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ORIGINAL ARTICLE *Fertility control*

One- and two-day dosing intervals between mifepristone and misoprostol in second trimester medical termination of pregnancy—a randomized trial

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BACKGROUND: The recommended time interval between mifepristone and misoprostol in medical second trimester termination of pregnancy (TOP) has been 36–48 h. However, a more flexible interval would be of value. The aim of this investigation was to compare one- and two-day intervals in second trimester medical TOP. The main outcome measures were induction-to-abortion time and the rate of surgical evacuation.

METHODS: This open randomized trial included 227 women undergoing TOP between gestational weeks 13–24. Mifepristone (200 mg) was followed by misoprostol (400 mcg) after one (17–28 h) or two (41– 45 h) days.

RESULTS: In intention-to-treat analysis, the median induction-to-abortion interval was 1 h longer in the one-day group (8.5 versus 7.2 h, $P = 0.038$), but in per-protocol analysis, the rate of surgical evacuation was higher in the 2-day group [30/115 (25%) versus 40/112 (37%); 95% confidence interval 0.3–24.1, $P = 0.044$]. A subgroup analysis showed that the median induction-to-abortion interval was 3 h longer in the one-day group, amongst women without previous vaginal deliveries (10.1 versus 7.6, $P = 0.013$) and when gestation exceeded 16 weeks (10.8 versus 7.2, $P = 0.024$).

CONCLUSIONS: Both one- and two-day dosing intervals seem to be suitable for second trimester medical TOP, but women with no previous deliveries and those whose gestation exceeds 16 weeks may benefit from the longer interval. However, evaluated on the basis of surgical evacuation, the one-day interval could be supported as an option for second trimester medical TOP. Effective use of both one- and two-day dosing intervals is important when optimizing clinical service.

Trial Registration: **ISRCTN09944151**.

Key words: dosing interval / second trimester / termination of pregnancy / mifepristone / misoprostol

Introduction

Termination of pregnancy (TOP) between 13 and 24 weeks of gestation (during the second trimester) constitutes ~6–12% of all induced abortions (Department of Health, 2010; Guttmacher Institute, 2010; Socialstyrelsen, 2010; THL, 2010). The method used for second trimester TOP can be controversial (Grimes, 2008; Lohr *et al.*, 2008; Lee *et al.*, 2010), but in Northern Europe second trimester TOP is largely performed by means of medical abortion (Department of Health, 2010; Socialstyrelsen, 2010; THL, 2010).

The most efficacious regimen for medical second trimester TOP appears to be the use of a combination of the antiprogestin, mifepristone, followed by the prostaglandin E_1 (PGE_1) analogue, misoprostol, (Gemzell-Danielsson and Lalitkumar, 2008; Lohr *et al.*, 2008). The most common regimen is oral mifepristone (200 mg) followed by an 800-mcg dose of misoprostol (Gemzell-Danielsson and Lalitkumar, 2008). Thereafter, 400-mcg doses of misoprostol are repeated every 3 h—up to five doses per 24 h (Gemzell-Danielsson and Lalitkumar, 2008). This regimen has had 97–99% efficacy, i.e. rate of abortion within 24 h (Ashok *et al.*, 2004; Hamoda *et al.*, 2005).

The recommended time interval between mifepristone and the first dose of misoprostol has been 36–48 h, as the maximal effect of mifepristone is reached at that point (Gemzell-Danielsson and Lalitkumar, 2008). However, in clinical practice this waiting time poses several problems. Thus, a more flexible time interval is needed when organizing clinical services throughout the week. Increased flexibility might also improve patient satisfaction—for example, by lowering the possible anxiety of aborting at home following mifepristone administration.

In previous studies, simultaneous administration of mifepristone and misoprostol has been found to be less effective than a regimen involving a 36- to 38-h dosing interval (Chai *et al*., 2009). However, the results of retrospective reviews (Heikinheimo *et al*., 2004; Nilas *et al*., 2007) and one randomized study (Hou *et al*., 2010) suggest that one- and two-day mifepristone–misoprostol intervals are both equally effective.

The objective of this randomized trial was to compare one- and two-day intervals between mifepristone and misoprostol administration in second trimester medical TOP. The primary outcome measures were induction-to-abortion time and the rate of surgical evacuation of retained placenta or placental tissue. The induction-to-abortion time was defined as the time from the first misoprostol dose to fetal expulsion. Secondary outcome measures were the rates of adverse events and complications (bleeding, infection and pain).

Materials and Methods

This open prospective randomized trial was conducted at the Department of Obstetrics and Gynaecology, Helsinki University Central Hospital. The trial had approval from the Ethics Committee of the Hospital district of Helsinki and Uusimaa, and the Finnish National Agency for Medicines. The trial was registered at Controlled Trials (web page: http://www.controlled-trials.com/ISRCTN09944151).

Doctors on duty assessed all women presenting themselves at the centre and requesting second trimester TOP. Medical history was reviewed and a clinical examination including gynaecological examination and ultrasonography (either transvaginal or abdominal) to determine the duration of gestation was performed. The hospital nurses or the investigator (M.M.) contacted the women after they had been found suitable for the study. Inclusion criteria were: age $\geq$18 years and a viable singleton pregnancy between 13 and 24 weeks of gestation (85–169 days of amenorrhoea), a legal indication for TOP and official approval from the Finnish Legal Authority for Medicolegal Affairs (Valvira, 2010) as required by Finnish legislation on TOP during these weeks of gestation (FINLEX, 2010). Written informed consent was obtained from the participants before their enrolment into the study.

Exclusion criteria were allergy to study medication, severe or complicated asthma not responding to medication, suspected ectopic pregnancy, coronary disease or high risk factors for it, intrauterine contraceptive device in the uterus at the time of termination and lack of a common language with the medical staff. Demographic characteristics of the women were collected at the time of the first visit to the hospital.

Randomization was performed using a computer-assisted random block system (R Development Core Team, 2010) with permuted randomization for random block clinical trials. Random blocks of 4–6 women were used. The investigators did not participate in randomization, which was done before the start of the study.

Calculation of sample size was based on the results of a pilot study (Heikinheimo *et al*., 2004). A difference of 2 h or more in induction-to-abortion time was considered clinically significant. Power analysis indicated that in order to show a 2-h difference in the induction-to-abortion time using *t*-tests with 80% power ($\beta = 0.20$) and a 5% significance level ($\alpha = 0.05$), both groups needed at least 92 subjects. In addition, the rate of surgical evacuation (Heikinheimo *et al*., 2004) was considered for the calculation of sample size. The rate of surgical evacuation was set to 36%. Assuming a 20% difference between the treatments, the required sample size was 102 per group using Fisher's exact test with 80% power and a 5% significance level. Subsequently, 230 subjects were randomized, assuming a possible dropout rate of one in five.

The group assignments were kept in sealed, opaque envelopes. Hospital nurses or the study investigator (M.M.) opened the randomization envelopes after recruitment. The women were randomized into two groups according to which misoprostol was administered one or two days after ingestion of 200 mg of mifepristone (Mifegyne®, Exelgyn, Paris, France). Mifepristone was taken during a short visit to the outpatient clinic, with no observation time. The women were asked to return as soon as possible if they vomited within 2 h after mifepristone intake. Thereafter, the subjects returned to the hospital early in the morning one (20–28 h) or two days (40–48 h) later for misoprostol administration. This took place at the hospital ward in an inpatient setting.

Misoprostol (200 mcg, Cytotec®, Pfizer Oy, Helsinki, Finland) was administered in 400 mcg doses every 3 h, with up to five doses per 24 h. It was administered vaginally as long as uterine bleeding was not heavy (as judged by the nurse in charge of the subject) and thereafter it was given sublingually. A 200 mg dose of mifepristone was repeated at midnight if no signs of imminent abortion were seen. If abortion had not occurred within 24 h of administration of the first misoprostol dose, a transvaginal ultrasonography was performed. A second (and third) course of vaginal misoprostol was administered if no signs of imminent abortion were seen.

Regarding prophylactic management of pain, oral ibuprofen (600–800 mg), paracetamol (500 mg) or paracetamol (500 mg) plus dihydrocodeine (10 mg) were administered at the time of the first misoprostol dose. Thereafter, oral non-steroidal anti-inflammatory drugs or oral paracetamol (500 mg) plus dihydrocodeine (10 mg) and oral or parenteral opioid analgesics were administered when needed. Antiemetics (oral or rectal metoclopramide hydrochloride and oral ondansetron) were used for nausea and vomiting.

Potential side effects (i.e. bleeding of $>$500 ml) axial temperature rise to over 38.0°C and clinical signs of infection were monitored by nurses on the ward. In cases of heavy bleeding, the amount was measured by weighing. In cases of clinical signs of temperature change (shivering, chills), axial temperature was taken. Clinical signs of infection were defined as temperature rise to over 38°C with lower abdominal pain and infectious smell in the vaginal discharge, being aware that the first two signs can be due to misoprostol use. Pain was assessed by a VAS (visual analogue scale) score of 0–10 before a misoprostol dose or any analgesics were administered. The VAS was explained to the subjects as zero representing no pain at all and number 10 as the worst possible pain they could imagine.

If the fetus and placenta were passed at the ward, the placenta appeared to be complete and there were no signs of continuous heavy vaginal bleeding, no further interventions were undertaken and the women were discharged. No routine ultrasonographic examination was performed.

Women who did not pass the placenta were examined and the remaining placenta was removed at the ward or in the operating theatre under general anaesthesia if needed. This occurred after administration of 400–800 mcg doses of misoprostol followed by an appropriate observation period (defined by the doctors on duty). There were no written instructions concerning the appropriate observation time, but a few

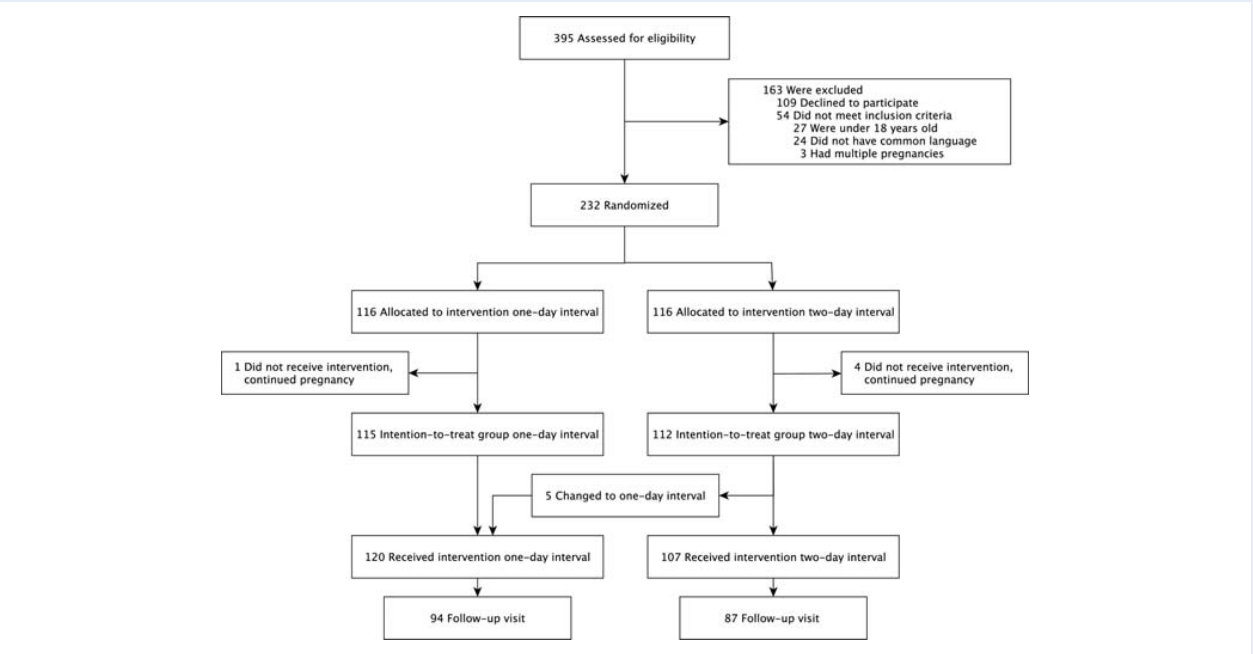

Figure 1 The study flow chart of the randomized trial of one- and two-day dosing intervals between mifepristone and misoprostol in second trimester medical TOP.

hours were commonly used. In cases of heavy bleeding, surgical evacuation was performed instantly. The diagnosis of residual tissue was based on continuous heavy bleeding and placental tissue that seemed to be incomplete (as judged by the staff in charge of the subject).

Sick leave of 3 days was recommended. Contraceptives were prescribed when necessary. Oral contraceptives were started immediately after abortion and contraceptive implants were inserted at the ward.

The women were scheduled to return for a follow-up assessment 2–4 weeks after the abortion. At the follow-up, they were asked about the development of any complications that may require treatment. Clinical examination and transvaginal ultrasonography were performed and the use of postabortal contraception was assessed. Intrauterine devices (either the levonorgestrel-releasing intrauterine system or a copper-IUD) were inserted if needed.

The diagnosis of residual tissue was based on continuous prolonged bleeding with ultrasound finding of uneven endometrial thickening. Ultrasound findings without abnormal bleeding or lower abdominal pain were not treated surgically. Routine histological analysis of the residual tissue was not performed, but in all cases the surgeon confirmed a suspicion of residual tissue. Analysis of heavy bleeding (over 500 ml) was based on measurements of bleeding at the hospital ward. Infection was defined as lower abdominal pain, infectious smell in bleeding or discharge and/or increased levels of circulating leukocytes and/or C-reactive protein. Thus, all infections from mild endometritis to severe pelvic inflammatory disease were taken into account.

Statistical analysis

Statistical analysis was performed using PASW 18.0 for Mac (SPSS Inc., Chicago, IL, USA).

Differences in continuous variables were analysed by means of the Mann–Whitney *U*-test for skewed data. The data are presented as medians (IQR, i.e. interquartile range or 5th–95th percentile range as appropriate). Confidence interval (CI) for the difference between two medians was analysed using the Hodges–Lehman method. Chi-square or Fisher's exact tests were used as appropriate for independent nominal data. Cox proportional hazards regression model was used in order to adjust for baseline covariates in time-to-event analysis. Statistical significance was defined as $P < 0.05$. Chi-square test for trend (with one degree of freedom) was used for analysis of misoprostol doses needed. 95% CI for differences of proportions were calculated using Newcombe's method (Newcombe, 1998). Kaplan–Meier survival analysis with the log rank test and the corresponding *P*-values was used to compare cumulative induction-to-abortion data. Analysis and comparison were performed on both the intention-to-treat (ITT) and a per-protocol (PP) basis.

Results

A total of 395 women underwent medical second trimester TOP between 7 May 2008 and 6 July 2010. However, 109 of them declined to participate and 54 were excluded for not fulfilling the inclusion criteria. Subsequently 232 (59%) were randomized into the study. Figure 1 shows how the study groups were formed. Five women decided to continue pregnancy before mifepristone was taken. Thus 227 women receiving treatment were included in the ITT analysis as originally randomized. Furthermore, five women changed the randomized time interval from 2 days to one and they were allocated into the actual treatment groups in the PP analysis.

One subject in the 2-day group failed to abort with medication and underwent surgical dilatation and evacuation. Misoprostol was used for 2 days, but thereafter there was a 36-h break in medication for

Table I Demographic characteristics (ITT basis) of the 227 women undergoing medical second trimester TOP between 7 May 2008 and 6 July 2010.

Variable	One-day interval (n = 115)	Two-day interval (n = 112)
Gestation at abortion		
Days of amenorrhoea [median (IQR)]	104 (98–119)	106 (98–122)
Gestational weeks 13–16	78 (67.8)	72 (64.3)
Gestational weeks 17–24	37 (32.2)	40 (35.7)
Age [years, median (IQR)]	23 (20–27)	23 (20–29)
Marital status		
Married	17 (14.8)	14 (12.5)
Cohabiting	19 (16.5)	22 (19.6)
Single	79 (68.7)	76 (67.9)
Socioeconomic status		
White-collar workers	11 (9.6)	13 (11.6)
Blue-collar workers	40 (34.8)	39 (34.8)
Students	30 (26.1)	27 (24.1)
Others	34 (29.6)	33 (29.5)
BMI [kg/m^2, median (IQR)]	23 (21–26)	23 (20–25)
Chlamydia trachomatis infection	8 (7.0)	10 (8.9)
Previous TOP	55 (47.8)	48 (42.9)
Previous vaginal delivery	38 (33.0)	28 (25.0)
Previous Caesarean section	11 (9.6)	9 (8.0)
Indication for TOP		
Fetal	8 (7.0)	8 (7.4)
Other	107 (93.0)	104 (97.2)

Data expressed as n (%) unless otherwise stated. IQR, interquartile range; ITT, intention-to-treat; TOP, termination of pregnancy.

non-medical reasons. This subject was analysed as a non-aborter up to 48 h, but left out of any other time analysis because of the protocol violation.

The demographic characteristics of the study groups on the basis of ITT are presented in Table I. No unexpected differences among these baseline characteristics were produced by the randomization. The same was true among baseline characteristics in PP analysis (data not shown).

The median (5th–95th percentile range) time interval between mifepristone and misoprostol was 24 (21–25) h in the one-day group and 42 (32–48) h in the 2-day interval group in the ITT analysis. In the PP analysis, the median (5th–95th percentile range) time interval was 24 (21–25) and 42 (41–48) h in the one- and two-day groups, respectively. None of the women aborted after mifepristone only. The median (IQR) number of misoprostol doses was 3 (3–4) in the one-day and 3 (3–4) in the 2-day-interval group ($P = 0.17$) in the ITT analysis.

Analysis of the primary outcome measures, the induction-to-abortion time and the rate of surgical evacuation, are shown in Table II. On ITT basis, the median induction-to-abortion interval was one hour longer in the one-day group (95% CI for difference 0.1–1.9; $P = 0.038$). In order to adjust for baseline covariates (Table I), cox regression model was used for induction-to-abortion event in ITT analysis. The 2-day interval was related to a shorter induction-to-abortion interval (unadjusted hazard ratio, HR 0.84; 95% CI 0.65–1.1, $P = 0.21$ and adjusted HR 0.74; 95% CI 0.46–0.89; $P = 0.03$).

The rate of surgical evacuation of retained placenta was higher in the 2-day interval group (percentage difference 11.4; 95% CI −23.0 to 0.6), but the difference did not reach statistical significance ($P = 0.06$) in ITT analysis. However, in the PP analysis the 2-day interval was related to a higher rate of surgical evacuation of residual tissue than the one-day interval (percentage difference 12.4; 95% CI 0.3–24.1; $P = 0.044$).

A subgroup analysis (Table II) on ITT basis showed that the median induction-to-abortion interval was 3 h longer in the one-day interval group on women without previous vaginal deliveries ($P = 0.013$) and when gestation exceeded 16 weeks ($P = 0.024$). On PP basis, this analysis showed that the median induction-to-abortion interval was 3 h longer on women without previous vaginal deliveries ($P = 0.022$).

The timing of surgical evacuation was further analysed (Table II). On ITT basis, the immediate surgical evacuation during the hospital stay at the time of TOP occurred more often in the 2-day interval group (percentage difference 9.1; 95% CI −19.2 to 0.9), although this difference was not statistically significant ($P = 0.07$). Later surgical evacuation occurred also more often in the 2-day interval group (percentage difference 3.3 and 95% CI −12.5 to 5.6), but also this difference was not statistically significant ($P = 0.45$).

The secondary outcome measures were not significantly different between the one-day and two-day interval groups (Table III). The rate of infection (percentage difference 2.4; 95% CI −5.8 to 10.5, ns.) as well as the occurrence of bleeding over 500 ml (percentage difference 0.7; 95% CI −6.3 to 7.7, ns.) was similar in the one- and two-day interval groups. The number of severe complications was low; altogether two subjects in the one-day interval group had a perforation of the uterus during the immediate surgical evacuation of residual tissue. The perforations were sutured in laparoscopic operations. The percentage difference of severe complications between the groups was 1.7 (95% CI −2.0 to 5.9).

The cumulative rate of abortion in ITT basis is shown in Fig. 2. The difference in the cumulative rates of abortion in the two study groups was not statistically significant ($P = 0.17$). The same was true when the cumulative abortion rate among women with no previous vaginal deliveries ($P = 0.13$) or when gestational weeks exceeded 16 ($P = 0.09$) were analysed separately (data not shown). These figures remained the same when analysed on the PP basis (data not shown). By 12 h, the success rate of abortion was 82 and 86% in the one- and two-day interval groups, respectively in the PP analysis ($P = 0.4$). By 24 h, the figures were 95 and 94% ($P = 0.7$).

Altogether, 46 women (20.4%) did not attend the scheduled follow-up visit. One-third of them were successfully contacted by telephone. However, none of the women not attending the follow-up visit had contacted a public hospital within 3 months after TOP in connection with abortion-related issues. We thus considered their outcome complete, with no serious complications.

Table II The primary outcome of the 227 women undergoing medical second trimester TOP between 7 May 2008 and 6 July 2010.

	Variable	One-day interval	Two-day interval	95% CI for difference	*P*-value
ITT basis		*n* = 115	*n* = 112		
	Induction-to-abortion (hours)[a]	8.5 (6.3–12.3)	7.2 (5.8–9.2)	0.1–1.9	0.038
	No previous deliveries	10.1 (7.0–12.7)	7.6 (5.8–10.6)	0.3–3.1	0.013
	Previous vaginal deliveries	7.0 (5.5–9.0)	6.8 (5.8–7.7)	−0.8 to 1.5	0.57
	≤16 weeks of gestation	7.6 (5.9–11.3)	7.2 (5.7–9.0)	−0.4 to 1.6	0.27
	>16 weeks of gestation	10.8 (7.2–13.1)	7.2 (6.2–10.6)	0.3–4.3	0.024
	Surgical evacuation of retained placenta	29 (25.2)	41 (36.6)	−23.0 to 0.6	0.06
	Immediate	15 (13.0)	25 (22.3)	−19.2 to 0.7	0.07
	Later	14 (12.2)	16 (14.3)	−11.1 to 6.8	0.64
PP basis		*n* = 120	*n* = 107		
	Induction-to-abortion (hours)[a]	8.5 (6.3–12.3)	7.2 (5.8–9.7)	0.0–1.8	0.055
	No previous deliveries	10.0 (7.0–12.5)	7.6 (5.8–10.6)	0.2–2.8	0.022
	Previous vaginal deliveries	7.0 (5.5–8.8)	6.8 (5.7–7.7)	−0.7 to 1.5	0.53
	≤16 weeks of gestation	7.8 (6.0–10.8)	7.2 (5.6–9.1)	−0.4 to 1.6	0.27
	>16 weeks of gestation	10.7 (7.2–12.5)	7.2 (6.2–10.9)	0.0–4.1	0.050
	Surgical evacuation of retained placenta	30 (25.0)	40 (37.4)	0.3–24.1	0.044
	Immediate	16 (13.3)	24 (22.4)	−19.2 to 0.9	0.07
	Later	14 (11.7)	16 (15.0)	−12.5 to 5.6	0.47

Data expressed as *n* (%) or median (IQR). ITT, intention-to-treat; PP, per-protocol.
[a]Without the subject who did not abort with medication.

Table III The secondary outcome measures analysed according to ITT basis of the 227 women undergoing medical second trimester TOP between 7 May 2008 and 6 July 2010.

Variable	One-day interval *n* = 115	Two-day interval *n* = 112	*P*-value
Misoprostol doses (400 mcg)			0.40[a]
1–2	24 (20.9)	26 (23.2)	
3	38 (33.0)	48 (42.9)	
4	25 (21.7)	17 (15.2)	
5	21 (18.3)	13 (11.6)	
6–18	7 (6.1)	8 (7.1)	
Infection[b]	13 (11.3)	10 (8.9)	0.66
Temperature over 38°C	14 (12.2)	16 (14.3)	0.64
Bleeding over 500 ml	8 (7.0)	7 (6.3)	0.84
Haemoglobin under 90 g/l	4 (3.5)	3 (2.7)	0.73
Blood transfusion	3 (2.6)	1 (0.9)	0.33
Severe complications[c]	2 (1.7)	0	0.16
VAS max (highest value in visual analogue scale)	6 (5–8)	7 (4–9)	0.07
The need of additional opiates for analgesia	106 (92.2)	100 (90.1)	0.58
The need of antiemetic drugs	30 (26.1)	24 (21.6)	0.43
Induction-to-placental-expulsion (hours)[d]	9 (6–12)	8 (6–10)	1.00

Data expressed as *n* (%) or median (IQR).
[a]Chi-square test for trend.
[b]Endometritis or pelvic inflammatory disease.
[c]Perforation during surgical evacuation of retained placenta.
[d]Without the subject who did not abort with medication.

Discussion

We found a 1-h difference in the induction-to-abortion times between one- and two-day intervals in administration of mifepristone and misoprostol for second trimester medical TOP. Although statistically significant, in clinical practice this is a small difference. Moreover the gold standard, 2-day interval between abortion-medication was

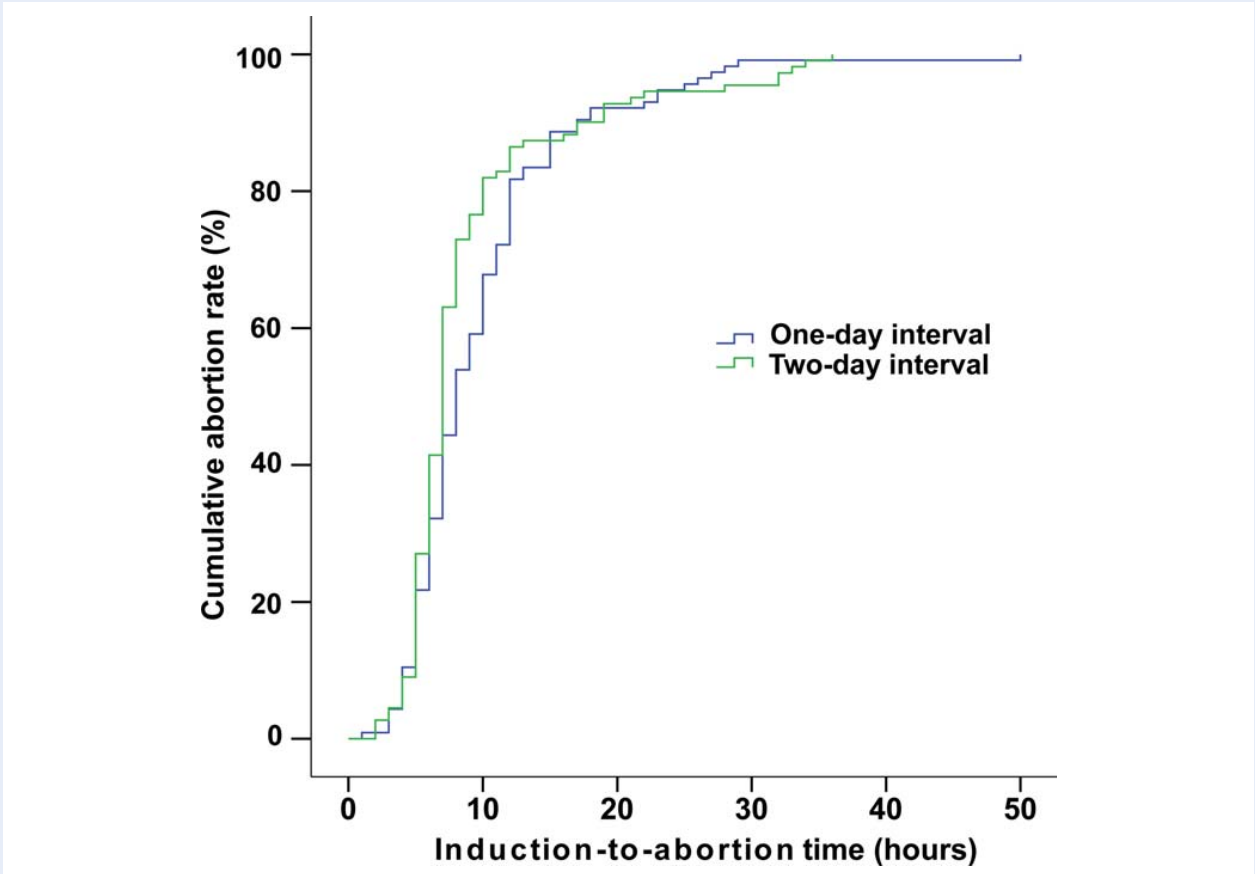

Figure 2 The cumulative rate of abortion in the one- and two-day mifepristone to misoprostol interval groups on ITT basis.

related to a higher rate of surgical evacuation of retained placenta. Otherwise, the two dosing regimens did not differ as regards adverse events during and after TOP. Thus both one- and two-day intervals seem to be suitable for clinical use in second trimester medical TOP.

However, there seems to be some subgroups of women who may benefit from the longer interval between mifepristone and misoprostol as the one-day interval was related to a clearly longer induction-to-abortion time in women with no previous vaginal deliveries and women with a pregnancy exceeding 16 weeks of gestation. This difference would result in a treatment that cannot be performed as a day-case within one nurse's shift. It may also be counted as more inconvenient for the patient, and more resources are needed in the hospital.

This prospective study provides data from a centre where all second trimester TOPs are performed medically. In the present series, fetal indications for TOP were less common than among the total of second trimester TOPs in our institute (Mentula *et al.*, 2010). As previous studies have described similar success and complication rates in medical second trimester TOP due to fetal or social indications (Nilas *et al.*, 2007; Brouns *et al.*, 2010; Dickinson *et al.*, 2010), this hardly had an effect on the results.

In the present study, five women changed intervention group. This confirmed the need to have a flexible dosing interval between mifepristone and misoprostol. Moreover, one-fifth of all women did not attend the scheduled follow-up visit. However, the investigators had access to the hospital record database concerning visits to public hospitals in the Helsinki University Hospital area. This database gives detailed information of all visits to specialist health care in public hospitals. Thus these patients were not considered as lost-to-follow-up.

The induction-to-abortion time in this study and the 24-h success rate were similar to those described earlier (Ashok *et al.*, 2004; Tang *et al.*, 2005; Carbonell *et al.*, 2008; Chai *et al.*, 2009; Hou *et al.*, 2010). Nonetheless, when seeking the highest success rate as well as the shortest induction-to-abortion time the answer may be related to the misoprostol dose. The highest 24-h success rate (97–100%) has been related to 600–800-mcg initiation dose of misoprostol (Ashok *et al.*, 2004; Carbonell *et al.*, 2008; Chai *et al.*, 2009) while the 400-mcg initiation dose of misoprostol has been related to 91–94% success rate within 24 h (Tang *et al.*, 2005; Hou *et al.*, 2010). Moreover, the initiation dose of a 200-mcg misoprostol has been related to the lowest (66–75%) 24-h success rate (Ngai *et al.*, 2003; Brouns *et al.*, 2010). Also the induction-to-abortion interval seems to relate to the initiation dose of misoprostol. The shortest

(5 h) induction-to-abortion interval has been related to a misoprostol initiation dose of 600–800 mcg (Chai et al., 2009), while the 400 and 200 mcg doses have been related to 7 (Hou et al., 2010) and 10 h induction-to-abortion times. Therefore, chancing the initiation dose of misoprostol to 800 mcg could further improve the protocol used in this study.

The longer induction-to-abortion time of women with no previous vaginal deliveries or gestation that exceeded 16 weeks was in line with previous studies where nulliparity and longer gestation have been related to a longer induction-to-abortion time also with the 36–48 h interval between mifepristone and misoprostol (Ashok et al., 2004). Uterine contractility in response to exogenous PG has been reported to be maximal at 36–48 h after mifepristone treatment (Swahn and Bygdeman, 1988). We thus speculate that optimizing myometrial contractility is important when treating women without previous vaginal deliveries and women whose gestation exceeds 16 weeks as they seem to be in a risk for longer induction-to-abortion time.

The rate of surgical evacuation in the present study was high, as much as 31%, compared with the 3–9% described earlier from a centre with extensive experience with the method (Ashok et al., 2004; Hamoda et al., 2005). While the study groups in our study and these studies seemed to be similar, the only difference being the initiation dose (400 versus 800 mcg) of misoprostol. Thus, the rate of surgical evacuation may also be related to the dosing of misoprostol. However, some 10 years ago surgical evacuation was used as a routine procedure following all second trimester medical TOPs in Finland, as is still the case in some countries (Carbonell et al., 2008; Chai et al., 2009). However, we assume that in the present study the criteria for evacuation were similar between the two groups.

In the present study, the 2-day interval between mifepristone and misoprostol was related to a higher rate of surgical evacuation than the one-day interval in PP analysis. This finding was in contrast to that in an earlier study where the 2-day interval was related to fewer incomplete abortions (30 versus 46%; $P < 0.001$) (Hou et al., 2010). In the study by Hou et al. (2010), TOP was performed between gestational weeks 13–16, while the present study included also TOP performed between 17 and 24 weeks of gestation. The misoprostol doses were the same in both studies, but in the study by Hou et al. (2010) the time interval between repeat misoprostol doses were 6 h as they were 3 h in our study. These differences may have an effect on the rate of surgical evacuation, as well as differences in the criteria for evacuation. However, we assume that the time interval between mifepristone and misoprostol may not be the only explanation for the evacuation rate after second trimester medical TOP. Thus, further evaluation of the factors related to the need of surgical evacuation after second trimester medical TOP is needed.

In conclusion, the present results confirm that both one- and two-day dosing intervals between mifepristone and misoprostol are suitable for clinical use for second trimester medical TOP. However, women with no previous deliveries and those with duration of gestation over 16 weeks may benefit from the longer interval. Clinical practice should also be evaluated on the basis of the need of surgical evacuation and in the present study the rate of surgical evacuation was higher in the 2-day interval group. Although the effect of the interval between abortion-medication on the rate of surgical evacuation may not be fully solved, this suggests that there are several aspects to be considered in clinical practice. Use and knowledge of both the one- and two-day intervals between mifepristone and misoprostol administration is of importance when optimizing patient care and organizing clinical services in second trimester TOP.

Authors' roles

All authors have equally participated in study design, analysis of the data, manuscript drafting and critical discussion. M.M. was involved in the execution of the study.

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References

Ashok PW, Templeton A, Wagaarachchi PT, Flett GM. Midtrimester medical termination of pregnancy: a review of 1002 consecutive cases. *Contraception* 2004;**69**:51–58.

Brouns J, Van Wely M, Burger M, Van Wijngaarden W. Comparison of two dose regimens of misoprostol for second-trimester pregnancy termination. *Contraception* 2010;**82**:266–275.

Carbonell JL, Torres MA, Reyes R, Ortega L, García-Gallego F, Sánchez C. Second-trimester pregnancy termination with 600-microg vs. 400-microg vaginal misoprostol and systematic curettage postexpulsion: a randomized trial. *Contraception* 2008;**77**:50–55.

Chai J, Tang OS, Hong QQ, Chen QF, Cheng LN, Ng E, Ho PC. A randomized trial to compare two dosing intervals of misoprostol following mifepristone administration in second trimester medical abortion. *Hum Reprod* 2009;**24**:320–324.

Department of Health. Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsStatistics/DH_099285 (6 January 2011, date last assessed) 2010.

Dickinson J, Brownell P, Mcginnis K, Nathan E. Mifepristone and second trimester pregnancy termination for fetal abnormality in Western Australia: worth the effort. *Aust N Z J Obstet Gynaecol* 2010;**50**:60–64.

FINLEX. FINLEX®-Ajantasainen lainsäädäntö: 24.3.1970/239. Available at: http://www.finlex.fi/fi/laki/ajantasa/1970/19700239. (6 January 2011, date last assessed) 2010.

Gemzell-Danielsson K, Lalitkumar S. Second trimester medical abortion with mifepristone-misoprostol and misoprostol alone: a review of methods and management. *Reprod Health Matters* 2008;**16**:162–172.

Grimes D. The choice of second trimester abortion method: evolution, evidence and ethics. *Reprod Health Matters* 2008;**16**:183–188.

Guttmacher Institute. *Facts on Induced Abortion Worldwide*. Guttmacher Institute. Available at: http://www.guttmacher.org/pubs/fb_IAW.html (6 January 2011, date last accessed) 2010.

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**:2348–2354.

Heikinheimo O, Suhonen S, Haukkamaa M. One- and 2-day mifepristone-misoprostol intervals are both effective in medical termination of second-trimester pregnancy. *Reprod Biomed Online* 2004;**8**:236–239.

Hou S, Zhang L, Chen Q, Fang A, Cheng L. One- and two-day mifepristone-misoprostol intervals for second trimester termination of pregnancy between 13 and 16weeks of gestation. *Int J Gynaecol Obstet* 2010;**111**:126–130.

Lee VC, Ng EH, Ho PC. Issues in second trimester induced abortion (medical/surgical methods). *Best Prac Res Clin Obstet Gynaecol* 2010; **24**:517–527.

Lohr PA, Hayes JL, Gemzell-Danielsson K. Surgical versus medical methods for second trimester induced abortion. *Cochrane Database Syst Rev* 2008:CD006714. DOI: 10.1002/14651858.CD006714.pub2.

Mentula MJ, Niinimäki M, Suhonen S, Hemminki E, Gissler M, Heikinheimo O. Young age and termination of pregnancy during the second trimester are risk factors for repeat second-trimester abortion. *Am J Obstet Gynecol* 2010;**203**:107.e1–7.

Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med* 1998;**17**:857–872.

Ngai SW, Tang OS, Ho PC. Prostaglandins for induction of second-trimester termination and intrauterine death. *Best Prac Res Clin Obstet Gynaecol* 2003;**17**:765–775.

Nilas L, Glavind-Kristensen M, Vejborg T, Knudsen UB. One or two day mifepristone-misoprostol interval for second trimester abortion. *Acta obstetricia et gynecologica Scandinavica* 2007; **86**:1117–1121.

R Development Core Team. *A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing, 2010;1. http://www.r-project.org (June 2011, date last accessed).

Socialstyrelsen. *Official statistics of Sweden 2010*. http://www.socialstyrelsen.se/publikationer2011/2011-6-1 (June 2011, date last accessed).

Swahn ML, Bygdeman M. The effect of the antiprogestin RU 486 on uterine contractility and sensitivity to prostaglandin and oxytocin. *BJOG* 1988;**95**:126–134.

Tang OS, Chan CC, Kan AS, Ho PC. A prospective randomized comparison of sublingual and oral misoprostol when combined with mifepristone for medical abortion at 12–20 weeks gestation. *Hum Reprod* 2005;**20**:3062–3066.

THL. Induced abortions—reproduction—statistics by themes—stakes. Available at: http://www.stakes.fi/EN/tilastot/statisticsbytopic/reproduction/abortions.htm. (6 January 2011, date last assessed) 2010.

Valvira. Valvira.fi2010. Available at: http://www.valvira.fi/en/ (6 January 2011, date last accessed).