Articles

Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial

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Summary

Background A single 10 mg dose of mifepristone, and two 0·75 mg doses of levonorgestrel 12 h apart, are effective for emergency contraception. Because no studies had compared the efficacies of both compounds, or investigated a single dose of 1·5 mg levonorgestrel, we undertook this three-arm trial.

Methods We did a randomised, double-blind trial in 15 family-planning clinics in 10 countries. We randomly assigned 4136 healthy women with regular menstrual cycles, who requested emergency contraception within 120 h of one unprotected coitus, to one of three regimens: 10 mg single-dose mifepristone; 1·5 mg single-dose levonorgestrel; or two doses of 0·75 mg levonorgestrel given 12 h apart. The primary outcome was unintended pregnancy; other outcomes were side-effects and timing of next menstruation. Analysis was by intention to treat, but we did exclude some patients from the final analyses.

Findings Of 4071 women with known outcome, pregnancy rates were 1·5% (21/1359) in those given mifepristone, 1·5% (20/1356) in those assigned single-dose levonorgestrel, and 1·8% (24/1356) in women assigned two-dose levonorgestrel. These proportions did not differ significantly (p=0·83). The relative risk of pregnancy for single-dose levonorgestrel compared with two-dose levonorgestrel was 0·83 (95% CI 0·46–1·50), and that for levonorgestrel (the two regimens combined) compared with mifepristone, 1·05 (0·63–1·76). Side-effects were mild and did not differ greatly between groups, and most women menstruated within 2 days of the expected date. Women who took levonorgestrel had earlier menses than did those who took mifepristone.

Interpretation The three regimens studied are very efficacious for emergency contraception and prevent a high proportion of pregnancies if taken within 5 days of unprotected coitus. Mifepristone and levonorgestrel do not differ in efficacy. A 1·5 mg single levonorgestrel dose can substitute two 0·75 mg doses 12 h apart.

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Introduction

Two 0·75 mg doses of levonorgestrel administered 12 h apart, taken up to 72 h after unprotected intercourse is better tolerated and more efficacious than the standard in hormonal emergency contraception—ie, the Yuzpe regimen (two doses of 0·1 mg ethinyloestradiol, 0·5 mg levonorgestrel, 12 h apart).[1] Results from a systematic review[2] that combined these data with those from another trial, in which treatment was administered up to 48 h after unprotected intercourse,[3] confirmed these conclusions. The two-dose regimen of levonorgestrel has been approved in more than 80 countries and is progressively replacing the Yuzpe regimen.

A comparison of three single doses of mifepristone (600 mg, 50 mg, and 10 mg) administered up to 120 h after intercourse for emergency contraception showed that the proportions of pregnancies (1·3%, 1·1%, and 1·2%, respectively) did not differ between these three doses.[4] The investigators concluded that a 60-fold reduction in the dose of mifepristone did not seem to decrease its effectiveness as an emergency contraceptive. No major side-effects occurred in any participants of that trial; however, the delay in the onset of next menstruation was significantly related to the mifepristone dose (p<0·01). A systematic review[2] combined results of trials that compared high doses of mifepristone (>50 mg) with low doses (≤10mg), or that compared mid-range doses (25–50 mg) with low doses (≤10 mg) and reported no

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evidence of a dose-related efficacy. However, the side-effect profile was better with low doses than with mid or high doses. These results suggest that mifepristone could improve existing emergency contraception options, because it can be administered in a single low dose with few side-effects. If levonorgestrel could also be given as a single dose, treatment would be simplified and compliance and patients' acceptance of the drug could be increased.

Our aim in this randomised, double-blind, multinational trial was, therefore, to compare the efficacy and side-effects of three treatments, when administered up to 120 h (5 days) after unprotected coitus: a single dose of 10 mg mifepristone; a single dose of 1·5 mg levonorgestrel; and two separate doses of 0·75 mg levonorgestrel given 12 h apart . The main outcomes were pregnancy rates, proportions of pregnancies prevented, side-effects and timing of the first menstrual period after treatment. We also planned to analyse the effect of treatment delay on efficacy.

Methods

Patients

This trial was done in 15 family-planning clinics in China, Finland, Georgia, Hungary, India, Mongolia, Slovenia, Sweden, Switzerland, and the UK (table 1).

We asked women presenting for emergency contraception to participate, and included those who were healthy, had regular menstrual cycles (24–42 days' duration), and who requested emergency contraception within 120 h of a single act of unprotected coitus in the present menstrual cycle. Participants also had to be willing to abstain from unprotected intercourse during that cycle, and be available for follow-up over the next 6 weeks. Women who had recently discontinued hormonal contraception or had been pregnant were included only if they had had at least one complete and normal menstrual cycle before the current cycle. Furthermore, the results of a sensitive pregnancy test (25 IU human chorionic gonadotropin) taken at admission had to be negative. We excluded women who were pregnant, breastfeeding, using hormonal contraception in the current cycle, using the rhythm method of natural family planning in the same cycle, uncertain about the date of the most recent menses, and those with contraindications for mifepristone use (chronic adrenal failure, a known allergy to mifepristone, severe asthma not controlled by corticosteroid therapy, or inherited porphyria). In addition, the centres did not enrol women likely to continue a pregnancy should emergency contraception fail. Relevant medical, gynaecological, and obstetric histories were recorded, as was the date of last menstruation, the expected date of next menses, and the date and clock time of unprotected intercourse.

All participants gave written informed consent. Institutional review boards at each of the participating centres and WHO Secretariat Committee on Research Involving Human Subjects gave ethics approval.

Randomisation

We used a computer-generated randomisation sequence developed by WHO to assign participants in each centre to one of three treatment groups: single-dose mifepristone; single-dose levonorgestrel; or two-dose levonorgestrel. Each centre received assignments by randomly-permuted blocks with a fixed block size of 10.

Allocation was concealed by the use of sealed, sequentially-numbered treatment packs, which were filled and labelled in accordance with the list of randomisation for each centre by Labatec, Geneva, Switzerland. Before and during the trial, we tested samples of the packed drugs to ensure the quality of supplies being sent to participating centres. The results confirmed correct labelling and drug content of the tablets.

In the 10 mg mifepristone group, women received two 5 mg tablets of mifepristone and two placebo tablets identical in appearance to levonorgestrel; in the single-dose levonorgestrel group, women were given two 0·75 mg levonorgestrel tablets and two placebo tablets identical in appearance to mifepristone; and in the two-dose levonorgestrel group women received one 0·75 mg levonorgestrel tablet, one placebo tablet identical in appearance to levonorgestrel, and two placebo tablets identical in appearance to mifepristone. The second dose comprised one dummy levonorgestrel tablet in the first two groups and one 0·75 mg levonorgestrel tablet in the third group. Mifepristone tablets and mifepristone placebo were provided by Roussel-Uclaf, Romainville, France, and levonorgestrel tablets and levonorgestrel placebo were provided by Gedeon Richter Ltd, Budapest, Hungary.The first dose was taken at the clinic, and the second was taken 12 h later at home.

Outcome measures

The primary outcome measure was unintended pregnancy, confirmed by a positive pregnancy test, or by vaginal ultrasound at follow-up, or both. We considered 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 intercourse 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 onset of the next menstrual period. We used estimated conception probabilities by cycle day from two data sets created by Trussell and colleagues,[5] which include only clinical pregnancies and exclude those diagnosed by biochemistry only (pooled-recognisable). Other outcome measures were side-effects in the week after the start of treatment and the timing of the first menstruation after treatment—ie, the difference between estimated and actual dates of menses onset.

Procedures

Women were advised not to have unprotected sex, and were given condoms. We asked participants to keep a diary of side-effects in the week after the treatment, and to record spotting or bleeding, acts of intercourse, and whether a condom was used, until the next menses or the follow-up visit, whichever came first. No incentives were given, and the trial drugs were supplied free of charge to participants.

A follow-up visit was arranged about 1 week after the estimated onset of the next menstrual bleeding, and the date of the visit was written on the diary card. If the woman had normal menstruation, she had completed the trial. If menstruation was not normal, or had not started by the time of the follow-up visit, we did a pregnancy test. For women with a negative test result, we arranged another follow-up appointment; however, if the test was positive, we did an ultrasound examination to estimate the duration of gestation. If menses had not occurred by the time of the second follow-up visit and the pregnancy test was negative, treatment was regarded as successful. WHO provided the centres with pregnancy tests and condoms.

Clinicians, participants, and investigators were unaware of drug assignments and this double-blinding was maintained until after the final analysis; only the person who prepared the random lists had access to them.

Principal investigators met before the trial to review the protocol and ensure uniform criteria for the assessment of outcomes. While the trial was in progress, the trial coordinator and other WHO staff visited trial sites. Principal investigators also monitored the trial, and all but one of the centres had previously participated in previous multicentre trials of emergency contraception. This trial was not monitored by an external independent committee, because the drugs used are already registered and available for widespread use. Data quality monitoring was done in accordance with the standard operating procedures presently used in WHO, Geneva.

Statistical analysis

The proposed sample size for this trial was 4200 women, with 1400 women per treatment group. This sample size was chosen to detect a minimum difference between a 1·2% failure rate in women treated with mifepristone[4] and a 2·9% failure rate[3] in women treated with levonorgestrel. These failure rates have been reported in previous studies. To have a power of 80% in a 5%-level two-sided test and assuming 10% loss to follow-up, a sample size of 1340 women per group (4020 total) was required. To be conservative, we increased our target sample size to 4200. This sample size would have 78% power to show non-inferiority (one-sided equivalence) between failure rates in the two levonorgestrel regimens within a margin of equivalence of 1·1% on the absolute scale with a 95% CI if the true failure rates are 1·1% in both regimens (as observed previously[1]). However, the power would be only 47% if the true failure rates are 2·9% in both regimens.

We excluded women who were lost to follow-up from the efficacy analysis, because we did not know their outcome. We also decided a priori to exclude women who requested emergency contraception if their single act of unprotected intercourse occurred after missed menses, but who had erroneously been treated. Otherwise, the analysis was as per randomisation. For the safety analysis, all women with at least some safety information were included.

To compare the efficacy of the three treatments, we calculated relative risks by standard methods, and their 95% CIs with Taylor series. We calculated the ratio of observed to expected pregnancies, the prevented fraction and its 95% CI in each group assuming the binomial distribution and taking into account the imprecision of conception probability estimates.[5] To take into account the standardisation by the expected pregnancies, we calculated the ratio of the standardised rates and its 95% CI assuming a ratio between two Poisson variables. We used logistic regression with SAS software (version 8) to adjust for centres and to test for interactions between regimens and the other four variables—centre, delay in treatment, additional acts of intercourse, and ethnic origin.

To investigate the observed pregnancies in greater detail we undertook subgroup analyses to compare the efficacy between regimens in women who adhered to protocol and were treatment compliant. We stratified our analyses by delay in treatment administration (women treated within 72 h and from 73 to 120 h after unprotected intercourse), acts of protected intercourse after treatment (yes/no), unprotected acts of intercourse (yes/no), and ethnic group (Chinese and non-Chinese).

We investigated the effect of delay in treatment on treatment efficacy in two ways. First, we compared the efficacy of each regimen among women treated within 72 h with those treated from 73 to 120 h after unprotected sex using a relative risk and a χ^2 test. Second, we calculated a χ^2 for trends with the crude pregnancy rates for each 24-h interval of delay.

Before the trial started we agreed that a failure rate of any of the three treatments higher than the 3·2% rate associated with the Yuzpe regimen[1] was not acceptable. We decided that if the lower 95% CI on the failure rate in a group was greater than 3·2%, we would investigate the reasons for such high failure rates, but there was no stopping rule.

Role of the funding source

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Results

4136 women were enrolled in the trial by 15 centres; each centre recruited between 122 and 447 women (table 1), 1380 were assigned mifepristone, 1379 single-dose levonorgestrel, and 1377 two-dose levonorgestrel (figure 1). We did not record the number of women who requested emergency contraception but were not enrolled.

	Mifepristone			Single-dose levonorgestrel			Two-dose levonorgestrel			All regimens		
	Enrolled	Lost to follow-up	Pregnant	Enrolled	Lost to follow-up	Pregnant	Enrolled	Lost to follow-up	Pregnant	Enrolled	Lost to follow-up	Pregnant
Beijing	99	0	1	100	0	3	97	0	3	296	0	7
Geneva	92	4	2	93	7	2	96	3	1	281	14	5
Helsinki	40	0	1	41	1	1	41	1	0	122	2	2
Hong Kong	99	8	1	99	4	1	99	7	1	297	19	3
Ljubljana	50	0	0	49	0	1	48	0	2	147	0	3
Manchester	49	2	1	49	3	0	49	2	0	147	7	1
Nanjing	149	0	2	149	2	3	149	0	3	447	2	8
New Delhi	48	5	0	49	0	3	50	0	2	147	5	5
Shanghai (IFPTI)	149	0	4	149	3	1	149	1	5	447	4	10
Shanghai (SIPPR)	149	0	4	149	0	2	149	1	4	447	1	10
Stockholm	99	1	1	100	1	1	98	4	1	297	6	3
Szeged	108	0	2	107	0	0	106	0	0	321	0	2
Tbilisi	49	0	0	49	0	0	49	0	0	147	0	0
Tianjin	100	0	1	97	0	1	99	0	0	296	0	2
Ulaanbaatar	100	0	1	99	1	1	98	0	2	297	1	4
All centres	1380	20	21	1379	22	20	1377	19	24	4136	61	65

IFPTI=Institute of Family Planning Technical Instruction. SIPPR=Shanghai Institute of Planned Parenthood Research.

Table 1: **Pregnancies by centre and treatment group**

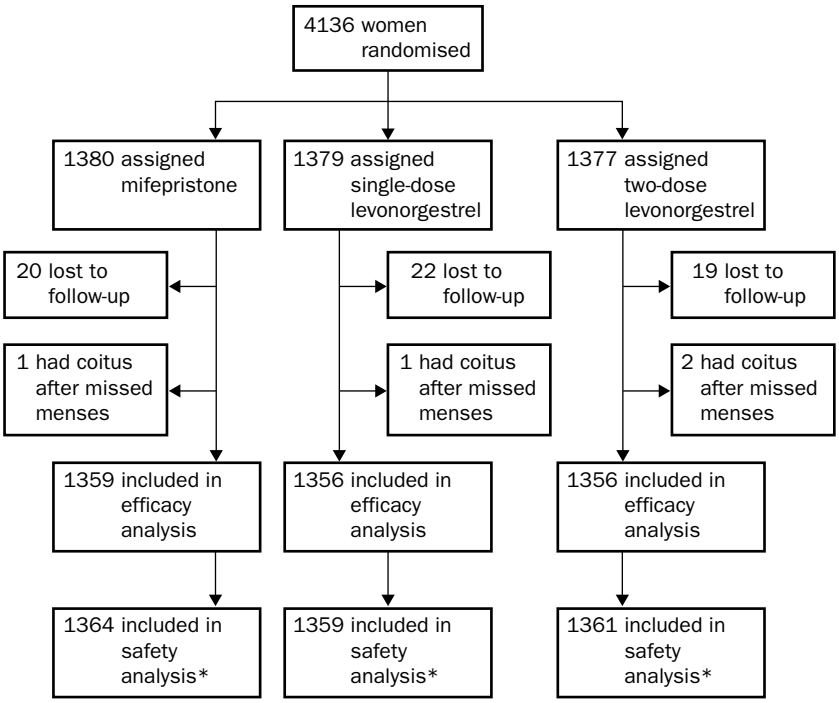

Figure 1: **Trial profile**
*Side-effects information available if first follow-up visit took place.

All women received the first dose of treatment. We did not have information about the second dose intake for 62 women, most of whom (52) missed the first follow-up visit (information on the second dose was collected retrospectively at this visit). 36 women took the second dose 24 h or more after the first dose, and 21 vomited in the first hour after either tablet intake. In all, 117 women had partial non-compliance or their compliance could not be assessed (two women had more than one reason for non-compliance).

Of 4136 women enrolled, 61 were lost to follow-up (1·5%), and we did not know the outcome of their treatment. Four women (0·1%) who requested emergency contraception and declared having unprotected intercourse after the expected date of menses were excluded from the efficacy analysis. Thus, 4071 women with outcome information remained in this analysis (figure 1), of whom 2202 (54%) were Chinese and 1869 (46%) non-Chinese, and most of these were white.

Baseline characteristics were similar among the three treatment groups (table 2). Women were young (mean age 27 years; range 14–52 years), had a mean weight of 56 kg, and about a quarter (26% [1075/4071]) had used emergency contraception in the past. More than half (60% [2460]) had been pregnant before, but there was a large variation between centres: from 8% (9/119) in Helsinki to 92% (410/445) in one of the Shanghai centres. The same trend was noted in the 48% (1971) of women who had had at least one induced abortion, which varied from 5% (6/119) to 78% (349/445) in the same centres. About half the women (52% [2131]) requested emergency contraception because they had not used any contraception at coitus, 44% (1799) reported condom failure, and 3–4% (141) had another contraceptive fail. In all, 44% (1792) of women requested treatment within 24 h, 72% (2933) within 48 h, and 88% (3596) within 72 h.

The 61 women lost to follow-up were younger (mean 22 years) than the other women, a smaller percentage had been pregnant before (33% [20]) and had induced abortion (28% [17]). The proportion of Chinese women was smaller among those lost to follow-up (43% [26]).

Of the 4071 women included in the efficacy analysis, 65 were pregnant (table 3). There were no significant differences in pregnancy rates between the three regimens (p=0·83). Adjustment for centre with the Mantel-Haenszel procedure produced almost identical results. There was no statistical heterogeneity between centres (p=0·84 for the comparison of the two levonorgestrel groups, p=0·49 for that of the two levonorgestrel groups combined *vs* mifepristone, from Breslow-Day tests of homogeneity of odds ratios). The four women excluded from the analysis who requested emergency contraception after the expected date of menses, were not pregnant. One pregnancy in the two-dose levonorgestrel group was in the fallopian tube, all others were intrauterine. All pregnant women opted to have induced abortion.

Unreported pregnancies in women lost to follow-up, if imbalanced, could bias the results; however, we have no reason to believe that this situation is likely to have happened.

The number of expected pregnancies if no treatment had been given, and the proportion prevented by treatment are shown in table 3. The risk of pregnancy for the single-dose levonorgestrel group compared with the

	Mifepristone (n=1359)	Single-dose levonorgestrel (n=1356)	Two-dose levonorgestrel (n=1356)
Demographic and anthropometric variables, mean (SD)			
Age (years)	27·2 (7·0)	27·1 (7·2)	27·4 (7·1)
Weight (kg)*	56·5 (8·6)	56·0 (8·7)	56·4 (8·7)
Height (cm)†	163·4 (5·8)	163·1 (6·2)	163·0 (6·0)
Length of cycle (days)‡	29·3 (2·7)	29·2 (2·7)	29·3 (2·8)
Duration of menstrual flow (days)	5·0 (1·3)	5·0 (1·3)	5·0 (1·2)
Time between ovulation and intercourse	0·6 (5·3)	0·8 (5·2)	0·6 (5·3)
Ethnic group			
Chinese	737 (54%)	733 (54%)	732 (54%)
Other Asian/black	157 (12%)	163 (12%)	166 (12%)
White	465 (34%)	460 (34%)	458 (34%)
History			
Pregnancy	832 (61%)	804 (59%)	824 (61%)
Induced abortion	681 (50%)	632 (47%)	658 (49%)
Use of EC	340 (25%)	390 (29%)	345 (25%)
Other contraceptive methods	1255 (92%)	1235 (91%)	1248 (92%)
Reasons for requesting EC			
No method	720 (53%)	725 (54%)	686 (51%)
Condom failure	585 (43%)	590 (44%)	624 (46%)
Other contraceptive failure	54 (4%)	41 (3%)	46 (3%)
Time from coitus to treatment (h)§			
0–24	598 (44%)	622 (46%)	572 (42%)
25–48	403 (30%)	377 (28%)	361 (27%)
49–72	214 (16%)	199 (15%)	250 (18%)
73–96	99 (7%)	87 (6%)	101 (7%)
>96	38 (3%)	63 (5%)	63 (5%)

EC=emergency contraception. *Two missing observations. †Three missing observations. ‡Five missing observations. §24 missing observations.

Table 2: **Baseline characteristics**

	Rate			Prevented fraction (95% CI)	Relative risks* (95% CI)	Relative risks* (95% CI)
	n	Pregnancies	Expected pregnancies			
Mifepristone	1359	21 (1·55%)	108	81% (69·2–87·8)	1	0·87 (0·49–1·56)
Single-dose levonorgestrel	1356	20 (1·47%)	111	82% (70·9–88·7)	0·95 (0·52 to 1·75)	0·83 (0·46–1·50)
Two-dose levonorgestrel	1356	24 (1·77%)	106	77% (64·9–85·4)	1·15 (0·64 to 2·05)	1
All levonorgestrel	2712	44 (1·62%)	216	80% (71·2–85·6)	1·05 (0·63 to 1·76)	–

*Crude relative risks.

Table 3: **Pregnancy rates and prevented fractions**

two-dose group, adjusted for the expected pregnancies in each group, was 0·80 (0·42–1·51). That for levonorgestrel (the two regimens combined) compared with mifepristone was 1·05 (0·61–1·85). These results are very similar to those noted before adjustment (table 3).

We repeated the analysis excluding 174 women who were not eligible according to inclusion and exclusion criteria and should not have been enrolled, or who did not comply fully with the treatment. Among these, 127 were not eligible: 32 were treated after 120 h had elapsed from the single act of unprotected intercourse, 16 had cycle length shorter than 24 days or longer than 42 days, one had used hormonal methods of contraception during the current cycle and 84 had used rhythm methods (six women met more than one exclusion criterion). The remaining 47 excluded women were partly non-compliant, or those with compliance information missing who were still left after the previous exclusions. Thus, of the 3897 women left after exclusions, 1·4% (18/1312) were pregnant in the mifepristone group, 1·5% (20/1303) in the single-dose levonorgestrel group and 1·7%(22/1282) in the two-dose levonorgestrel group. Comparisons of pregnancy proportions did not differ greatly from those noted before exclusions: the crude relative risk of pregnancy for single-dose levonorgestrel compared with two-dose levonorgestrel was 0·89 (0·49–1·63); that for levonorgestrel (the two regimens combined) compared with mifepristone was 1·18 (0·68–2·05).

We investigated whether the length of time between unprotected intercourse and treatment (ie, delay of treatment) was an effect modifier, and whether it also had an effect on efficacy (table 4). There was no evidence of an interaction between regimens and timing of treatment within 72 h of unprotected intercourse, or after 72 h (p=0·90). For the three regimens combined, women who were treated after 72 h had higher pregnancy rates, 2·4% (11/451) than those treated within 72 h, 1·5% (54/3596), but the difference was not significant (p=0·16). However, there was a significant trend in pregnancy rates in the 5 successive days from the time of unprotected intercourse (χ^2 5·5, p=0·0190; p=0·0034 from logistic regression). The numbers were too few to assess this trend separately for mifepristone and for the two levonorgestrel groups: the pregnancy rates on days 1, 2, 3, 4, and 5 were 1·2% (7/598), 1·2% (5/403), 2·8% (6/214), 1·0% (1/99), and 5·3% (2/38), respectively, in the mifepristone group. The corresponding results for both levonorgestrel groups combined were 1·7% (20/1194), 0·7% (5/738), 2·5% (11/449), 1·1% (2/188), and 4·8% (6/126), respectively.

Having intercourse (with or without contraception) between treatment and expected menstruation resulted in higher pregnancy rates (p=0·0005): 2836 women reported not having had intercourse, and 1235 women reported at least one act of intercourse. Of women who did not have coitus after treatment, there were 32 pregnancies (1·1%) and of women who did have intercourse, there were 33 pregnancies (2·7%). There was no interaction by regimen (p=0·18; table 4). On the other hand, having unprotected intercourse (without contraception) between treatment and expected menstruation resulted in much higher pregnancy rates in the mifepristone group (9/41 [22·0%]) than the levonorgestrel groups (4/61 [6·6%]). By contrast, in women who did not report having intercourse after treatment, there were 12 pregnancies out of 1318 (0·9%) in the mifepristone group and 40 out of 2651 (1·5%) in the two levonorgestrel groups combined; the interaction was significant (p=0·02).

Chinese women were pregnant more frequently than non-Chinese, but the difference was not significant (p=0·45; table 4). Of 2202 women in Chinese centres who completed the follow-up, 40 (1·8%) were pregnant.

	Group	Observed pregnancies/total	Prevented fraction (95% CI)
Delay in treatment after intercourse (days)*			
1–3	Mifepristone	18/1215 (1·48%)	82% (70·5 to 89·0)
	Single-dose levonorgestrel	16/1198 (1·34%)	84% (73·0 to 90·5)
	Two-dose levonorgestrel	20/1183 (1·69%)	79% (66·2 to 86·8)
4–5	Mifepristone	3/137 (2·19%)	58% (–23·8 to 86·0)
	Single-dose levonorgestrel	4/150 (2·67%)	63% (1·5 to 85·7)
	Two-dose levonorgestrel	4/164 (2·44%)	60% (–5·9 to 84·6)
Intercourse after treatment†			
Yes	Mifepristone	14/443 (3·16%)	60% (30·5 to 76·6)
	Single-dose levonorgestrel	7/404 (1·73%)	81% (59·0 to 90·9)
	Two-dose levonorgestrel	12/388 (3·09%)	64% (36·0 to 80·0)
No	Mifepristone	7/916 (0·76%)	91% (79·7 to 95·5)
	Single-dose levonorgestrel	13/952 (1·37%)	83% (69·0 to 90·1)
	Two-dose levonorgestrel	12/968 (1·24%)	83% (70·0 to 90·8)
Ethnic group‡			
Chinese	Mifepristone	13/737 (1·76%)	78% (60·6 to 87·3)
	Single-dose levonorgestrel	11/733 (1·50%)	81% (65·0 to 89·6)
	Two-dose levonorgestrel	16/732 (2·19%)	70% (50·3 to 82·3)
Non-Chinese	Mifepristone	8/622 (1·29%)	84% (67·5 to 92·2)
	Single-dose levonorgestrel	9/623 (1·44%)	83% (66·7 to 91·3)
	Two-dose levonorgestrel	8/624 (1·28%)	85% (68·7 to 92·4)

*p delay=0·17. p regimen×delay=0·90. †p further acts p=0·0005. p regimen×further acts=0·18. ‡p ethnic group=0·45. p regimen×ethnic group=0·79.

Table 4: **Efficacy analysis stratified by intercourse-treatment interval, intercourse after treatment, and ethnic group**

	Group	Number of cases	p*
Nausea	Mifepristone	196/1364 (14%)	0·86
	Single-dose levonorgestrel	189/1359 (14%)	
	Two-dose levonorgestrel	199/1361 (15%)	
Vomiting	Mifepristone	12/1364 (1%)	
	Single-dose levonorgestrel	19/1359 (1%)	0·37
	Two-dose levonorgestrel	19/1361 (1%)	
Diarrhoea	Mifepristone	61/1364 (5%)	
	Single-dose levonorgestrel	53/1359 (4%)	0·24
	Two-dose levonorgestrel	44/1361 (3%)	
Fatigue	Mifepristone	208/1364 (15%)	
	Single-dose levonorgestrel	184/1359 (14%)	0·30
	Two-dose levonorgestrel	182/1361 (13%)	
Dizziness	Mifepristone	123/1364 (9%)	
	Single-dose levonorgestrel	132/1359 (10%)	0·82
	Two-dose levonorgestrel	126/1361 (9%)	
Headache	Mifepristone	140/1364 (10%)	
	Single-dose levonorgestrel	142/1359 (10%)	0·71
	Two-dose levonorgestrel	130/1361 (10%)	
Breast tenderness	Mifepristone	114/1364 (8%)	
	Single-dose levonorgestrel	113/1359 (8%)	0·99
	Two-dose levonorgestrel	115/1361 (8%)	
Lower abdominal pain	Mifepristone	191/1364 (14%)	
	Single-dose levonorgestrel	183/1359 (14%)	0·72
	Two-dose levonorgestrel	198/1361 (15%)	
Bleeding	Mifepristone	258/1364 (19%)	
	Single-dose levonorgestrel	426/1359 (31%)	<0·0001
	Two-dose levonorgestrel	426/1361 (31%)	
Delay of menses more than 7 days†	Mifepristone	118/1327 (9%)	
	Single-dose levonorgestrel	62/1334 (5%)	<0·0001
	Two-dose levonorgestrel	63/1332 (5%)	

*Bonferroni adjustment for simultaneous inferences: significance at 1% level if p<0·0010. †Non pregnant only.

Table 5: **Side-effects within 7 days and delay of menses**

Of the 1869 corresponding women in non-Chinese centres, 25 (1·3%) were pregnant. The comparison of regimens stratified by ethnic group yielded similar results to those without stratification (p=0·79 for the regimen by ethnic group interaction).

In the mifepristone group, there was no association between the timing of treatment in relation to the cycle day and the timing of menses (p=0·79 for the linearity component from a linear model adjusting for centres). For the two levonorgestrel groups combined, the earlier in the cycle the treatment occurred, the earlier the menses started (the linearity component was significant, p<0·0001).

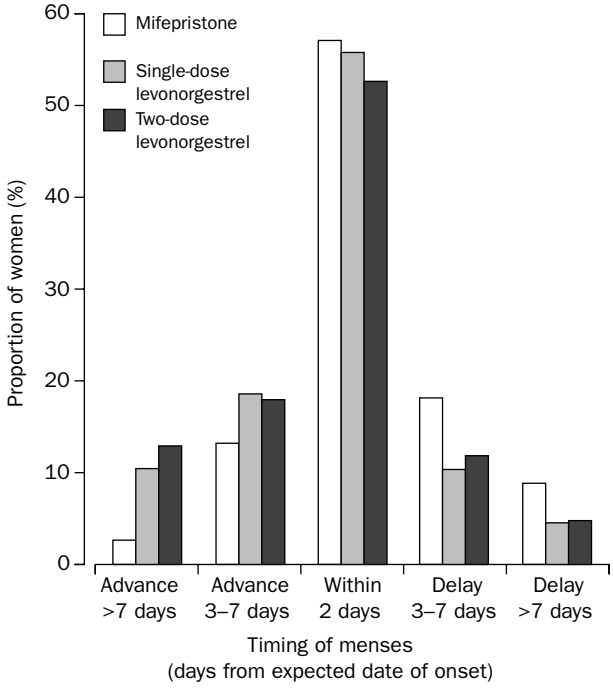

Figure 2: **Timing of menses after postcoital contraception**

Women recorded side-effects day by day, and complaints were uncommon in all treatment groups in the 7 days after the start of treatment (table 5). Only about 1% (50/4084) of women reported vomiting. There was no significant difference in the proportion of women with each side-effect between regimens except for bleeding and delay of menses for more than 7 days. During the first day after treatment, 9% of women or less reported side-effects (data not shown). During the second and third day combined, these proportions were all less than 11% and less than 8% during days 4 to 7.

Bleeding within the first 7 days was more common in the two levonorgestrel groups (31% or 852/2720) than the mifepristone group (19% [258/1364], p<0·0001, table 5). If women who had menses starting within these 7 days are excluded, the rates were about 16% for the two levonorgestrel groups (168/1011 and 150/967 for single-dose and two-dose levonorgestrel, respectively) and 9·4% (107/1142) for mifepristone (p<0·0001), so that bleeding not related to menses seemed to be more common in women who had received levonorgestrel.

More than half the women in all groups had menses within 2 days of the expected date (figure 2). More of the remaining women in the two levonorgestrel groups tended to have menses earlier than expected, and more women in the mifepristone group tended to have it later (p<0·0001). About 9% (118/1327) of women in the mifepristone group had a delay of more than 7 days in the onset of the first menses after treatment, compared with 5% (125/2666) in the two levonorgestrel groups combined.

Although the total rate of side-effects was low, there were differences between centres, such that women in developed countries reported more side-effects after treatment than women in developing countries. For example, within 7 days of treatment, three women out of 147 (2%) reported nausea in New Delhi, but 41 out of 147 (28%) did so in Manchester. There were three reports of serious adverse events during the trial: one ectopic pregnancy that required surgical treatment (two-dose levonorgestrel group); one of pyelonephritis that required treatment in hospital between treatment and follow-up (mifepristone group); and one of a ruptured corpus luteum cyst that required surgery between treatment and follow-up (single-dose levonorgestrel group). There is no evidence of any relation between these events and trial treatment.

Discussion

We started this trial with the objective of comparing the efficacy of three regimens in prevention of pregnancy, and we noted no difference between the treatments. However, because of our sample size, we cannot discard the possibility that the single-dose levonorgestrel regimen increases the risk of pregnancy up to 1·5-fold compared with the two-dose regimen, or that the two-dose regimen increases the risk of pregnancy up to more than two times that of the single dose regimen. To prove equivalence within a smaller margin would have required a larger trial.

In our two earlier international trials, we reported slightly lower pregnancy rates than in this trial for the two-dose levonorgestrel regimen,[1] and for the single-dose regimen of 10 mg of mifepristone.[4] These differences can be explained by chance, because they were not significant (p=0·27 and p=0·76, respectively, from a continuity-adjusted χ^2 test).

After adjustment for expected pregnancies with the same conception probabilities,[4] the two-dose levonorgestrel regimen in the previous trial prevented 89% of pregnancies,[1] but in this trial it prevented 79% when administered within 72 h after coitus. As for mifepristone, in the previous trial the 10 mg dose prevented 85% of pregnancies[4] compared with 81% in this trial.

However, the comparison of pregnancy rates and prevented fractions between trials is subject to bias, because the actual rates will depend on the sample of women studied. Inclusion and exclusion criteria might vary between protocols, and women's characteristics could influence results: cultural and social determinants of women's reporting might also vary across trials. When seeking post-coital emergency contraception, some women could be reluctant to provide reliable information—for example, they might have had several earlier acts of intercourse in that cycle, or even suspect an early pregnancy, which cannot be detected at admission. Thus, our comparison of efficacy between groups in this trial is unbiased, but we warn against the limitations of absolute estimates of pregnancy rates and prevented fractions within studies, and hence also of crude comparisons between studies.

We are aware of only one published study[6] comparing levonorgestrel (two 0·75 mg doses) and 10 mg mifepristone, which was done by S Wu and colleagues using locally manufactured drugs, and launched at about the same time as this trial. It was a double-blind, randomised, multicentre trial with 643 and 633 women, respectively, in the levonorgestrel and mifepristone groups. The treatment was administered up to 72 h after coitus. The failure rate of the two-dose regimen of levonorgestrel was 3·1% and that of mifepristone 1·4% (relative risk 2·17, 95% CI 1·00–4·77). In our trial the failure rates of the two regimens among Chinese women within 72 h of coitus were 2·2% and 1·8%, respectively (1·24, 0·60–2·56), and were not significantly different. In addition to the differences between the participants in the two trials, there might be also a difference in the characteristics of the drugs used.

For all treatment regimens combined, pregnancy rates were slightly higher, in Chinese than non-Chinese women, although not significantly so (1·8% *vs* 1·3%, respectively). We observed the same trend in our previous trial with levonorgestrel (2·0% *vs* 0·8%) as well as with the Yuzpe regimen (5·7% *vs* 2·3%), but these differences were not significant.[1] We are not aware of higher pregnancy rates in Chinese who use regular hormonal contraception than women of other ethnic origins. However, Chinese women had higher pregnancy rates in studies of the efficacy of intrauterine devices[7] and of women with lactational amenorrhoea.[8] In addition to ethnic differences in metabolism of steroids,[9] there could also be variations in fertility between populations.

We have reported previously, a significant increasing trend in failure rates with delay in treatment for levonorgestrel and the Yuzpe regimen combined.[10] However, when considering levonorgestrel alone, the numbers were small and the trend was not significant. There was no evidence that a delay in the administration of mifepristone affected efficacy.[4] When we compared the efficacy of treatment in women starting the treatment within 3 days of unprotected intercourse and those starting treatment with a delay of 4 or 5 days, we did not detect an effect of treatment delay on the efficacy. However, a trend towards a lower efficacy with longer delay was present for the three regimens combined when considering the pregnancy rates in the 5 successive days. An assessment of this trend is desirable for the two drugs separately, but the small number of women given delayed treatments in this trial makes our estimation very imprecise. There is a need for meta-analyses of the two regimens, with pooled data from different trials at the patient level and adjustment for confounders to obtain more power in the assessment of this clinically relevant effect. The adjustment for confounders is important because the comparison between delay categories is observational in nature—ie, it is not randomised.

Side-effects were rare, but there was variation between centres such that women in developed-country centres reported side-effects more often than women in developing countries. Overall, women reported fewer side-effects in this trial after levonorgestrel than did those in our previous trial.[1] For example, the occurrence of nausea after two doses of levonorgestrel was 23% in the previous trial and about 15% in this trial, and the rates of vomiting were 5·0% and 1·4%, respectively. Because proportions of women with side-effects vary widely between centres, the variation between trials could be explained by different centres participating in the trials.

Mifepristone has been shown to delay ovulation,[11] which means a longer cycle and later return of menses than if ovulation was not delayed. Furthermore, there is a continued risk of pregnancy after treatment if women have further unprotected intercourse. Our results confirm this finding, because we noted that the delay of menses happened significantly more often in the mifepristone group, and pregnancy rate was as high as 22% in women who continued to have unprotected coitus after mifepristone treatment compared with 0·9% in women who did not have unprotected intercourse after treatment in that group. For example, ultrasonography showed that one woman in the mifepristone group had conceived more than 3 weeks after treatment. When counselling women on emergency contraception, the risk of pregnancy after treatment should be highlighted, especially if mifepristone is used. Contraception should be recommended in cases where abstinence is not possible.

The occurrence of delay in the start of the next menses was related to the dose of mifepristone in the previous mifepristone trial.[4] The proportion of women in the 10 mg group who had a delay of more than 7 days was 18% (97/553) in that trial, and 9% (117/1326) in this one ($p<0·0001$ from a χ^2 test). The difference might be partly attributable to the fact that in the previous trial, any bleeding that occurred within 5 days of treatment was regarded as treatment-related and not as menses, and thus, menses delay might have been somewhat over-reported.

We believe that this trial has internal validity because treatments were randomly allocated, participants, clinicians, and investigators were unaware of treatement allocation, and our sample size was large enough to show a clinically relevant difference if it existed. This trial also has external validity, because it enrolled women of several different populations in developing and developed countries.

Our findings show that the levonorgestrel dose does not need to be split, but that a single dose of 1·5 mg can be used. The use of a single dose simplifies the use of levonorgestrel for emergency contraception without an increase in side-effects. Compared with mifepristone, either of the levonorgestrel regimens has the advantage of being associated with early, rather than late, menses after treatment. With early or on-time menses, women are relieved from anxiety about an unwanted pregnancy sooner, and can begin a regular and effective method of contraception more quickly than if menstruation is delayed. Evidence of higher efficacy with earlier treatment

from this trial was weak, suggesting that further research is needed. In any case, even if a declining trend in efficacy with time were verified, the regimens studied still prevent a high proportion of pregnancies even up to 5 days after coitus.

Contributors

H von Hertzen, in collaboration with the members of the steering committee, was responsible for the conception of the trial and selection of centres. H von Hertzen and G Piaggio prepared the protocol. H von Hertzen supervised the trial. J Ding, J Chen, S Song, G Bártfai, E Ng, K Gemzell-Danielsson, A Oyunbileg, S Wu, W Cheng, F Lüdicke, A Pretnar-Darovec, R Kirkman, S Mittal, A Khomassuridze, and D Apter contributed to the final trial protocol and implemented the trial in their respective countries. G Piaggio and A Peregoudov were responsible for data management and the statistical analysis. H von Hertzen and G Piaggio wrote the paper with inputs from the investigators.

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Conflict of interest statement

None declared.

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