



Original research article

# Risk factors of surgical evacuation following second-trimester medical termination of pregnancy<sup>☆,☆☆</sup>

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Received 26 August 2011; revised 25 November 2011; accepted 29 November 2011

## Abstract

**Background:** Second-trimester medical termination of pregnancy (TOP) is associated with a higher risk of surgical evacuation than earlier medical TOP. Little is known about risk factors of surgical evacuation. Therefore, we assessed these risk factors among women undergoing second-trimester medical TOP.

**Study Design:** Data on 227 women were derived from a prospective randomized trial comparing 1- and 2-day mifepristone–misoprostol intervals in second-trimester medical TOP between 2008 and 2010.

**Results:** The rate of surgical evacuation was 30.8%. The risk of surgical evacuation was increased by a history of curettage [odds ratio (OR) 4.4; 95% confidence interval (CI) 1.7–11.7], fetal indications for TOP (OR 6.1; 95% CI 1.1–34.4), age above 24 years (OR 2.4; 95% CI 1.1–5.3) and a 2-day interval (OR 2.2; 95% CI 1.1–4.1).

**Conclusions:** History of curettage, fetal indication, increasing age and 2-day interval between mifepristone and misoprostol increase the risk of surgical evacuation in cases of second-trimester medical TOP. These findings are important when optimizing clinical service in second-trimester TOP.

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**Keywords:** Surgical evacuation; Second trimester; Mifepristone; Misoprostol; Termination of pregnancy.

## 1. Introduction

Medical induction with mifepristone and misoprostol is an effective and acceptable method to use in second-trimester termination of pregnancy (TOP) [1]. However, in comparison with first-trimester TOP, it is associated with an increased risk of retained placenta and surgical evacuation [2]. The risk of surgical removal of the placenta or placental tissue has been reported to vary from 5% to 30% in second-trimester medical TOP [3–10]. However, few studies have been carried out to analyze the risk factors of surgical evacuation after

second-trimester medical TOP performed with mifepristone and misoprostol.

An elevated risk of surgical evacuation in medical second-trimester TOP has been related to higher maternal age, a higher number of prostaglandin doses needed [5], previous termination of pregnancy and increasing duration of gestation [5,8]. The role of the time interval between mifepristone and misoprostol is controversial. In our previously published study concerning randomized comparison of 1- vs. 2-day intervals between mifepristone and misoprostol, the 2-day interval was associated with a higher risk of surgical evacuation [9]. However, in a study by Hou et al. [11], the 1-day interval was related to a higher rate of retained placenta.

As data on this subject are sparse, the purpose of the present study was to assess the risk factors for retained placenta and residual tissue in second-trimester medical TOP. Additionally, various demographic and procedure-related factors and the risk of surgical evacuation after medical second-trimester TOP were evaluated.

<sup>☆</sup> Conflict of interest statement: The authors have no conflict of interest in relation to this work.

<sup>☆☆</sup> This study was supported by Helsinki University Central Hospital Research funds.

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## 2. Material and methods

The present data were derived from an open prospective randomized trial in which 1- and 2-day intervals between mifepristone and misoprostol administration in second-trimester medical TOP were compared [9]. The study was performed at Helsinki University Central Hospital between 2008 and 2010. Details of the study are summarized in a previous publication [9]. In brief, 395 women who underwent medical TOP during the second trimester, between 13 to 24 weeks of gestation (85 to 169 days of amenorrhea), were assessed for eligibility, and the participants signed a written consent for the study. Inclusion criteria for the study were age  $\geq 18$  years and a singleton pregnancy with a live fetus. Exclusion criteria were allergy to the medication used, severe asthma, ectopic pregnancy, coronary disease or an intrauterine contraceptive device in the uterus. Altogether, 54 women did not meet the inclusion criteria, and 109 women declined to participate [9]. Both treatment groups had 116 women allocated to a 1- or 2-day interval between mifepristone and misoprostol. However, five women continued pregnancy, and five women changed to the 2-day interval group. Finally, 120 women received the intervention with the 1-day interval, and 107 women had the 2-day interval between mifepristone and misoprostol.

The study involved comparison of two dosing intervals of misoprostol (400 mcg; 2 $\times$ 200 mcg, Cytotec<sup>®</sup>, Pfizer Oy, Helsinki, Finland) administered after 1 (range 17–28 h) or 2 days (range 37–49 h) following ingestion of 200 mg of mifepristone (Mifegyne<sup>®</sup>, Exelgyn, Paris, France). The study protocol included repeat misoprostol (400-mcg doses) every 3 h up to 2000 mcg per 24 h. The administration route was vaginal as long as uterine bleeding was not heavy (as judged by staff in charge of the subject); thereafter, it was sublingual. If abortion had not occurred after 24 h, the women were reassessed by means of gynecological examination. When necessary, a second (and third) course of misoprostol was administered.

Pain was managed with a prophylactic dose of oral ibuprofen (600 or 800 mg) or paracetamol (500 mg), and paracetamol (500 mg) plus dihydrocodeine (10 mg) administered at the time of the first misoprostol dose. Thereafter, oral nonsteroidal anti-inflammatory drugs (NSAIDs) or oral paracetamol (500 mg) plus dihydrocodeine (10 mg) and oral or parenteral opioid analgesics were administered on demand.

Nurses at the ward monitored potential side effects, bleeding, axial temperature rise to over 38°C and clinical signs of infection. In cases of heavy bleeding, the volume was measured by weighing the blood. When the fetus and placenta were passed at the ward, the placenta appeared to be complete and there were no signs of continuous heavy bleeding, no further interventions were undertaken, and the women were discharged.

Women who did not pass the placenta were examined within some hours or instantly in cases of heavy bleeding.

The remaining placenta was removed at the ward or in the operating theater under general anesthesia. This occurred after administration of an additional 400–800-mcg dose of misoprostol vaginally or sublingually followed by an appropriate observation period (defined by the doctors on duty). There were no written instructions concerning the appropriate observation time. In cases of heavy bleeding, surgical evacuation was performed without delay. In cases of manual or surgical removal of the placenta, the fetal-to-placental expulsion time was calculated from expulsion of the fetus to the surgical procedure. 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).

A follow-up assessment at 2 to 4 weeks after TOP was scheduled and performed by the investigator (M.M.). It included clinical examination and transvaginal ultrasonography. A diagnosis of residual tissue was based on clinical judgment of continuous prolonged heavy bleeding together with an ultrasonographic finding of uneven endometrial thickening. Ultrasonographic findings without abnormal bleeding or lower abdominal pain were not treated by means of surgical evacuation. Routine histological analysis of the residual tissue was not performed. Heavy bleeding was defined according to measurements of bleeding at the hospital ward when it exceeded approximately 300 mL and continued. Infection was defined as lower abdominal pain and increased levels of circulating leucocytes or C-reactive protein. Infections from mild endometritis to severe pelvic inflammatory disease were taken into account. Altogether, 181 (79.9%) women participated in their scheduled follow-up visits. The missing patients could be traced from the electronic patient records of our hospital system that shows all visits to public hospitals in the Helsinki and Uusimaa area. In Finland, practically all surgical evacuations or treatments of postabortal complications are performed in public hospitals.

The background characteristics were gathered during the first visit at the hospital (Table 1). Previous curettage represents previous surgical TOP(s) or curettage(s) due to other reasons. The type of previous curettage, sharp or suction curettage, was not known.

The trial had approval from the Ethics Committee of the Hospital District of Helsinki and Uusimaa and from the Finnish National Agency for Medicines. Registration of the trial was at Controlled Trials (web page: <http://www.controlled-trials.com/ISRCTN09944151>).

### 2.1. Statistical analysis

Analysis of the data was performed on a per-protocol basis. Statistical analysis was performed using PASW 18.0 for Mac (SPSS Inc., Chicago, IL, USA). The background factor data are presented as medians [and interquartile range (IQR) or 5th to 95th percentile range, as appropriate] or  $n$  (%). Binary logistic regression models were used to assess

Table 1  
Characteristics of 227 women undergoing second-trimester medical TOP between 2008 and 2010

Variable	Definition	Study population <i>n</i> =227
Gestation at TOP	13 to 14 weeks	65 (28.6)
	15 to 16 weeks	85 (37.4)
	17 to 18 weeks	35 (15.4)
	19 to 22 weeks	42 (18.5)
Age (years)	18 to 19 years	46 (20.3)
	20 to 24 years	75 (33.0)
	25 to 29 years	50 (22.0)
	30 to 34 years	24 (10.6)
	35 to 39 years	18 (7.9)
Mifepristone–misoprostol interval	≥40 years	14 (6.2)
	1 day	120 (52.9)
Marital status	2 days	107 (47.1)
	Married	31 (13.7)
	Cohabiting	41 (18.1)
Socioeconomic status	Single	155 (68.3)
	White-collar workers	24 (10.6)
	Blue-collar workers	79 (34.8)
	Students	57 (25.1)
BMI (kg/m <sup>2</sup> )	Others	67 (29.5)
	<30	207 (91.2)
Smokers	≥30	20 (8.8)
		139 (61.2)
Nulliparae		85 (37.4)
Previous TOP		103 (45.4)
Previous miscarriage		45 (19.8)
Previous vaginal delivery		66 (29.1)
Previous cesarean section		20 (8.8)
History of uterine curettage		70 (30.8)
Indication for TOP	Fetal	16 (7.0)
	Other	211 (93.0)
NSAID analgesia during TOP		173 (76.2)

Data expressed as *n* (%) unless otherwise stated.

the effect of background demographics in uni- and multivariable analysis. The background characteristics that could be related to each other and to the risk of surgical evacuation were selected for multivariable analysis. The results of uni- and multivariable analyses are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Differences in continuous variables were analyzed by means of the Mann–Whitney *U* test for skewed data. Confidence intervals for the differences between two medians were analyzed by using the Hodges–Lehman method. Statistical significance was defined as *p*≤.05.

### 3. Results

The study population consisted of 227 women undergoing second-trimester medical TOP. Only one woman (0.4%) failed to abort the fetus with this medical treatment. After 48 h of mifepristone–misoprostol treatment, dilatation and

evacuation were performed. This was considered as a need for surgical treatment in the analysis.

The demographics of the study population are shown in Table 1. The median IQR gestation at TOP was 15 (14–17) weeks. The median (IQR) age of the women was 24 (20–29) years. The median (IQR) body mass index (BMI) was 22.6 (20.8–25.2) kg/m<sup>2</sup>. The randomization into 1- and 2-day mifepristone–misoprostol interval groups did not produce any unexpected differences among baseline characteristics (data not shown). Moreover, there were no significant differences between these groups regarding the dose or administration route of misoprostol (data not shown).

Altogether, 70 (30.8%) women underwent surgical evacuation of the placenta or residual tissue after expulsion of the fetus. Evacuation was performed during the initial stay at hospital among 40 women (40/227, 17.6%) and after leaving the hospital among 30 women (30/187 women without surgical evacuation, 16.0%). Immediate surgical evacuation during the initial hospital stay was performed more often in cases of completely retained placenta (31/40 women, 77.5%) and less often in cases of partially delivered placenta associated with heavy bleeding (9/40 women, 22.5%). During the follow-up period, all the surgical evacuations were performed (*n*=30) because of clinical signs of residual tissue, i.e., bleeding and pain and/or infection with ultrasonographic findings of residual tissue.

Table 2 shows the results of the uni- and multivariable analyses of the effects of background factors on the risk of surgical evacuation. For the analyses, age and gestation were dichotomized into two categories. In the multivariable analysis, age ≥25 years significantly increased the risk of surgical evacuation in comparison to younger age (OR 2.4; 95% CI 1.1–5.3). Also, the 2-day interval between mifepristone and misoprostol doubled the risk of surgical evacuation (OR 2.2; 95% CI 1.1–4.1) compared with the 1-day interval. Moreover, previous curettage of the uterus (OR 4.4; 95% CI 1.7–11.7) and fetal indications for TOP (OR 6.1; 95% CI 1.1–34.4) significantly increased the risk of surgical evacuation. Marital and socioeconomic status, BMI, smoking and NSAID analgesia did not have statistically significant effects on the risk of surgical evacuation (data not shown). The route of misoprostol administration (vaginal vs. sublingual) did not have a significant effect on the rate of surgical evacuation (data not shown). Most of the misoprostol administration was vaginal; sublingual-only administration route was used in seven women.

Assessment of the effect of age and gestational weeks was also done according to the age categories shown in Table 1 (data not shown). In univariable analysis, the age of 30 to 34 years tripled the risk for evacuation (OR 3.5; 95% CI 1.2–10.3, *p*=.02) similarly as the age of 35 to 39 years (OR 3.3; 95% CI 1.0–10.7, *p*=.048) compared with the age of 18 to 19 years. The age of ≥40 years raised the risk fivefold (OR 5.5; 95% CI 1.5–19.8, *p*=.009) compared with the age of 18 to 19 years. However, in multivariate analysis, these results were not statistically significant. Also, increasing weeks of

Table 2  
Risk factors associated with surgical evacuation among the 227 women undergoing second-trimester medical TOP

Variable		OR	95% CI	p Value	Adjusted OR <sup>a</sup>	95% CI	p Value
Gestation at TOP	≤16 weeks	1.07	0.59–1.95	.82	1.02	0.52–2.00	.96
	>16 weeks	Ref.					
Age	18 to 24 years	Ref.					
	<b>25 to 48 years</b>	<b>2.18</b>	<b>1.23–3.87</b>	<b>.008</b>	<b>2.43</b>	<b>1.11–5.34</b>	<b>.03</b>
Mifepristone–misoprostol interval	1 day	Ref.					
	<b>2 days</b>	<b>1.79</b>	<b>1.01–3.17</b>	<b>.045</b>	<b>2.16</b>	<b>1.13–4.11</b>	<b>.02</b>
Previous TOP <sup>b</sup>	Yes	1.02	0.58–1.80	.95	0.49	0.20–1.22	.13
Previous miscarriage <sup>b</sup>	Yes	1.88	0.96–3.68	.07	1.34	0.59–3.07	.49
Previous vaginal delivery <sup>b</sup>	Yes	1.07	0.58–1.98	.84	0.53	0.23–1.22	.14
Previous cesarean section <sup>b</sup>	Yes	1.23	0.47–3.23	.67	0.65	0.20–2.19	.49
History of uterine curettage <sup>b</sup>	<b>Yes</b>	<b>2.40</b>	<b>1.33–4.36</b>	<b>.004</b>	<b>4.41</b>	<b>1.66–11.71</b>	<b>.003</b>
Indication for TOP	<b>Fetal</b>	<b>4.19</b>	<b>1.46–12.05</b>	<b>.008</b>	<b>6.14</b>	<b>1.09–34.45</b>	<b>.04</b>
	Other	Ref.					

Significant results are bolded.

<sup>a</sup> Results of the multivariable analysis. Odds ratio adjusted for the categorical variables presented in Table 1.

<sup>b</sup> None as reference.

gestation did not have a statistically significant effect on the risk of surgical evacuation.

Heavy bleeding [defined as bleeding over 500 mL ( $n=15$ )] increased the total risk of surgical evacuation (OR 10.6; 95% CI 2.9–39.0;  $p<.001$ ). However, only four women (1.8%) in this study required blood transfusion, which did not have a statistically significant effect on the risk of surgical evacuation (OR 7.0; 95% CI 0.7–68.4;  $p=.1$ ). Infection following TOP was associated with an increased total risk of surgical evacuation (OR 14.3; 95% CI 4.6–43.8;  $p<.001$ ). Only three out of 22 (13.6%) women having infection after TOP did not have residual tissue inside the uterus as judged on clinical grounds. Thus, surgical evacuation was not performed in these women.

The effect of induction-to-abortion time (the time interval from the first misoprostol dose to fetal expulsion) vs. the need of surgical evacuation was evaluated. The median (with

5th to 95th percentile range) induction-to-abortion time was shorter in the group without surgical evacuation [7 h 15 min (3 h 40 min to 23 h 10 min)] than in the group undergoing surgical evacuation [8 h 20 min (4 h 58 min to 33 h 45 min);  $p=.02$ ; difference between medians 1 h 5 min and 95% CI for the difference 10 min to 2 h 23 min].

The effect of fetal-to-placental expulsion time on the need of surgical evacuation was also of interest. The median fetal-to-placental expulsion time (with 5th to 95th percentile range) was 10 min (0 min to 2 h 40 min) in the group that did not need any surgical evacuation. In the group undergoing surgical evacuation ( $n=70$ ), the median fetal-to-placental expulsion time was 1 h 40 min (0 min to 5 h 25 min;  $p<.001$ ; difference between medians 1 h 30 min and 95% CI for the difference 15 min to 3 h 10 min). Longer fetal-to-placental expulsion interval increased the risk of surgical evacuation of the placenta (Fig. 1).

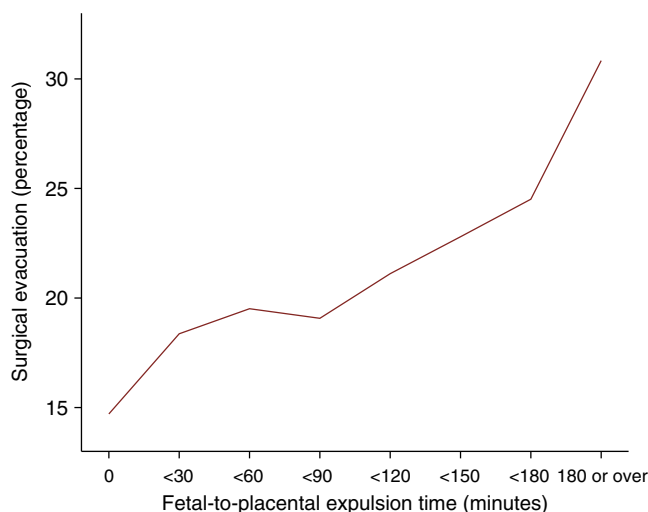


Fig. 1. Fetal-to-placental expulsion time and its effect on surgical evacuation among 227 women undergoing second-trimester medical TOP.

#### 4. Discussion

We found that the main risk factors associated with surgical evacuation following medical second-trimester TOP were a history of uterine curettage and fetal indications for TOP. Age of 25 years or more, and the 2-day interval between mifepristone and misoprostol also increased the risk of surgical evacuation.

This study provides information from a prospective study and from a center where all second-trimester TOPs are performed medically. However, the power calculation for this study was not based on analysis of the risk factors of surgical evacuation, and the number of participants might be a limitation. Although the investigator (M.M.) treated these patients most of the time, several other physicians participated in their treatment as well. The decision to perform a surgical evacuation was based on the individual judgment of the physician on duty. The decision to perform a surgical

evacuation may therefore also be dependent on a will to speed up the procedure, not only due to patient characteristics. During the follow-up, the suspicion of retained parts of placenta was based on clinical examination.

The rate of surgical evacuation in this study represents the high end of figures earlier described [5,11]. This may be due to small differences in the demographic characteristics of the subjects. Not all background characteristics in the various studies can be compared, but our study involved more women with previous TOP (45 vs. 29%) and fewer women with previous live birth (30 vs. 46%) in comparison with a study by Ashok et al. [5]. Another explanation for the high figures might be that surgical evacuation after fetal expulsion was routine in Finland some 10 years ago and the number of surgical evacuations is decreasing slowly [12]. Nevertheless, the risk factors of surgical evacuation highlighted by the present study should also be useful in centers in which fewer evacuations are performed.

Previous abortion has been associated with an increased risk of incomplete second- [5] as well as first-trimester medical TOP [13–15]. Given the time of these publications, most previous abortions must have been surgical ones. In the present study, a history of uterine curettage, but not that of TOP, increased the risk of surgical evacuation in second-trimester medical TOP. We therefore speculate that uterine curettage results in endometrial, cervical and/or uterine changes that hinder full emptying of the uterus or detachment of the placenta. Unfortunately, we could not specify the type of the previous curettage in order to evaluate its effect on the risk of surgical evacuation. Nevertheless, careful consideration of the need of curettage can be advised, at least in order to decrease the risk of surgical evacuation in cases of possible future TOP or deliveries. Moreover, an association between placenta previa and induced abortion has been suggested, but there seems to be a lack of information about the role of surgical evacuation after medical abortion and the risk of curettage in subsequent pregnancies [16].

In our previous publication concerning this study, we reported that the overall induction-to-abortion time was slightly shorter following the 2-day interval between mifepristone and misoprostol compared to the 1-day interval [9]. However, in women without previous vaginal deliveries and in cases in which the duration of gestation exceeded 16 weeks, the induction-to-abortion time associated with the 1-day interval was markedly longer than that with the 2-day interval. These data are in line with previous results [11]. Surprisingly, the need of surgical evacuation was significantly higher following the 2-day interval [9]. This finding is in contrast with previous data [11]. Given the randomized nature of the study, a purely chance finding is unlikely. The relatively small number of participants and small differences in the baseline demographics, especially in the number of previous pregnancies and previous abortions [11], might be potential explanations for this phenomenon. Unfortunately, very detailed comparison of the demographics cannot be

performed because of slightly different styles of describing them [11]. Nevertheless, the potentially increased need of surgical evacuation also needs to be taken into consideration when providing a clinical service in second-trimester medical TOP.

Women in the older age group had an increased risk of surgical evacuation, this finding being in line with previously published data [5]. As older women and those with early menarche have been shown to be at higher risk of cesarean section [17], a phenomenon of decreasing myometrial contractility in response to prolonged hormonal stimulation has been proposed. Such a phenomenon could explain the present results—uteri of the women in the older age bracket might respond less well to the contractile effects of mifepristone and misoprostol.

A fetal indication for TOP and the associated raised risk of surgical evacuation in our study need further evaluation. The elevated risk might be a result of speeding up the procedure of second-trimester TOP by carrying out surgical evacuation. However, in previous studies, fetal indications for second-trimester TOP have not been separated from other indications [3,10], and their effect remains unclear.

The risk of surgical evacuation was raised when the fetal-to-placental expulsion time was longer. Unfortunately, we did not provide any detailed instructions about the optimal expectant management time in this study. It can be assumed that surgical evacuation or manual removal of the placenta was mostly performed to expedite discharge from the hospital, as fewer surgical evacuations were performed because of heavy bleeding. Previous studies also have little data on the optimal expectant management time for placental expulsion. Expectant management to allow spontaneous expulsion of the placenta over a period of at least 4 h has not been associated with serious morbidity [18], and the same was shown in this study.

Our results have practical implications. A history of uterine curettage and older age increase the risk of residual tissue and/or surgical evacuation in TOP. Both the median induction-to-abortion interval and the median fetal-to-placental expulsion interval were longer in the group of women undergoing surgical evacuation than among women who did not need surgical treatment. This suggests that the factors that mature the cervix or induce uterine contractility have an effect on the risk of surgical evacuation. In addition, clinically diagnosed infection and bleeding over 500 mL were valuable clinical indicators as regards the need of surgical evacuation in this study. These data should be of value when planning clinical services for women undergoing second-trimester medical TOP.

## 5. Conclusion

The results of the present study suggest that special focus on curettage of the uterus and on the interval between mifepristone and misoprostol is needed in order

to lower the risk of surgical evacuation in potential future TOPs and possibly in other pregnancies as well. However, studies aimed at assessing the means to lower this risk are needed. The acceptability and efficacy of different methods of TOP are widely debated. However, more data about the effect of different methods of TOP and their implications in connection with future pregnancies are urgently needed.

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