Original Research

Mifepristone and Oral, Vaginal, or Sublingual Misoprostol for Second-Trimester Abortion

A Randomized Controlled Trial

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OBJECTIVE: To compare the efficacy of the vaginal and sublingual administration of the synthetic prostaglandin misoprostol with the currently used oral administration route in second-trimester medical abortion.

METHODS: This was a prospective randomized trial of medical abortion with misoprostol after mifepristone priming at 14–24 weeks of gestation. From 2009 to 2013, recruited women received 200 mg mifepristone orally followed 24–48 hours later by an 800-microgram vaginal loading dose of misoprostol. Women were then randomized to receive additional 400-microgram misoprostol doses orally every 3 hours, vaginally every 4 hours, or sublingually every 3 hours. The main outcome was the duration of abortion with emphasis on the proportion of women undelivered 12 hours after the misoprostol loading dose in the three groups.

RESULTS: A total of 302 women were randomized: 100 to oral, 100 to vaginal, and 102 to sublingual misoprostol. The median gestation at recruitment was oral 19.1 weeks (interquartile range 17.2–20.8), vaginal 19.4 weeks (interquartile range 17.3–20.4), and sublingual 19.7 weeks (interquartile range 17.6–21.0). The overall abortion duration was longer in women receiving oral misoprostol: oral 9.5 hours (95% confidence interval [CI] 8.5–11.4), vaginal 7.4 hours (95% CI 6.5–8.2), and sublingual 7.8 hours (95% CI 7.0–9.2). Overall, 84 of 302 (27.8%) women were undelivered at 12 hours, comprising 37.0% (95% CI 28.7–47.8) oral, 20.5% (95% CI 14.0–30.1) vaginal, and 21.0% (95% CI 14.3–30.7) sublingual groups.

CONCLUSION: Vaginal or sublingual misoprostol administered after a vaginal loading dose in second-trimester medical abortion with mifepristone priming is associated with a shorter time to pregnancy termination compared with an oral regimen.

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Both surgical and medical methods are used to effect abortion in the second trimester and each technique has its advantages and complications. The sequential use of the antiprogesterone mifepristone and the synthetic prostaglandin misoprostol is a widely used and effective combination for medical abortion in the second trimester.[1–5] However, there are recognized complications with medical abortion.[6] Increasing gestation at termination is associated with an increase in the procedural duration and complication rate.[7] There is an ongoing requirement to refine the techniques used to effect abortion in the second trimester to both decrease the duration of the procedure and the potential complications.

Most published mifepristone and misoprostol regimens have been based on medical abortions at median gestations of 16 weeks.[1,5] This bias to earlier second-trimester gestations provides abortion durations of approximately 6 hours with greater than 90% of women delivering in less than 24 hours.[1] However, there is an increase in abortion duration with an increase in gestation.[7] This gestation effect probably relates in part to the need for greater cervical dilatation as gestation advances as a result of the larger fetal size.

The bioavailability of vaginally administered misoprostol is three times higher than that of orally administered misoprostol.[8,9] Sublingually administered misoprostol has a higher serum peak concentration and bioavailability compared with vaginal administration.[9] We therefore hypothesize that altering the route of administration of misoprostol after mifepristone priming may reduce the overall abortion duration at later gestations.

The aim of this study was to compare the efficacy of the vaginal and sublingual administration of the synthetic prostaglandin misoprostol with the currently used oral administration route in second-trimester medical abortion.

MATERIALS AND METHODS

This study was conducted as a randomized clinical trial. The investigational protocol was approved by the King Edward Memorial Hospital Institutional Ethics Committee before the start of the study.

Women admitted to King Edward Memorial Hospital for Women, Perth, Western Australia, for second-trimester medical abortion for fetal abnormality or maternal medical complication at 14–24 weeks of gestation between April 2009 and April 2013 were invited to participate in the study. Gestational age was assigned on the basis of certain menstrual dates with confirmatory ultrasonography or ultrasound dating if the menstrual dates were uncertain or varied significantly from the menstrual dates. As a result of the potential confounding effect of feticide (the administration of a lethal injection to the fetus) on the abortion process, we did not recruit women who were beyond 22 weeks of gestation in whom a feticide was required. All women received 200 mg oral mifepristone 24–48 hours before hospitalization.

Once informed consent was obtained, the women were randomized to one of three study protocols using a series of sequentially numbered opaque envelopes with group allocations concealed from the clinician and every participant until the start of the procedure. The group allocation for the participants was generated independently using a computer-generated random sequence in blocks of 30 with 10 protocols per group. Women allocated to oral received a loading dose of 800 micrograms misoprostol vaginally followed by 400 micrograms misoprostol orally every 3 hours for a maximum of five doses (the standard regimen at the time of the trial). Women randomized to vaginal received a loading dose of 800 micrograms misoprostol vaginally followed by 400 micrograms misoprostol vaginally every 4 hours for a maximum of five doses. Those women allocated to sublingual received a loading dose of 800 micrograms misoprostol vaginally followed by 400 micrograms misoprostol sublingually every 3 hours for a maximum of five doses. As a result of the nature of the study protocol, it was not practical to blind the women and staff to the randomization allocation.

If delivery of the fetus did not occur after the completion of the allocated initial misoprostol regimen, the regimen was repeated 12 hours after the final misoprostol dose was completed. The mifepristone was not repeated. Maternal pulse, blood pressure, and temperature were recorded 3-hourly. A visual analog assessment of pain and nausea was performed 3-hourly. The women performed these assessments with a visual analog ruler scaled from 0 to 100 with 0 reflecting no symptom and 100 perceived as the most intense symptom ever experienced. Analgesia was provided on patient request by intramuscular morphine with metoclopramide 10 mg intramuscularly as the standard antiemetic medication. After expulsion of the fetus, 10 units of oxytocin was administered intramuscularly into the upper thigh to facilitate placental delivery.[10] Spontaneous expulsion of the placenta within 60 minutes of delivery was awaited with digital exploration of the uterine cavity and blunt curettage in the operating room reserved for those cases in which expulsion did not occur or was incomplete on the basis of clinical signs and symptoms.

Maternal blood loss was assessed clinically by the ward and operating room nursing staff. A full blood count was performed before the start of the termination process and within 24 hours of delivery for all women. Before hospital discharge, the women were provided with a short 4-point satisfaction questionnaire with responses provided on a visual analog ruler scaled from 0 to 100 with 0 perceived as "much better than expected" and 100 as "much worse than expected."

The primary outcome measure was the duration from the start of the misoprostol loading dose until expulsion of the fetus with the percentage of women delivered within 12 and 24 hours of prostaglandin commencement compared among the three study arms. It was expected from our previous observations that at least 62% of women recruited into the standard treatment arm would deliver in less than 12 hours and 88% within 24 hours.[4] We planned that 300 women would be recruited to the study (100 per group). This sample size was selected to attain 80% power to detect the proportions of women remaining undelivered at 12 hours are 38% and 20%, respectively (ie, "surviving proportions with expected hazard ratio of 1.66=In[0.2]:In[0.38]) for the standard regimen at the time of the trial (oral) and either of the experimental treatments (vaginal or sublingual) when performing a two-sided log rank test at an overall significance level of .05 using PASS 2008 for Windows.

Medians and interquartile ranges or means and standard deviation were used to summarize continuous outcomes. Categorical data were summarized using frequency distributions. Univariate comparisons if continuous outcomes were conducted using Kruskal-Wallis nonparametric analysis of variance and comparisons of categorical outcomes were performed using χ^2 tests using exact inference. Probability estimates of time required until the abortion was completed were obtained using the Kaplan-Meier method.

The primary end point of duration of termination was compared between the groups using a log rank test and Cox proportional regression model after adjusting for gestation. The influence of other factors such as maternal characteristics on the duration of abortion were examined using Cox proportional hazards regression modeling and where covariate effects were summarized using hazard ratios (HRs) and their 95% confidence intervals (CIs). In comparisons of duration of abortion between treatment regimens where shorter abortion duration is the preferred outcome, the HR less than 1 reflects longer abortion duration and the HR greater than 1 reflects a shorter abortion duration.

SPSS 18.0 and StatXact 8.0 statistical software were used for data analysis. All hypothesis testing was two-sided and *P* values $<.05$ were considered statistically significant.

RESULTS

Three hundred two women were recruited to the study. One hundred women were randomized to oral, 100 women to vaginal, and 102 received the sublingual protocol (Fig. 1). We had expected some recruit withdrawal from the allocated study groups and thus some additional women were recruited before it was evident that there were no study group losses. Groups were balanced with respect to maternal age, race, and prior uterine surgery (Table 1). For all groups, the mean gestational age at recruitment was approximately 19 weeks (Table 1).

There was a significant difference in the median duration of abortion among the three groups (Table 2; Fig. 2). Women randomized to the oral protocol (median duration 9.5 hours, CI 8.5–11.4) had a significantly longer duration of abortion than those receiving the vaginal or sublingual regimen (median 7.4 hours, CI 6.5–8.2, *P*=.021 and 7.8 hours, CI 7.0–9.2, *P*=.001, respectively). At 12 hours the percentage of women remaining undelivered was 37% (CI 28.7–47.8%) in the oral regimen, 20.5% (CI 14.0–30.1%) in the vaginal regimen, and 21.0% (CI 14.3–30.7%) in the sublingual regimen, representing 84 of 302 (28.8%) of all recruited women. At 24 hours after prostaglandin commencement, the percentage of women undelivered was 11.0% (CI 6.3–19.2%) in the oral regimen, 3.9% (CI 1.5–10.2%) in the vaginal, and 4.0% (CI 1.5–10.5%) in the sublingual regimen.

Advancing gestation, nulliparity, and prior cesarean delivery significantly prolonged the duration of abortion independently of the randomized allocation group and their effects were similar in all three groups. Relative to earlier gestations (less than 17 weeks), gestations between 17 and 19 weeks and greater than 20 weeks were both associated with longer abortion duration (HR 0.47, CI 0.34–0.65, *P*<.001 and HR 0.40, CI 0.28–0.55; *P*<.001, respectively) (Fig. 3). Relative to parous women without a history of cesarean delivery, nulliparous women were more likely to experience a prolonged termination (HR 0.36, CI 0.28–0.48, *P*<.001). Parous women with a history of cesarean delivery had a higher likelihood of prolonged abortion (HR 0.49, CI 0.36–0.68, *P*<.001). Maternal age, body mass index, and racial origin were not associated with the duration of abortion (*P*=.473, *P*=.504, and *P*=.164, respectively). Similarly, the interval between mifepristone administration and misoprostol commencement was not associated with abortion duration (*P*=.463).

There was no significant difference in maternal pulse or blood pressure among the three groups. The median maximal maternal temperature was 37.0°C (interquartile range 37.1, 37.7) for the oral, 37.4°C (37.1, 37.9) for the vaginal, and 37.4°C (37.1, 37.8) for the sublingual regimen (*P*=.963). A temperature 38°C or higher was recorded in four (4%) of women in the oral, two (2%) in the vaginal, and one (1%) in the sublingual regimen (*P*=.671). Pain scores did not differ among the three misoprostol regimens (*P*=.190; median maximal scores of 60, 50, and 50 for oral, vaginal, and sublingual regimens, respectively). Similarly, there was no significant difference among the three groups for the occurrence of vomiting (*P*=.782; median maximum scores of 0 for all three regimens) or diarrhea (*P*=.606; 75th percentiles of 0 for all three regimens).

There was no difference in estimated postpartum blood loss among the three groups (*P*=.941) (Table 2). Similarly, no significant difference in the pre- and postdelivery hematocrit among the three groups was observed (Table 2). Five women received a blood transfusion in this study: two women in the oral regimen experienced uterine atony after expulsion of the placenta but did not require any operative interventions and two women in the sublingual regimen had

Table 1. Maternal Characteristics

Characteristic	Oral (n=100)	Vaginal (n=100)	Sublingual (n=102)	*P*
Maternal age (y)	32 (28–36)	31 (28–35)	32 (28–37)	.504
Age group (y)				
Younger than 20	3 (3)	2 (2)	1 (1.0)	.633
20–29	32 (32)	34 (34)	30 (29.4)	
30–39	50 (50)	56 (56)	60 (58.8)	
40 or older	15 (15)	8 (8)	11 (10.8)	
Race (caucasian)	87 (87)	90 (90)	91 (89.2)	.785
BMI (kg/m^2)	24.8 (22.5–27.9)	24.1 (22–27.8)	24.6 (22.2–27.8)	.606
Gravidity	2 (1, 3)	2 (2, 4)	3 (2, 4)	.281
Parity	1 (0, 1)	1 (0, 2)	1 (0, 1)	.429
Nulliparity	45 (45)	37 (37)	35 (34.3)	.270
Prior cesarean delivery	22 (22)	16 (16)	28 (27.4)	.144
Gestation (wk)	19.1 (17.2–20.8)	19.4 (17.3–20.4)	19.7 (17.6–21.0)	.577
Gestation group (wk)				
Less than 17	20 (20)	20 (20)	20 (19.6)	.958
17–19	41 (41)	44 (44)	40 (39.2)	
20–24	39 (39)	36 (36)	42 (41.2)	

BMI, body mass index.
Data are median (interquartile range) or n (%) unless otherwise specified.

a retained placenta with significant hemorrhage. There was one case of uterine scar rupture in this study in a woman allocated to the vaginal regimen with a single prior low-transverse uterine cesarean delivery 12 months before the abortion. The uterine rupture was managed by laparotomy and suture repair.

Satisfaction scores did not differ among the three groups (Table 3). It was notable that women did not rate their pain control highly and many women felt this could have been managed better. The majority of women required morphine for analgesia: 78% in oral, 87% in the vaginal, and 82% in the sublingual regimen (*P*=.372). The median duration of hospital stay was not different among the three groups (Table 2). We observed the main factor affecting on duration of stay postabortion was the provision of fetal viewing for the parents and hospital support services such as chaplaincy and psychological medicine.

DISCUSSION

This randomized clinical trial demonstrates both the sublingual and vaginal routes of misoprostol administration resulted in a shorter duration of abortion compared with the oral route. Increasing gestational age and maternal parity were key factors independently affecting the duration of the abortion process. This is important information to provide to women during the preprocedure counseling process, because

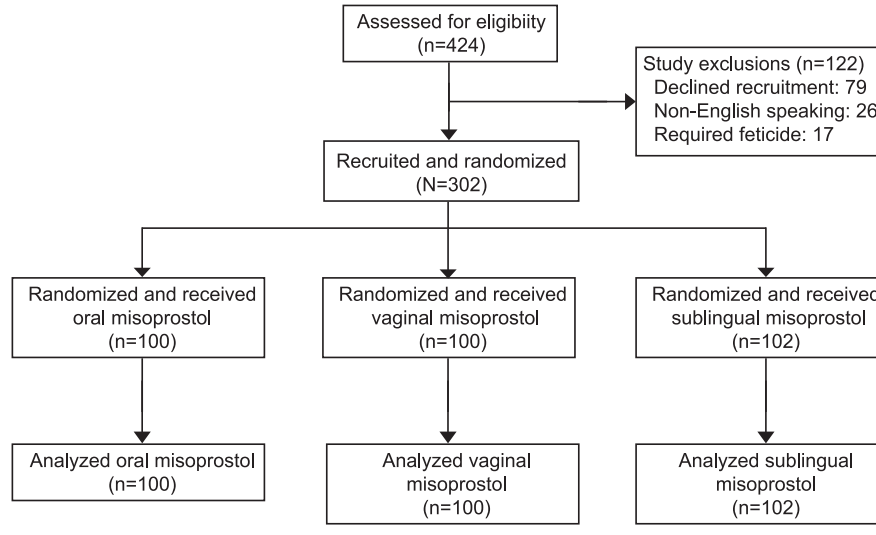

Fig. 1. Consolidated Standard of Reporting Trials (CONSORT) flow chart.

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Table 2. Delivery Characteristics

Characteristic	Oral (n=100)	Vaginal (n=100)	Sublingual (n=102)	*P*
Mifepristone–misoprostol duration (h)	37.4 (27.8–42.8)	31.9 (26.8–41.7)	29.7 (26.1–41.6)	.177
Median duration of termination (h)	9.5 (8.5–11.4)	7.4 (6.5–8.2)	7.8 (7.0–9.2)	.005
Undelivered at 12 h	37.0 (28.7–47.8)	20.5 (14.0–30.1)	21.0 (14.3–30.7)	
Undelivered at 24 h	11.0 (6.3–19.2)	3.9 (1.5–10.2)	4 (1.5–10.5)	
Number of subsequent misoprostol doses	2 (2–4)	1 (1–2)	2 (1–3)	<.001
Total misoprostol dosage (micrograms)*	1,600 (1,600–2,400)	1,200 (1,200–1,600)	1,200 (1,200–1,600)	<.001
Placenta retained	18 (18)	18 (18)	20 (19.6)	.945
Blood loss (mL)	100 (50–250)	100 (50–250)	100 (50–200)	.941
Transfusion	2 (2)	1† (1)	2 (2)	1.000
Predelivery hematocrit	0.35 (0.34–0.35)	0.35 (0.33–0.38)	0.36 (0.34–0.38)	.905
Postdelivery hematocrit	0.35 (0.32–0.37)	0.34 (0.33–0.38)	0.35 (0.32–0.36)	.684
Duration of stay (h)	26.5 (24–31.6)	26.3 (24–29.3)	25.8 (23–29)	.077

Durations presented as median (95% confidence interval); proportion undelivered presented as rate (95% confidence interval). Dosage and hematocrit presented as median (interquartile range). Other variables are presented as n (%) unless otherwise specified.
* Total misoprostol dosage includes the 800-microgram loading dose.
† Case complicated by uterine rupture.

they typically desire data on the abortion duration and this should be tailored to her individual obstetric characteristics.

There are several regimens reported for misoprostol in second-trimester medical abortion, varying in the route of administration and the dose.[11] When the misoprostol is preceded by mifepristone, 24–48 hours before prostaglandin commencement, the amount of prostaglandin required is substantially reduced and the misoprostol commencement–delivery interval significantly shorter. This study has demonstrated that administering the misoprostol either vaginally or sublingually results in both a shorter median delivery interval and a reduction in the proportion of women undelivered at 12 and 24 hours after commencement of prostaglandin. The side effect profile was not significantly different, and women's preferences were not different among the three regimens; however, it is difficult to separate the effect of the intensive nursing support and compassion, which is highly valued by the women, from the actual procedure. We speculate that it may be possible to omit the vaginal loading dose of misoprostol if oral misoprostol is no longer to be used, and this is the basis of a planned clinical trial.

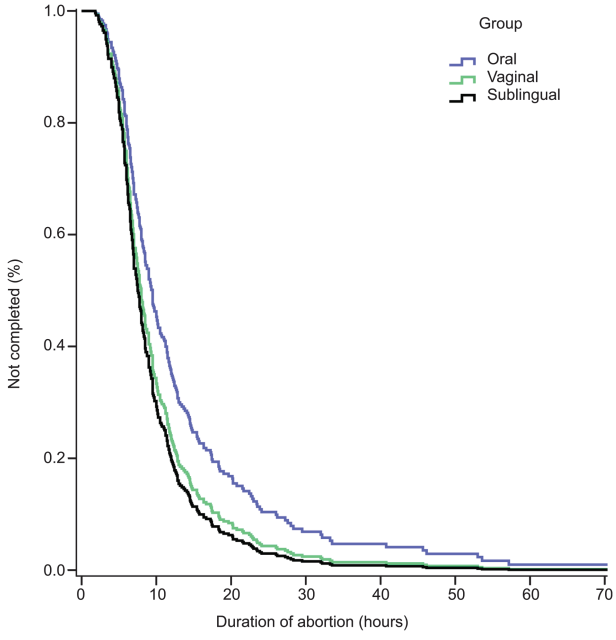

Fig. 2. Survival curves of the percentage of women undelivered for each of the three misoprostol regimens. Significantly longer median duration of abortion was experienced by women receiving the oral misoprostol regimen (*P*=.021 and *P*=.001 for vaginal and sublingual regimens, respectively).

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A prior publication in 1995 comparing vaginal and oral misoprostol after mifepristone pretreatment did not find a difference in the abortion duration between these two administration routes.[12] However, that study of 70 women had a median gestation at termination of 16 weeks; earlier gestation has consistently been associated with a shorter abortion interval. Review of the cumulative abortion rates demonstrated a shift toward a longer abortion duration for the women receiving the doses orally and although not reaching statistical significance, the vaginal group required less misoprostol to effect abortion compared with the oral group (1,000 micrograms compared with 1,400 micrograms, vaginal compared with oral, respectively).[12] We speculate that the greater median gestation in our study exposed the delay in abortion duration in this earlier study with the oral route.

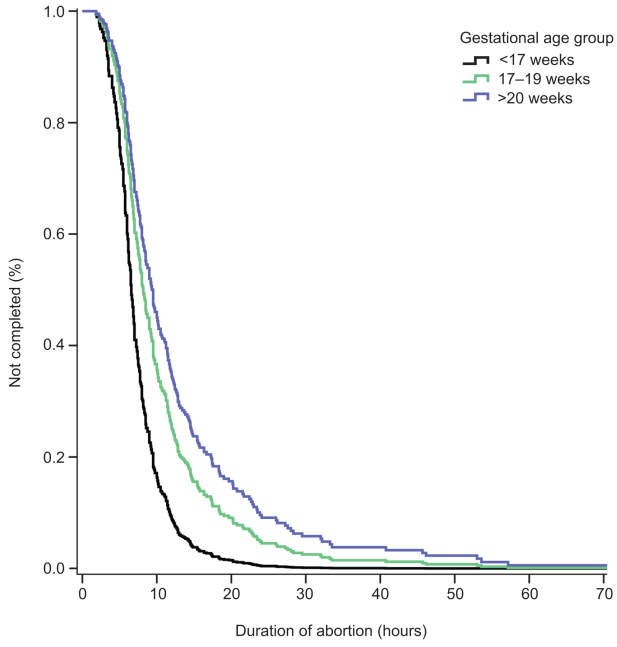

Fig. 3. Survival curves of the effect of increasing gestation on abortion duration.

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Although medical abortion in the second trimester with mifepristone and misoprostol is an effective therapeutic regimen, this study shows that procedural complications may arise. The most common serious complication occurring was placental retention, although the rate was substantially lower than reported in a recent publication where it was 30.8%.[13] This group provided an additional dose of 400–800 micrograms misoprostol either vaginally or orally after delivery of the fetus to assist with placental expulsion. We have previously shown that 600 micrograms oral misoprostol was no better than expectant management in the third stage.[10] Intramuscular oxytocin provided a significant reduction in placental retention in the randomized trial, and this protocol is now our standard practice.[10] Notwithstanding the improvement in placental expulsion rates with routine oxytocin, 1.7% of women required a blood transfusion secondary to acute hemorrhage and 5.0% had an estimated blood loss 1,000 mL or greater. Whereas uterine rupture after prior cesarean deliveries is not a frequent occurrence with medical abortion regimens, it certainly does occur and all women should be counseled in regard to the potential for this complication.[14,15] It is recognized that second-trimester abortion is associated with higher complication rates than those performed in the first trimester.[6] Institutions performing second-trimester medical abortions should have ready access to facilities to manage potential complications.

Feticide was not used in this study, which could potentially limit its generalizability to situations where this technique is used. Feticide is offered in our unit for gestations greater than 22 weeks but is not mandatory in situations where the fetal anomaly is not compatible with life.[16] Because the effect of feticide on the abortion duration is unclear, we did not recruit women in whom feticide was required to remove the possibility of a confounding influence, if it exists.[17] A second limitation to this study was that the time between the mifepristone administration and the commencement of the misoprostol was variable, although the randomization process ensued the time was consistent between the three groups and also is more reflective of actual clinical practice. We only recruited women who chose to have a medical abortion and have no comparative data on surgical abortion. The use of surgical and medical abortion varies throughout the world with surgical techniques common in the United States and medical techniques common in Europe.[18] There are advantages and complications with both techniques, and the procedural choice usually is based on the expertise of the health care practitioner and the preference of the woman.

Table 3. Women's Perceptions of the Procedure

Perception	Oral (n=100)	Vaginal (n=100)	Sublingual (n=102)	*P*
Opinion of procedure	50 (20–50)	50 (26–50)	50 (19–50)	.990
Pain perception	50 (38–66)	50 (46–71)	50 (43–74)	.813
Recommendation	21 (0–150)	27 (0–50)	25 (3–50)	.452
Impression of control	39 (10–50)	38 (15–50)	34 (15–50)	.754

Data are median (interquartile range) of a 0–100 visual analog scale (0=best; 100=worst) unless otherwise specified.

REFERENCES

1. Ashok PW, Templeton A, Wagaarachchi PT, Flett GM. Midtrimester medical termination of pregnancy: a review of 1002 consecutive cases. Contraception 2004;69:51–8.
2. Kapp N, Borgatta L, Stubblefield PG, Vragovic O, Moreno N. Mifepristone in midtrimester medical abortion: a randomized controlled trial. Obstet Gynecol 2007;110:1304–10.
3. Danielsson-Gemzell K, Lalitkumar S. Second trimester medical abortion with mifepristone–misoprostol and misoprostol alone: a review of methods and management. Reprod Health Matters 2008;16(suppl):162–72.
4. Dickinson JE, Brownell P, McGinnis K, Nathan E. Mifepristone and second trimester pregnancy termination for fetal abnormality in Western Australia: worth the effort. Aust NZ J Obstet Gynaecol 2010;50:60–4.

5. Ngoc NT, Shochet T, Raghavan S, Blum J, Nga NT, Minh NT, et al. Mifepristone and misoprostol compared with misoprostol alone for second-trimester abortion. Obstet Gynecol 2011;118:601–8.
6. Grossman D, Blanchard K, Blumenthal P. Complications after second trimester surgical and medical abortion. Reprod Health Matters 2008;16(suppl):173–82.
7. Dickinson JE, Doherty DA. Factors influencing the duration of pregnancy termination with vaginal misoprostol for fetal abnormality. Prenat Diagn 2009;29:520–4.
8. Tang OS, Schweer H, Seyberth HW, Lee SW, Ho PC. Pharmacokinetics of different routes of administration of misoprostol. Hum Reprod 2002;17:332–6.
9. Tang OS, Gemzell-Danielsson K, Ho PC. Misoprostol: pharmacokinetic profiles, effects on the uterus and side-effects. Int J Gynecol Obstet 2007;99(suppl 2):S160–7.
10. Dickinson JE, Doherty DA. Optimization of third-stage management after second-trimester medical pregnancy termination. Am J Obstet Gynecol 2009;201:303.e1–7.
11. Borgatta L, Kapp N; Society of Family Planning. Clinical Guidelines. Labor induction abortion in the second trimester. Contraception 2011;84:4–18.
12. el-Refaey H, Templeton A. Induction of abortion in the second trimester by a combination of misoprostol and mifepristone: a randomized comparison between two misoprostol regimens. Hum Reprod 1995;10:475–8.
13. Mentula M, Heikinheimo O. Risk factors of surgical evacuation following second-trimester medical termination of pregnancy. Contraception 2012;86:141–6.
14. Daskalakis GJ, Mesogitis SA, Papantoniou NE, Moulopoulos GG, Papapanagiotou AA, Antsaklia AJ. Misoprostol for second trimester pregnancy termination in women with prior caesarean section. BJOG 2005;112: 97–9.
15. Dickinson JE. Misoprostol for second-trimester pregnancy termination in women with a prior cesarean delivery. Obstet Gynecol 2005;105:352–6.
16. Royal College of Obstetricians and Gynaecologists. The care of women requesting induced abortion. Evidence-based clinical guideline. London (UK): Royal College of Obstetricians and Gynaecologists Press; 2011.
17. Diedrich J, Drey E; Society of Family Planning. Induction of fetal demise before abortion. Contraception 2010;80:462–73.
18. Lee VC, Ng EH, Ho PC. Issues in second trimester induced abortion (medical/surgical methods). Best Pract Res Clin Obstetrics Gynaecol 2010;24:517–27.