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Lowering the doses of mifepristone and gemeprost for early abortion: a randomised controlled trial

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Participants are listed on page 742

Objective To test the efficacy of lower doses of mifepristone and gemeprost for medical induction of early abortion.

Design Randomised controlled trial. Participants were blinded as to the therapy and physicians to the dose of mifepristone.

Setting Thirteen hospital gynaecological units in different continents.

Participants 1224 healthy pregnant women requesting medical abortion at <57 days from last menses.

Intervention Random allocation to one of four regimens: mifepristone 50 mg by mouth followed by either 0.5 mg or 1.0 mg gemeprost vaginally on day 3; mifepristone 200 mg by mouth followed by either 0.5 mg or 1.0 mg gemeprost vaginally. We concealed the allocation sequence from clinicians enrolling participants, and maintained double blinding throughout.

Main outcome measures Incidence of complete abortion; subordinate outcome measures included side effects such as vomiting and fall in haemoglobin, as well as the need for emergency curettage and blood transfusion.

Results The success rate was significantly related to the dose of mifepristone. The relative risk of failure to have a complete abortion with the lower dose of mifepristone was 1.6 (95% CI: 1.1-2.3) times that with the higher dose. The relative risk of failure with the lower dose of gemeprost (1.3; 95% CI: 0.9-1.8) did not reach statistical significance.

Conclusions A single dose of mifepristone 50 mg followed by gemeprost is inadequate for early medical abortion. There was no significant difference in side effects between the four treatment groups.

INTRODUCTION

While the sequential regimen of mifepristone (RU486) plus a prostaglandin administered two days later can safely induce abortion in early pregnancy, the optimal regimen remains unknown[1]. A randomised controlled trial[2] showed that mifepristone given in repeated doses of 25 mg every 12 h (total 125 mg) followed by gemeprost has comparable efficacy as does a single 600 mg dose followed by gemeprost. Other trials[3,4] found that reducing the single dose of mifepristone from 600 mg to 200 mg did not impair the efficacy of the mifepristone-prostaglandin regimen.

Lowering the dose of mifepristone and gemeprost might reduce both the cost of the regimen and the incidence of unpleasant side effects, such as diarrhoea and vomiting. For example, the regimen of mifepristone 200 mg orally followed by gemeprost 1mg vaginally 36-48 h later induces complete abortion in 94% of patients at <57 days of gestation[3]. Nevertheless, a quarter of women have unpleasant gastrointestinal side effects, and many request narcotic analgesia. This randomized controlled trial examined the efficacy and side effects of lower doses of both mifepristone and gemeprost comparing four regimens: 1. 50 mg mifepristone followed by 0.5 mg gemeprost; 2. 50 mg mifepristone followed by 1 mg gemeprost; 3. 200 mg mifepristone followed by 0.5 mg gemeprost; and 4. 200 mg mifepristone followed by 1 mg gemeprost.

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METHODS

Centres in 13 cities participated in this trial: Aberdeen, Chandigarh, Edinburgh, Havana, Hong Kong, Ljubljana, Lusaka, Shanghai, Singapore, Stockholm, Szeged, Tbilisi and Tianjin. The protocol was approved by the institutional review board of the World Health Organization and that of each of the participating centres.

The study population included pregnant women in good general health, who had had regular menstrual cycles of 25-35 days duration and had a normal intrauterine pregnancy of gestational age of <57days from the first day of the last menses to the day of mifepristone administration. Each participant had opted to use other than hormonal or intrauterine contraception until the first menses after abortion.

Women were excluded from the study if they had

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medical conditions which would contraindicate the use of either mifepristone (e.g. adrenal disease) or gemeprost (e.g. hypertension or glaucoma); or a history of thromboembolism, liver disease or pruritus of pregnancy. We also excluded women who had an intrauterine device *in situ* or who were breastfeeding or were heavy smokers.

Each woman signed an informed consent before enrolment and was requested to maintain a diary card to note days of bleeding and the occurrence of side effects. After admission to the study the women gave a blood sample for haemoglobin measurement and received two oral tablets: either 50 mg of mifepristone and a placebo tablet or 200 mg of mifepristone and a placebo tablet. Women returned to the clinic 48 hours later for a brief interview, review of symptoms recorded in the diary card and medical evaluation. Then the women received either a whole (1 mg) or a half (0.5 mg) vaginal pessary of gemeprost and remained under observation for 4 hours. They returned for three follow-up visits on day 8, 15, and 48 after admission.

The primary outcome measure was complete abortion, confirmed by passage of the products of conception, a negative pregnancy test, or an empty uterus on ultrasonography, and no emergency or elective curettage during the period up to first menstruation. Incomplete abortion included those requiring curettage for completion. A missed abortion included a non-viable pregnancy (a retained non-viable embryo), and a failed attempted abortion was a continuing pregnancy. Those who had vacuum aspiration before the outcome was known (e.g. women who discontinued their participation before follow up) or who were lost to follow-up were classified as undetermined. Secondary outcome measures included side effects (e.g. abdominal pain, nausea, vomiting and fall in haemoglobin) and the need for emergency curettage or blood transfusion.

The *a priori* hypothesis was that the 50 mg dose of mifepristone followed by 0.5 mg gemeprost would be less effective. We assumed a complete abortion rate of 94% with mifepristone 200 mg followed by gemeprost 1mg[3]and 87% for mifepristone 50 mg plus 0.5 mg gemeprost. With $\alpha = 5$ and a power of 80%, to show a significant difference between rates of 94% and 87%, the trial would require 302 participants per group[5]. To account for difficulties in recruiting study centres and for attrition of participants after enrolment, we attempted to enlist 16 centres, each enrolling 100 women. We felt this strategy would result in more than 1200 participants.

Two stopping rules were established for the trial before enrolment began. For safety reasons, we planned to suspend enrolment should two or more participants at any centre experience the same severe side effect attributable to the regimen. In addition, we determined that the upper 95% CI for the complete abortion rate must not fall below 90%. A data safety monitoring committee composed of WHO staff made interim reviews of the data after 50 participants, 100 participants, and every 100 participants thereafter to assess efficacy. Investigators enrolling participants were not involved in stopping decisions concerning efficacy.

The individual woman served as the unit of randomisation. We used a computer-generated random number sequence developed by staff in Geneva. The allocation sequence was concealed from investigators and participants by using sealed, opaque envelopes labelled with the study number, the name of the centre, the sequentially-assigned participant number and the expiry date of the drugs. Each envelope contained a packed mifepristone tablet and a placebo tablet and instructions for the gemeprost dose.

We maintained blinding of treatment for participants at all sites. Clinicians were kept unaware of the mifepristone dose. The mifepristone tablets (50 mg or 200 mg) and the corresponding placebo tablets supplied by Roussel-Uclaf (Romainville, France) were identical in size and external appearance. Since we could not distribute the gemeprost pessaries in envelopes, each envelope contained a method indicator card for the gemeprost dose. After opening each envelope, a person not involved with enrolment of participants gave the clinician an intact gemeprost 1mg pessary or half a pessary (divided by a sterile knife). No deviations from assigned treatment occurred. The allocation sequence was kept by the staff in Geneva and was not provided to the investigators in the centres. Analysts were not blinded as to treatment.

The data were analysed centrally in Geneva. The analyses were by intention-to-treat including participants eventually found to have been ineligible for the study. Treatment outcome was dichotomised into complete abortion or failure which includes all other categories. Crude rates for complete abortion with exact confidence intervals were calculated by the binomial distribution. Crude relative risks (RR) of failure with its 95% CI were estimated using contingency table and the adjusted Relative risks were estimated using the Generalized Linear Model. Between women and within women differences in categorical secondary outcomes were compared using Pearson's χ^2 and McNemar's tests, respectively. ANOVA was used to compare between and within women differences in continuous measurements.

RESULTS

Thirteen of 16 projected centres participated, enrolling 1224 participants. We exercised the stopping rule for efficacy during the study: the efficacy for the lowest dose regimen (mifepristone 50 mg followed by gemeprost 0.5mg) was below the predetermined cutoff at an interim analysis and we discontinued that arm of the study. A total of 249 women were enrolled in this regimen and 325 in each of the other three regimens. Nineteen participants (1.6%) were found not to be eligible

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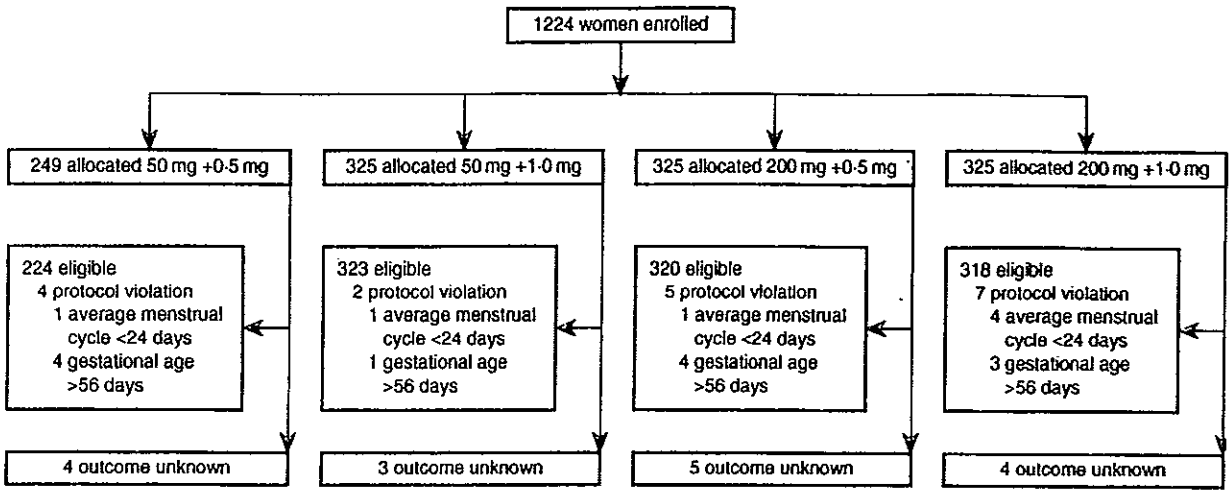

Fig. 1. Trial profile.

after randomisation (Fig. 1). These included seven who had menstrual cycles shorter than 24 days and 12 who had a gestational age >56 days. All these women were, however, included in the final analysis. The analysis thus includes all the 1224 recruited participants.

Randomisation produced similar treatment groups in baseline characteristics (Table 1). The distributions by gestational age, parity, woman's age, height and haemoglobin level were uniform across treatments. Mean weights, however, varied by 2.4 kg between groups and we examined the possible effects of this disparity in later analyses.

Of the 1224 women recruited, 1101 (90.1%) had a complete abortion (Table 2). The outcome was unknown for 16 (1.3%) women (Fig. 1). To provide the most conservative estimates of efficacy, we considered the outcomes of these 16 participants to be failures.

The abortifacient efficacy (Table 2) was related to the dose of mifepristone: the crude complete abortion rates with 95% confidence intervals were 87.6% (84.6%-90.2%) and 92.3% (90.0%-94.2%) in the 50mg and 200mg dose groups, respectively. There was an effect of the dose of gemeprost on efficacy, but it was not statistically significant: 88.7% (85.8%-91.1%) and 91.4% (88.9%-93.4%) in the 0.5mg and 1mg dose groups, respectively. The effect of mifepristone was greater with the lower dose of gemeprost (Table 2), but the difference was not statistically significant ($P = 0.49$ for the interaction).

Stated differently, the relative risk of failure to have a complete abortion with the lower dose of mifepristone was 1.6 (95% CI 1.1-2.3) times that with the higher dose regimen (Table 3). The relative risk of failure to have a complete abortion with the lower dose of gemeprost was 1.3 (95% CI 0.9-1.8) times that with the higher dose regimen. When the regimen with the lower dose of both drugs is compared with the regimen with the higher dose of both drugs, the relative risk of failure with the former (mifepristone 50mg followed by gemeprost 0.5mg) was 2.2 (95% CI 1.3-3.5) times that with the latter (mifepristone 200mg followed by gemeprost 1mg). As shown in Table 3, when adjusted for the effect of centre, the results were similar. Also the higher weight of women in the group treated with the lower doses of mifepristone

Table 1. Baseline characteristics, by treatment group. Values are given as mean (SD). GA = gestational age; PI = ponderal index; SBP = systolic blood pressure.

	Mifepristone 50 mg				Mifepristone 200 mg			
	Gemeprost 0.5 mg ($n = 249$)		Gemeprost 1.0 mg ($n = 325$)		Gemeprost 0.5 mg ($n = 325$)		Gemeprost 1.0 mg ($n = 325$)	
Age (years)	26.6	(5.1)	26.6	(5.2)	25.9	(5.4)	26.2	(5.2)
Total pregnancies[a]	2.6	(2.7)	2.6	(2.2)	2.6	(2.9)	2.5	(3.2)
GA (days)	47.8	(5.3)	48.0	(5.4)	48.1	(5.0)	47.4	(5.0)
Height (cm)	162.7	(7.2)	162.0	(6.8)	162.4	(6.6)	162.3	(6.5)
Weight (kg)	58.6	(9.2)	57.8	(8.9)	56.4	(8.2)	56.4	(8.2)
PI	22.1	(3.5)	22.0	(3.0)	21.4	(2.7)	21.4	(2.7)
SBP (mmHg)	110.8	(11.2)	110.9	(10.2)	110.1	(10.6)	110.6	(10.9)
Haemoglobin (g/dl)	12.7	(1.1)	12.5	(1.1)	12.6	(1.2)	12.6	(1.2)

[a] Previously pregnant women only.

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Table 2. Treatment outcome by group. Values are given as *n* (%).

	Mifepristone 50 mg				Mifepristone 200 mg					
Abortion type	Gemeprost 0.5 mg		Gemeprost 1.0 mg		Gemeprost 0.5 mg		Gemeprost 1.0 mg		Total	
Complete	211	(84.7)	291	(89.8)	297	(91.7)	302	(92.9)	1101	(90.1)
Incomplete	18	(7.2)	22	(6.8)	15	(4.6)	16	(4.9)	71	(5.8)
Missed	5	(2.0)	1	(0.3)	5	(1.5)	1	(0.3)	12	(1.0)
Failed attempted	11	(4.4)	7	(2.2)	2	(0.6)	2	(0.6)	22	(1.8)
Undetermined	4	(1.6)	3	(0.9)	5	(1.5)	4	(1.2)	16	(1.3)

and gemeprost did not explain the lower efficacy of this treatment.

Among the subordinate analyses, the time to onset of bleeding was strongly related to mifepristone dose. About 30% of women who received mifepristone 50mg began to bleed before the gemeprost administration, compared with 50% of those given the higher dose ($P < 0.001$). Also, in the interval between mifepristone and gemeprost administration, the relative risk of reporting dizziness was 1.3 times higher (95% CI 1.1-1.7) among women given the higher mifepristone dose compared with those given the 50 mg dose. Similarly, the relative risk of lower abdominal pain was 1.2 times higher (95% CI 1.1-1.4) in that interval in the 200 mg/group. No important differences appeared between groups in nausea, vomiting, blood pressure, pulse or temperature. Before prostaglandin administration haemoglobin levels were lower in women who received the 200 mg dose of mifepristone ($P < 0.05$), and compared with values at admission to the study they were significantly lower ($P < 0.001$) in all groups one week and two weeks after treatment. In all 29 women (2.3%) had vacuum aspiration due to heavy bleeding. Among them six (0.5%) women (two, two, one and two in different groups) were given blood transfusions. One woman had heavy bleeding the day after taking 50mg of mifepristone, and another woman had a haemorrhagic shock while still in the hospital after gemeprost administration and had to be resuscitated.

DISCUSSION

Earlier trials have shown that lowering the single dose of mifepristone from 600mg to 200mg[3,4] or to five doses of 25 mg repeated at 12-hour intervals[2] did not compromise efficacy, provided that a prostaglandin was also used. This trial now suggests that a dosage threshold exists for mifepristone when followed by gemeprost, as the efficacy declined despite the use of this effective prostaglandin in the combination regimen. Further, the decrease in the dose did not have an effect on noxious side effects, such as nausea or vomiting and the difference between two doses of gemeprost in the occurrence of abdominal pain was also insignificant.

The lack of a linear relationship between mifepristone dose and abortifacient efficacy when the drug is given in single doses higher than 100 mg may relate to the non-linear pharmacokinetics of the drug above that dose[6]. The pharmacokinetics of doses between 2mg and 25 mg appear to be linear[7] although no studies have investigated the pharmacokinetics of the 50 mg dose. Administration of mifepristone initiates degradation of the endometrium, the clinical sign of which is uterine bleeding. There appeared to be a dose-related difference in the percentage of women who started bleeding prior to prostaglandin administration in this study. Mifepristone also increases uterine contractility[8] and softens the cervix[9]. It is not known to what extent these effects are dose-related, although they seem to be related to the time interval since administration of the drug. Abdominal pain has been somewhat less with higher doses of mifepristone in previous studies[3], although not significantly so, but it may indicate better softening of the cervix with higher doses. Vomiting is a common side effect related to the use of prostaglandins. This study suggested that lowering the dose of gemeprost to a half does not significantly reduce this side effect.

This trial has both strengths and weaknesses. Its sample size was sufficiently large to detect a clinically important difference in efficacy. The participants came

Table 3. Relative risk (RR) of failure of complete abortion.

	n	%	Unadj RR	(95%CI)	Adj RR[a]	(95%CI)
Mifepristone						
200 mg	50	7.7	1.00		1.00	
50 mg	71	12.4	1.61	(1.14-2.27)	1.62	(1.15-2.27)
Gemeprost						
1.0 mg	56	8.6	1.00		1.00	
0.5 mg	65	11.3	1.31	(0.94-1.85)	1.33	(0.95-1.86)

[a] Adjusting for centres only.

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from diverse countries, which increases its relevance to broad populations of women. Randomisation and allocation concealment[10] minimised selection bias. We masked the treatment assignments for both participants and clinicians to the extent possible and used uniform outcome measures to minimise ascertainment bias. While clinicians could identify whether participants received a whole or half gemeprost pessary, we doubt this influenced the results. No prior studies have examined the effect of lowering the gemeprost dose, and previous studies[3,4] have only looked at doses above 100 mg of mifepristone. We believe that the differences in body mass observed between the groups were due to chance, but we found no evidence of confounding by Ponderal index. With single mifepristone doses of 50mg and 200mg, a dose-response relationship with efficacy is evident despite prostaglandin augmentation.

CONCLUSION

A single dose of mifepristone 50mg is significantly less effective than mifepristone 200mg, both followed by gemeprost 0.5 or 1mg. Gemeprost 0.5mg appeared to be less effective than 1mg, but this difference was not statistically significant.

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References

1. Van Look PFA, von Hertzen H. Post-ovulatory fertility regulation: the emergence of antiprogestogens. In: Van Look PFA, Perez-Palacios G, editors. *Contraceptive Research and Development 1984 to 1994*, Delhi: Oxford University Press, 1994:151–201.
2. World Health Organization. Pregnancy termination with mifepristone and gemeprost: a multicenter comparison between repeated doses and a single dose of mifepristone. *Fertil Steril* 1991;56:32–40.
3. World Health Organization Task Force on Post-ovulatory Methods of Fertility Regulation. Termination of pregnancy with reduced doses of mifepristone. *BMJ* 1993;307:532–537.
4. McKinley C, Thong KJ, Baird DT. The effect of dose of mifepristone and gestation on the efficacy of medical abortion with mifepristone and misoprostol. *Hum Reprod* 1993;8:1502–1505.
5. Machin D, Campbell MJ, Fayers PM, Pinol APY. *Sample Size Tables for Clinical Studies*. London: Blackwell Science, 1997.
6. Heikinheimo O, Kekkonen R. Doseresponse relationship of RU486. *Ann Med* 1983;25:71–76.
7. Kekkonen R, Heikinheimo O, Mandelin E, Lähteenmäki P. Pharmacokinetics of mifepristone after low oral doses. *Contraception* 1996;54:229–234.
8. Swahn ML, Bygdeman M. The effect of the antiprogestin RU486 on uterine contractility and sensitivity to prostaglandin and oxytocin. *BJOG* 1988;95:126–134.
9. Rådestad A, Bygdeman M, Green K. Induced cervical ripening with mifepristone (RU486) and bioconversion of arachidonic acid in human pregnant uterine cervix in the first trimester. *Contraception* 1990;41:283–292.
10. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodologic quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273:408–412.

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