Original Research

Simultaneous Administration Compared With a 24-Hour Mifepristone–Misoprostol Interval in Second-Trimester Abortion

A Randomized Controlled Trial

Dina Fatima Abbas, MPH, Jennifer Blum, MPH, Nguyen Thi Nhu Ngoc, MD, MSc, Nguyen Thi Bach Nga, MD, Huynh Thi Kim Chi, MD, Roxanne Martin, and Beverly Winikoff, MD, MPH

OBJECTIVE: To compare outcomes with simultaneous administration of mifepristone and misoprostol with a regimen in which the drugs are administered at a 24-hour interval for second-trimester abortion.

METHODS: In this placebo-controlled, double-blind trial, participants were randomized to receive mifepristone either 24 hours before or at the same time as misoprostol. Participants were hospitalized to receive 400 micrograms buccal misoprostol at 3-hour intervals up to 48 hours or until uterine expulsion. The primary outcome was the proportion of women who experienced uterine expulsion within 24 hours after the first misoprostol dose and this required 504 women to examine our hypothesis that this rate would be 85% in the 24-hour interval arm compared with 70% in the simultaneous arm. Secondary outcomes included total abortion time from mifepristone and misoprostol.

RESULTS: From February 2013 to April 2014, 509 women were enrolled. Women in the 24-hour interval arm were more likely to abort within 24 hours (94.4% compared with 85.0%, relative risk 1.11, 95% confidence interval [CI] 1.05–1.18). At 48 hours, the rate was similar in the two arms (96.8% [24-hour interval] and 95.7% [simultaneous], relative risk 1.01, 95% CI 0.97–1.04). Median misoprostol dosing time was shorter in the 24-hour interval arm (7.7 compared with 13 hours; $P<.001$) and consistent with the median misoprostol doses required (three compared with five; $P<.001$). Median time from mifepristone to uterine expulsion was longer in the 24-hour interval arm (32.3 compared with 13 hours; $P<.001$). Both regimens had high acceptability rates and reported similar side effects and pain scores.

CONCLUSION: Administering mifepristone and misoprostol simultaneously results in lower expulsion rates within 24 hours of taking misoprostol, longer median misoprostol treatment times, and requires more misoprostol doses. At 48 hours, both regimens work equally well. Simultaneous dosing results in less total time from the first clinical contact to complete abortion.

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Mifepristone+misoprostol is a safe and effective alternative to surgery for second-trimester abortion.[1] Pretreatment with mifepristone 24–48 hours before initiating misoprostol dosing results in decreased induction to abortion time in the second trimester.[2–4] However, this time interval lengthens the total abortion time when calculated from administration of mifepristone to expulsion.

In the second trimester, few studies have explored a shorter mifepristone and misoprostol dosing interval, which increases the induction to abortion time

From the Gynuity Health Projects, New York, New York; the Center for Research and Consultancy in Reproductive Health, Ho Chi Minh City, Vietnam; and Hung Vuong Hospital and Binh Duong Hospital, Ho Chi Minh City, Vietnam.

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Corresponding author: Dina Fatima Abbas, MPH, Gynuity Health Projects, 15 East 26th Street, Suite 801, New York, NY 10010; e-mail: dabbas@gynuity.org.

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and lowers the success rate.[5–8] However, one previous trial examined simultaneous administration in second-trimester abortions and found that 98.6% of women who used the drugs simultaneously has a successful abortion within 48 hours.[5]

In Vietnam, as in parts of the United States, second-trimester abortion services are typically offered at higher level health facilities and may necessitate multiple clinic visits that are inconvenient and increase overall cost in the form of travel and overnight housing.[5,9] Evidence suggests that women prefer quicker abortion procedures, fewer clinic visits,[10,11] and a shorter interval between administration of mifepristone and misoprostol.[12,13]

Simultaneous use of mifepristone–misoprostol and no limit to the number of misoprostol doses are two strategies that could shorten the overall process time and clinic visits, yet few prospective studies have explored either strategy. This trial sought to compare administration of 200 mg mifepristone simultaneously with or 24 hours before 400 micrograms buccal misoprostol followed by misoprostol doses every 3 hours for medical abortion at 13–22 weeks of gestation.

MATERIALS AND METHODS

This double-blind placebo-controlled randomized trial was conducted at Hung Vuong Obstetrics and Gynecology Hospital in Ho Chi Minh City (tertiary care facility) and Binh Duong Obstetrics and Newborn Hospital (secondary facility) in Binh Duong Province in Vietnam. The protocol was approved by the ethical review boards at both hospitals.

The trial enrolled women with a live fetus presenting for termination of intrauterine pregnancy 13–22 weeks of gestation by ultrasonography and who were eligible for medical abortion as determined by clinical history and examination. Inclusion criteria were closed cervical os, no vaginal bleeding, and no known contraindications to the study drugs. Exclusion criteria were history of transmural uterine incision, contraindications to vaginal delivery, parity greater than five, active labor, or signs of infection. Consenting women were randomized to receive 200 mg mifepristone either 24 hours before or at the same time as the start of treatment with misoprostol.

Participants received either 200 mg mifepristone or placebo (study packet one) at the first visit and were hospitalized 24 hours later to receive the drugs in study packet two: placebo or 200 mg mifepristone (per randomization) followed immediately by 400 micrograms misoprostol. Misoprostol was administered buccally with one 200-microgram tablet in each cheek for 30 minutes before swallowing remaining fragments. Additional doses of 400 micrograms buccal misoprostol were administered every 3 hours until fetal expulsion or for up to 48 hours. An additional 200 micrograms buccal misoprostol was administered to facilitate placental expulsion if it did not occur within 30 minutes of fetal expulsion. Women who did not abort by 48 hours were discharged from the study and could opt for surgical management or repeat medical abortion, both of which are standard care at these hospitals.

Every 3 hours, midwives recorded blood pressure, temperature, and asked participants to rate their pain using a seven-level visual analog scale. In keeping with hospital protocols, a 5-day regimen of 100 mg doxycycline was prescribed as well as oral analgesics, as needed. Before discharge, midwives interviewed all participants about their experience, side effects, and acceptability.

The sample was stratified by gestational age categories: 13–16 weeks and 17–22 weeks. Randomization was stratified by the two gestational age groups with a one-to-one allocation using blocks of six. Mifepristone and placebo were sealed in envelopes that were color-coded by gestational age (13–16 weeks; 17–22 weeks). Trial arm was blinded until completion of data collection.

The primary outcome was proportion of woman who had a complete abortion 24 hours after the first misoprostol dose. Removal of the placenta (manually or with sponge forceps) and uterine massage were not considered additional interventions. Based on findings from a previous study,[4] we hypothesized that 85% of women receiving misoprostol 24 hours after mifepristone would experience complete uterine evacuation within 24 hours compared with 70% of women who received the drugs simultaneously. A sample of 249 participants in each arm was necessary to detect the difference between 70% and 85% given a two-tailed test, a type 1 error of 5%, and 80% statistical power. We increased this sample by 5% (504) to account for loss to follow-up. Secondary outcomes included time from both the mifepristone and from the first misoprostol dose to complete uterine evacuation, additional interventions, total misoprostol dose, side effects, and acceptability.

All data were collected, entered, and analyzed using SPSS 19 and 21. Data on continuous variables are summarized as medians and ranges or means and standard deviation. Categorical data are summarized using frequency distributions. Mann-Whitney, Pearson χ^2 tests, Fisher exact test, or t test were used as appropriate. Relative risks with 95% confidence intervals were calculated to measure treatment effect for the primary and secondary outcomes. The Kaplan-Meier

Table 1. Participant Baseline Demographic and Clinical Characteristics

Outcome	24-h Interval Arm (n=252)	Simultaneous Arm (n=257)
Age (y)	24±6 (13–46)	24±6 (13–47)
13–16 wk	24±6	24±6
17–22 wk	24±6	24±6
Gravidity	82 (32.5)	98 (38.1)
13–16 wk	45/127 (35.4)	49/130 (37.7)
17–22 wk	37/125 (29.6)	49/127 (38.6)
Parity (1 or greater)	58 (23)	61 (23.7)
13–16 wk	32/127 (25.2)	35/130 (26.9)
17–22 wk	26/125 (20.8)	26/127 (20.5)
Gestational age (wk)	16.4±2.9 (12–22)	16.4±2.8 (12–22)
13–16 wk	13.9±0.9	14.1±1.1
17–22 wk	18.6±1.7	18.8±1.6
Prior induced abortion	14 (5.6)	23 (8.9)
13–16 wk	6/127 (4.7)	8/130 (6.2)
17–22 wk	8/125 (6.4)	15/127 (11.8)

Data are mean±standard deviation (range), n (%), or n/N (%).
There were no statistical differences in the baseline demographic and clinical characteristics.

method was used to generate probability estimates of time intervals to complete abortion. Stratified analyses by gestation age group (13–16 weeks and 17–22 weeks) are shown for all outcomes. Logistic and linear regression analyses were conducted to assess potential confounding factors and to determine whether any associations existed between median misoprostol dosing time and mean pain score.

RESULTS

From February 19, 2013, to April 29, 2014, 509 women were enrolled to receive mifepristone and misoprostol at either a 24-hour interval (n=252) or simultaneously (n=257). Baseline characteristics were comparable in the two trial arms (Table 1.) Four cases are excluded from the analysis: two women (one in each arm) did not return to the clinic for the second visit; one woman (simultaneous arm) received a study packet that erroneously included two tablets (of mifepristone, placebo, or both) and in one case (simultaneous arm), data on the expulsion were not recorded. All available data were analyzed for 505 women (24-hour interval n=251; simultaneous n=254). Figure 1 shows the consort flow chart for this trial.[14]

Women who waited 24 hours to take misoprostol after mifepristone were significantly more likely to expel both the fetus and placenta within 24 hours of the first misoprostol dose compared with those who took the drugs simultaneously (94.4% compared with 85%) (Table 2). Among women who took the drugs at a 24-hour interval, the rate was almost identical in the 13- to 16-week and 17- to 22-week groups (Table 2). However, in the simultaneous arm, there was a difference in this rate between these two gestational age groups (87.5% compared with 82.5%, respectively). Both regimens performed similarly by 48 hours after

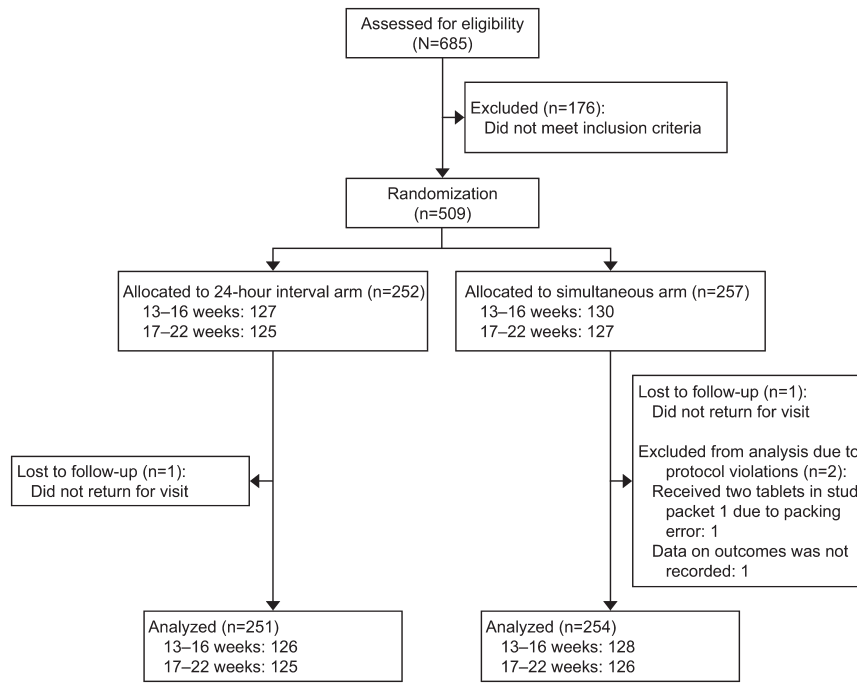

Fig. 1. Flow diagram of participants.
Abbas. Mifepristone–Misoprostol Interval in Abortion at 13–22 Weeks of Gestation. Obstet Gynecol 2016.

Table 2. Rates of Complete Uterine Evacuation and Time to Expulsion

Outcome	24-h Interval Arm (n=251)	Simultaneous Arm (n=254)	RR (95% CI)	*P*
Complete uterine evacuation at 24 h	237 (94.4)	216 (85.0)	1.11 (1.05–1.18)	<.001
13–16 wk	119/126 (94.4)	112/128 (87.5)	1.09 (1.00–1.18)	.05
17–22 wk	117/125 (93.6)	104/126 (82.5)	1.13 (1.03–1.24)	.007
Complete uterine evacuation at 48 h	243 (96.8)	243 (95.7)	1.01 (0.97–1.04)	.64
13–16 wk	122/126 (96.8)	120/128 (93.8)	1.03 (0.98–1.09)	.25
17–22 wk	121/125 (96.8)	123/126 (97.6)	0.99 (0.95–1.03)	.69
Intervention rate*	8/251 (3.2)	9/254 (3.5)†	0.89 (0.35–2.29)	.83
Oxytocin	7/251 (2.8)	7/254 (2.8)	—	
Surgical evacuation	1/251 (0.003)	2/254 (0.007)	—	
Time to complete abortion from initial misoprostol dose‡§	7.7 (2.1–40.3)	13 (4.9–47.8)	—	<.001‖
13–16 wk	6.5 (2–40.3)	12.3 (4.9–47.8)	—	<.001‖
17–22 wk	9.5 (4.6–37.1)	14.6 (5.8–47)	—	<.001‖
Time to complete abortion from mifepristone‡§	32.3 (26.9–64.8)	13.0 (4.9–47.8)	—	<.001‖
13–16 wk	33.8 (28.8–47)	12.3 (4.9–47.8)	—	<.001‖
17–22 wk	30.9 (26.9–64.8)	14.6 (5.8–47.0)	—	<.001‖
No. of misoprostol doses‡	3.3±1.9, 3 (1–14)	5.3±2.4, 5 (2–16)	—	<.001‖
13–16 wk	3.1±1.9	4.7±2.3	—	<.001‖
17–22 wk	3.9±1.7	5.8±2.5	—	<.001‖
Received greater than 5 misoprostol doses	26 (22.6)	89 (77.4)		<.001

RR, relative risk; CI, confidence interval.
Data are n (%), n/N (%), median (range), or mean±standard deviation unless otherwise specified.
* The use of sponge forceps, manual removal of placenta, and uterine massage were not considered additional interventions.
† There were two additional failures, in which both women did not expel within 48 hours. In one case the woman expelled shortly after 48 hours with the assistance of sponge forceps. In another case, the woman elected to have a repeat medical abortion.
‡ No time recorded for three cases (two in the 24-hour interval arm; one in the simultaneous arm).
§ Among women with uterine expulsion at 48 hours after receipt of the first misoprostol dose.
‖ *P* value calculated with the Mann-Whitney test.

the first misoprostol dose (24-hour interval: 96.8%; simultaneous: 95.7%) (Table 2).

The rate of additional interventions, defined as oxytocin or surgical evacuation, was low in both trial arms (24-hour interval: 3.2%; simultaneous: 3.5%). The majority of these women received oxytocin to help facilitate expulsion. Three women (24-hour interval: one; simultaneous: two) underwent surgical evacuation (Table 2). Additionally, there were two failures in the simultaneous arm: one woman elected to repeat the medical abortion and a second woman expelled shortly after 48 hours.

The median time to abortion from the first misoprostol dose was significantly shorter for women who took the mifepristone and misoprostol at a 24-hour interval (7.7 compared with 13 hours) (Table 2). This time interval was compared by Kaplan-Meier survival analysis (Table 3; Fig. 2). These times are consistent with the median misoprostol dose of 1,200 micrograms (three doses) and 2,000 micrograms (five doses) given to women in the 24-hour interval and simultaneous arms, respectively (Table 2). Regardless of regimen used, the duration of dosing with misoprostol was longer among women at

Table 3. Proportion of Women Requiring Ongoing Management by 6-Hour Time Intervals*

	Hours							
	6	12	18	24	30	36	42	48
24-h interval arm	189 (76.5)	64 (25.9)	22 (8.9)	13 (5.3)	12 (4.9)	9 (3.6)	6 (2.4)	6 (2.6)
Simultaneous arm	245 (98)	154 (61.6)	65 (26)	36 (14.4)	21 (8.4)	15 (6)	10 (4)	8 (3.2)

Data are n (%).
* Eight cases are excluded from this analysis. In five cases (two in the 24-hour interval arm and three in the simultaneous arm), women received additional interventions before 48 hours. No time was recorded in three cases (two in the 24-hour interval arm and one in the simultaneous arm).

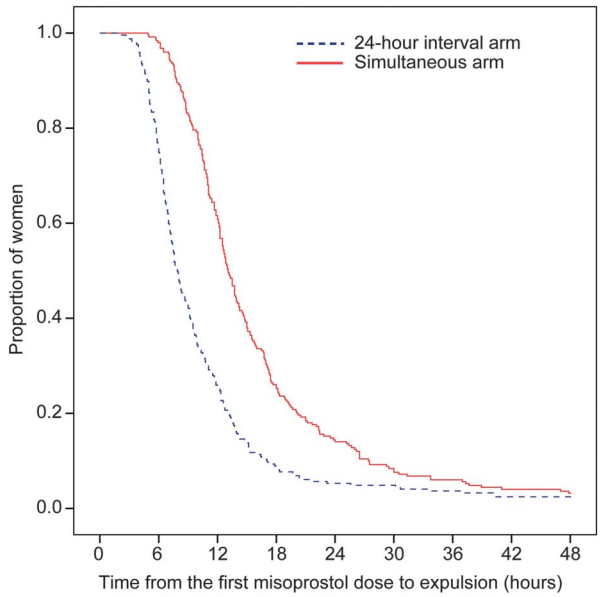

Fig. 2. Kaplan-Meier survival estimates of proportion of women with complete abortion by trial arm.

Abbas. Mifepristone–Misoprostol Interval in Abortion at 13–22 Weeks of Gestation. Obstet Gynecol 2016.

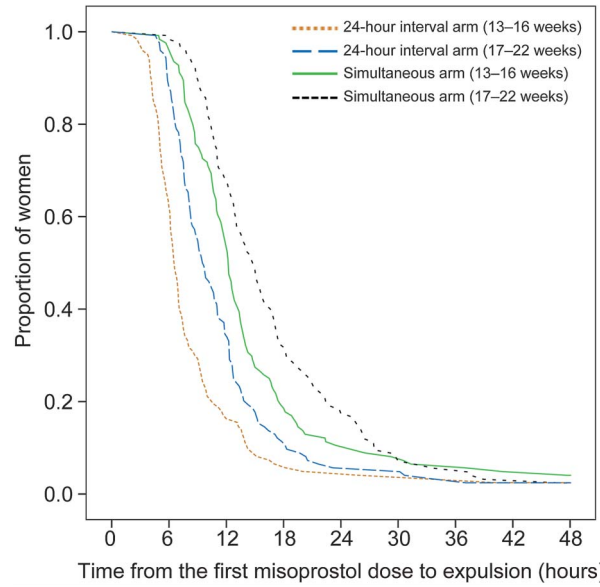

Fig. 3. Kaplan-Meier survival estimates of proportion of women with complete abortion by trial arm and gestational age group.

Abbas. Mifepristone–Misoprostol Interval in Abortion at 13–22 Weeks of Gestation. Obstet Gynecol 2016.

17–22 weeks of gestation compared with those at 13–16 weeks of gestation. Kaplan-Meier survival estimates of the proportion of women with complete abortion by trial arm illustrate the differences between gestational age groups (Fig. 3). When calculated from receipt of mifepristone, median time to abortion was significantly longer in the 24-hour interval arm (32.3 compared with 13 hours) (Table 2).

Parity did not affect rates of complete uterine evacuation or time to expulsion with the exception of the subgroup of nulliparous women presenting at 17–22 weeks of gestation and who received the drugs simultaneously. For these women the time to complete abortion from the first dose of misoprostol was longer (P=.005) (data not shown).

In both arms, participants reported similar experiences with pain with no statistically significant differences in median pain scores, severity, and acceptability of pain (Table 4). Regression analysis showed that a longer time to complete abortion from the initial misoprostol dose was significantly associated with a higher mean pain score (P=.004) (data not shown). There were no reported differences in nausea, chills, fever, and vomiting, but significantly fewer women randomized to the 24-hour interval arm experienced diarrhea. Acceptability and satisfaction data are shown in Table 4.

Two women randomized to the 24-hour interval arm were diagnosed with infection as a result of retained placenta and heavy bleeding postabortion that prolonged their hospital stay. Both women were treated with intravenous oxytocin and antibiotics. One woman in the simultaneous arm experienced heavy bleeding and received a blood transfusion. In all three cases, the women completed their abortions without recourse to surgical intervention and were discharged in stable condition.

DISCUSSION

These findings demonstrate that both regimens are effective and acceptable to terminate pregnancies in the second trimester. A 24-hour interval significantly increases the likelihood that the abortion will be complete within 24 hours of the first misoprostol dose. By 48 hours, more than 95% of women in both trial arms (P=.64) had expelled the fetus and placenta without recourse to additional interventions. In this trial, the proportion of women who experienced uterine evacuation within 24 hours in the simultaneous arm (85%) was considerably higher than those (48.3–72%) documented in previous studies of misoprostol alone in the second trimester,[2,3] indicating that the pretreatment with mifepristone was beneficial.

The 24-hour interval also shortens the median misoprostol dosing time by 5.3 hours, consequently reducing duration of labor, yet the extra 24 hours between administration of the two drugs increases the total time of the procedure nearly threefold if

Table 4. Pain, Side Effects, Acceptability, and Satisfaction as Reported by Women

Outcome	24-h Interval Arm (n=251)	Simultaneous Arm (n=254)	*P*
Pain score over time	2.1±1.1 2 (0–6)	2.2±1.2 2 (0–7)	.17*
Pain reported as			
5 or greater at least once during dosing with misoprostol	69 (27.5)	60 (23.6)	.36
5 or greater for 2 consecutive misoprostol doses	33 (13.1)	38 (15)	.61
Diarrhea	83 (33.1)	137 (53.9)	<.001
Nausea	68 (27.1)	66 (26.0)	.84
Vomiting	57 (22.7)	63 (24.8)	.60
Fever	44 (17.5)	55 (21.7)	.26
Chills	41 (16.3)	54 (21.3)	.17
Pain acceptable or very acceptable	242/250 (96.8)	249 (98.0)	.41
Side effects acceptable or very acceptable	251 (100.0)	250 (98.4)	.12
Procedure satisfactory or very satisfactory	249 (99.2)	252 (99.2)	1.0
Serious adverse events	2† (0.01)	1‡ (0.004)	

Data are mean±standard deviation, median (range), n (%), or n/N (%) unless otherwise specified.
* *P* value calculated with *t* test.
† Diagnosed with infection as a result of retained placenta (one) or heavy bleeding (one) resulting in an extended hospital stay.
‡ Transferred to emergency department as a result of heavy bleeding resulting in an extended hospital stay.

calculated from time of mifepristone (32.3 compared with 13 hours).

Gestational age and parity did not significantly affect uterine evacuation rates. However, women at 17–22 weeks of gestation received more misoprostol doses and experienced a longer time to completion, paralleling findings from other studies.[8,15–18] This difference may be the result of larger fetal size requiring more cervical dilation. Nulliparous women at 17–22 weeks of gestation randomized to the simultaneous regimen were also more likely to have a longer time to completion.

Reports of pain and most side effects are largely similar to findings from a previous second-trimester medical abortion study in this population[4] but lower than those documented in other second-trimester abortion studies.[3,5] Previous studies suggest that more misoprostol doses and longer induction to abortion are associated with significantly more analgesic use.[19] As with other measurements of pain, the information from this trial may be context-specific.

There were no safety issues reported among women who received more than five doses of misoprostol (the maximum number of doses recommended in most international guidelines).[20,21] This finding suggests that continuous dosing is clinically safe, improves expulsion rates, and is also beneficial because it shortens hospitalization. This information merits revision of dose limits in international guidelines.

A trial strength was the double-blind placebo-controlled design, which reduced the potential influence of confounding variables and health care provider bias on clinical outcomes. A limitation was that this design required all participants to make two clinic visits, thereby limiting comparisons of acceptability of these two service delivery regimens. Moreover, we were not able to analyze effects on length of hospitalization associated with each regimen because hospital administrative polices rather than medical condition heavily influenced discharge times.

Eliminating the interval between the mifepristone and misoprostol has the potential to reduce hospital visits, inherent extra time, transportation, accommodations, and other costs to receive a tablet of mifepristone. However, other strategies may also be used to alleviate some of the logistic burdens on women seeking second-trimester abortions. Decades of research has established that mifepristone is a benign drug with hardly any side effects, and indeed, taking mifepristone at home is becoming the norm for some first-trimester abortions.[22] Provision of mifepristone at a pharmacy or a geographically proximate primary health clinic would allow some women to skip the extra hospital visit to procure the mifepristone and take it 24 hours before the misoprostol. Our data from the 24-hour interval are consistent with other second-trimester abortion studies[17] and suggest that same-day outpatient care is a viable option for some women.

Although these findings show that administering the mifepristone and misoprostol at 24-hour intervals results in better clinical outcomes, the programmatic

advantages of a simultaneous regimen support the need for continued efforts to structure second-trimester abortion services to be more client-centered and provide women flexibility and autonomy without compromising the quality of clinical care.

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