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Comparison of three single doses of mifepristone as emergency contraception: a randomised trial

*Task Force on Postovulatory Methods of Fertility Regulation**

Summary

Background Mifepristone is a highly effective and well-tolerated emergency contraceptive when given in a dose of 600 mg within 72 h of unprotected coitus. We assessed whether the same effectiveness can be achieved with lower doses of mifepristone (50 mg and 10 mg) and a longer postcoital treatment period (120 h).

Methods We undertook a multicentre, single-masked, randomised trial in 11 family-planning clinics in Australia, China, Finland, Georgia, the UK, and the USA. 1717 healthy women with regular menstrual cycles who requested emergency contraception within 120 h of unprotected coitus were randomly assigned to three treatment groups.

Findings 32 women were lost to follow-up and one was pregnant before treatment. The 600 mg, 50 mg, and 10 mg groups did not differ in the proportions of pregnancies (seven [1·3%] of 559, six [1·1%] of 560, and seven [1·2%] of 565). Two pregnancies (both in the 50 mg group) were tubal. Among women without further acts of intercourse, treatment delay did not appear to influence the effectiveness. No major side-effects occurred, except a delay in the onset of next menses, significantly ($p<0·01$) related to the mifepristone dose.

Interpretation Lowering the dose of mifepristone sixty-fold did not decrease its effectiveness as an emergency contraceptive under typical use, though a study of this size cannot exclude differences in effectiveness up to almost three-fold. Lower doses of mifepristone were associated with less disturbance of the menstrual cycle. Thus, a dose as low as 10 mg seems preferable to the 600 mg dose.

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*Members and study organisation given at end of paper

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Introduction

Two UK randomised controlled trials of emergency contraception compared a single dose of 600 mg mifepristone with the Yuzpe regimen of oral contraceptives (ethinylestradiol 100 μg plus levonorgestrel 500 μg, repeated after 12 h) given within 72 h of unprotected coitus.[1,2] Mifepristone seemed to be a better option—three pregnancies were reported among 597 women who received mifepristone, compared with nine pregnancies among 589 women who received the Yuzpe regimen. The difference in proportions of pregnancies was not significant, but women who received mifepristone had significantly less nausea and vomiting, which are major drawbacks of the Yuzpe regimen. Women who received mifepristone were, however, more likely to have a delay in the onset of the next menses, presumably because antiprogestagen administered in the preovulatory phase of the menstrual cycle delays or blocks ovulation.[3] Such delay can worry women already fearful of an unintended pregnancy. In addition, delayed ovulation means a conception risk later in the prolonged cycle if no contraception is used. In one of the UK trials,[2] the three pregnant women were reported to have conceived 10–15 days after mifepristone treatment.

Research on the effects of mifepristone on ovarian and endometrial functions suggests that doses lower than 600 mg may confer protection against pregnancy when used for emergency contraception.[4–6] Lower doses would reduce the cost and are consistent with the principle that the lowest effective dose of a drug should be used.

This randomised controlled trial aimed to compare the effectiveness and side-effects, including the timing of the subsequent menstrual period, of single doses of 600 mg, 50 mg, and 10 mg mifepristone when the treatment was given within 120 h (5 days) of unprotected coitus.

Methods

Protocol

This trial was carried out in 11 family planning clinics in six countries on four continents. We obtained approval for the

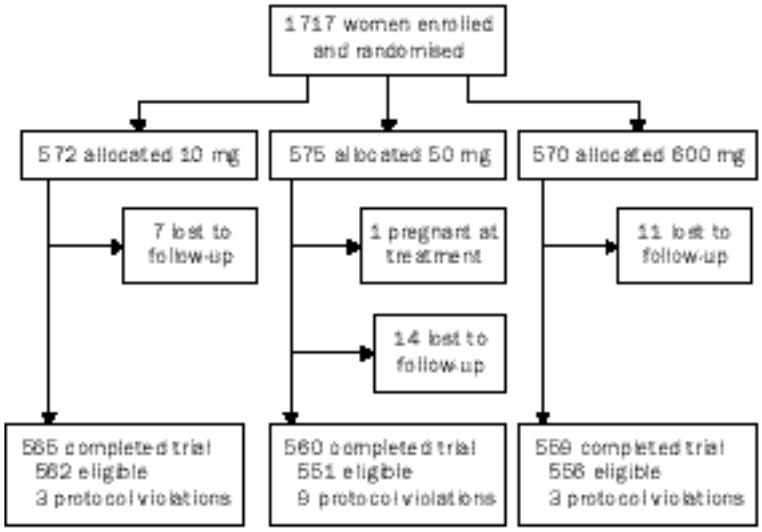

Figure 1: **Trial profile**

study from the WHO Secretariat Committee on Research Involving Human Subjects and from the institutional review board of each of the participating centres. Eligible participants were healthy women with regular menstrual cycles (24–42 days' duration) who requested emergency contraception within 120 h of a single, and only, act of unprotected coitus in the present menstrual cycle; who were willing to avoid further acts of unprotected intercourse during that cycle; and who were available for follow-up over the next 6 weeks. Women who had lately discontinued hormonal contraception or been pregnant were included in the study only if they had had at least one normal menstrual cycle before the current cycle. Exclusion criteria were current pregnancy or breastfeeding, use of hormonal contraception in the current menstrual cycle, uncertainty about the date of the last menstrual period, and contraindications to use of mifepristone. In addition, centres did not enrol women likely to continue a pregnancy should contraception fail.

After participants had given written informed consent they were included in the study. Relevant gynaecological, obstetric, and medical history was recorded. In some cases, a pregnancy test was done or a urine or blood sample was taken for retrospective analysis. Each participant received three tablets, at the assigned dose of mifepristone, at the clinic.

Women were advised to abstain from further acts of intercourse until the onset of the next menses, or to use barrier methods if further acts took place. They 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. Bleeding occurring within 5 days of mifepristone administration was not regarded as normal menstruation. Women were asked to come for a follow-up visit about a week after the expected onset of next menses. If menses had not resumed by that time, a second follow-up visit was scheduled a week later. Human chorionic gonadotropin (HCG) was measured in blood or urine at the first or second follow-up visit for women whose menses had not started. If the result suggested that conception had occurred, ultrasonography was used to estimate the duration of gestation.

Analysis

The primary outcome was unintended confirmed pregnancy. Secondary outcome measures included side-effects and delay in the onset of next menses.

The proposed sample size for this trial was 700 women per dose group (2100 women in total), calculated on the basis of method failures only, obtained from previous studies.[1,2] With the assumption of 10% loss to follow-up and no failures in the 600 mg group, this sample size would allow the demonstration of a significant difference with 1·2% of failures in either of the other dose groups, in a two-sided test with α=0·05, with 80% power. If typical use had been taken as a risk of 0·5% (three of 597) with the 600 mg dose, obtained by pooling of data from the two previous trials,[1,2] this sample size would allow the demonstration of a significant difference with a risk of 2·4% or higher in the 10 mg or 50 mg groups. If the sample size had been obtained as an equivalence trial, on the assumption of the same pregnancy risk of 0·5% in the two dose groups, the sample size of 700 per group would allow the demonstration of equivalence within a difference of 1·2% between any two doses with 93% power and one-sided 95% CI. For a risk of 1·2%, however, the power is 66%.

Analyses were by intention to treat. We measured effectiveness in two ways, calculating crude and adjusted pregnancy risks as well as the estimated reduction in expected pregnancies, or prevented fraction (1 minus the ratio of observed pregnancies to 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 obtained from the recognisable conceptions pooled by Trussell and colleagues[7] from British data[8] and North Carolina data.[9] The estimates include only clinical pregnancies (pregnancies diagnosed only by biochemistry are excluded).

We calculated proportions of pregnancies and crude relative risks by standard methods and their 95% CI from the binomial distribution (proportions) and Taylor series (relative risks). To standardise the proportions of pregnancies by cycle day, we calculated the ratio of observed to expected pregnancies and the prevented fractions with 95% CI using the Poisson distribution. Then we calculated the ratio of the standardised pregnancy risks and their 95% CI as a ratio of Poisson variables.

To examine observed pregnancies in greater detail, we undertook a subgroup analysis of women with no further acts of intercourse, by excluding women who had further acts of intercourse between treatment and the follow-up visit or visits and those for whom this information was missing. We repeated this analysis for women with no further unprotected acts of intercourse (no intercourse or use of barrier contraceptions). We examined the effect of the delay in treatment administration (within 72 h and more than 72 h) and the effect of further acts of intercourse.

Logistic regression with SAS software (version 6.12) was used to assess the effectiveness of the three regimens, with adjustment for various factors, and to look for interactions. We assessed each interaction in a separate model owing to the limited number of pregnancies. Since unreported pregnancies among women lost to follow-up could bias the comparison between groups, we did analyses of worst-case and best-case scenarios. We did a secondary analysis excluding women with protocol violations. For non-pregnant women, we also carried out a survival analysis with log-rank tests to estimate the effect of dose on delay in onset of next menses, defined as the difference in days between expected and actual day of onset.

Assignment

The individual participant was the unit of randomisation. We used a computer-generated randomisation sequence developed by WHO staff to assign participants to treatment groups within centres. Each centre received assignments by randomly permuted blocks with a fixed block size of nine.

The manufacturer (Roussel-Uclaf, Paris, France) supplied sequentially numbered bottles of pills for each participating

	10 mg group		50 mg group		600 mg group		All regimens	
	Enrolled*	Pregnant	Enrolled*	Pregnant	Enrolled*	Pregnant	Enrolled*	Pregnant
Centre								
Ashfield	49 (0)	1	48 (3)	1	48 (1)	1	145 (4)	3
Melbourne	16 (0)	0	15 (0)	1	17 (1)	2	48 (1)	3
Edinburgh	63 (0)	1	60 (2)	0	62 (1)	0	185 (3)	1
Helsinki	50 (0)	0	51 (0)	0	49 (0)	2	150 (0)	2
Hong Kong	99 (1)	1	101 (0)	1	100 (0)	0	300 (1)	2
Manchester	51 (2)	1	49 (5)	1	49 (5)	0	149 (12)	2
Nanjing	78 (3)	1	82 (2)	0	80 (3)	1	240 (8)	2
San Francisco	16 (0)	1	17 (0)	1	17 (0)	0	50 (0)	2
Shanghai	50 (1)	1	51 (0)	0	49 (0)	1	150 (1)	2
Tbilisi	50 (0)	0	50 (2)	1	50 (0)	0	150 (2)	1
Tianjin	50 (0)	0	51 (0)	1	49 (0)	0	150 (0)	1
All centres	572 (7)	7	575 (14)	7	570 (11)	7	1717 (32)	21

*Numbers in parentheses=numbers with unknown pregnancy outcome.

Table 1: **Numbers of women enrolled and pregnancies by centre and treatment group**

centre, according to the randomisation sequence. We attempted to maintain allocation concealment by having three pills in each bottle: two 5 mg tablets plus one placebo tablet for the 10 mg dose; one 50 mg tablet plus two placebo tablets for the 50 mg dose; and three 200 mg tablets for the 600 mg dose. Each bottle was sealed and labelled sequentially with the number of the centre, participant number, and expiry date. Participants took the three pills under observation.

Each pill bottle contained three white tablets. The 200 mg tablets were somewhat larger than the 50 mg and 5 mg tablets or placebos. Clinicians and participants were not told the composition of the three pills.

Results

We enrolled 1717 participants in 11 centres (figure 1). We intended to enrol 150 women at each of 14 sites, but three of the selected sites were unable to join the trial. Among the participating centres, some (Melbourne and San Francisco) had slower enrolment than expected, and others (Edinburgh, Hong Kong, Nanjing) agreed to recruit additional participants (table 1). Despite several attempts to trace them, 32 (1·9%) participants were lost to follow-up. One woman was found to have been pregnant at the time of treatment and was excluded from the analysis. 15 participants had protocol violations (four delay >120 h, six cycle length <24 days, five further use of emergency contraception), but they were included in the primary analysis in the groups to which they had been assigned. Thus, the final analysis included 1684 women. With this sample size, the power obtained to show equivalence is 88% (instead of 93%) for a risk of 0·5% or 57% (instead of 66%) for a risk of 1·2%.

The three randomised treatment groups were similar in baseline characteristics (table 2). Overall, the mean age was 27·8 years, weight 57·4 kg, height 163·4 cm, and cycle length 29·0 days. More than half of the women (58·2%) had been pregnant before, and 27·9% had used emergency contraception in the past. About 57% reported a condom failure, and about 41% had used no contraception at coitus. The proportions of women with an interval of more than 72 h between coitus and mifepristone treatment were 16%, 18%, and 14% in the 10 mg, 50 mg, and 600 mg groups. The 32 participants lost to follow-up were younger (mean 23 years) than the other women, but they were similar in all other important respects.

21 enrolled women were found to be pregnant after treatment (table 3), including the woman who was pregnant at the time of treatment (pregnancy 14). Six women (pregnancies 1, 8, 15, 16, 17, and 18) may have conceived 2 weeks or more after the act of intercourse that prompted treatment. These pregnancies were regarded as user failures and kept in the main analysis. Only eight of the 21 pregnant women had pregnancy tests at admission, but most had ultrasonography at follow-up (only one woman with a normal pregnancy had neither, but she had repeated HCG tests at follow-up). Two women in the 50 mg group had tubal pregnancies. The remaining 19 pregnant women opted to have induced abortion.

The proportions of pregnancies were similar in all three treatment groups (table 4). For all three pairwise comparisons between groups, the relative risks of pregnancy did not differ significantly from 1·0.

With expected number of pregnancies based on recognisable conceptions,[7] the prevented fractions for the 600 mg, 50 mg, and 10 mg groups were 84%, 86%, and 85% (table 4). Thus, overall, mifepristone prevented 85% of the pregnancies that would have occurred without treatment.

There were deviations from the study protocol for 15 participants. Ten were found retrospectively to have been wrongly recruited: four were beyond the 120 h limit; and six had usual menstrual cycles shorter than 24 days. Five women had used further hormonal emergency contraception (two used the Yuzpe regimen for additional acts of coitus during the cycle, and three received other hormonal emergency contraception).

Variable	10 mg group (n=565)	50 mg group (n=560)	600 mg group (n=559)
Demographic and anthropometric variables*			
Age (years)	27·7 (6·5)	27·9 (6·4)	27·7 (6·4)
Weight (kg)	57·0 (10·1)	57·2 (9·1)	57·9 (9·6)
Height (cm)	163·2 (5·9)	163·3 (6·2)	163·5 (6·2)
Body-mass index (kg/m^2)	21·4 (3·3)	21·4 (2·9)	21·6 (3·2)
Cycle length (days)	28·8 (2·3)	29·1 (2·6)	29·1 (2·5)
History			
Previous pregnancy	327 (57·9%)	324 (57·9%)	329 (58·9%)
Previous induced abortion	246 (43·5%)	249 (44·5%)	261 (46·7%)
Previous use of emergency contraception	175 (31·0%)	149 (26·6%)	145 (25·9%)
Previous use of other contraceptive method	525 (92·9%)	530 (94·6%)	511 (91·4%)
Reasons for requesting emergency contraception			
No method used	231 (40·9%)	227 (40·5%)	228 (40·8%)
Condom failure	321 (56·8%)	326 (58·2%)	311 (55·6%)
Other contraceptive failure	13 (2·3%)	7 (1·3%)	20 (3·6%)
Time from coitus to treatment (h)			
≤24	205 (36·3%)	185 (33·0%)	189 (33·8%)
25–48	154 (27·3%)	181 (32·3%)	173 (30·9%)
49–72	117 (20·7%)	94 (16·8%)	119 (21·3%)
73–96	61 (10·8%)	70 (12·5%)	47 (8·4%)
>96	28 (5·0%)	30 (5·4%)	31 (5·6%)

*Mean (SD).

Table 2: **Baseline characteristics of participants**

	Time from coitus to treatment (h)	Time from coitus to conception (days)	Further acts of coitus	Other features
10 mg group				
1	67	15	Unprotected	User failure*
2	114	–1	Protected	Bodyweight 126 kg
3	35	–5	Unprotected	. .
4	41	–6	None	. .
5	84	1	Protected	. .
6	56	2	Protected	. .
7	15	–5	Protected	. .
50 mg group				
8	33	24	Not known	User failure*
9	65	–7	Protected	. .
10	12	0	None	. .
11	110	–3	None	. .
12	44	NA	None	Tubal pregnancy
13	38	NA	Protected	Tubal pregnancy
14	106	–15	None	Pregnant before study
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	. .

NA=not applicable.
*Defined as a discrepancy of more than 14 days (based on ultrasonography and/or pregnancy test) between act of coitus that prompted treatment and estimated date of conception.

Table 3: **Details of pregnancies**

Omission of these 15 participants from the analysis produced almost identical results. The results for the comparison of the three doses were similar when we calculated the odds ratios by logistic regression to adjust for centre, day of the cycle in which intercourse took place, interval between intercourse and treatment, and further acts of intercourse after treatment.

Differences in the number of unreported pregnancies among the women lost to follow-up in the three treatment groups are unlikely to affect the conclusions. Even if all seven women who were lost to follow-up from the 10 mg group had been pregnant and none of those lost to follow-up from the other groups had, the relative risk of pregnancy of the 10 mg group compared with the 600 mg group would have been 2, not significantly different from 1 at the 5% level (p=0·13). On the other hand, in the best-case scenario (all women lost to follow-up included in the analysis and counted as not pregnant), the results are almost identical to those reported above.

943 women had no further acts of intercourse after the act that prompted treatment. Of 328 who received 600 mg mifepristone, one (0·3%) became pregnant; of 308 who received 50 mg, three (1·0%) became pregnant; and of 307 who received 10 mg, one (0·3%) became pregnant. Information on this variable was missing for 13 women. The comparison of the risks for these three groups showed no significant difference, but the power of the test was low owing to the small numbers of pregnancies.

For the larger group of 1651 women with no further acts of unprotected intercourse (ie, no intercourse or use of a barrier method), the pregnancy rates in the 600 mg, 50 mg, and 10 mg groups were five of 553, five of 549, and five of 549 (all 0·9%). Information on this variable was missing for 14 women. The relative risks of pregnancy of the 50 mg group and the 10 mg group compared with the 600 mg group were 1·0 (95% CI 0·3–3·4) and 1·0 (0·3–3·5).

Women who had repeated acts of coitus after treatment had a higher risk of pregnancy than those with no further acts (14 [1·9%] of 728 vs five [0·5%] of 943; relative risk 3·6 [1·3–10·0]). Women without further acts of intercourse who received treatment more than 3 days after coitus had a similar risk of pregnancy to those who received treatment earlier (one [0·7%] of 154 *vs* four [0·5%] of 789; relative risk 1·3 [0·1–11·4]).

The delay in onset of next menses was significantly (p<0·01) related to the dose of mifepristone. With women who became pregnant excluded, the proportion of women with menses delay of more than 7 days was 36% (196/547) after 600 mg, 23% (128/550) after 50 mg, and 18% (97/553) after 10 mg (figure 2). Bleeding within 5 days after mifepristone was significantly related to the dose: the proportions of women with such bleeding were 15·2% (86/565) with 10 mg, 30·7% (172/560) with 50 mg, and 35·4% (198/559) with 600 mg (p<0·01). There were no other differences in side-effects, although the proportion of women with fatigue/weakness increased with the dose (19·6% [110/562], 20·6% [115/557], and 24·2% [135/558] with 10 mg, 50 mg, and 600 mg; p=0·06). Overall, 17·4% (291/1677 [95% CI 15·6–19·3]) of women had nausea, 12·6% (211/1677 [11·0–14·3]) headache, 12·6% (212/1677 [11·1–14·3]) dizziness, and 1·7% (28/1677 [1·1–2·4]) vomiting.

Discussion

In previous trials,[1,2] mifepristone 600 mg given within 72 h of unprotected coitus was associated with no pregnancies under ideal conditions (women who conceived after treatment administration were not included in analyses). In this trial, with a larger sample size, including various populations and extending the treatment period up to 120 h, the 600 mg dose was associated with a pregnancy rate of 0·9% among women with no unprotected further acts of intercourse. The pregnancy rate including all women in that group was 1·3%; this rate is close to that found in one of the earlier trials[2] when women who conceived after treatment administration were included (three [1·55%] of 195).

	Observed pregnancies/ total	Proportion pregnant (%; 95% CI)	Relative risk (95% CI)	Number of pregnancies expected	Prevented fraction (%; 95% CI*)
Group					
600 mg	7/559	1·3 (0·5–2·6)	1·00	45	84 (67–93)
50 mg	6/560	1·1 (0·4–2·3)	0·85 (0·29–2·51)	43	86 (69–94)
10 mg	7/565	1·2 (0·5–2·5)	0·99 (0·35–2·80)†	48	85 (67–93)
All participants	20/1684	1·2 (0·7–1·8)	. .	136	85 (76–91)

*Reference category.
†1·2 (0·4–3·4) when 50 mg is reference category.

Table 4: **Pregnancy rates and prevented fractions by treatment group**

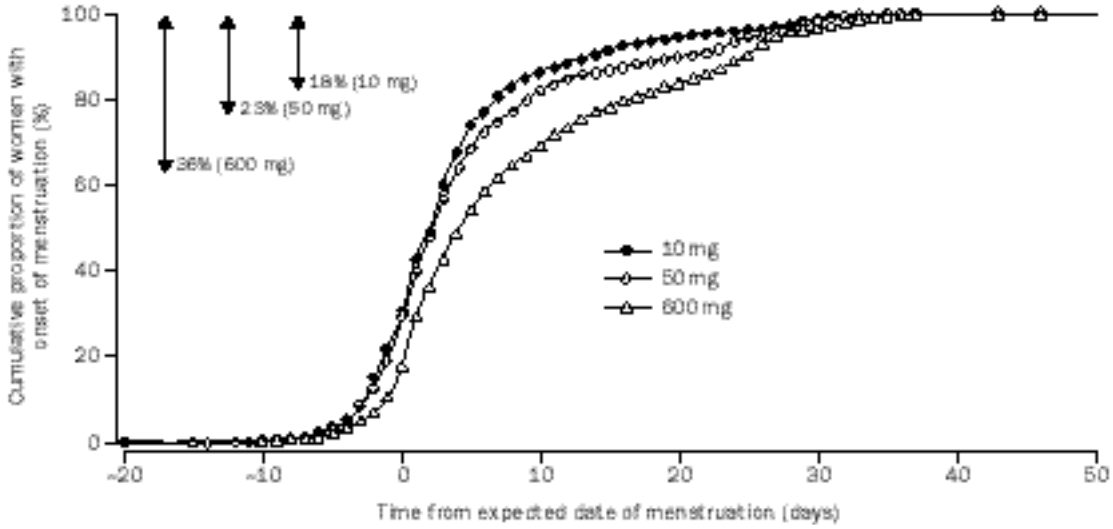

Figure 2: **Cumulative proportions of women with onset of menstruation in relation to time from expected date of menstruation**
Proportions of women with delay of more than 7 days indicated by arrows.

Lowering of the dose of mifepristone from 600 mg to 10 mg did not significantly impair its effectiveness as an emergency contraceptive measured under normal conditions or with typical use,[10] though the power in this study was such that differences in effectiveness up to almost three-fold cannot be excluded. The finding of similar results for women with no further acts of coitus and those with no unprotected acts suggests that the dose did not affect efficacy (ie, how well the method works under ideal conditions).[10]

This finding has several practical implications. A lower dose of mifepristone would be substantially cheaper. Although effective and better tolerated than the commonly used Yuzpe regimen,[1,2] mifepristone 600 mg would probably prove to be too expensive for use as an emergency contraceptive. After lower doses, women are less likely to have a delay in the onset of next menses, as shown in this trial. Not only does such delay add to worry about an unintended pregnancy, but also later ovulation exposes the woman to the risk of pregnancy should she have further acts of unprotected intercourse.

Mifepristone blocks or delays ovulation when administered during the preovulatory phase of the cycle.[3] Thus, ovulation occurs later than anticipated and women who have further acts of unprotected intercourse are at risk of getting pregnant. The delay in the onset of menses in our study was significantly related to the dose of mifepristone and was more likely to occur in the 600 mg group. This finding is consistent with the delay of menses found in previous studies.[1,2] When we looked at the discrepancy between the date of intercourse and the estimated date of conception for each pregnant woman, we found that six women apparently conceived more than 2 weeks after the act of intercourse for which they sought treatment. The possibility that three of them (1, 16, and 17 in table 3) conceived in their next cycle cannot be ruled out: they had a bleeding episode a few days after treatment which, according to the protocol, was judged to be drug-induced and not menses.

In a previous study comparing levonorgestrel and the Yuzpe regimen for emergency contraception,[11] earlier treatment within 72 h of intercourse was more effective than later treatment. Under similar conditions in this study, no effect of treatment delay was observed.

Two tubal pregnancies occurred in this study, both in the 50 mg group. No information is available about possible influence of antiprogestagens on tubal transport of the fertilised egg in women, although accelerated transport has been reported in rats.[12] If a woman already has a tubal pregnancy, mifepristone does not disturb it.[13] The two women in the study with tubal pregnancies did not have any known risk factors. Without treatment, we would have expected 136 pregnancies to occur among the participants (table 4). The proportion of extrauterine pregnancies observed in this study (two [1·5%] of 136) accords with the incidence reported in a review of ectopic pregnancy.[14]

We believe that this trial has internal validity. The randomisation produced treatment groups similar in all important respects. We attempted to conceal the allocation by using a central pharmacy; however, the pill bottles were not opaque, and the tablets used were not identical. Clinicians may have deduced that bottles containing three identical pills (200 mg tablets) were those for the 600 mg dose, but we doubt whether investigators selectively enrolled participants on the basis of that discovery.[15] We believe that participants were unaware of their treatment assignments. The objective nature of the outcome measure should have minimised the potential impact of any unmasking of the assigned treatment by clinicians involved in the study. Fewer than 2% of participants were lost to follow-up. Fewer than 1% of enrolments deviated from the protocol, and reanalysis without these women did not change the results. Although our sample size fell short of that planned, it was large enough to provide good precision for the pregnancy proportions (table 4).

We believe the trial also has external validity. The trial enrolled a heterogeneous group of women from four continents. In some centres, such as Edinburgh and Hong Kong, emergency contraception is widely known and commonly used; in others, such as Melbourne or San Francisco, this is not the case.

In much of the world, use of emergency contraception is still rare. Easy access to it may decrease numbers of unintended pregnancies.[16] Lowering the mifepristone dose from 600 mg to 10 mg has important advantages without significantly compromising effectiveness. Since mifepristone seems to be an effective emergency

contraceptive at doses much lower than those required to induce abortion, it may prove valuable in preventing unwanted pregnancies and recourse to abortion.[17] Whether mifepristone is a better choice than levonorgestrel[11] awaits the results of a randomised comparison of these two regimens. We are currently conducting such a multicentre randomised trial.

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