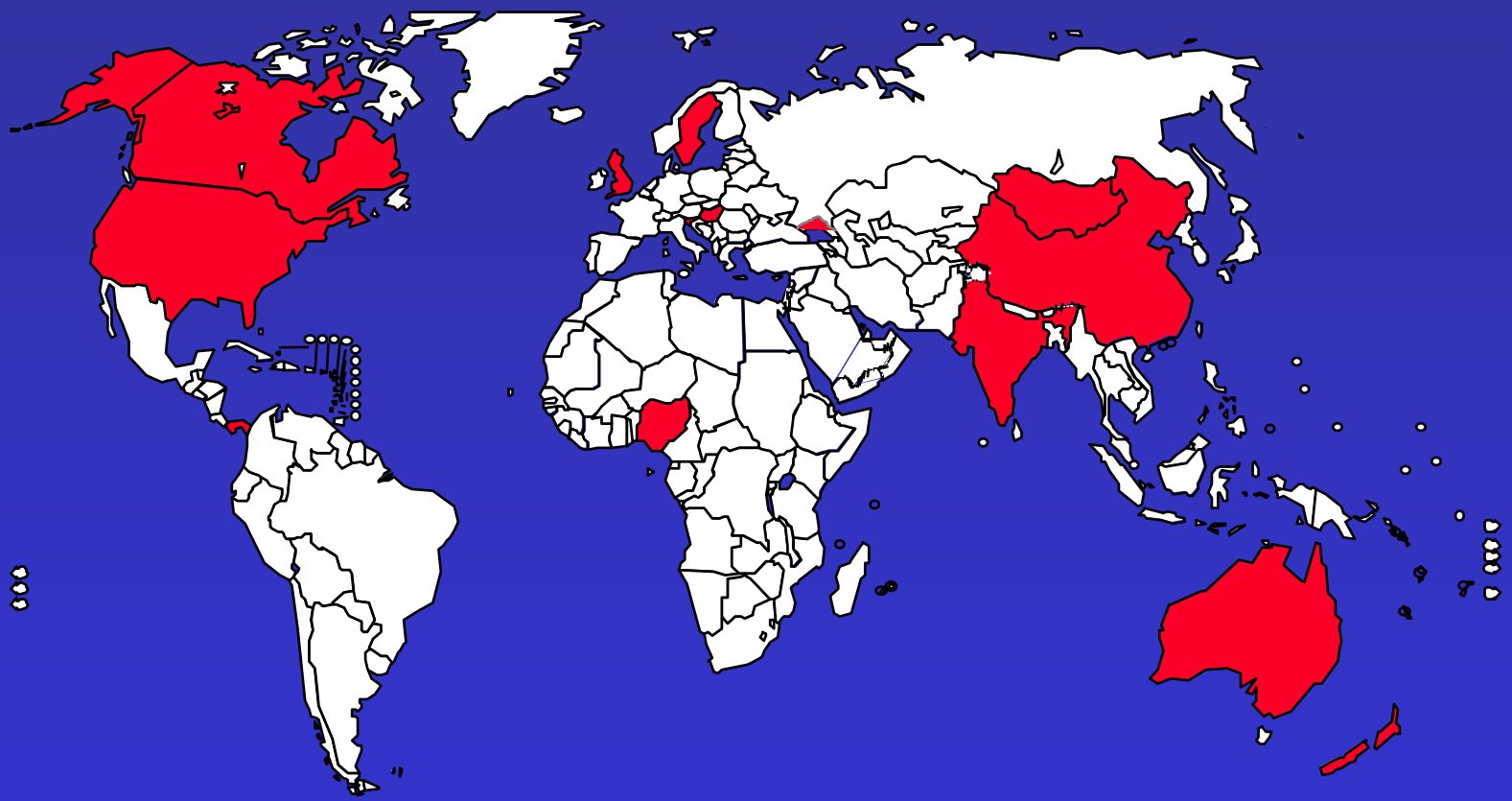
LEVONORGESTREL / YUZPE regimen

Design

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

(Lancet, 352:428-33)

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



(WHO 1998)

LEVONORGESTREL / YUZPE regimen

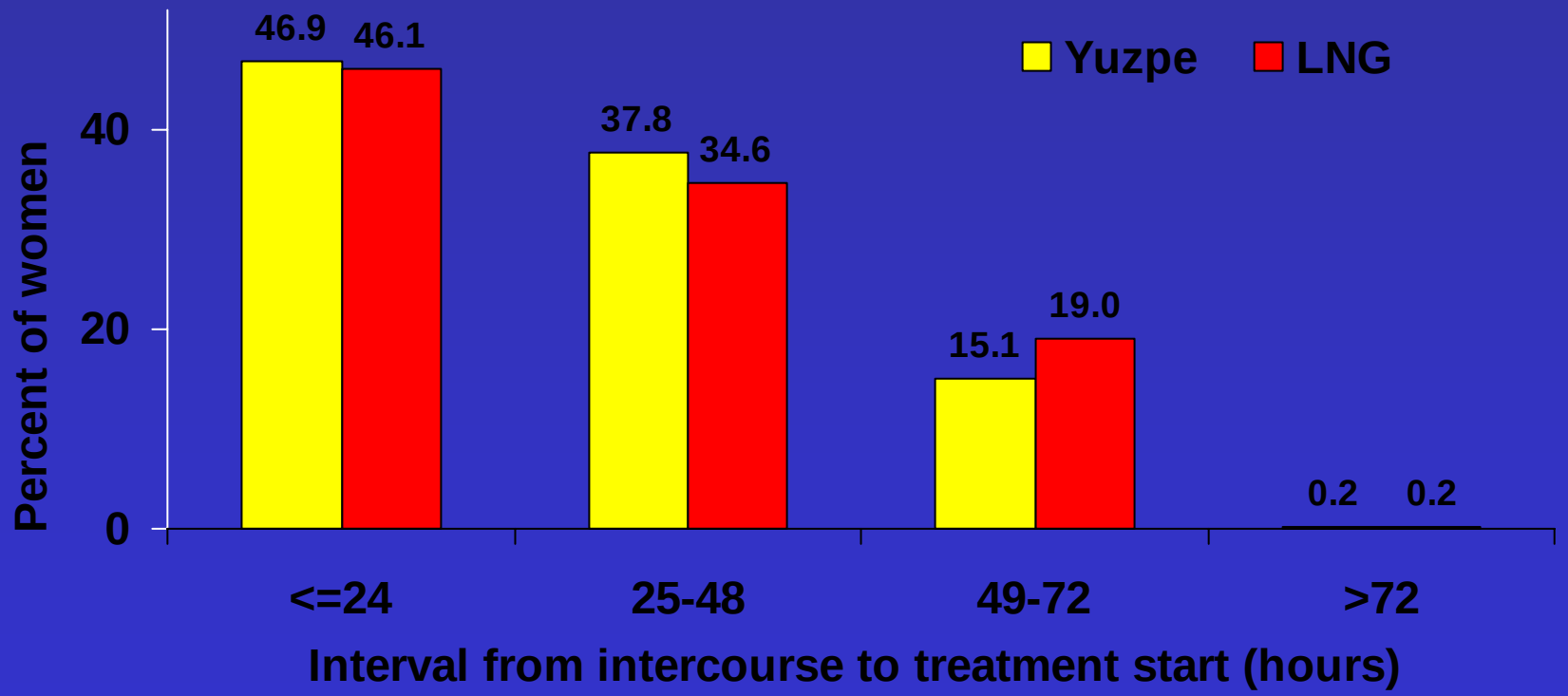
Reason for requesting emergency contraception

	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 / YUZPE regimen

Delay in taking emergency contraceptive



(Lancet, 352:428-33)

Efficacy of Emergency Contraception

1. ‘Failure rate’ = % of women pregnant after EC

2. Proportion of pregnancies prevented =

$$1 - \frac{\text{no. pregnancies observed after treatment}}{\text{no. pregnancies expected without treatment}}$$

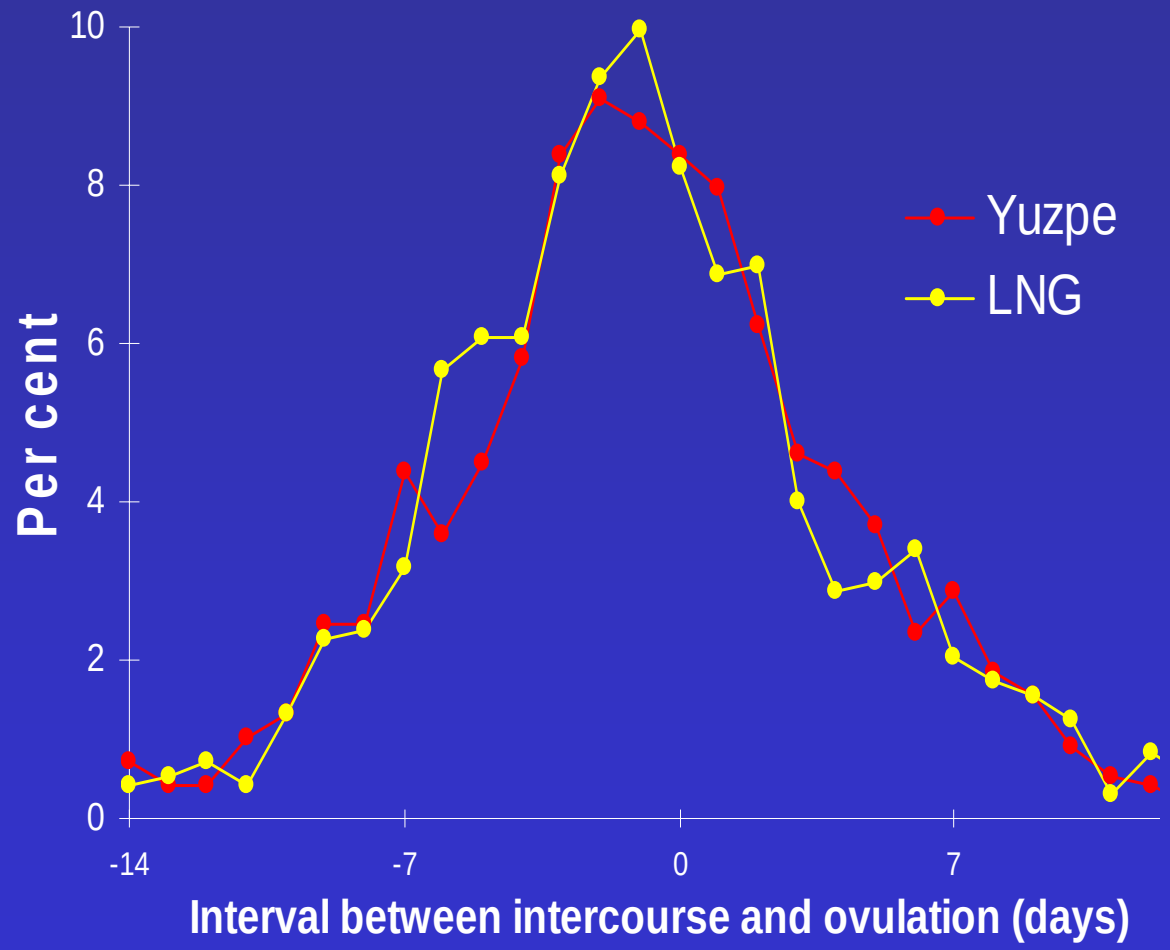
Note: women may not be at risk of pregnancy

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

Day of intercourse in relation to estimated day of ovulation



Problems with efficacy calculations

- There are no placebo controlled trials
- Efficacy is based on estimations = real risk of pregnancy is unknown
  - real cycle day of intercourse uncertain
  - real number of acts of intercourse before and after EC
  - assumed that both partners are fertile

Levonorgestrel versus the Yuzpe regimen

Efficacy: prevented fraction

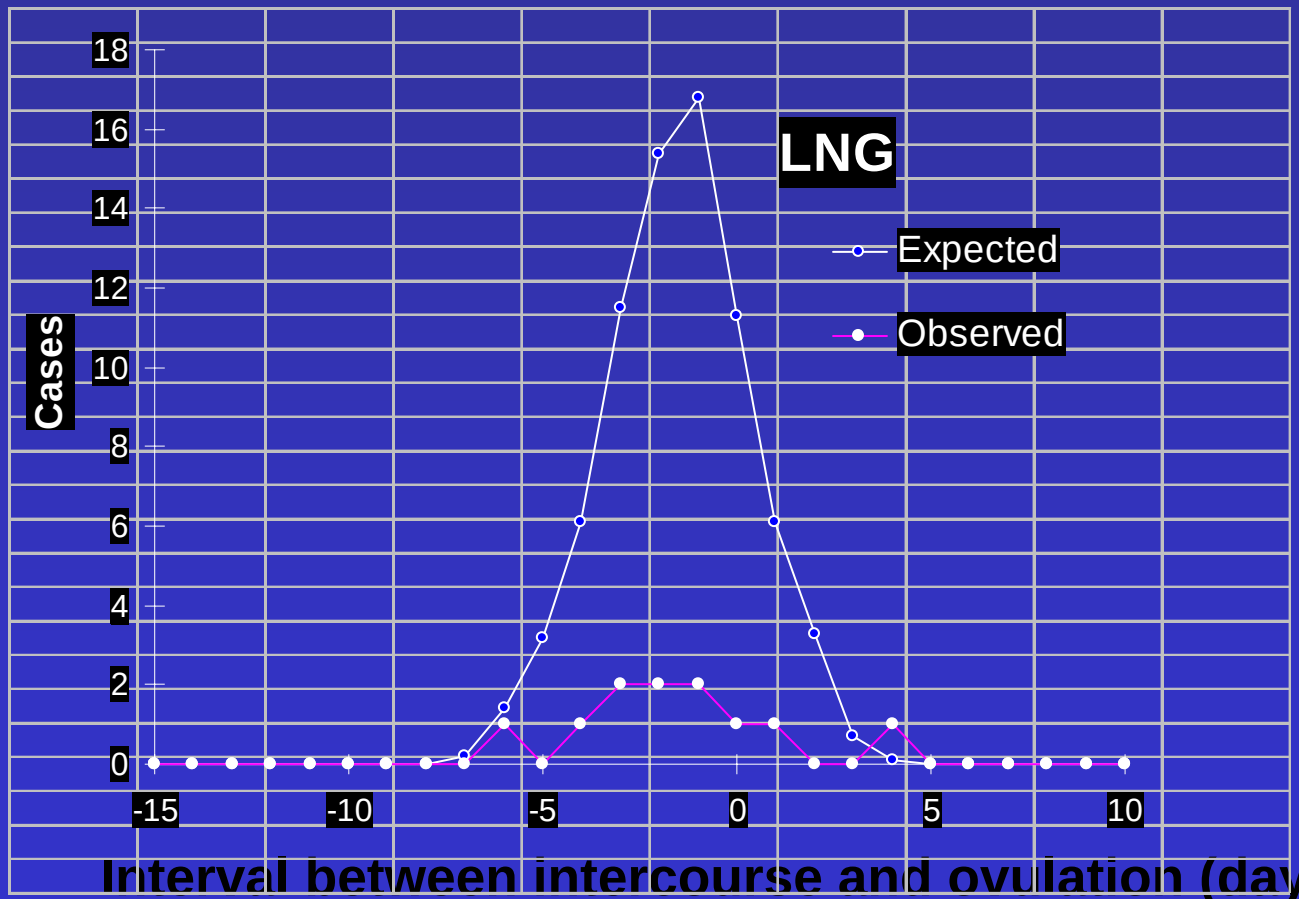
Group	No. of women	No. of pregnancies		Efficacy**	
		Observed	Expected*	(%)	95% CI
Yuzpe	979	31	74.2	58	(41, 72)
LNG	976	11	76.3	86	(74, 93)

* Using Dixon's estimates of conception probabilities

** Prevented fraction

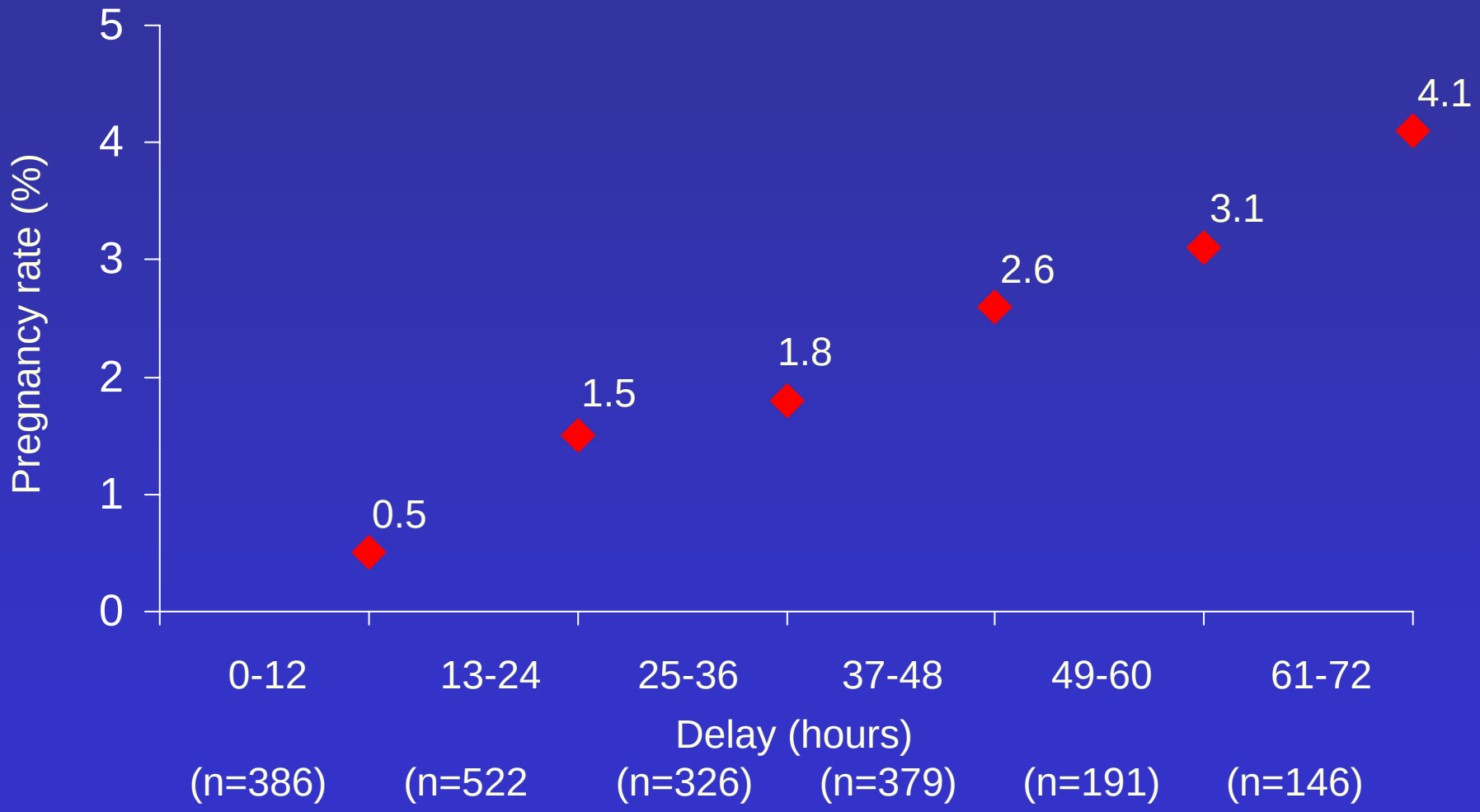
(Lancet, 352:428-33)

Observed vs expected pregnancies by day of intercourse



(Lancet, 352:428-33)

Pregnancy rates and treatment delay



Which regimen works best -> comparison of treatments

- To undertake large randomized comparative trials

Absolute effectiveness of each treatment is not known, but the comparison is valid

LEVONORGESTREL / 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)

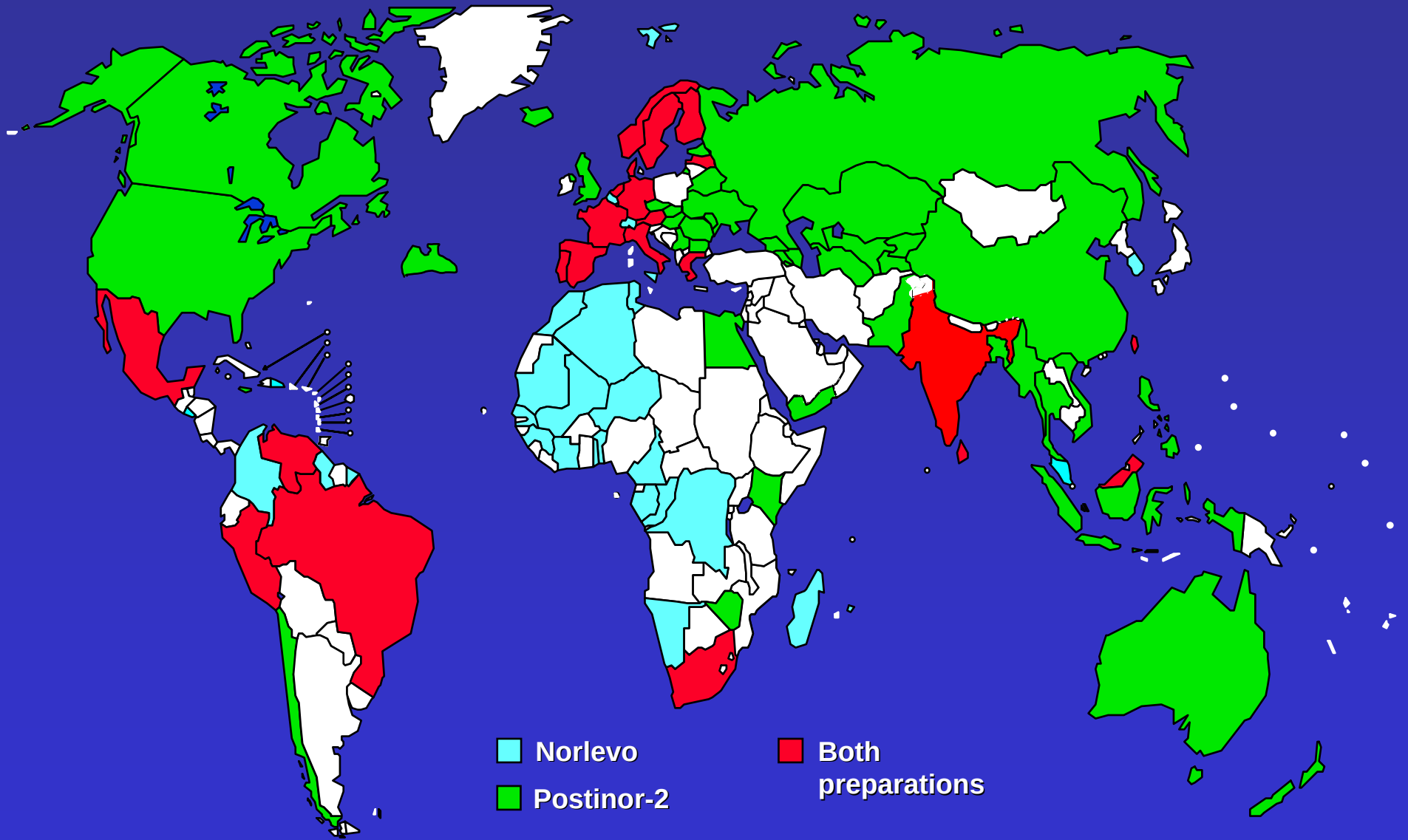
LEVONORGESTREL / YUZPE regimen

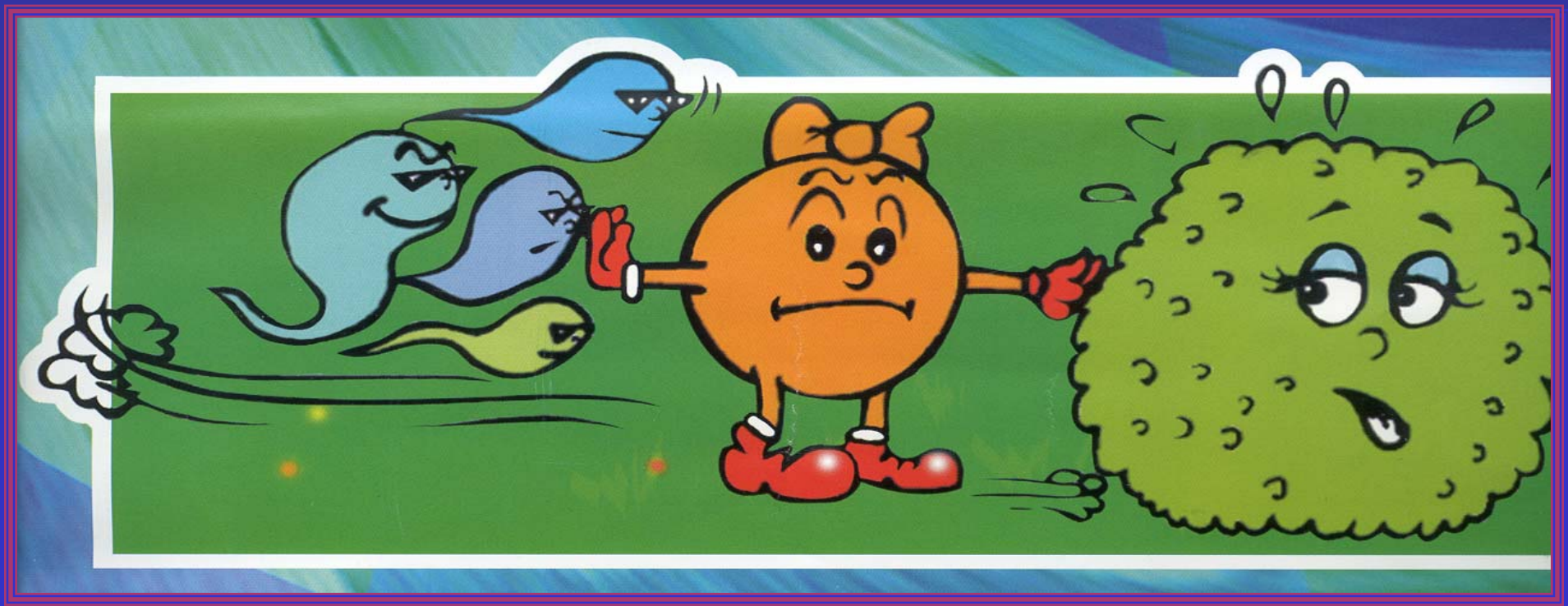
Conclusions

- 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)

Registration of levonorgestrel preparations for emergency contraception (as of October 2003)





MECHANISMS OF ACTION

(Yuzpe regimen; levonorgestrel)

- Do not cause abortion
- Precise mechanism in a particular case cannot be known and may depend on time in menstrual cycle when intercourse occurred and pills are taken
  - **ovulation inhibition or delay**
  - trapping of sperm in cervical mucus (?)
  - alteration in transport of sperm, egg or embryo (?)
  - inhibition of fertilization (?)

Effect of LNG EC on ovulation

Follicle size	No. of women	No ovulation
12-14 mm	18	83%
15-17	22	38%
> 18 mm	17	12%

Croxatto et al. 2003

No ovulation, or abnormal luteal phase

Follicle size	LNG	Placebo	
12-14 mm	94%	61%	ns
15-17 mm	91%	45%	p=0.003
> 18 mm	47%	13%	ns
Total	79%	41%	p=0.0001

Croxatto et al. 2003

Repeated postcoital use of LNG 0.75 mg

Study site	No. of pregnancies	No. of women-years	Rate*	95% CI
Chengdu	0	29.8	0.0	0.0-12.4
Havana	0	3.9	0.0	0.0-94.6
Karachi	5	30.3	16.5	5.4-38.5
Ljubljana	3	24.4	12.3	2.5-35.9
Shanghai	1	22.9	4.9	0.1-24.3
St. Petersburg	0	21.7	0.0	0.0-17.0
Total	9	133.0	6.8	3.1-12.9

** Per 100 woman-years*

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

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

Mifepristone and levonorgestrel do not differ in efficacy

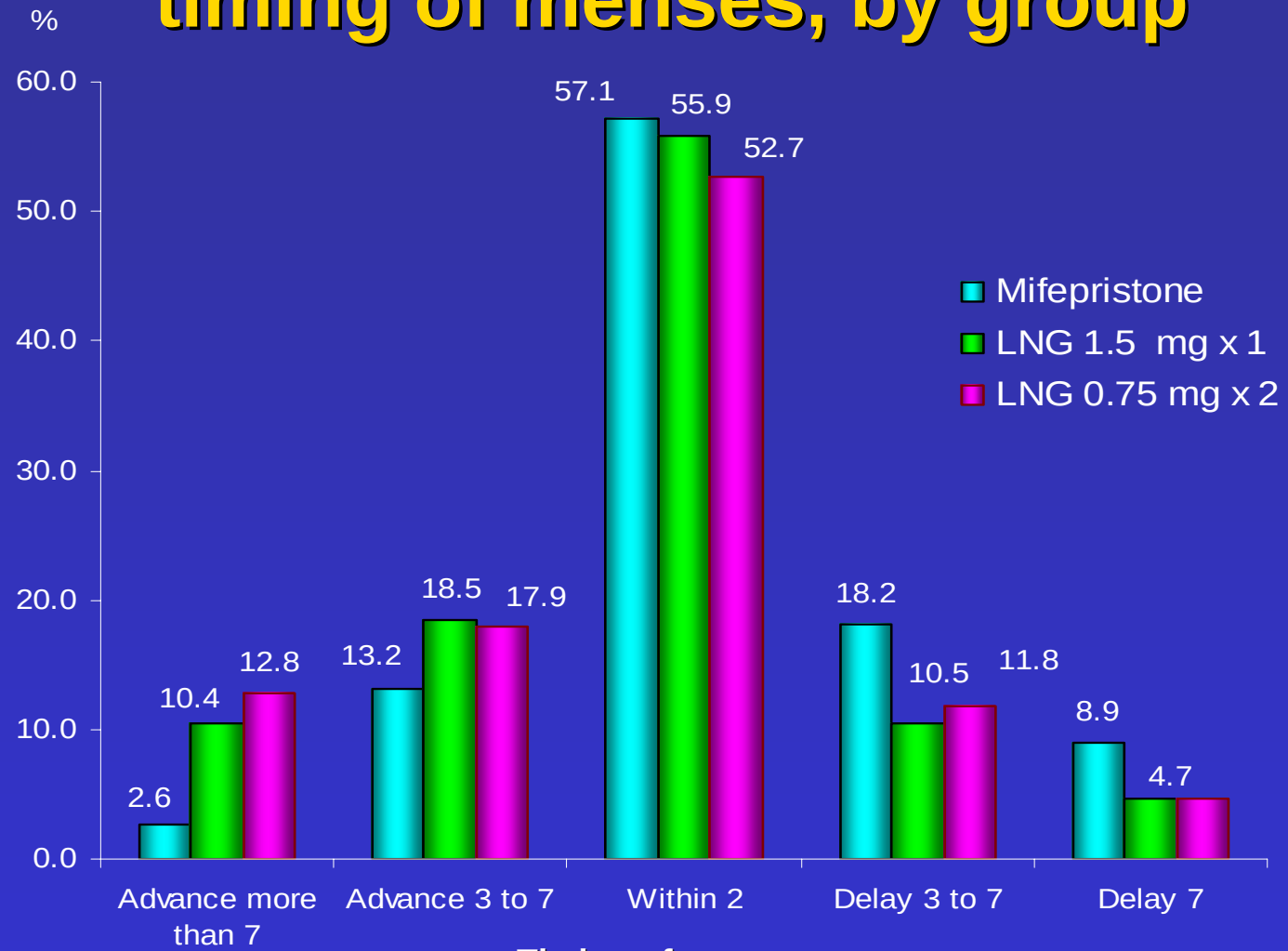
Group	Observed pregnancies /total	Rate
Mifepristone	21/1359	1.55%
LNG 1.5 mg x 1	20/1356	1.47%
LNG 0.75 mg x 2	24/1356	1.77%
All LNG	44/2712	1.62%

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)

Percentages of women in categories of timing of menses, by group



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%**

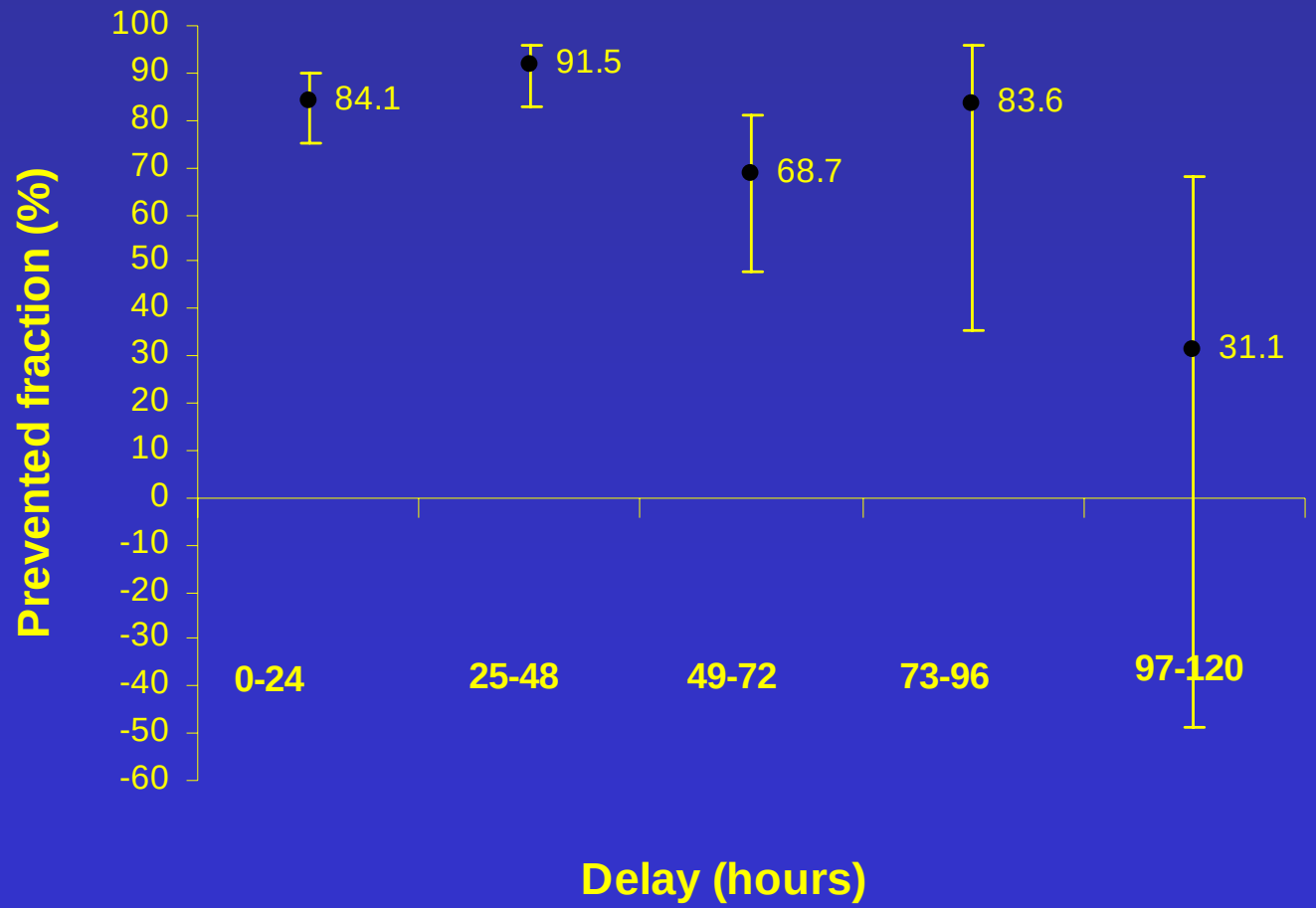
Interaction p=0.0226

(Mifepristone and two LNG regimens)

Effect of delay on pregnancy rates 10 mg mifepristone - meta-analysis

Delay (hours)	No. of women	No.of pregnancies	%	Prevented fraction (%)
0-24	1644	22	1.3	84.1
25-48	1075	8	0.7	91.5
49-72	636	16	2.5	68.7
73-96	188	2	1.1	83.6
97-120	126	6	4.8	31.1

Effect of delay on effectiveness levonorgestrel - meta-analysis



Efficacy of Emergency Contraception

Absolute effectiveness of EC pills not known

They prevent pregnancies but are not as effective as regular contraception

EC pills should never replace regular methods of family planning

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

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