

Mifepristone Followed by Misoprostol or Oxytocin for Second-Trimester Abortion

A Randomized Controlled Trial

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OBJECTIVE: To compare two methods for induction of second-trimester abortion after priming the cervix with mifepristone.

METHODS: This was a randomized prospective trial carried out between January 2009 and February 2012. The participants were healthy women between 14 and 24 weeks of gestation with missed miscarriage or need for termination of pregnancy. All participants received oral 200 mg mifepristone and, after 36 hours, after randomization, were given either a high-concentration oxytocin drip (maximal dose of 150 milli-international units/min) for up to 36 hours or 800 micrograms misoprostol vaginally followed by 400 micrograms oral misoprostol every 3 hours with a maximum of four oral doses. If expulsion of the fetus was not achieved, another 200 mg mifepristone was administered and another course of misoprostol was delivered as described previously. The primary outcome measure was success expulsion of the fetus in 36 hours since starting on uterotonic agent. Secondary outcomes included time until expulsion of the fetus and rate of adverse outcomes.

RESULTS: Success rates in the mifepristone–misoprostol and mifepristone–oxytocin arms were 100% (70/70 patients) and 95.8% (69/72), respectively (relative risk 1.043, 95% confidence interval 0.99–1.10, $P=.13$). Time until fetal expulsion was shorter in the mifepristone–misoprostol arm (7.0 ± 4.9 hours compared with 11.3 ± 7.4 hours, $P<.001$). However, the rate of adverse

effects in the misoprostol group was higher than in the oxytocin group. Factors associated with a shorter time until expulsion were missed miscarriage compared with therapeutic abortion, increased ultrasonographic gestational age, and increased parity.

CONCLUSION: The two regimens studied had comparable efficacy for induction of second-trimester abortion; however, the mifepristone–oxytocin regimen has a longer time until expulsion but with fewer side effects.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, www.clinicaltrials.gov, NCT00784797.

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LEVEL OF EVIDENCE: I

Second-trimester abortion is a common procedure and contributes to 12.5% of the total abortions in the United States.¹ Both surgical (ie, dilatation and evacuation) and medical induction of labor options are available, each with its own advantages and complications. However, health care practitioners not experienced with surgical abortion may be distressed in cases of advanced gestation, and medical abortion, which is more common, especially in European countries,² may be preferable.

Mifepristone has been used to induce second-trimester abortion.^{3,4} It has potent antiprogesterone effects, acting as a competitive inhibitor of the progesterone receptor. As a result, it decreases the contractility threshold of the uterus, ripens the cervix, and therefore facilitates the abortion process. Administration of mifepristone is followed by an uterotonic agent, like prostaglandins. Usually misoprostol^{5,6} is used because of its relative stability at room temperature, ease of administration, and cost. Side effects are the main disadvantage of misoprostol and can occur in up to 30% of the patients.⁷ Recently we investigated the application of mifepristone before administering

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a high-concentrated oxytocin drip.⁸ We showed in a randomized placebo-controlled trial that induction with mifepristone before oxytocin shortened time until expulsion of the fetus and increased success rates in second-trimester abortions.

In this study, we compared in a randomized trial our protocol of mifepristone–oxytocin with the commonly used protocol of mifepristone–misoprostol to produce a regimen that would lead to the highest success rates with minimal side effects and the shortest duration until expulsion of the fetus.

MATERIAL AND METHODS

The study group included healthy women who underwent second-trimester missed or therapeutic abortion (defined as abortion between 14 and 24 weeks of gestation) at the gynecology department in Hadassah Hebrew University Medical Center in Jerusalem. Gestational age was defined by last menstrual period and fetal size by ultrasonic estimation. Indications for the procedure were either the need for termination of pregnancy or late missed miscarriage. Exclusion criteria included women after more than one previous cesarean delivery; known allergy to mifepristone, misoprostol, or oxytocin; premature preterm rupture of the membranes; history of recent asthma; a known coagulation disorder or past thromboembolic event; history of chronic adrenal failure or concurrent long-term corticosteroid treatment; and porphyrias.

After allocation, the patients were given a detailed explanation about the study protocol and signed an informed consent if they agreed to participate in the study. The study protocol was approved by our institutional review board (HMO-0516-08) and registered with www.clinicaltrials.gov (NCT00784797). Patients were randomized into two groups by choosing a sealed envelope from a pile shuffled by the nurses. All women received 200 mg mifepristone orally. Thirty-six hours after the administration of mifepristone, all patients were offered epidural analgesia before being given an uterotonic agent and 99% accepted this modality. Each patient, according to previous randomization, was given either a high concentrated oxytocin drip (starting dose of 50 milli-international units/min with increase by 50 milli-international units/min every 20 minutes to a maximal dose of 150 milli-international units/min) for up to 36 hours or 800 micrograms misoprostol vaginally followed by 400 micrograms oral misoprostol every 3 hours with a maximum of four oral doses. If expulsion of the fetus was not achieved, another 200 mg mifepristone was administered and another course of misoprostol was delivered as described previously. After fetal expulsion, all women underwent evacuation of the uterus from remaining gestational contents by a Bumm curette (large sharp curette) under the same regional analgesia. Protocol failure was defined as inability to evacuate the uterus within 36 hours since the administration of either oxytocin or misoprostol (Fig. 1).

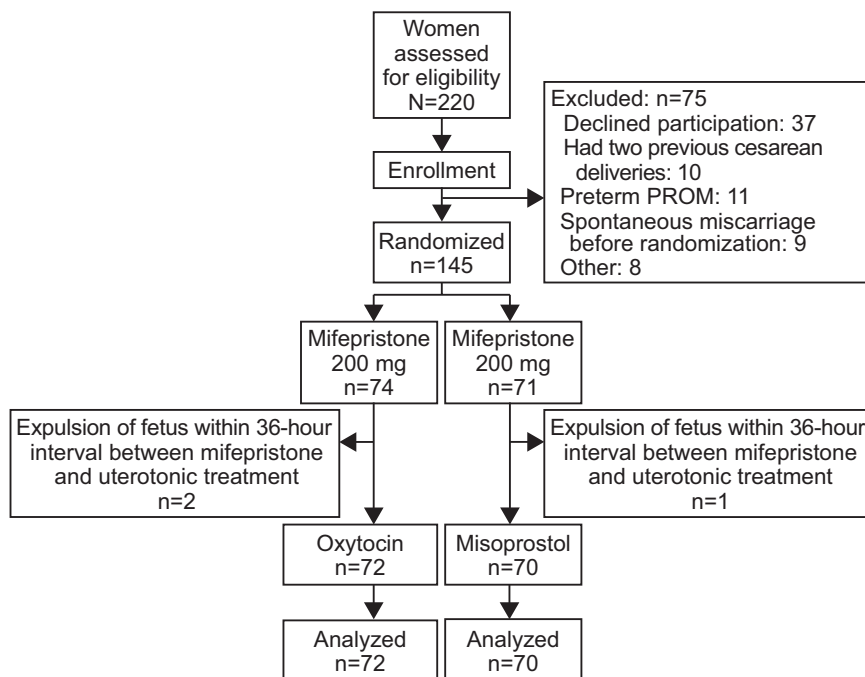


Fig. 1. Flow of participants through the study. PROM, premature rupture of membranes. Elami-Suzin. Mifepristone–Oxytocin in Second-Trimester Abortion. *Obstet Gynecol* 2013.



Demographic and clinical data were collected after informed consent. The primary outcome measure was successful expulsion of the fetus in 36 hours after starting on the uterotonic agent. Secondary outcomes included time until expulsion of the fetus and rate of adverse outcomes.

Sample size was calculated assuming equivalent success rates between the two treatments. Based on previous studies,^{8–11} the expected success rate in the mifepristone–misoprostol group was 95% and assuming that a difference of up to 10% between the groups is clinically negligible, with a significance level of 5% (one-tailed) and a power of 90%, a sample size of 63 participants in each group will be sufficient to prove equivalence. To allow for potential dropoff, we allocated an extra 10% of participants.

SPSS/PC+ software was used for statistical analysis. Analysis was based on the intent-to-treat principle. A χ^2 test was used to test the association between two categorical variables. The two-sample *t* test as well as the Mann-Whitney nonparametric test was applied to compare quantitative variables between two independent groups. The Pearson correlation coefficient was computed to estimate the strength of a linear association between two quantitative variables. The four-way analysis of variance model was used to assess the effect of treatment method controlling for confounders, which were found to be significantly associated in the univariate analysis, with the outcome of “time to expulsion.” Intervention until expulsion time was presented using a Kaplan-Meier survival graph and a Cox regression survival model was applied to assess the effect of treatment method on success of treatment, taking into account time to expulsion and controlling for other variables. All tests applied were two-tailed and a *P* value of 5% or less was considered statistically significant.

RESULTS

The study was carried out from January 2009 to February 2012. Of 220 women who were examined for eligibility for the study, 145 women were randomized into the study group arms (mifepristone–oxytocin compared with mifepristone–misoprostol) and final analysis was made on 142 patients (Fig. 1). The two groups did not differ in age, parity, indication for abortion, gestational age, number of previous vaginal deliveries, or marital status (Table 1).

Both study arms demonstrated high success rates: 70 of 70 patients (100%) in the mifepristone–misoprostol arm and 69 of 72 patients (95.8%) in the mifepristone–oxytocin arm. This difference was not statistically significant (relative risk 1.043, 95% confidence interval [CI] 0.99–1.10, *P* = .13). However, seven of the 70 successful

Table 1. Demographics of Participants in the Oxytocin and Misoprostol Groups

Variable	Oxytocin (n=72)	Misoprostol (n=70)	<i>P</i>
Age (y)			.11
18–25	10 (14.7)	15 (21.4)	
26–35	32 (47.1)	33 (50)	
36–40	18 (26.4)	14 (20)	
41 and older	8 (8.8)	6 (8.6)	
Gestational age (wk)*	18.76±3.2	18.41±3.0	.509
Family status			.2
Married	57 (83.8)	53 (75.7)	
Single	8 (11.8)	14 (20.0)	
Divorced	3 (4.4)	1 (1.4)	
No. of previous births			.129
0	10 (14.5)	20 (28.6)	
1–4	48 (69.9)	40 (57.1)	
4 or more	12 (15.9)	10 (14.3)	
Reasons for abortion			.98
Missed abortion	27 (37.5)	27 (38.6)	
Planned abortion	45 (62.5)	43 (61.4)	
Week of pregnancy			.40
19 or less	40 (47.6)	32 (55.2)	
More than 19	44 (52.4)	26 (44.8)	

Data are n (%) or mean±standard deviation unless otherwise specified.

* Estimated by ultrasonography.

participants in the misoprostol group needed an alternative treatment (usually oxytocin) because of adverse effects that precluded the continued use of misoprostol (predominantly high fever that will be aggravated by the prostaglandin effect on the thermostat center in the brain).

The interval between administration of the pharmacologic intervention until expulsion of the fetus was shorter in the mifepristone–misoprostol group (7.0±4.9 hours compared with 11.3±7.4 hours, *P* < .001; Fig. 2). Patients with a missed miscarriage had a shorter time until expulsion than patients after termination of pregnancy: 10.3±7.4 hours compared with 12±7.3 hours (*P* < .001) in the mifepristone–oxytocin arm and 5±3.6 hours compared with 8.3±5.2 hours (*P* < .001) in the mifepristone–misoprostol arm. There was no correlation between the time that elapsed since the missed abortion event and the time to expulsion of the fetus.

Other factors that were associated with a shorter time until expulsion were parity and gestational age as measured by ultrasonographic parameters rather than by last menstrual period. The mean intervention to expulsion time was 7.7±6 hours in both study arms when the ultrasonographic gestational age was 19 weeks or younger compared with 11.2±6.9 hours in pregnancies above 19 weeks of gestation (*P* = .002;



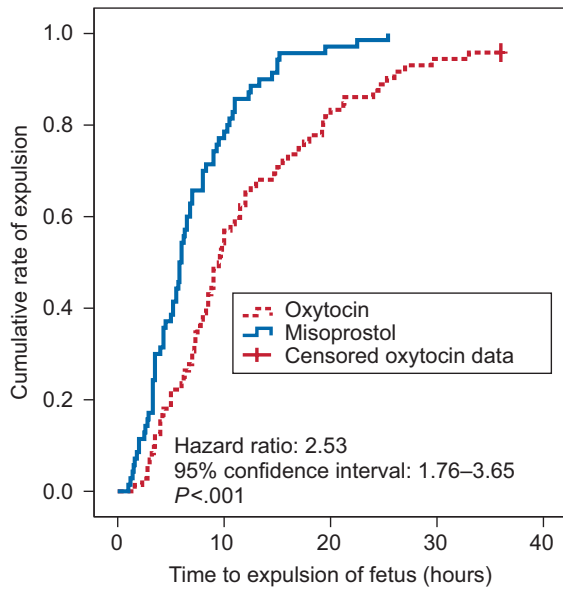
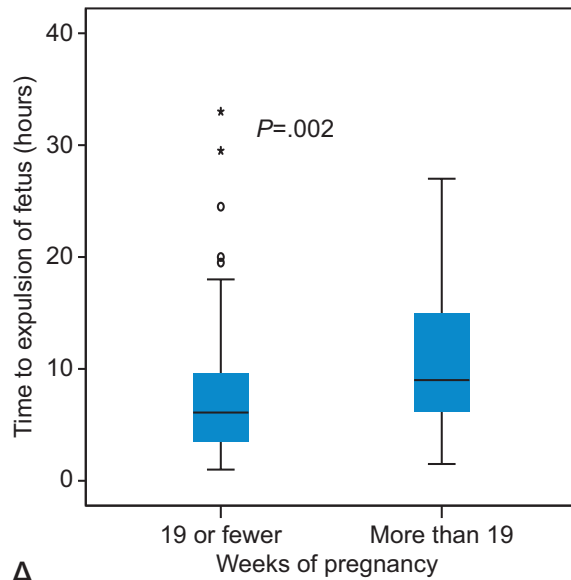


Fig. 2. Kaplan–Meier curve for induction to expulsion of fetus for the two study groups. Time until expulsion was shorter in misoprostol group compared with oxytocin treatment (hazard ratio 2.53, 95% confidence interval 1.76–3.65, $P<.001$).

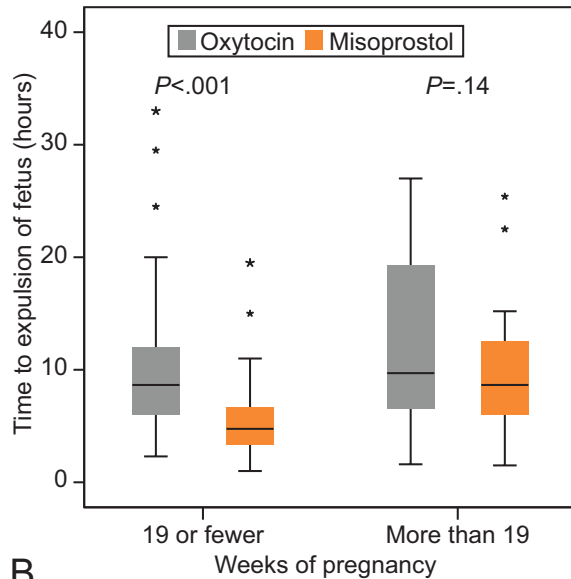
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Fig. 3A). Moreover, when comparing the efficacy of the two treatments for pregnancy 19 weeks of gestation or less, women in the mifepristone–misoprostol group aborted faster (5.4 ± 0.55 hours compared with 10.4 ± 1.1 hours, $P<.01$, Fig. 3B). However, there was no significant difference between the groups for abortions above 19 weeks of gestation (9.7 ± 1.1 hours compared with 12.4 ± 1.4 hours, respectively, $P=.14$; Fig. 3B). The time to expulsion was decreased in women with at least one previous delivery compared with nulliparous women (7.9 ± 7 compared with 12.4 ± 10.3 hours, $P=.002$).

The shorter time until expulsion of the mifepristone–misoprostol arm compared with the mifepristone–oxytocin arm remained statistically significant even after correcting for confounding factors including the abortion type (ie, missed miscarriage or termination of pregnancy), ultrasonographic gestational age, patient’s age, and previous vaginal delivery ($P<.001$). Factors that remained independently significant after multiple regression analysis regarding time until fetal expulsion were type of abortion, ultrasonographic gestational age, and whether the patient had at least one previous vaginal delivery. A Cox regression survival model, taking into account “time until expulsion” with controlling for type of treatment, gestational age, type of abortion, age, and parity, revealed that the two significant



A



B

Fig. 3. Time until expulsion of fetus by gestational age. **A.** Box plot of all participants in early (19 weeks of gestation or earlier) and late (after 19 weeks of gestation) second-trimester abortion. The central line represents the medians with the box indicating the interquartile range and the whiskers indicating the range. Asterisks and circles indicate outliers. **B.** Box plot of time until expulsion of fetus for the two study groups in early (19 weeks of gestation or earlier) and late (after 19 weeks of gestation) second-trimester abortions. Asterisks and circles indicate outliers.

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parameters are type of treatment (hazard ratio 2.53, 95% CI 1.76–3.65, $P<.001$) and at least one previous vaginal delivery (hazard ratio 2.28, 95% CI 1.44–3.50, $P<.001$).



The rate of adverse effects in the misoprostol group was higher than in the oxytocin group. There were increased incidences of fever 38°C or higher (38.6% compared with 7.2%; relative risk 3.83, 95% CI 1.69–8.69, $P < .001$) and shivers (46.4% compared with 22.4%; relative risk 1.79, 95% CI 1.20–2.66, $P = .005$) in misoprostol and oxytocin arms, respectively (Table 2).

DISCUSSION

Our results show that both high concentration oxytocin drip and misoprostol have similar efficacy for second-trimester abortion after induction with mifepristone. The mifepristone–misoprostol combination was associated with a shorter time until expulsion compared with mifepristone–oxytocin, especially in cases of missed abortion and for fetuses measured at 19 gestational weeks of gestation or less by ultrasonography. However, the mifepristone–oxytocin regimen had fewer side effects.

The adverse effects of misoprostol were the main reason for discontinuation of treatment and necessity for alternative protocol in seven participants (predominantly high fever as a result of a direct effect of prostaglandins on the thermostat center in the brain). This tendency toward a more favorable adverse outcome profile of oxytocin had been described previously.¹² Our proposed high-concentration oxytocin drip regimen with a maximal dose of 150 milli-international units/min (high dose because of a reduced number of oxytocin receptors at early pregnancy) is lower than that originally described by Winkler et al¹² (maximal dose of 5,000 milli-international units/min) and therefore was less prone to adverse outcomes (in particular water intoxication). Excessive water imbalance was controlled by water restriction during the treatment.

The study by Ramin et al,¹³ comparing misoprostol with oxytocin, demonstrated a shorter induction-to-delivery interval in the misoprostol cohort (15.2 ± 6.7 hours) compared with those treated with oxytocin (21.7 ± 11.0 hours; $P = .02$). Moreover, the

success rate, defined as an evacuation of the uterus within 24 hours, was higher in the misoprostol group (91% compared with 62%; $P = .04$). Previous studies have confirmed that priming of the cervix with mifepristone, before inducing labor with a prostaglandin, shortened the induction-to-delivery interval and improved the overall success rate of the medical evacuation.^{14,15} Our group has previously demonstrated that mifepristone has the same effect when the induction of labor was preceded by a high-concentration oxytocin drip.⁸ This can explain the higher and identical success of oxytocin compared with misoprostol in such regimen.

In our study, factors that were associated with a shorter time until expulsion were missed abortion, multiparity, and ultrasonographic gestational age 19 weeks of gestation or less. Multiparity and early gestational age have been associated with a shorter time-to-expulsion interval in previous studies.^{16–19} Missed abortion has also been associated with a shorter interval²⁰ and several physiologic processes were suggested, including nitric oxide release.²¹ It is generally thought that a delay in medical abortion would allow natural physiologic processes to facilitate a shorter expulsion of the fetus; however, in our study, we found no association between a longer time from the initiation of the nonviable pregnancy and a shorter time-to-expulsion interval. Therefore, we are of the opinion that there is no benefit to the patient in recommending a delay before the medical abortion.

Prostaglandins have been associated with uterine rupture, especially in the previously scarred uterus.^{22,23} Nevertheless, this complication is rarely observed and previous systematic review has confirmed the safety of prostaglandins in women with no more than one low transverse cesarean delivery.²⁴ Priming of the cervix with mifepristone probably lowers the incidence of this rare complication, because reduced force is needed to efface and dilate the cervix. However, the ability to use oxytocin (which has a serum half-life of minutes compared with several hours with misoprostol) with similar efficacy compared with misoprostol increases safety margins in grand-multiparous women or women with a previously scarred uterus because the infusion can be stopped whenever prerupture symptoms appear. Other advantages of oxytocin, compared with misoprostol, are reduced risk of amnionitis and no need for the physician to administer the medication.

The present study showed that the regimen of mifepristone with oxytocin had a comparable efficacy to misoprostol with fewer side effects, but took longer, especially in missed miscarriage with gestational age below 19 weeks. Even in those earlier miscarriages,

Table 2. Side Effects Reported by Women During Treatment

	Oxytocin	Misoprostol	<i>P</i>
Weakness	29/66 (43.9)	33/70 (47.1)	.708
Nausea	20/66 (30.3)	18/70 (25.7)	.551
Vomiting	11/67 (16.4)	10/70 (14.3)	.729
Diarrhea	2/66 (3.0)	7/70 (10.0)	.167
Shivers	20/66 (30.3)	39/69 (56.5)	.002
Fever 38°C or higher	7/72 (7.2)	27/70 (38.6)	.001

Data are n/N (%) unless otherwise specified.



the physician should present the patient the advantages and disadvantages of each protocol so together they can decide which of the two would be the most beneficial treatment for the patient.

REFERENCES

1. Hammond C. Recent advances in second-trimester abortion: an evidence-based review. *Am J Obstet Gynecol* 2009;200:347–56.
2. Esteve JL, Gallego FG, Llorente MP, Bermudez SB, Sala ES, Gonzalez LV, et al. Late second-trimester abortions induced with mifepristone, misoprostol and oxytocin: a report of 428 consecutive cases. *Contraception* 2008;78:52–60.
3. Rodger MW, Baird DT. Pretreatment with mifepristone (RU 486) reduces interval between prostaglandin administration and expulsion in second trimester abortion. *Br J Obstet Gynaecol* 1990;97:41–5.
4. Urquhart DR, Templeton AA. The use of mifepristone prior to prostaglandin-induced mid-trimester abortion. *Hum Reprod* 1990;5:883–6.
5. Wildschut H, Both MI, Medema S, Thomee E, Wildhagen MF, Kapp N. Medical methods for mid-trimester termination of pregnancy. *The Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD005216. DOI: 10.1002/14651858.CD005216.pub2.
6. Vargas J, Diedrich J. Second-trimester induction of labor. *Clin Obstet Gynecol* 2009;52:188–97.
7. Tang OS, Gemzell-Danielsson K, Ho PC. Misoprostol: pharmacokinetic profiles, effects on the uterus and side-effects. *Int J Gynaecol Obstet* 2007;99(suppl 2):S160–7.
8. Ben-Meir A, Erez Y, Feigenberg T, Hamani Y, Laufer N, Rojansky N. Mifepristone followed by high-dose oxytocin drip for second-trimester abortion: a randomized, double-blind, placebo-controlled, pilot study. *J Reprod Med* 2009;54:511–6.
9. Bartley J, Baird DT. A randomised study of misoprostol and gemeprost in combination with mifepristone for induction of abortion in the second trimester of pregnancy. *BJOG* 2002; 109:1290–4.
10. Chai J, Tang OS, Hong QQ, Chen QF, Cheng LN, Ng E, et al. A randomized trial to compare two dosing intervals of misoprostol following mifepristone administration in second trimester medical abortion. *Hum Reprod* 2009;24:320–4.
11. 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.
12. Winkler CL, Gray SE, Hauth JC, Owen J, Tucker JM. Mid-second-trimester labor induction: concentrated oxytocin compared with prostaglandin E2 vaginal suppositories. *Obstet Gynecol* 1991;77:297–300.
13. Ramin KD, Ogburn PL, Danilenko DR, Ramsey PS. High-dose oral misoprostol for mid-trimester pregnancy interruption. *Gynecol Obstet Invest* 2002;54:176–9.
14. Hamoda H, Ashok PW, Flett GM, Templeton A. A randomized trial of mifepristone in combination with misoprostol administered sublingually or vaginally for medical abortion at 13–20 weeks gestation. *Hum Reprod* 2005;20:2348–54.
15. Hamoda H, Ashok PW, Flett GM, Templeton A. A randomised controlled trial of mifepristone in combination with misoprostol administered sublingually or vaginally for medical abortion up to 13 weeks of gestation. *BJOG* 2005;112:1102–8.
16. Kai K, Karakida S, Kono M, Sasaki T, Togo K, Tsuno A, et al. Effects of parity and gestational age on second-trimester induction-abortion interval in combination with osmotic dilators and gemeprost. *Contraception* 2012;86:147–52.
17. Vitner D, Deutsch M, Paz Y, Khatib N, Baltiter T, Rosenberg S, et al. Association between gestational age and induction-to-abortion interval in mid-trimester pregnancy termination using misoprostol. *Eur J Obstet Gynecol Reprod Biol* 2011; 156:140–3.
18. Gomez O, Borrás A, Rabanal A, Palacio M, Carceller A, Coll O, et al. Mifepristone-misoprostol midtrimester abortion: impact of gestational age on the induction-to-abortion interval. *Contraception* 2010;81:97–101.
19. Wagner N, Abele H, Hoopmann M, Grischke EM, Blumenstock G, Wallwiener D, et al. Factors influencing the duration of late first and second-trimester termination of pregnancy with prostaglandin derivatives. *Eur J Obstet Gynecol Reprod Biol* 2011;155:75–8.
20. Jain JK, Mishell DR Jr. A comparison of misoprostol with and without laminaria tents for induction of second-trimester abortion. *Am J Obstet Gynecol* 1996;175:173–7.
21. Vaisanen-Tommiska M, Mikkola TS, Ylikorkala O. Increased release of cervical nitric oxide in spontaneous abortion before clinical symptoms: a possible mechanism for preabortal cervical ripening. *J Clin Endocrinol Metab* 2004;89: 5622–6.
22. Al-Hussaini TK. Uterine rupture in second trimester abortion in a grand multiparous woman. A complication of misoprostol and oxytocin. *Eur J Obstet Gynecol Reprod Biol* 2001;96: 218–9.
23. Berghahn L, Christensen D, Droste S. Uterine rupture during second-trimester abortion associated with misoprostol. *Obstet Gynecol* 2001;98:976–7.
24. Goyal V. Uterine rupture in second-trimester misoprostol-induced abortion after cesarean delivery: a systematic review. *Obstet Gynecol* 2009;113:1117–23.

