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Mifepristone and Misoprostol Administered Simultaneously Versus 24 Hours Apart for Abortion

A Randomized Controlled Trial

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OBJECTIVE: Mifepristone and oral misoprostol are typically used for medical abortion in women up to 49 days of gestation, with a 36- to 48-hour interval between the medications. Alternative routes of misoprostol administration allow for use beyond 49 days of gestation. We designed this randomized, noninferiority trial to compare the efficacy, adverse effects, and acceptability of misoprostol 800 mcg vaginally administered simultaneously with, or 24 hours after, mifepristone 200 mg orally for abortion in women up to 63 days of gestation.

METHODS: The 1,128 participants swallowed mifepristone 200 mg and were then randomized to self-administer misoprostol intravaginally immediately in the office (group 1) or 24 hours later at home (group 2). Subjects returned for an evaluation, including transvaginal ultrasonography, 7±1 days after initiating treatment. Women who had not aborted were offered a second dose of misoprostol and returned for another evaluation in approximately 1 week. A phone contact was also attempted approximately 5 weeks after treatment. Treatment was considered a failure if a suction aspiration was performed for any indication.

RESULTS: The complete abortion rate for group 1 (95.1%, 95% confidence interval [CI] 93.0–96.8%) was statistically noninferior to that for group 2 (96.9%, 95% CI 95.1–98.2%) (*P*=.003). The abortion rates between groups did not significantly differ by gestational age. Adverse effects were mostly similar, although nausea, diarrhea, and warmth or chills were significantly more common in group 1.

CONCLUSION: Mifepristone 200 mg and misoprostol 800 mcg vaginally used simultaneously is as effective for abortion as compared with regimens using a 24-hour dosing interval.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, www.clinicaltrials.gov, NCT00269568

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LEVEL OF EVIDENCE: I

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** For members of the MAST Study Trial Group, see the Appendix.*

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Medical abortion techniques have evolved over the past 2 decades based on scientific advances. The original mifepristone and misoprostol regimens included 600 mg of oral mifepristone, followed 36–48 hours later by 400 mcg of oral misoprostol in women up to 49 days of gestation. Large, prospective, randomized trials support equal efficacy with regimens using a lower dose of mifepristone (200 mg).[1–3] Addi-

tionally, alternative methods of administration of misoprostol, including vaginal,[4–6] buccal,[7] and sublingual,[8,9] allow for use of the medications for gestations beyond 49 days of gestation.

Over the past 5 years, multiple studies have focused on the time interval between medications. Regimens with oral misoprostol are not very effective when the time interval decreases below the recommended 36–48 hours.[10] Buccal regimens appear effective with dosing intervals as little as 24 hours in women up to 56 days of gestation.[7] The largest trials include vaginal misoprostol, with which efficacy is maintained in women up to 63 days of gestation when the time interval is as little as 6–8 hours.[11] Decreasing the time interval allows most women to complete a medical abortion in less than 1 day. Additionally, because approximately 50% of women have vaginal bleeding during the 48-hour interval between mifepristone and misoprostol administration with the standard regimen,[10,12,13] administering the drugs on the same day would decrease undesirable adverse effects like bleeding.

The natural progression in the evaluation of the effect of time between mifepristone and vaginal misoprostol administration is simultaneous administration of the agents. Such studies appear scientifically rational based on available pharmacokinetic and clinical data. Vaginal administration appears to act as a depot of misoprostol acid.[14] Typically, cramping begins approximately 2 hours and bleeding about 3 to 3½ hours after misoprostol placement.[11,15,16] Significant serum levels of misoprostol acid are still present 4 hours after administration based on the pharmacokinetic profile,[14] thereby rationalizing simultaneous application.

Pilot trials were performed with the primary objective of evaluating 24-hour expulsion rates after simultaneous administration of mifepristone 200 mg and vaginal misoprostol 800 mcg.[17,18] These trials included 120 women, with 40 women in each of the gestational age ranges of 49 days or less, 50–56, and 57–63 days of gestation. The expulsion rates of 90%, 88%, and 85%, respectively, were similar to those seen in regimens with intervals of 6–8 hours,[15,16] demonstrating the potential efficacy of these drugs for medical abortion when administered simultaneously. We performed this prospective, randomized, multicenter trial to compare the efficacy, adverse effects, and acceptability of misoprostol 800 mcg vaginally administered simultaneously with, or 24 hours after, mifepristone 200 mg orally in women up to 63 days of gestation. This study is designed as a noninferiority trial, with efficacy as the primary outcome variable.

MATERIALS AND METHODS

The study was conducted at four centers: the University of Pittsburgh, Oregon Health and Science University, Northwestern University, and the University of Southern California. The study was reviewed and approved by the institutional review boards of the respective institutions and by the U.S. Food and Drug Administration (FDA). The University of Pittsburgh served as the sponsoring institution; all protocol changes were submitted and approved by the University of Pittsburgh Institutional Review Board before submission to other institutions. All participants provided written consent before participation in the study.

We enrolled 1,128 healthy women who were requesting an elective abortion, had an intrauterine pregnancy at 63 days of gestation or less on the day of mifepristone administration as confirmed by vaginal ultrasonography, were willing to comply with the visit schedule, were willing to have a surgical abortion if indicated, and had access to a telephone. Potential subjects were excluded if they had any contraindication to mifepristone, including chronic systemic corticosteroid administration or adrenal disease; had any contraindications to misoprostol, including glaucoma, mitral stenosis, sickle cell anemia, poorly controlled seizure disorder, or known allergy to prostaglandin; had a hemoglobin level less than 10 g/dL; had cardiovascular disease, including angina, valvular disease, arrhythmia, or cardiac failure; had a known coagulopathy or were receiving treatment with anticoagulants; had a pregnancy with an intrauterine device in utero; had an ultrasound examination that demonstrated any evidence of an early pregnancy failure; had active cervicitis on examination; were breastfeeding; or had previously participated in the trial.

After obtaining informed consent, a medical history was reviewed, hemoglobin and blood type were obtained, and pelvic and transvaginal ultrasound examinations performed. Only women with a visible intrauterine gestational sac were eligible. Mean sac diameter ([length+width+depth]/3) was used to determine estimated gestational age (EGA) when an embryonic pole was absent using the formula: mean sac diameter (EGA [days]=mean sac diameter [mm]+30).[19] For gestations with an embryonic pole, the formula embryonic pole (EGA [days]=embryonic pole [mm]+42) was used.[20] Last menstrual period (LMP) was used to determine EGA if the LMP was within 3 days of the ultrasound EGA, but the ultra-

sound estimate was used if it differed by 4 days or more from the EGA by LMP.

At the University of Pittsburgh, subjects returned for enrollment at least 24 hours after signing informed consent as required by the Pennsylvania Abortion Control Act. At all other sites, screening and enrollment occurred at the same visit. Once entry criteria were confirmed, each woman was counseled further about the correct method of inserting the misoprostol. She then swallowed mifepristone 200 mg, after which the randomization envelope was opened by the research staff. Women randomized to immediate insertion (group 1) went into an examination room in the office and inserted 4 tablets of misoprostol 200 mcg as high up as possible into the vagina within 15 minutes of swallowing the mifepristone. Those women randomized to routine insertion (group 2) were given the misoprostol tablets to take home with instructions to insert the misoprostol tablets 23–25 hours after taking the mifepristone. Group assignment was performed in a randomized fashion using sequentially numbered opaque envelopes containing a card with computer-generated assignment information and prepared for each center by the Data Coordinating Center. Randomization was stratified by center with equal frequency to the two treatment arms. Random allocations were performed in a permuted block design with varying block sizes as described by Pocock.[21]

Rh-immune globulin 50 mcg intramuscularly was administered to all subjects who were Rh-negative. Subjects were given written instructions regarding pain medication use and bleeding parameters. Women were advised to contact the research office if vaginal bleeding exceeded two soaked sanitary pads per hour for 2 consecutive hours. Participants were given a prescription for or supply of 20 tablets of codeine phosphate (30 mg), oxycodone (5 mg), acetaminophen with codeine (300 mg/30 mg) (with instructions not to take more than 13 tablets in a 24-hour period), or acetaminophen with hydrocodone (500 mg/5 mg) (with instructions not to take more than 8 tablets in a 24-hour period). Subjects were instructed to use ibuprofen or acetaminophen initially and to use the prescribed narcotic only if necessary. Subjects were asked to maintain a daily diary of medication use and adverse effects throughout the study. At each follow-up visit, the diary was reviewed and data collected regarding bleeding, cramping, other adverse effects, and medication use since the prior visit. An investigator was available 24 hours a day in the case of emergency and to answer subjects' questions.

Participants were scheduled to return for a follow-up examination 7 (±1) days after taking mifepristone, during which transvaginal ultrasonography was performed. Women who had not expelled the gestational sac were offered a repeat dose of misoprostol and scheduled to return. Subjects who missed the first follow-up visit and were not seen again until 12 or more days after receiving the mifepristone could not receive a second dose of misoprostol.

All women had a follow-up contact scheduled at 14 (±2) days after mifepristone administration. Those women who had expelled the pregnancy received a phone call from the researchers, and those who had not expelled the gestational sac returned for a visit that included transvaginal ultrasonography. Subjects who had not aborted by the second follow-up and had a viable gestation were offered a surgical abortion. Women with a nonviable persistent gestation at the second follow-up were offered a surgical abortion or scheduled to return again in another 3 weeks. If the abortion had not been completed by this final follow-up visit, subjects were offered a surgical abortion or weekly follow-up. Suction aspiration was also performed at any time if it was clinically necessary because of uterine hemorrhage or incomplete abortion, or at the subject's request.

Five weeks after initiating the study, we attempted to contact by telephone all women who had expelled the gestational sac by the first or second follow-up visit to review if there have been any problems since the abortion. The procedure was considered successful if the abortion occurred without requiring a suction aspiration. Neither the study staff, investigators, or participants were blinded to treatment group, as is common in medical abortion trials.[11]

Immediately before enrollment, women completed a questionnaire regarding their prior experience with abortion and a visual analog scale (VAS)[22,23] measuring the amount of pain and bleeding they anticipated. At each participant's final follow-up visit, she was questioned about her satisfaction with this medical abortion regimen and completed a VAS measuring the amount of perceived bleeding and pain experienced during the abortion process and her preference for medical or surgical abortion if she needed an abortion again in the future. On a 100-mm line, with 0 equaling no bleeding and 100 equaling heavy bleeding, subjects were asked to mark the amount of bleeding they experienced. In a similar fashion, level of pain was recorded, with 0 equaling no pain and 100 representing severe pain. Likewise, preference for abortion method was recorded, with 0

equaling medical abortion and 100 representing surgical abortion.

On-site monitoring was performed by staff from the Data Coordinating Center at a minimum of every 4 weeks or upon request of the Principal Investigator. The monitor reviewed the center's documents to ensure appropriate institutional review board approval and communication as well as accurate and appropriate reporting of source data.

Sample size was estimated to demonstrate noninferiority of the study treatment (simultaneous administration) to standard treatment (24-hour interval). The complete abortion rate in the standard care group (group 2) was set at 97%.[11] Using a one-sided, two-group test of equivalence, 552 subjects per group were required to demonstrate equivalence within a 3% observed difference (upper 95% confidence interval of 5%).[24] This sample size was statistically able to establish noninferiority with the same 3% observed difference, with an efficacy in the standard group as high as 100% and as low as 95%. To allow for 2% of subjects to not have documentation of a final outcome, the total sample size was increased to 1,128 women. Because individual adverse effects in medical abortion regimens using these agents typically occur at a rate exceeding 10%,[11,13,15,16,25] this sample size had 80% power to detect at least a 60% difference in the rates of adverse effects between the two treatment groups. For adverse effects occurring at rates of 20%, this study had 80% power to detect at least a 45% difference between the two groups.

Baseline demographic data were compared according to treatment group using Student *t* test, Fisher exact test, χ^2 test, or χ^2 test for linear trend, where appropriate, to assess for clinically significant differences. An intent-to-treat analysis was performed to include all women with adequate follow-up defined as having at least one follow-up visit, more than one phone contact beyond 7 days after using the medications with a history by phone consistent with expulsion, or by review of outside records that confirmed expulsion.

The primary objective of this study was to compare complete abortion rates in women who received mifepristone followed by vaginal misoprostol within 15 minutes (experimental group) and 24 hours later (standard care group) using a one-sided equivalence test of proportions, with an equivalence limit of 5%. The null hypothesis for the test of equivalence is that two treatments are not equivalent. Rejecting the null hypothesis, indicated in this study by $P \leq .05$, implies that the two treatments are equivalent.[24] Interim analyses based on the complete abortion rate (both overall and stratified by gestational age) were conducted when 360 women and 720 women (approximately 33% and 66% of the study population, respectively) completed their follow-up visits. This interim analysis reduced the alpha for the final analysis to 0.0472 according to the O'Brien and Fleming method.[26]

Secondary outcomes included evaluation of the efficacy of mifepristone and one dose of misoprostol, adverse effects, bleeding, and acceptability data. Gestational age efficacy (overall, within group, and after mifepristone and a single dose of misoprostol) and the rate of adverse effects by gestational age were evaluated using the χ^2 for linear trend. Efficacy within groups by study site was evaluated using the χ^2 test. The rate of adverse effects (nausea, vomiting, and pain medication use), bleeding, and acceptability, as measured by positive or negative answers, between the two abortion regimens was compared using Fisher exact test. The length of bleeding after treatment, and the pre- and posttreatment VAS assessments were compared between treatment groups using the Mann-Whitney *U* test because these data did not appear to be normally distributed when their frequency distributions were graphically displayed. For analyses of adverse effects, bleeding, and acceptability data, two-tailed *P* values less than .05 were considered statistically significant.

RESULTS

Between April 2004 and May 2006, 1,128 subjects were enrolled (Fig. 1). Both groups were similar in demographic characteristics (Table 1). The gestational age was set by LMP and confirmed by ultrasonography in 49% and 45% of women in groups 1 and 2, respectively. The remaining women had their gestational ages adjusted by the ultrasound examination.

A final outcome was established for 1,100 women, with 26 (2.3%) women lost to follow-up (Fig. 1). A small number of women (19, 1.7%) had follow-up consisting only of multiple phone contacts or by review of medical records subsequent to the occurrence of the medical abortion; all of these women had histories consistent with expulsion and no signs of a continuing pregnancy. The median times of misoprostol administration in groups 1 and 2 were 5 minutes and 24 hours after mifepristone, respectively. All subjects in group 1 (0.2%) except for one used the misoprostol within 15 minutes of the mifepristone; the one outlier used her dose at 24 minutes. In group 2, four (0.7%) women did not use the misoprostol at the correct time, defined as more than 15 minutes outside of the assigned time interval. These four women used

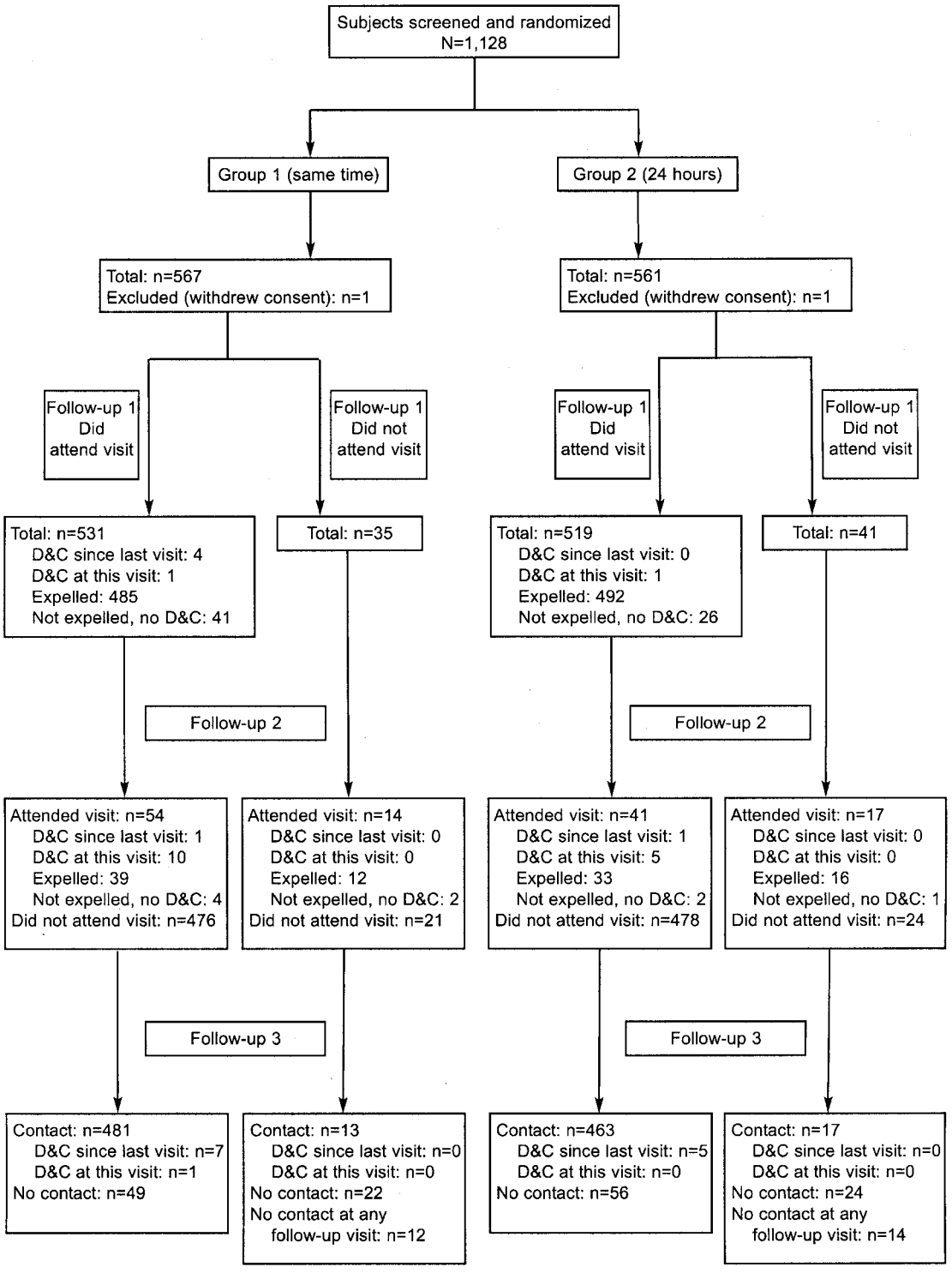

Fig. 1. Flow of study participants. Group 1: mifepristone 200 mg orally followed within 15 minutes by misoprostol 800 mcg vaginally. Group 2: mifepristone 200 mg orally followed by misoprostol 800 mcg vaginally 23–25 hours later. Follow-up 1: scheduled visit 7 (±1) days after mifepristone. Follow-up 2: scheduled visit 14 (±2) days after mifepristone. Follow-up 3: scheduled visit (if patient had not expelled pregnancy by follow-up 2 and pregnancy was nonviable) or scheduled phone call 5 weeks after mifepristone. Two subjects in group 1 and five subjects in groups 2 had dilation and curettage (D&C) after the final scheduled follow-up contact. One subject in group 1 received additional misoprostol at the day 35 visit and was considered a treatment failure.

Creinin. Medical Abortion. Obstet Gynecol 2007.

Table 1. Baseline Demographics of Study Population

	Study Treatment (Interval 0–15 min) (n=554)	Standard Treatment (Interval 23–25 h) (n=554)
Gestational age (d)	50±8	51±8
49 or less	266 (48)	229 (42)
50–56	159 (29)	172 (32)
57–63	129 (23)	145 (27)
Age (y)	26±6	26±6
Gravidity		
1	161 (29)	143 (26)
2	111 (20)	108 (20)
3	100 (18)	105 (19)
4	67 (12)	83 (15)
5 or more	115 (21)	107 (20)
Parity		
0	246 (44)	216 (40)
1	147 (27)	140 (26)
2	88 (16)	127 (23)
3 or more	73 (13)	63 (12)
Race		
White	371 (67)	331 (61)
Black	152 (27)	175 (32)
Other/none of these	31 (5)	40 (7)
Hispanic ethnicity	60 (11)	69 (13)
Marital status		
Single	426 (77)	430 (79)
Married	80 (14)	66 (12)
Divorced/separated	48 (8)	50 (9)
Living with partner*	218 (39)	182 (33)
Prior elective abortion(s)	234 (42)	231 (42)
Prior medical abortion(s)	56 (10)	68 (12)

Data are expressed as n (%) or mean±standard deviation.
* P=.04. All other variables P>.05 by Fisher exact test, χ^2 test, χ^2 test for linear trend, or Student t test, where appropriate.

the misoprostol at 21.45 hours, 22.75 hours, 25.33 hours, and 44.75 hours. Additionally, one subject in group 2 swallowed her misoprostol; she was at 57 days of gestation and failed treatment but was included in the analysis.

The efficacy of treatment in women with simultaneous administration was noninferior to that in women who administered the medications 24 hours apart (Table 2) (P=.003). If the women who were lost to follow-up were included as treatment failures, the outcomes were still equivalent (data not shown). However, the success rates with mifepristone followed by a single dose of misoprostol were different (Table 2) (91% versus 94%, respectively, P=.1 for noninferiority). There was no trend for decreasing success overall or with mifepristone and a single dose

Table 2. Complete Abortion Rate With Mifepristone 200 mg Followed by Misoprostol 800 mcg Vaginally*

	Study Treatment (Interval 0–15 min)	Standard Treatment (Interval 23–25 h)	P†
Overall (d)	95.1 (93.0–96.8) (n=554)	96.9 (95.1–98.2) (n=546)	.003
49 or less	95.5 (92.3–97.6) (n=266)	98.3 (95.6–99.5) (n=229)	.08
50–56	94.3 (89.5–97.4) (n=159)	95.3 (91.0–98.0) (n=172)	.051
57–63	95.3 (90.2–98.3) (n=129)	96.6 (92.1–98.9) (n=145)	.06
With single dose misoprostol (d)	91.0 (88.3–93.2) (n=554)	94.0 (91.6–95.8) (n=546)	.1
49 or less	90.6 (86.4–93.8) (n=266)	94.3 (90.4–96.9) (n=229)	.3
50–56	89.9 (84.2–94.1) (n=159)	93.0 (88.1–96.3) (n=172)	.3
57–63	93.0 (87.2–96.8) (n=129)	94.5 (89.4–97.6) (n=145)	.1

Data are expressed as % (95% confidence interval).
* Women who were lost to follow-up are excluded.
† Values are from Fisher exact test; P<.05 implies noninferiority.

of misoprostol with increasing gestational age within study groups ($P>.3$ for all comparisons). There was also no difference for overall efficacy within study groups by study site (data not shown).

Treatment failures in groups 1 and 2 included viable pregnancy at the second follow-up visit (four women and one woman, respectively), persistent nonviable pregnancy at the second follow-up visit (seven and four women, respectively), persistent nonviable pregnancy at the third follow-up visit (two women and 1 woman, respectively), incomplete abortion (12 and 11 women, respectively), and subject request (two and no women, respectively).

Cramping began after a median of 2.5 hours (range 0 to 143 hours) and 1.7 hours (range –24 to 115 hours) after misoprostol administration in groups 1 and 2, respectively ($P<.001$). Bleeding began after a median of 3.7 hours (range 0 to 74 hours) and 2.0 hours (range –23 to 24 hours), respectively ($P<.001$). Pad count data were available for 549 (99.1%) and 544 (99.6%) women in groups 1 and 2, respectively. For these women, 31.5% and 36.8% reported that the heaviest amount of bleeding they experienced was soaking at least two pads in 1 hour ($P=.07$). There was also no difference in the number of women who reported that the heaviest amount of bleeding exceeded two pads in 1 hour (9.7% versus 10.1%, $P=.8$). Bleeding and spotting duration was not different between groups, lasting a median of 10 and 15 days, respectively, for women in group 1, and 10 and 14 days, respectively, for women in group 2 (Table 3).

Adverse effects are presented in Table 4. Women in group 1 had statistically significantly higher rates of nausea, diarrhea, and warmth or chills after misoprostol administration. Bleeding, cramping, and acceptability information are presented in Table 3. Complete pre- and posttreatment VAS assessments were available for 533 (96%) and 527 (97%) women in groups 1 and 2, respectively. The median level of pain reported on the post-questionnaire was 64 mm and 62 mm, respectively. The indicated level of pain was 3 mm higher in group 1 and 2 mm lower in group 2 than that anticipated on pretreatment VAS assessment in both groups. The findings were similar for bleeding, with a median posttreatment severity of bleeding of 63 mm and 64 mm for groups 1 and 2, respectively, and the differences as compared with pretreatment estimation of bleeding, 8 mm and 7 mm lower, respectively.

Serious adverse events occurred in 17 (1.5%) women. Four women (0.4%) received a transfusion, all in group 2, with gestational ages at initiation of treatment of 50, 51, 57, and 63 days. One subject in group 1 had a heterotopic pregnancy and had surgery for the tubal gestation after a successful medical abortion. Two other women had hospitalizations for events unrelated to the medical abortion. In addition to these serious events, 10 women (0.9%), five in each group, were diagnosed with acute pelvic infection after the medical abortion but were treated as outpatients. One of these infections (in group 2) occurred after a suction aspiration for an incomplete abortion.

Table 3. Cramping, Bleeding, and Acceptability Information With Mifepristone 200 mg Followed by Misoprostol 800 mcg Vaginally

	Study Treatment (Interval 0–15 min) (n=554)	Standard Treatment (Interval 23–25 h) (n=546)	*P*
Cramping			
Onset (h, median)	2.5	1.7	<.001*
Range (h)	0–143	24–115	
Bleeding			
Onset (h, median)	3.7	2.0	<.001*
Range (h)	0–74	−23–24	
Bleeding duration			
Spotting (d, median)	10	10	.98*
Bleeding (d, median)	15	14	.4*
Heaviest bleeding (%)†			
Soaked 2 pads/h or more	31.5	36.8	.07‡
Soaked 3 pads/h or more	9.7	10.1	.8‡
Acceptability (%)§			
Would recommend to a friend	94	94	1.0‡
Would choose method again	88	89	.5‡

* *P* value from Mann Whitney *U* test.
† Greatest number of pads soaked in 1 hour; data available for 549 (99.1%) and 544 (99.6%) women in groups 1 and 2, respectively.
‡ *P* value from Fisher exact test.
§ Data available from 545 (98%) and 536 (98%) women in groups 1 and 2, respectively.

Table 4. Adverse Effects After Treatment With Mifepristone and Misoprostol

	Standard Treatment (Between Mifepristone and Misoprostol) (n=544)	Standard Treatment (After Misoprostol) (n=544)	Study Treatment (n=550)	P*
Nausea	29	51	58	.04
Vomiting	9	31	31	1.0
Diarrhea	5	26	35	.002
Warmth/chills	15	56	69	<.001
Headache	18	36	40	.2
Dizziness	9	37	39	.5
Cramping	21	96	97	.3
Spotting	9	–	–	–
Bleeding	6	100	100	.2

Data are expressed as percentages.
All subjects received mifepristone 200 mg and misoprostol 800 mcg vaginally. Women receiving standard treatment inserted the misoprostol 23–25 hours after mifepristone; those receiving study treatment inserted the misoprostol within 15 minutes of mifepristone administration.
* Comparing adverse effects after misoprostol treatment.

DISCUSSION

We have demonstrated that simultaneous administration of mifepristone and vaginal misoprostol is at least as effective as administration of the medications 24 hours apart. The sample size was calculated to evaluate noninferiority for the overall study sample and was not large enough to determine noninferiority at each gestational age range. However, even with smaller samples within each gestational age range, the abortion rates within each gestational age range were almost noninferior, with *P* values of .051 to .08 (Table 2), suggesting that larger trials would likely demonstrate equivalence. The point difference between the two treatment groups was 3%, the value declared a priori for noninferiority of the overall complete abortion rates. Given that the standard treatment group had a single-dose efficacy below 95%, the sample was not large enough to demonstrate this 3% difference to be noninferior.

The complete abortion rates[4,11,27] and adverse effect rates[11] in the standard treatment groups were similar to those previously published for this regimen, inferring external validity. In a prior trial comparing dosing intervals of 6–8 hours and 23–25 hours, women in the shorter interval group experienced fewer adverse effects and were less likely to experience significant bleeding.[11] Further shortening the interval to simultaneous dosing does not appear to create these same benefits in relation to adverse effects or bleeding. It is possible that the lack of a decrease is, in reality, the result of women experiencing adverse effects from both the mifepristone and misoprostol when administered simultaneously. Importantly, the differences, albeit statistically significant, are relatively small and are not likely to have clinical relevance as evidenced by the high and equal satisfaction in both treatment groups.

When this study was initiated, the "evidence-based" use of vaginal misoprostol was very common in the United States. In December 2005, Fischer et al[28] reported four deaths in the United States from *Clostridium sordellii* infection in women who had received mifepristone and vaginal misoprostol. A fifth infectious death, related to *C perfringens*, was reported at a Centers for Disease Control and Prevention meeting in May 2006.[29] One theory about infection and medical abortion is that mifepristone causes immunosuppression[30]; however, more widespread and serious infections would be occurring with more common organisms. In our current study, mild infection was diagnosed in less than 1% of subjects, a rate that is too low to support the idea of significant immunosuppression. Another theory is that use of the misoprostol vaginally increases the likelihood of infection with rare organisms. Such a finding would obviate the importance of this study. Additional recent reports have linked *C sordellii* infection to the deaths of eight women who recently had delivered infants either vaginally or by caesarean, two women who had miscarriages, and one woman who was infected during her menstrual period.[29] Obviously, neither mifepristone nor vaginal misoprostol was routinely used in these cases. For now, the evidence does not allow any inference as to whether the use of vaginal misoprostol as opposed to other routes impacts this risk. It is unclear if these rare infectious deaths with medical abortion are a direct effect of the medications used or a result of the process of medical abortion caused by the medications.

We, as providers and policy makers, may not be able to globally categorize how women assess risks and benefits of pregnancy options, and it is likely that such decisions are complex and personal. If there really is an increased risk of death with medical as compared with early surgical abortion, that difference

is likely 1 per 100,000 with medical abortion[31] and 1 per million with early surgical abortion.[32] For perspective, the mortality risk with a term delivery is 1 per 10,000.[33] The risk of death is small regardless of pregnancy outcome, but the experience of each process for the woman is vastly different. The current study shows that women can use regimens with vaginal misoprostol without any time delay between medications with efficacy that is similar to those with a delay. Studies with a 6–8 hour interval demonstrate fewer adverse effects than those with a 24-hour interval. For women, what is the relative value of all of these differences? Would women prefer a vaginal route with fewer adverse effects or the ability to have their abortion completed sooner? Are changes in mortality from very, very rare to very, very, very rare more relevant to a woman than significant decreases in adverse effects or timing issues? These are questions we need to understand better to provide the best options for women.

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APPENDIX

The following institutions and persons participated in the MAST Study Trial. The principal investigators at each center are indicated by asterisks.

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