

Effects of slow release misoprostol on uterine contractility in early pregnancy

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BACKGROUND: The effect of a novel slow release form of misoprostol (SR misoprostol) on uterine activity during early pregnancy was investigated in a pilot study. **METHODS:** Thirty women with a pregnancy between 8 and 12 weeks requesting surgical abortion were allocated to treatment according to computerized randomization. SR misoprostol (400 and 800 µg) was compared to 400 µg of conventional misoprostol, all given orally. Intrauterine pressure was recorded using a pressure transducer inserted extra-amniotically and connected to a computer 30 min before treatment until 4 h thereafter when suction curettage was performed. Uterine tonus (mmHg) and contractility in Montevideo Units (MU) were calculated. **RESULTS:** An increase in uterine tonus occurred after a significantly shorter time interval and was significantly more pronounced following conventional misoprostol compared to SR misoprostol. Regular uterine contractions developed in only a few patients treated with 400 µg conventional misoprostol or 400 µg SR misoprostol. In contrast the increase in uterine contractility (MU) was significantly more pronounced following 800 µg SR misoprostol treatment and was still continuing at 4 h of recording. **CONCLUSIONS:** SR misoprostol acts less on uterine tonus than orally administered conventional misoprostol but leads to development of regular uterine contractions.

Key words: misoprostol/pregnancy/slow release/sublingual administration/uterine contractility

Introduction

Conventional misoprostol (Cytotec®; Pfizer, USA) is a commercially available prostaglandin E₁ analogue approved for the prevention and treatment of gastric ulcer. It is marketed in ~90 countries, is licensed for oral use and supplied in tablet form containing 200 µg of misoprostol. Although licensed for oral use it was shown that the efficacy of mifepristone–misoprostol medical abortion regimens could be increased and the rate of ongoing pregnancies as well as side-effects reduced when misoprostol is administered vaginally as compared to orally (El-Refaey *et al.*, 1995). Several clinical studies have confirmed that vaginal administration is more effective than oral administration (El-Refaey *et al.*, 1995; von Hertzen *et al.*, 2003). The difference in effect of oral and vaginal administration can be explained by studies on pharmacokinetics and uterine contractility (Zieman *et al.*, 1997; Gemzell-Danielsson *et al.*, 1999; Tang *et al.*, 2002). Following vaginal administration the absorption and metabolism of misoprostol is slower, resulting in a prolonged elevation of plasma levels of misoprostol. Thus the bioavailability of conventional misoprostol was shown to be 3-fold higher than following oral administration (Zieman *et al.*, 1997). The prolonged stimulation of the myometrium resulted in more regular and long-lasting increase in uterine contractility (Gemzell-Danielsson *et al.*, 1999).

However, the vaginal route of administration may not be acceptable to many women due to religious and social reasons (Ho *et al.*, 1997). The degree of absorption also showed a pronounced individual variation leading to a low plasma concentration of conventional misoprostol in some women (Gemzell-Danielsson *et al.*, 1999; Tang *et al.*, 2002). It has recently been shown that sublingual administration could be an alternative to the other routes of administration. Regimens using mifepristone and sublingual misoprostol are clinically effective and result in plasma concentrations of misoprostol which are significantly greater than those following both oral and vaginal administration (Tang *et al.*, 2002, 2003).

A drawback with sublingual administration is that some women complain about the taste of the tablets, experience more gastrointestinal side-effects and find it easier to swallow the pills (Aronsson *et al.*, 2004a,b; Hamoda *et al.*, 2004). The effect of sublingual misoprostol may also be shorter-lasting than that of vaginal misoprostol (Aronsson *et al.*, 2004b). Recently a randomized controlled study on repeated doses of vaginal versus sublingual conventional misoprostol in the second trimester was done. The number of complete abortions was higher in the vaginal group at 24 h while there was no difference at 48 h, which is consistent with a shorter-lasting effect of sublingual conventional misoprostol (Tang *et al.*, 2004).

Another approach has been to repeat the dose of oral conventional misoprostol after a 3 h interval in order to increase efficacy and reduce side-effects by dividing the dose, taking into account the pharmacokinetics of the drug (Aubeny, 1997).

An alternative would be to administer misoprostol in a slow-release form that would allow a longer lasting stimulation of the myometrium. Recently a slow-release or sustained-release form of misoprostol was synthesized and the chemical properties described (Chen *et al.*, 2000). Pharmacokinetic studies (Chen *et al.*, 2000) indicate that intake of this SR misoprostol may result in a longer duration of elevated plasma concentration of the active misoprostol free acid that may allow development of uterine contractility similar to vaginal treatment but without the drawbacks of this route.

The aim of the present pilot study was to compare the effect of orally administered conventional misoprostol and the novel SR misoprostol in two different doses on uterine contractility in women with 8–12 weeks gestation.

Materials and methods

Thirty healthy women with a normal intrauterine pregnancy between 8 and 12 weeks gestation calculated from the last menstrual period and confirmed by gynaecological examination and vaginal ultrasound who requested termination of pregnancy by vacuum aspiration were recruited. For practical reasons, only women requesting vacuum aspiration were included. The routine in the clinic is to perform vacuum aspiration between 8 and 12 weeks of gestation. The women did not have any signs of local infection. All women gave their written informed consent and the study was approved by the ethics committee at the Karolinska University Hospital/Institutet. All women received 400 µg of conventional misoprostol (Cytotec®; Pfizer, USA) or either 400 µg or 800 µg SR misoprostol orally. The slow-release tablets have previously been characterized (Chen *et al.*, 2000).

The women were randomized into the three treatment groups according to a computer generated randomization schedule. The allocations were put in opaque sealed envelopes. The subjects were asked to remain fasted overnight and were admitted to the hospital on the morning of the operation. All patients received the study drugs from the same research nurse. The envelopes were opened in front of the patients and just before they swallowed the tablets. The rest of the staff and the researchers were unaware of the treatment allocations. The tablets were taken with water. Either one or two tablets were administered of SR misoprostol (400 µg tablets). The conventional misoprostol is 200 µg tablets and two tablets were given. The nurse who administered the drug and the patients were advised not to mention or discuss the number of tablets with the investigators.

Intrauterine pressure was recorded using a computer (polygraph and software from Medtronic, Stockholm, Sweden) connected to a pressure transducer (Millar Microtips PC-771; Miller Instruments, Inc., USA). The sterilized transducer was inserted through a speculum under sterile conditions after cleansing the cervix with chlorhexidin, through the cervical canal into the uterine cavity extra-amniotically so that its tip was placed 1–2 cm from the uterine fundus. The women remained in a supine position during the entire recording session. Intrauterine pressure was monitored starting 30 min before misoprostol intake and was maintained up to 4 h thereafter. The recording would have been excluded from further

analysis if it had been interrupted before 135 min. At the end of the recording session, the pregnancy was terminated by vacuum aspiration under general anaesthesia by administration of intravenous propofol (1.5–2.0 mg/kg) and fentanyl (0.5 mg/kg). The degree of cervical priming was assessed before mechanical dilatation, noting the largest Hegar dilator that could enter the cervix without any force.

The primary outcome measure of the study was the effect on uterine activity. Elevation of uterine tonus, above the resting level, in mmHg and uterine contractility in Montevideo Units (MU) (Caldeyro-Barcia and Poserri, 1959) were calculated before and for 10 min intervals after misoprostol administration in each subject. Analysis of the individual recordings was performed in a blinded fashion, i.e. without knowledge on the treatment allocations.

The difference in effect on uterine contractility measured in MU previously observed between oral and vaginal administration of conventional misoprostol was used to calculate the sample size. Our previous studies have reported a difference in uterine contractility between oral and vaginal misoprostol at 135 min after administration (184 MU, SD 65) (Aronsson *et al.*, 2004a). A sample size of at least six subjects per group was calculated to give 80% power in detecting a similar difference between oral and SR misoprostol at 5% level of significance assuming a SD of 65. To compensate for possible loss of subjects due to technical problems or discontinuations for other reasons, a sample size of 10 women per treatment group was chosen.

Repeated measurement analysis of variance was performed using the SAS software, testing whether there were differences between the three treatment groups. A significant overall test was followed by the corresponding pairwise comparisons. When overall differences between two treatments were found to be significant, differences at each time-point were tested in Stats Direct, version 2.4.1 (www.statsdirect.com) by unpaired *t*-tests, in order to locate where in time the most substantial differences appeared. Instead of *t*-tests we also performed Mann–Whitney *U*-test to verify that the conclusions were not dependent on choice of statistical method. The differences between the groups in demographic data, time needed for dilatation and surgery and the amount of bleeding were tested using the Mann–Whitney *U*-test.

Two-sided *P*-values were reported, and the level of significance was set at *P* < 0.05.

Results

Thirty women, 10 per group, were randomized, treated and completed recording of intrauterine pressure for a period of 3.5–4 h prior to vacuum aspiration. For practical reasons (e.g. availability of anaesthesiologist) some registrations had to be stopped before 4 h (three at 3 h 30 min, two at 3 h 40 min and another two at 3 h 50 min). The quality of all recordings was high and allowed analysis in all cases. The clinical characteristics of the patients are shown in Table I. Women in the three groups did not differ significantly in age, parity or gestational age. All women were at 8–12 weeks of gestation and mean parity was 0.8, 1.2 or 1.1 respectively (range 0–3).

The first effect of misoprostol treatment was an increase in uterine tonus independent of regimen. However, this increase was more rapid and more pronounced following oral administration of conventional misoprostol than following SR treatment. The mean uterine tonus for all groups was <2 mmHg

Table I. Patient characteristics

	400 µg misoprostol	400 µg SR misoprostol	800 µg SR misoprostol
Age (years)	26 (18–38)	29.5 (18–40)	32 (19–39)
Parity	0.8 (0–2)	1.2 (0–3)	1.1 (0–3)
Gestational age (days of amenorrhoea)	61.5 (48–80)	60 (44–83)	58 (45–75)

Values are median (range).

prior to administration of misoprostol. The mean time to increase in tonus was 6.6 (±2.0) min for 400 µg oral conventional misoprostol compared to 14.3 (±8.2) and 13.5 (±5.5) min for 400 µg SR misoprostol and 800 µg SR misoprostol respectively ($P < 0.05$ and $P < 0.01$). The mean time to maximum tonus was also shorter for oral conventional misoprostol 56.2 (±43.6) compared to 108.9 (±72.8) min for 400 µg SR misoprostol and 111.6 (±69.0) min for 800 µg SR misoprostol ($P < 0.07$ and $P < 0.05$ respectively, compared to oral conventional misoprostol) (Table II, Figure 1).

The overall test showed that the development of uterine activity over time was not identical for the three different treatments, neither for tonus ($P < 0.001$) nor contractility ($P < 0.001$).

For tonus measurements there was a significant overall difference between conventional 400 µg and SR 400 µg ($P < 0.001$), and conventional 400 µg and SR 800 µg ($P < 0.001$), but not between SR 400 µg and SR 800 µg ($P = 0.5676$). The difference between the conventional 400 µg and SR 800 µg misoprostol for each 10 min interval is indicated in Figure 1. A significant difference between conventional 400 µg and SR 400 µg misoprostol for each 10 min interval was found from 50 min onwards ($P < 0.05$ or 0.01).

The effect of SR misoprostol on uterine contractility was dose dependent. For contractility measurements there was an overall significant difference between conventional 400 µg and SR 800 µg ($P < 0.001$), SR 400 µg and SR 800 µg ($P < 0.001$), but not between conventional 400 µg and SR 400 µg ($P = 0.0912$). The effect on uterine contractility following 400 µg SR misoprostol was less pronounced, whereas 800 µg had a more persistent and stronger effect; the difference between the two doses of SR was significant from 50 min onwards ($P < 0.05$ or < 0.01). A significant difference in uterine activity measured in MU between 400 µg conventional misoprostol and 800 µg SR misoprostol was

Table II. The effect of misoprostol by different release forms on uterine tonus

Release form	Dose (µg)	Time to increase in tonus (min)	P	Time to maximum tonus (min)	P
Oral	400	6.6 ± 2.0		56.2 ± 43.6	
Slow release	400	14.3 ± 8.2	0.01	108.9 ± 72.8	0.07
Slow release	800	13.5 ± 5.5	0.003	111.6 ± 69.0	0.05

Values are mean ± SD.

P -value calculated versus oral 0.4 mg (two-sided Student's t -test).

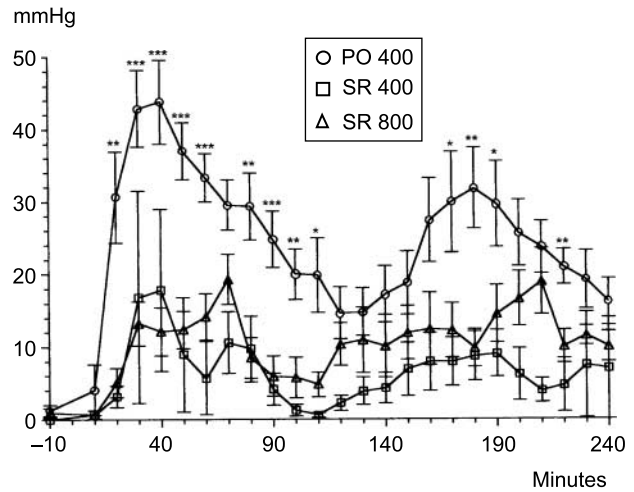


Figure 1. Uterine tonus was measured in mmHg. Significant differences were found in tonus following treatment with 400 µg (PO 400) conventional misoprostol compared to 400 µg SR (SR 400) misoprostol (not indicated) and following treatment with 400 µg conventional misoprostol compared to 800 µg SR (SR 800) misoprostol (as indicated by *). There was no significant difference between the two doses of SR misoprostol. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

found from 60 min after start of treatment ($P < 0.05$). Between 100 and 160 min the difference in effect between the groups did not reach significance. However, from 170 min the difference was significant and remained so until the end of recording when the effect of SR misoprostol appeared still to increase ($P < 0.01$ or $P < 0.001$ respectively) (Figure 2).

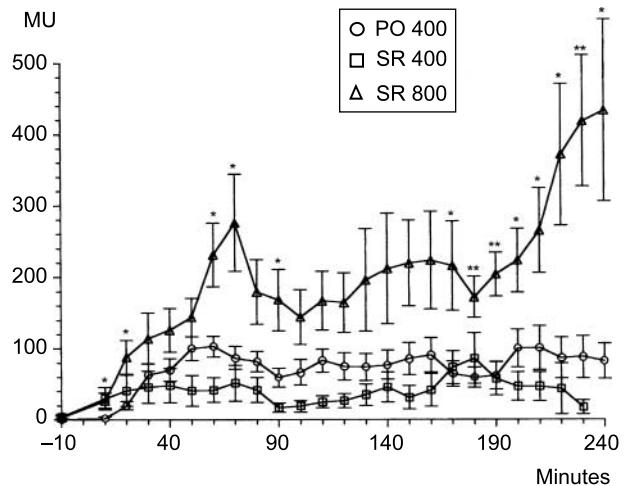


Figure 2. Uterine activity was measured in Montevideo Units (MU). There was a significantly increased uterine activity following treatment with 800 µg SR (SR 800) misoprostol compared to 400 µg (PO 400) conventional misoprostol (indicated by *). In contrast, treatment with 400 µg SR (SR 400) misoprostol resulted in a less pronounced uterine activity (significant difference, $P < 0.05$ to conventional misoprostol 400 µg only at 50, 60, 90–120 and 230 min). The difference between the two doses of SR was significant from 50 min onwards ($P < 0.05$ or $P < 0.01$). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Table III. Findings at surgery

	400 µg misoprostol	400 µg SR misoprostol	800 µg SR misoprostol
Cervical diameter (mm)	8 (5–11)	7 (4–10)	7 (5–9)
Time for dilatation (s)	8.75 (0–150)	13.5 (0–160)	7.75 (1–65)
Total time for surgery (min)	5.5 (2–30)	4 (2–6)	3.5 (2–5.4)
Blood loss (ml)	30 (3–40)	30 (10–100)	25 (2.5–90)

Values are median (range).

There were no significant differences between the groups.

At some time intervals (50, 60, 90–120, 230 min) the effect of 400 µg conventional misoprostol on uterine contractility was significantly more pronounced than that of 400 µg SR misoprostol ($P < 0.05$) (Figure 2).

For both tonus and contractility data, additional analyses with a non-parametric method (Mann–Whitney U -test) did not alter the results.

One woman per group reported nausea and two vomited, both following 800 µg SR misoprostol. Vomiting occurred 1.5–2.5 h following administration. These recordings were not excluded from analysis.

The differences between the groups in time needed for dilatation and surgery and the amount of bleeding was not statistically significant (Table III).

Discussion

Ever since medical abortion was first described, research has focused on finding the optimal type, dose and route of administration of the prostaglandin. Because prostaglandin is responsible for side-effects such as pain, diarrhoea and nausea, the dose and type of prostaglandin is a balance between efficacy and side-effects.

In the present study we investigated the effect of a novel form of slow or sustained release (SR) orally administered misoprostol on uterine activity during early pregnancy. The doses used were the standard dose of 400 µg of conventional misoprostol, which was compared to two different doses of SR misoprostol. *In vitro* data on SR misoprostol showed that <40% of misoprostol is released after 4 h in a water solution with a pH of 1.2. These data indicate that the amount of both 400 and 800 µg SR misoprostol released after 4 h of oral administration would be less than following oral administration of 400 mg conventional misoprostol. But the plasma levels would be elevated for a longer period of time for the SR.

The typical response of the pregnant uterus to oral administration of conventional misoprostol is a short increase in uterine tonus, if the uterus is not prepared with mifepristone (Norman *et al.*, 1991; Gemzell-Danielsson *et al.*, 1997; Aronsson *et al.*, 2004a).

The effect of vaginal administration of misoprostol is different in that the initial increase in tonus is less marked and is followed by an increase in uterine contractility (development of regular contractions) (Gemzell-Danielsson *et al.*,

1997). The effect on uterine activity is in accordance with available pharmacokinetic data. Following oral administration misoprostol is rapidly absorbed, reaching a peak plasma level after 30 min and thereafter declining. Vaginal administration of misoprostol results in a slower absorption rate, no 'first-passage' liver metabolism and elevated plasma levels during several hours (Zieman *et al.*, 1997; Gemzell-Danielsson *et al.*, 1999; Tang *et al.*, 2002). In the study by Norman *et al.* (1991), a dose of 200–600 µg of oral conventional misoprostol resulted in a dose-dependent increase in uterine tonus but not in the development of regular uterine contractions. The effect of a dose of 800 µg of oral conventional misoprostol on uterine activity has not been studied but would most likely be of limited value from a clinical point of view due to gastrointestinal side-effects. It therefore seems that the duration of stimulation is of importance for the development of uterine contractions while the increase in tonus more reflects the dose of misoprostol.

In the present study the time interval between oral administration of both 400 and 800 µg SR misoprostol and the initial increase in uterine tonus was significantly longer than following conventional misoprostol. These results indicate that the SR misoprostol preparation releases the active substance more slowly *in vivo* than the conventional misoprostol tablet. Rapid increases in plasma levels have been demonstrated for both oral and sublingual administration (Tang *et al.*, 2002) and are associated with a pronounced increase in uterine tonus (Aronsson *et al.*, 2004a). High peak plasma levels and a pronounced effect on uterine tonus also seem to give more side-effects. SR misoprostol had a less pronounced effect on uterine tonus in contrast to oral and similar to vaginal administration of conventional misoprostol.

Available clinical data have shown that oral misoprostol is significantly less effective than vaginal misoprostol to induce an abortion during early pregnancy if the patient is not pre-treated with mifepristone. The findings in the present study show that the effect of orally administered SR misoprostol on uterine tonus and contractility was similar to vaginally administered conventional misoprostol (Gemzell-Danielsson *et al.*, 1997). This indicates that SR misoprostol could be an orally administered alternative to vaginal misoprostol in medical abortion.

Unfortunately contractility recordings in the present study could not be continued for more than a maximum of 4 h for practical reasons. Pharmacokinetic data will be needed to gain further knowledge on the duration of the effect of SR misoprostol.

A review on women's attitudes towards medical abortion showed that women prefer oral administration of misoprostol, a shorter interval until complete abortion is diagnosed and fewer visits to the clinic (Winikoff *et al.*, 1995). If both drugs could be given within a shorter interval or at the same time this would make the treatment even easier and more convenient. An alternative to the present regimen with an interval between administrations of the drugs would be to give misoprostol in a slow release form at the same time as mifepristone or the following day. The effect on cervical ripening (time needed for dilation) following SR misoprostol

was as pronounced as for oral conventional misoprostol at 4 h after administration and did not differ between the three groups.

Only very few previous studies have investigated the effect of SR prostaglandin analogues in induced abortion. Bygdeman *et al.* (1984) used a slow-release vaginal prostaglandin analogue in second trimester induced abortion. Two years later another vaginal prostaglandin that was released during a 24 h period was studied for termination of early abortion up to 56 days gestation (Cameron and Baird, 1986). Both regimens were used without pre-treatment with mifepristone. An oral slow-release preparation of misoprostol, if effective during a sufficient time period, is likely to be more acceptable to women. A slower release of misoprostol following mifepristone may result in a lower total dose of prostaglandin needed and a lower rate of side-effects compared to oral and sublingual administration, which have rapid and strong effects on uterine tonus.

This is the first clinical pilot study on a novel SR form of orally administered misoprostol. To date, there is no slow release or sustained release dosage form of misoprostol available on the market. Further studies will investigate the pharmacokinetics of the SR misoprostol when administered during early pregnancy, the efficacy and acceptance when used for medical abortion and the potential for use in other indications.

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References

- Aronsson A, Bygdeman M and Gemzell-Danielsson K (2004a) Effects of misoprostol on uterine contractility following different routes of administration. *Hum Reprod* 19,81–84.
- Aronsson A, Helstrom L and Gemzell-Danielsson K (2004b) Sublingual compared with oral misoprostol for cervical dilatation prior to vacuum aspiration: a randomized comparison. *Contraception* 69,165–169.
- Ashok PW, Penney GC, Flett GMM and Templeton A (1998) An effective regimen for early medical abortion: a report of 2000 consecutive cases. *Hum Reprod* 13,2962–2965.
- Aubeny E (1997) Evolution since 1989 in France of Abortion by mifepristone (RU 486) associated with an analogue of prostaglandin [Evolution depuis 1989, en France, des interruptions volontaires de grossesse par mifépristone (RU 486) associée à un analogue de prostaglandine]. *Contracept Fertil Sex* 25,777–781.
- Bygdeman M, Christensen NJ, Dimov V and Green K (1984) Termination of pregnancy by a slow release device containing 16, 16-dimethyl-trans-delta 2 PGE1 methyl ester. *Asia Oceania J Obstet Gynaecol* 10,359–365.
- Cameron IT and Baird DT (1986) A controlled release form of 16,16-dimethyl-trans-delta 2-PGE, methyl ester for early abortion. *Contraception* 33,121–125.
- Caldeyro-Barcia R and Poserri JJ (1959) Oxytocin and contractility of the human pregnant uterus. *Am NY Acad Sci* 75,813–830.
- Chen D, Tsay R-J, Lin H-I, Chen H, Chao SC and Ku H (2000) Stabilization and sustained-release effect of misoprostol with methacrylate copolymer. *Int J Pharm* 203,141–148.
- El-Refaei H, Rajasekar D, Abdalla M, Calder L and Templeton A (1995) Induction of abortion with mifepristone (RU 486) and oral or vaginal misoprostol. *New Engl J Med* 332,983–987.
- Gemzell Danielsson K, Marions L, Rodriguez A, Spur BW, Wong PY and Bygdeman M (1999) Comparison between oral and vaginal administration of misoprostol on uterine contractility. *Obstet Gynecol* 93,275–280.
- Hamoda H, Ashok PW, Flett GM and Templeton A (2004) A randomized controlled comparison of sublingual and vaginal administration of misoprostol for cervical priming before first-trimester surgical abortion. *Am J Obstet Gynecol* 190,55–59.
- Ho PC, Ngai SW, Liu KL, Wong GC and Lee SW (1997) Vaginal misoprostol compared with oral misoprostol in termination of second trimester pregnancy. *Obstet Gynecol* 90,735–738.
- Norman JE, Thong KJ and Baird DT (1991) Uterine contractility and induction of abortion in early pregnancy by misoprostol and mifepristone. *Lancet* 16,338(8777),1233–1236.
- Tang OS, Schweer H, Seyberth HW, Lee SW and Ho PC (2002) Pharmacokinetics of different routes of administration of misoprostol. *Hum Reprod* 17,332–336.
- Tang OS, Chan CC, Ng EH, Lee SW and Ho PC (2003) A prospective, randomized, placebo-controlled trial on the use of mifepristone with sublingual or vaginal misoprostol for medical abortions of less than 9 weeks gestation. *Hum Reprod* 18,2315–2318.
- Tang OS, Lau WN, Chan CC and Ho PC (2004) A prospective randomised comparison of sublingual and vaginal misoprostol in second trimester termination of pregnancy. *Br J Obstet Gynaecol* 111,1001–1005.
- von Hertzen H, Honkanen H, Piaggio G, Bartfai G, Erdenetungalag R, Gemzell-Danielsson K, Gopalan S, Horga M, Jerve F, Mittal S *et al.* (2003) WHO Research Group on Post-Ovulatory Methods for Fertility Regulation. WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion. I: Efficacy. *Br J Obstet Gynaecol* 110,808–818.
- Winikoff B (1995) Acceptability of medical abortion in early pregnancy. *Fam Plann Perspect* 185,142–148.
- Zieman M, Fong SK, Benowitz NL, Banskter D and Darney PD (1997) Absorption kinetics of misoprostol with oral or vagina administration. *Obstet Gynecol* 90,88–92.

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