Randomised controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception

*Task Force on Postovulatory Methods of Fertility Regulation**

Summary

Background A previous randomised study suggested that the progestagen, levonorgestrel, given alone in two separate doses each of 0·75 mg caused nausea and vomiting in fewer women and might be more effective than the Yuzpe regimen of combined oral contraceptives for emergency contraception, although the difference was not significant. We compared these two regimens when started within 72 h of unprotected coitus.

Methods We enrolled in the double-blind, randomised trial 1998 women at 21 centres worldwide. Women with regular menses, not using hormonal contraception, and requesting emergency contraception after one unprotected coitus, received levonorgestrel (0·75 mg, repeated 12 h later) or the Yuzpe regimen (ethinyloestradiol 100 μg plus levonorgestrel 0·5 mg, repeated 12 h later).

Findings Outcome was unknown for 43 women (25 assigned levonorgestrel, 18 assigned Yuzpe regimen). Among the remaining 1955 women, the crude pregnancy rate was 1·1% (11/976) in the levonorgestrel group compared with 3·2% (31/979) in the Yuzpe regimen group. The crude relative risk of pregnancy for levonorgestrel compared with the Yuzpe regimen was 0·36 (95% CI 0·18–0·70). The proportion of pregnancies prevented (compared with the expected number without treatment) was 85% (74–93) with the levonorgestrel regimen and 57% (39–71) with the Yuzpe regimen. Nausea (23·1 *vs* 50·5%) and vomiting (5·6 *vs* 18·8%) were significantly less frequent with the levonorgestrel regimen than with the Yuzpe regimen ($p<0·01$). The efficacy of both treatments declined with increasing time since unprotected coitus ($p=0·01$).

Interpretation The levonorgestrel regimen was better tolerated and more effective than the current standard in hormonal emergency contraception. With either regimen, the earlier the treatment is given, the more effective it seems to be.

Lancet 1998; **352:** 428–33
See Commentary page ????

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Introduction

The Yuzpe regimen of combined oral contraceptives (ethinyloestradiol 100 μg plus levonorgestrel 0·5 mg or *dl*-norgestrel 1·0 mg, repeated 12 h later) is the most commonly used emergency contraceptive.[1] When started within 72 h of unprotected coitus, this regimen prevented about 75% of pregnancies that would have occurred without treatment.[2] However, about 50% of treated women report nausea and more than 20% vomit after the regimen.[3] Thus, there is a need for more effective and better tolerated methods.

Levonorgestrel is marketed in several countries for occasional postcoital contraception in packs containing 0·75 mg tablets (Gedeon Richter, Budapest, Hungary). A previous WHO-supported study in Hong Kong tested the efficacy and side-effects of this formulation as an alternative hormonal emergency contraceptive.[3] The levonorgestrel regimen (two 0·75 mg tablets taken with a 12 h interval) was compared with the Yuzpe regimen in a randomised controlled trial of women who requested emergency contraception within 48 h of unprotected coitus. Levonorgestrel was slightly, but not significantly, more effective than the Yuzpe regimen in preventing pregnancy. In addition, the proportion of women with vomiting was much lower with levonorgestel (2·7 *vs* 22·4%), a clinically important difference. We designed a larger multicentre trial to compare the regimens when started within 72 h of unprotected coitus.

Our a-priori hypothesis was that the two regimens would have similar efficacy in preventing pregnancy. Outcome measures included pregnancy rates, proportions of pregnancies prevented, and side-effects. All women with outcome information were included in the analysis. We planned two secondary analyses: the first would exclude women who were pregnant at admission; and the second would include only those who met predefined criteria for correct use of the assigned method. We also studied how the timing of treatment in relation to coitus influenced treatment efficacy.

Methods

Protocol

The research protocol was approved by the WHO Secretariat Committee on Research Involving Human Subjects and by the corresponding institutional review board of each of the participating centres in 21 cities in 14 countries.

Eligible participants were healthy women with regular menstrual cycles of 24–42 days' duration who had had during the treatment cycle only one act of unprotected intercourse; the act had to have occurred no longer than 72 h before the start of treatment. Participants were asked to avoid further acts of unprotected coitus during that cycle. Women who had recently used hormonal contraception or who had recently been pregnant were included in the study only if they had had at least one cycle of normal length before the current cycle.

Reasons for exclusion were breastfeeding or use of hormonal

contraception within the current menstrual cycle, contraindications to hormonal contraception, or uncertainty about the date of last menses.

After participants had provided written informed consent they were included in the study. Relevant gynaecological, obstetric, and medical history was recorded, and height and weight were measured. Pregnancy was excluded by means of a urine or serum pregnancy test, or by collection and storage of a urine or blood sample for later analysis should the woman be found to be pregnant at follow-up.

Each participant received two sets of two tablets. The levonorgestrel regimen consisted of a levonorgestrel tablet (0·75 mg) plus a placebo tablet, followed by a 0·75 mg levonorgestrel tablet plus a placebo tablet 12 h later. The Yuzpe regimen was two tablets each containing 50 μg ethinyloestradiol plus 0·25 mg levonorgestrel, followed 12 h later by two more of these tablets. Women received the first dose under supervision at the clinic and took the second dose at home. We also provided each woman with a third dose of her assigned treatment to use in case she vomited within 4 h of taking a dose.

Women were asked to keep a diary of side-effects in the week after drug administration and to record their bleeding patterns and any further acts of intercourse up to the follow-up visit or onset of menses, whichever came first. Investigators instructed women to return for follow-up about 1 week after the expected onset of next menses. If menses had not resumed by that time, a pregnancy test was done. No incentives were given to participants; study drugs were supplied free of charge to participants.

Detailed instructions about trial conduct and completion of preprinted data-recording forms were issued to all investigators, and compliance was monitored through site visits and data verification of completed forms by established standard operating procedures.

Outcome measures

The primary outcome measure was unintended pregnancy. We measured both crude and adjusted pregnancy rates as well as the estimated reduction in expected pregnancies, or prevented fraction (1 minus observed pregnancies/expected pregnancies). We estimated the expected number of pregnancies in each group by multiplying the number of women having unprotected coitus on each day of the menstrual cycle by the probability of conception on that cycle day. We estimated the date of ovulation by subtracting 14 days from the expected date of the next menstrual period. The probabilities of conception by cycle day were estimated from the results of Wilcox and colleagues,[4] modified to include only clinical pregnancies (ie, chemical pregnancies were excluded).[5] Secondary oucome measures included side-effects and changes in bleeding patterns.

For the secondary analysis that included only women who had used the assigned method correctly, correct use was defined by four criteria: the first dose of the treatment within 72 h of unprotected coitus; the interval to the second dose less than 24 h; no further acts of coitus (with or without barrier contraception) until the next menses; and no other hormonal contraception during the rest of the cycle.

Analysis

Our sample-size estimate was based on published efficacy rates for the Yuzpe regimen. In one review,[6] the overall pregnancy rate associated with the Yuzpe regimen was 1·8%. Using the equivalence criterion,[7] with an incidence of 1·8% in each group, α=0·05, and power of 80%, we estimated that 857 participants would be needed in each group to show equivalence within 1·8% (two-sided alternative hypothesis).[8] To compensate for anticipated loss to follow-up, we decided to enrol at least 1900 women. If we had used the pregnancy rate of 3·5% observed for the Yuzpe regimen in the Hong Kong study,[3] we would have needed a sample size of 1820 per group to demonstrate equivalence within a difference of 1·8%, and 482 per group to demonstrate equivalence within a difference of 3·5%. With 976 participants per group (close to the actual number of women who provided information on the outcome of treatment), the approximate power obtained to show superiority of levonorgestrel compared with the Yuzpe regimen or equivalence within a difference of 2·0%, 2·5%, 3·0%, or 3·5% was 77%, 91%, 97%, and 98%, respectively.[7,8] These power calculations assume normality, and the approximation may be poor with low rates.

	Yuzpe regimen		Levonorgestrel regimen		Both regimens	
	Enrolled	Pregnant	Enrolled	Pregnant	Enrolled	Pregnant
Centre						
Auckland	20 (2)	2	22 (5)	1	42 (7)	3
Beijing	50 (1)	5	50 (2)	1	100 (3)	6
Christchurch	25	1	25 (1)	1	50 (1)	2
Jos	50	0	50 (1)	0	100 (1)	0
Lagos	50	0	50	1	100	1
Ljubljana	50 (2)	0	49 (2)	0	99 (4)	0
Manchester	29	3	29 (2)	0	58 (2)	3
Nanjing	100 (1)	4	100 (1)	2	200 (2)	6
New Delhi	50	2	50 (1)	0	100 (1)	2
Northbridge	37 (2)	0	39	1	76 (2)	1
Panama City	30	2	30 (1)	1	60 (1)	3
Pittsburgh	38 (2)	2	36 (3)	0	74 (5)	2
Quebec City	30 (1)	0	33 (2)	0	63 (3)	0
Sagamu	75	1	75	0	150	1
Shanghai	50 (1)	4	50 (1)	0	100 (2)	4
Stockholm	49 (1)	1	49 (1)	1	98 (2)	2
Szeged	39	0	39	0	78	0
Tbilisi	50	0	50	0	100	0
Tianjin	50	1	50	2	100	3
Ulaanbaatar	75	0	75	0	150	0
Wellington	50 (5)	3	50 (2)	0	100 (7)	3
All centres	997 (18)	31	1001 (25)	11	1998 (43)	42

Numbers in parentheses are women with unknown pregnancy outcome.

Table 1: **Numbers of women enrolled and pregnancies reported**

We analysed the data by intention to treat. Rates and crude relative risks were calculated by standard methods and their 95% CI from the binomial distribution (rates) and Taylor series (relative risks). To standardise the pregnancy rates by cycle day, we calculated the ratios of observed to expected pregnancies, the prevented fraction, and their 95% CI using the Poisson distribution. Then we calculated the ratio of the standardised rates and its 95% CI assuming a ratio between two Poisson variables. Odds ratios and their 95% CI were calculated by exact methods with StatXact (version 2.11, 1992) to adjust in turn for centres, cycle day on which intercourse took place, age, body-mass index, and reason for requesting emergency contraception (no method used or failure of barrier method). Homogeneity of odds ratios was assessed across all these factors. Logistic regression with SAS software (version 6.12) was used to assess the efficacy of the two regimens with adjustment for these factors and to look for interactions. Each interaction was assessed in a separate model owing to the limited number of pregnancies.

Assignment

The unit of randomisation was the individual woman. We used a computer-generated randomisation sequence developed in Geneva to assign participants to treatment groups. Each centre received assignments by random permuted blocks with a fixed block size of ten.

The allocation was concealed by use of sealed, sequentially numbered, tinted pill bottles, which were filled and labelled by the manufacturer. Clinicians and participants were unaware of the next assignment. The intention was to enrol 100 women at each of 19 sites. Interest in the trial was greater than anticipated, however, and 21 centres eventually participated. Some centres had slower enrolment than expected, and Nanjing, Sagamu, and Ulaanbaatar agreed to recruit additional participants.

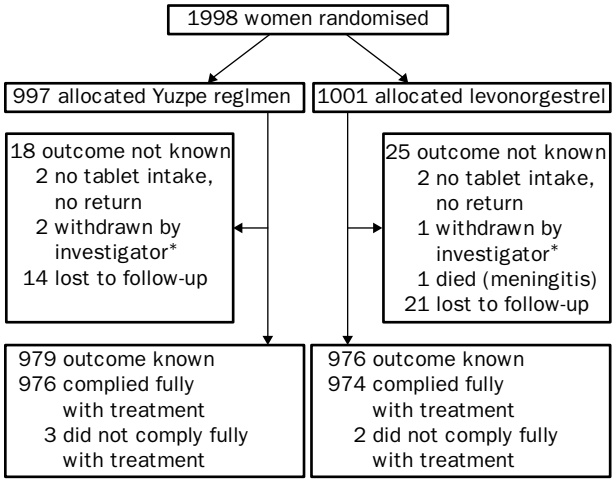

Figure 1: **Trial profile**
*To be treated with further emergency contraception.

Masking

Double blinding was maintained throughout the trial. Each pill bottle contained two identical tablets. Bottles containing a levonorgestrel tablet had an identical placebo tablet. The supplier formulated, especially for the trial, tablets containing the Yuzpe regimen, of identical appearance to the levonorgestrel tablets. The allocation sequence was kept in Geneva, and assignments were not revealed to investigators or participants during the trial.

Results

1998 women were enrolled (table 1), of whom 997 were assigned the Yuzpe regimen and 1001 the levonorgestrel regimen. The number of eligible women who were not randomised is not known, since the protocol did not require centres to record this information. In all, outcome was unknown for 43 women (2·2%) most of whom (39) were lost to follow-up despite attempts to reach them. Thus, 1955 women (979 in Yuzpe regimen group and 976 in levonorgestrel group) with outcome information remained in the analysis (figure 1).

The randomisation produced similar baseline characteristics of women in both treatment groups (table 2). The participants were young (mean 27 years), and a minority had used emergency contraception before this trial. Similar proportions cited lack of contraception and failure of a barrier method as the reason for requesting emergency contraception. Treatment started within 24 h of unprotected coitus in nearly 50% of the women in each group and within 48 h in more than 80%.

Characteristic	Treatment group	
	Yuzpe (n=979)	Levonorgestrel (n=976)
Mean (SD) baseline characteristics		
Age (years)	27·2 (6·8)	27·3 (7·0)
Body-mass index (kg/m²)	22·1 (3·3)	22·0 (3·6)
Menstrual cycle length (days)	28·8 (2·5)	28·9 (2·4)
Reproductive history		
⩾1 previous pregnancy	619 (63·2%)	633 (64·9%)
Previous use of emergency contraception	227 (23·2%)	203 (20·8%)
Failure of barrier method	431 (44·0%)	425 (43·5%)
Interval from coitus to ovulation		
>1 day previously	444 (45·4%)	452 (46·4%)
Day of ovulation ±1 day	246 (25·1%)	244 (25·0%)
>1 day afterwards	289 (29·5%)	279 (28·6%)
Time from coitus to treatment (h)		
⩽24	459 (46·9%)	450 (46·1%)
25–48	370 (37·8%)	339 (34·7%)
49–72	148 (15·1%)	185 (19·0%)
>72	2 (0·2%)	2 (0·2%)

Data exclude 43 women with unknown pregnancy outcome.

Table 2: **Characteristics of participants**

Coitus-to-treatment interval	Pregnancies/total	Pregnancy rate (95% CI)	Relative risk (95% CI)
All women			
Yuzpe	31/979	3·2 (2·2–4·5)	1·0
Levonorgestrel	11/976*	1·1 (0·6–2·0)	0·36 (0·18–0·70)
⩽24 h			
Yuzpe	9/459	2·0 (0·9–3·7)	1·0
Levonorgestrel	2/450	0·4 (0·1–1·6)	0·23 (0·05–1·04)
25–48 h			
Yuzpe	15/370	4·1 (2·3–6·6)	1·0
Levonorgestrel	4/338	1·2 (0·3–3·0)	0·29 (0·10–0·87)
49–72 h			
Yuzpe	7/150	4·7 (1·9–9·4)	1·0
Levonorgestrel	5/187	2·7 (0·9–6·1)	0·57 (0·19–1·75)

*1 woman did not have information on coitus-to-treatment interval.

Table 3: **Pregnancy rates by treatment group and time since unprotected coitus**

42 women were found to be pregnant after treatment (table 1). Retrospective urine analysis revealed, however, that four of them were already pregnant on enrolment. For another five women, pregnancy status at admission to the study was unknown (no pregnancy test on admission or ultrasonography done later to establish the duration of pregnancy). We decided to keep all these women in the main analysis. All pregnancies were intrauterine. Five women continued their pregnancies with normal outcomes, the others opted to have induced abortion.

The pregnancy rate was 3·2% (95% CI 2·2–4·5) among women assigned the Yuzpe regimen and 1·1% (0·6–2·0) among those assigned levonorgestrel (table 3). The crude relative risk of pregnancy for levonorgestrel compared with the Yuzpe regimen was 0·36 (95% CI 0·18–0·70). Adjustment for centre of enrolment produced the same result in terms of odds ratio (0·35 [0·16–0·72]). Almost identical results were obtained after adjustment in turn for cycle day on which intercourse took place, age, body-mass index, and reason for requesting emergency contraception. In all cases relative risks were homogeneous.

Unreported pregnancies among the women lost to follow-up could affect the results. For example, if there were no pregnancies among the 18 women assigned the Yuzpe regimen who had unknown outcomes and seven or more pregnancies occurred among women assigned levonorgestrel who had unknown outcomes, the result would be less significant. However, this detraction from significance would not occur with less than seven pregnancies (16%) among the 43 lost to follow-up. A reversal of the effect is less plausible, since this scenario would require at least 21 unreported pregnancies (49%) among the 43 women lost to follow-up. Examples of extreme cases with a reversal of the effect are no pregnancies among the 18 women assigned the Yuzpe regimen who had unknown outcomes and at least 21 among those assigned levonorgestrel who had unknown outcomes, the most extreme being the case with 25 in the latter group.

On the other hand, in the best-case scenario (ie, all women with unknown outcome included in the analysis and counted as not pregnant), the results are almost identical to those reported above. When we excluded the four women already pregnant at enrolment (three

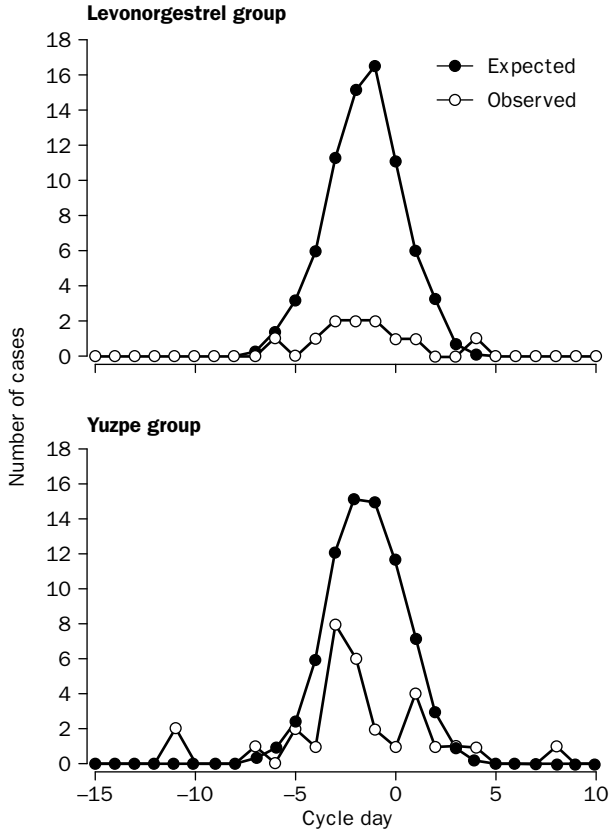

Figure 2: **Observed and expected numbers of pregnancies by timing of coitus in relation to predicted ovulation, by treatment group**

assigned the Yuzpe regimen, one the levonorgestrel regimen), the pregnancy rate was 2·9% (95% CI 1·9–4·1) for the Yuzpe regimen and 1·0% (0·5–1·9) for the levonorgestrel regimen (p=0·01), with a relative risk of 0·36 (0·17–0·73).

The earlier either emergency contraceptive treatment was given, the greater its efficacy (table 3), with a downward gradient in efficacy from treatment within 24 h to treatment within 49–72 h (p=0·01). Within each of these strata, however, the Yuzpe regimen was associated with a higher pregnancy rate than the levonorgestrel regimen. The relative risk of pregnancy associated with levonorgestrel compared with the Yuzpe regimen increased from 0·23 (0·05–1·04) at 24 h or less to 0·57 (0·19–1·75) at 49–72 h; a test for interaction of group by delay in treatment was not significant (p=0·58).

In both treatment groups women who had further acts of intercourse (with or without barrier contraception) had higher pregnancy rates than women without further intercourse (Yuzpe regimen 5·3% [19/360] *vs* 1·9% [12/619]; levonorgestrel 1·6% [6/372] *vs* 0·8% [5/602]).

Figure 2 shows the observed and expected numbers of pregnancies by timing of coitus in relation to predicted ovulation. Analysis of the prevented fraction (1−observed pregnancies/expected pregnancies) gave similar results to those for pregnancy rates. Based on the modified Wilcox estimates of conception probabilities,[5] the levonorgestrel regimen (11 pregnancies observed, 75·3 expected) prevented 85% (74–93) of the expected pregnancies (95% up to 24 h, 85% for 25–48 h, and 58% for 49–72 h). The Yuzpe regimen (31 pregnancies observed, 72·0 expected) prevented 57% (39–71) of

Side-effect	% with symptom (95% CI)		p
	Yuzpe (n=979)	Levonorgestrel (n=977)	
Nausea	50·5 (47·3–53·6)	23·1 (20·5–25·9)	<0·01
Vomiting	18·8 (16·4–21·4)	5·6 (4·3–7·3)	<0·01
Dizziness	16·7 (14·4–19·1)	11·2 (9·3–13·3)	<0·01
Fatigue	28·5 (25·7–31·4)	16·9 (14·6–19·4)	<0·01
Headache	20·2 (17·8–22·9)	16·8 (14·5–19·3)	0·06
Breast tenderness	12·1 (10·1–14·3)	10·8 (8·9–12·9)	0·40
Low abdominal pain	20·9 (18·4–23·6)	17·6 (15·3–20·1)	0·07
All other adverse effects*	16·7 (14·4–19·1)	13·5 (11·4–15·8)	0·06

Based on women for whom full information was available.
*Mostly diarrhoea and some irregular bleeding or spotting.

Table 4: **Side-effects**

expected pregnancies (77% up to 24 h, 36% for 25–48 h, and 31% for 49–72 h). The standardised pregnancy rates were 15% and 43% for the levonorgestrel and the Yuzpe regimens, respectively. The ratio of the two respective standardised rates was 0·34 (0·15–0·69).

In a subgroup analysis of the 1157 women who met criteria for correct use of the assigned regimen, there were 11 pregnancies among 583 women who received the Yuzpe regimen (1·9% [1·0–3·4]) and five among 574 women who received the levonorgestrel regimen (0·9% [0·3–2·0]; p=0·22). The crude relative risk of pregnancy for levonorgestrel compared with the Yuzpe regimen for this subgroup of women was 0·46 (0·16–1·32). The prevented fraction was 89% in the levonorgestrel group and 76% in the Yuzpe group. Since the classification as a correct user was based on verbal information, which was provided by the woman and could not be objectively verified, we do not know whether the pregnancies observed among correct users are true treatment failures or instances of faulty assignment based on misinformation provided by the women.

To examine the effect of ethnic origin, we grouped the 21 centres into five categories according to predominant ethnic group and geography. The differences in odds ratios across the five categories were statistically insignificant (p=0·89). We tested for homogeneity across individual centres also and found the odds ratios to be homogeneous (p=0·37).

Levonorgestrel was better tolerated than the Yuzpe regimen (table 4). Nausea, vomiting, dizziness, and fatigue were all significantly less common among women who received levonorgestrel; other side-effects were also less common in the levonorgestrel group but the differences were not significant. Significantly fewer women who received levonorgestrel alone required an extra dose because of vomiting.

The time to resumption of menses was similar for women in the two groups (p=0·67). For both groups combined, 13% of women had a delay of more than 7 days beyond the anticipated onset of next menses; 15% had a delay of 3–7 days; 57% had menses return within 3 days of the expected day; and 15% had an early onset. The mean duration of next menses was 4·7 days (SD 1·4) for both groups.

Discussion

This trial produced two findings of public-health importance. First, the levonorgestrel regimen was better tolerated than the Yuzpe regimen. Efficacy was greater, in terms of both crude and adjusted pregnancy rates and pregnancies prevented. The clustering of observed pregnancies around predicted ovulation (figure 2)

validates our estimates of conception probabilities in this large sample. Because of the biological variability in cycle length and the need to rely on calculated estimates of the day of ovulation, the occasional pregnancy after intercourse apparently outside the fertile period (figure 2) is to be expected.

We are aware of only one other randomised trial comparing these regimens.[3] Among 834 women in that trial who started treatment within 48 h of unprotected coitus, the intention-to-treat pregnancy rate was 3·5% with the Yuzpe regimen and 2·9% with the levonorgestrel regimen. After exclusion of women with further acts of intercourse in the cycle, the pregnancy rates were 2·7% (1·0–4·1) and 2·4% (0·8–4·1), respectively. Thus, although the difference observed was not significant, its direction is consistent with our finding of a greater efficacy of levonorgestrel.

The pregnancy rate for the Yuzpe regimen found in this study, even though greater than the overall pregnancy rate of 1·8% reported in an earlier review of 11 studies,[6] was within the range of pregnancy rates for the individual studies (0·2% to 7·4%). Such variability can be expected because study populations differ across studies in several respects. Variables likely to influence failure rates include the distribution of the timing of intercourse with respect to ovulation among participants, the proportion of women who had unprotected intercourse as opposed to a failure of the barrier method being used, the proportion of women in less fertile age-groups, and, possibly, the ethnic origin of the participants. We found slightly, but not significantly, higher pregnancy rates in the four Chinese centres than in the non-Chinese centres (Yuzpe regimen 5·7% [3·1–9·3] *vs* 2·3% [1·4–3·7]; levonorgestrel 2·0% [0·6–4·7] *vs* 0·8% [0·3–1·8]). The effect of cycle day on combined failure rates was significant (p=0·04), although we did not find a significant effect of age or of reason for requesting emergency contraception.

The second finding of public-health importance relates to the timing of treatment. For both methods combined, efficacy was significantly and inversely related to time since unprotected coitus (p=0·01). The trend was also significant for each treatment group separately. The smaller previous trial,[3] limited to 48 h from coitus, found the same trend (not significant) of decreasing efficacy with time for each regimen. Another prospective study in New Zealand suggested that the Yuzpe regimen worked better the earlier it was taken after intercourse.[9]

By contrast, a summary[10] of nine published reports of the Yuzpe regimen found no significant relation between efficacy and timing of treatment. Since the two randomised controlled trials and one prospective study have shown this trend, we suspect that the discrepancy is due to the lack of bias in the randomised controlled trials as compared with observational studies. Although the earlier randomised controlled trial[3] was included in the summary,[10] most of the summary's data came from observational studies.

Because of the rarity of treatment failures with either emergency contraceptive method, studies with sufficient statistical power to address the timing question are unlikely to be done. Hence, we believe women should receive treatment as soon as is practicable after unprotected coitus. Extrapolating from the significant trend found in our trial, we expect that treatment after 72 h will have even lower efficacy.[11]

Neither regimen substantially delayed the onset of next menses. Randomised controlled trials[12,13] comparing the 600 mg dose of the antiprogestagen mifepristone with the Yuzpe regimen showed an important difference in this regard. Treatment with this high dose of mifepristone caused a significant delay in the onset of the next menses. Such delays can worry women who are already concerned about the possibility of an unintended pregnancy. Also, when the reason for this delay is postponement of ovulation by the treatment, further unprotected acts of intercourse expose women to a risk of pregnancy.

Little is known about the mechanisms of action of the drugs in preventing pregnancies to explain why the Yuzpe regimen of levonorgestrel with ethinyloestradiol is less effective than the regimen of levonorgestrel alone. The lower efficacy could be due to an interaction between the oestrogen and the progestagen as well as to the lower dose of levonorgestrel used in the Yuzpe regimen. A separate assessment of the effects of the oestrogen, the dose of levonorgestrel, and the interaction between the hormones would require randomised clinical trials of questionable ethical value, given the superiority of the levonorgestrel regimen in side-effects shown in this study and the likelihood that oestrogen alone in the dose used in the Yuzpe regimen is unlikely to be effective.

Replacement of the Yuzpe regimen, the current standard for emergency contraception, with levonorgestrel should improve the acceptability of hormonal emergency contraception, and family-planning programmes providing emergency contraception should consider making this change. With either regimen, the sooner treatment starts, the better it works.

Task Force on Postovulatory Methods of Fertility Regulation: World Health Organization

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Acknowledgments

This study was funded by the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, WHO.

Gedeon Richter, Budapest, Hungary, provided the drugs used in the study and packaged them for the study centres.

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International randomised controlled trial of acetazolamide and furosemide in posthaemorrhagic ventricular dilatation in infancy

International PHVD Drug Trial Group

Summary

Background Furosemide and acetazolamide are widely used in the treatment of posthaemorrhagic ventricular dilatation (PHVD) in the hope of avoiding the need for surgical management, but this approach has not been evaluated in a controlled trial. This multicentre randomised controlled trial tested the hypothesis that these drugs would reduce the rate of shunt placement and increase disability-free survival at 1 year of age.

Methods Between 1992 and 1996, 177 infants aged less than 3 months past term, and with ventricular width more than 4 mm above 97th centile after intraventricular haemorrhage, were randomly assigned standard therapy alone or standard therapy plus treatment with acetazolamide (100 mg/kg daily) and furosemide (1 mg/kg daily). A minimisation algorithm ensured balance between groups with respect to both referral centre and the presence of a cerebral parenchymal lesion on cerebral ultrasonography at enrolment. The trial was stopped in September, 1996, because the data showed a clear advantage with standard therapy.

Findings We report outcomes for 151 infants whose expected date of delivery was before the end of 1995, with complete information at 1 year for 129 infants. The median gestational age was 28 weeks, mean birthweight 1299 g, and mean postnatal age at enrolment 25 days. 44% had a parenchymal lesion at randomisation. Death or shunt placement occurred in 49 of 75 infants allocated drugs plus standard therapy, compared with 35 of 76 allocated to standard therapy alone. The relative risk was 1·42 (95% CI 1·06–1·90; p=0·026), which is equivalent to one extra death or shunt placement for every five infants allocated drug therapy. 84% (52/62) of infants assigned drug therapy had died or were disabled or impaired at 1 year, compared with 60% (40/67) of those assigned standard therapy (relative risk 1·40 [1·12–1·76]; p=0·012).

Interpretation These preliminary results suggest that the use of acetazolamide and furosemide in preterm infants with PHVD is associated with a higher rate of shunt placement and increased neurological morbidity, and so cannot be recommended.

Lancet 1998; **352:** 433–40
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Introduction

Posthaemorrhagic ventricular dilatation (PHVD) affects 17 in 1000 infants born at less than 32 weeks of gestation[1] and has a poor neurodevelopmental prognosis.[1–6] Outcome may be affected in two ways—either by the cerebral parenchymal injury that may occur in association with the haemorrhage, or by secondary damage caused by hydrocephalus and its treatment. Mild PHVD resolves with conservative management in most cases.[7] In the UK, moderate to severe PHVD is usually managed at first by intermittent removal of cerebrospinal fluid (by ventricular taps with or without a reservoir, or by lumbar puncture). Controlled trials, however, have been unable to demonstrate any benefit of this treatment.[6,8,9] In particular a large multicentre randomised study showed that early removal of cerebrospinal fluid in PHVD did not reduce the need for subsequent shunt placement, and was associated with a higher incidence of infections of the central nervous system.[6] At the follow-up examinations at 1 year and 2·5 years, 85% of survivors had abnormal neuromotor signs and 73% were disabled, irrespective of treatment allocation.[6,10]

Ventriculoperitoneal shunting is an effective treatment if conservative management fails to halt the progression of PHVD. It is, however, fraught with complications, particularly in small infants with disorders affecting many systems, reduced immunity, and high concentrations of protein in cerebrospinal fluid, and carries lifelong risks associated with late infection or shunt failure.[11] Third