Taiwanese Journal of Obstetrics & Gynecology 54 (2015) 408–411

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Factors influencing the abortion interval of second trimester pregnancy termination using misoprostol

Wan-Hua Ting [a, 1], Fu-Hsiang Peng [a, 1], Ho-Hsiung Lin [b], Hsin-Fen Lu [a], Sheng-Mou Hsiao [a, *]

[a] Department of Obstetrics and Gynecology, Far Eastern Memorial Hospital, Banqiao District, New Taipei, Taiwan
[b] Department of Obstetrics and Gynecology, National Taiwan University College of Medicine and National Taiwan University Hospital, Taipei, Taiwan

ARTICLE INFO

Article history:
Accepted 18 August 2014

Keywords:
medical abortion
mid-trimester
prostaglandin analog

ABSTRACT

Objectives: To determine the factors influencing the abortion interval (AI) for medical termination of second-trimester pregnancy using misoprostol.
Materials and Methods: All patients who were admitted for second-trimester pregnancy termination between January 2008 and August 2013 were reviewed. Those who received either 200 μg or 400 μg of priming vaginal misoprostol, followed by 200 μg of misoprostol orally at 6-hour intervals were enrolled.
Results: In a total of 101 patients, delivery occurred within 24 hours of commencement in 62 patients (61%) and within 48 hours in 84 patients (83%), and the median AI was 16.5 hours. One patient (1%) failed to deliver. The remaining 100 fetuses were delivered successfully, and the median AI was 16.3 hours. Higher parity [hazard ratio (HR) = 1.28, $p = 0.04$], the presence of intrauterine fetal demise (HR = 2.66, $p = 0.003$), and the presence of premature preterm rupture of membranes (HR = 4.51, $p = 0.003$) were associated with shorter AI. Additionally, all women with premature preterm rupture of membranes delivered successfully within 12 hours; higher parity (odds ratio = 2.12, $p = 0.01$) and lower fetal birth body weight (odds ratio = 0.992, $p = 0.01$) were associated with successful delivery within 12 hours. There was no significant difference in AI in the groups that received different doses of priming vaginal misoprostol (200 μg vs. 400 μg).
Conclusion: Higher parity, intrauterine fetal demise, and preterm premature rupture of membranes were associated with shorter AI. The regimen of 200 μg oral misoprostol at 6-hour intervals following a 200 μg or 400 μg priming vaginal dose is feasible and efficacious for second trimester pregnancy termination.

Introduction

The termination of a second trimester pregnancy can be accomplished either medically or surgically. During the last 2 decades, medical methods for induced abortion have become preferable to surgical techniques because of lower maternal mortality and morbidity rates [1].

Of the various abortifacients available, misoprostol has emerged as the agent of choice for the induction of labor due to its low cost, long shelf life at room temperature, ease of administration, and worldwide availability. Although the United States Food and Drug Administration has not approved the use of misoprostol for medical abortion, pregnancy was removed from the label as an absolute contraindication in 2002 [2]. Since then, it has been widely used off-label for a variety of indications in the practice of obstetrics and gynecology including medical abortion, the induction of labor, cervical ripening prior to surgical procedures and the treatment of *postpartum* hemorrhage.

Misoprostol is a synthetic prostaglandin E1 analog that is effective not only in preventing gastric ulcers, but also in inducing cervical effacement and uterine contractions. The effectiveness of misoprostol alone for second trimester pregnancy is 80–90% [3]. The potency of misoprostol's effect varies with maternal and fetal factors, as well as the route of administration, dosing interval, dose, and cumulative dose. The ideal dosing regimen for second trimester pregnancy termination remains to be determined.

* Corresponding author. Department of Obstetrics and Gynecology, Far Eastern Memorial Hospital, 21 Section 2, Nanya South Road, Banqiao District, New Taipei City, Taiwan.
E-mail address: smhsiao2@gmail.com (S.-M. Hsiao).
[1] Equal contribution.

http://dx.doi.org/10.1016/j.tjog.2014.08.008

Knowledge about the abortion interval (AI) and associated influencing factors is important for counseling women who need termination of a second trimester pregnancy; however, few studies mention such findings [4,5], and the inclusion criteria in these studies merely includes cases with fetal anomalies or selected medical indications. Thus, the aim of this retrospective study was to estimate the AI in all enrolled women who needed medical termination by a combination of vaginal and oral misoprostol and to identify the factors that affect the AI.

Materials and methods

The medical profiles of all patients who were admitted for medical termination of a second-trimester pregnancy between January 2008 and August 2013 were reviewed. Previous cesarean delivery was not considered a contraindication for medical termination with misoprostol. The Research Ethics Committee of the Far Eastern Memorial Hospital approved this study.

Those women who received a priming dose of 200 μg or 400 μg misoprostol administered vaginally on admission, followed by 200 μg of misoprostol orally at 6-hour intervals, were enrolled. The patient characteristics and AI were recorded. The AI was calculated from the time of administration of vaginal misoprostol to the time of delivery of the fetus with labor pains or by surgical evacuation.

STATA software (Version 11.0; Stata Corporation, College Station, TX, USA) was used for the statistical analyses. The survival curve of the AI was estimated using the Kaplan–Meier method [6]. Cox proportional-hazards modeling was performed to evaluate the factors affecting the AI. A value of $p < 0.05$ was considered significant.

Results

This retrospective study included 101 patients with a median maternal age of 30 years (Table 1). Thirty-five patients (35%) had at least one prior vaginal delivery. Thirty-three patients (33%) required < 12 hours to terminate the pregnancy, 62 patients (61%) required < 24 hours to terminate the pregnancy, and 84 patients (83%) required < 48 hours to terminate the pregnancy (Figure 1A). The median AI of all 101 patients was 16.5 hours [25–75% interquartile range (IQR) = 9.3–32.7 hours]. One patient failed to deliver at 63 hours after misoprostol administration, and the abortion was completed via cervical dilatation and evacuation. The remaining 100 fetuses were delivered successfully, and the median AI was 16.3 hours (IQR = 9.1–32.5 hours); however, three patients were later subjected to placenta evacuation under intravenous anesthesia due to a retained placenta. There was no difference in AI between the different doses of priming vaginal misoprostol (200 μg vs. 400 μg; Figure 1B, log-rank test, $p = 0.17$).

By the Cox proportional-hazards model, higher parity, the presence of intrauterine fetal demise and the presence of premature preterm rupture of membranes were the significant factors associated with shorter AI (Table 2).

Six women had prior cesarean delivery. The method of induction in women with prior cesarean delivery was no different to those without. Three of these patients received a 200-μg vaginal priming dose, while the remaining three patients received a dose of 400 μg. All delivered successfully without any adverse events. The median AI of women with prior cesarean delivery was shorter than those without (median = 7.9 hours, IQR = 6.1–19.5 hours vs. median = 17.7 hours, IQR = 9.5–40.6 hours, $p = 0.025$, log-rank test). However, when we included prior cesarean delivery in the

Table 1
Baseline characteristics of patients receiving misoprostol for the termination of second trimester pregnancy ($n = 101$).

Variables	Values[a]
Maternal age (y)	30 (20–34)
Body mass index (kg/m^2)	21.7 (20.2–24.4)
Nulliparous	61 (60)
History of prior vaginal delivery	35 (35)
200 μg priming dose of vaginal misoprostol	53 (52)
Gestational age (wk)	15 (13–17)
Indication for termination	
IUFD	13 (13)
PPROM	5 (5)
Fetal anomaly	29 (29)
Other reasons[b]	54 (53)
Abortion interval (h)[c]	16.3 (9.1–32.5)
Delivery within 24 h	62 (61)
Male fetus	49 (49)
BBW (g)	80 (30–160)

BBW = birth body weight; IUFD = intrauterine fetal demise; PPROM = preterm premature rupture of membranes.
[a] Median (25–75% interquartile range) or number (%).
[b] Other reasons: unintended pregnancy.
[c] The pregnancy not successfully terminated by misoprostol was excluded (i.e., $n = 100$).

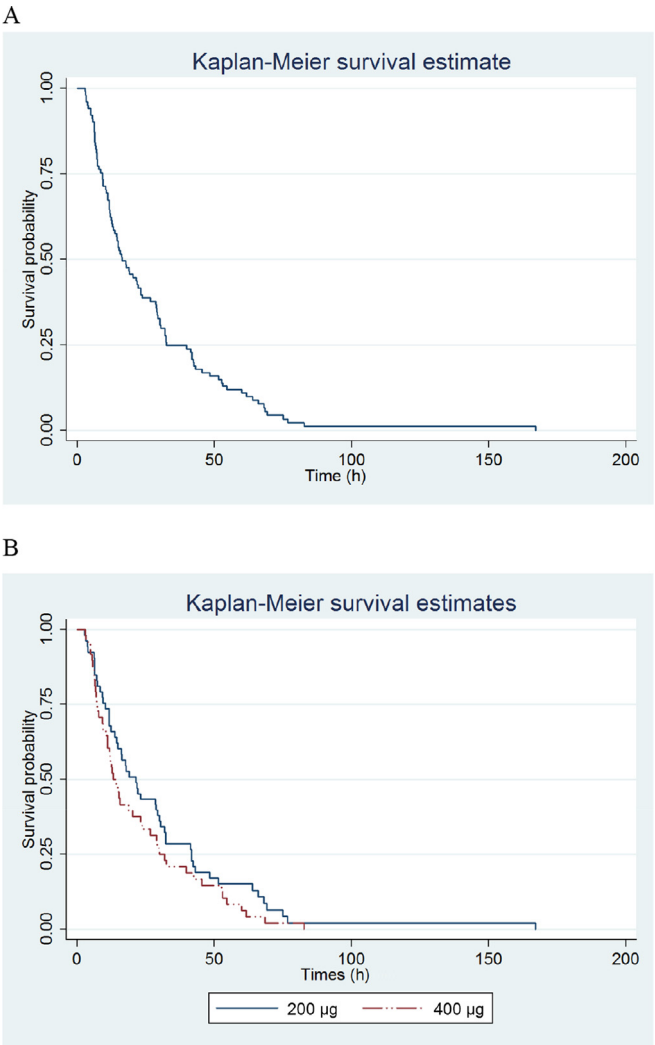

Figure 1. Kaplan–Meier probability curve of time required until fetal expulsion for (A) all patients undergoing medical termination, and (B) different priming doses of vaginal misoprostol (200 μg vs. 400 μg).

Table 2
Cox proportional-hazards modeling for factors influencing the abortion interval of second trimester termination using misoprostol ($n = 101$).

Variables	Univariate analysis			Multivariate analysis[a]		
	Hazard ratio	95% CI	p	Hazard ratio	95% CI	p
Maternal age (y)	1.03	1.00–1.06	0.03	—	—	—
Body mass index (kg/m^2)	1.03	0.99–1.08	0.15	—	—	—
Parity	1.27	1.01–1.60	0.04	1.28	1.01–1.62	0.04
Gestational age (wk)	1.04	0.96–1.13	0.33	—	—	—
The presence of IUFD	3.10	1.66–5.77	< 0.001	2.66	1.39–5.07	0.003
The presence of PPROM	6.73	2.59–17.47	< 0.001	4.51	1.69–12.02	0.003
The presence of fetal anomaly	0.90	0.58–1.41	0.66	—	—	—
Male fetus	1.05	0.61–1.81	0.87	—	—	—
Birth body weight (g)	1.00	0.998–1.001	0.74	—	—	—
Vaginal dose (200 μg = 0, 400 μg = 1)	1.32	0.89–1.96	0.17	—	—	—

CI = confidence interval; IUFD = intrauterine fetal demise; PPROM = preterm premature rupture of membranes.
[a] By the backward stepwise method until all the remaining values are $p < 0.05$.

Cox proportional-hazards model, the significance of prior cesarean delivery disappeared.

If we defined a success as the delivery of the fetus within 12 hours, the presence of premature preterm rupture of membranes perfectly predicted a success, and higher parity and lower fetal birth weight were two additional independent factors predicting success (Table 3).

There were no major maternal morbidities or mortalities during the course of termination.

Discussion

There were three main factors that significantly reduced the AI in our study: parity; the presence of intrauterine fetal demise; and preterm premature rupture of membranes. Multiparous women demonstrated a better response to the regimen with a shorter AI, which was consistent with the results of a prior study by Dickinson and Doherty [4] using 400 μg vaginal misoprostol alone at 4-hour intervals [4]. The median AI was reduced by 37% in multiparous women compared with the nulliparous women in our study (12 hours vs. 19 hours), a phenomenon that can be explained by better cervical compliance in the multiparous women. Additionally, we found that our median AI (16.5 hours) was similar to that of Dickinson and Doherty (16.1 hours) [4].

In our study, the presence of intrauterine fetal demise was a significant factor affecting the AI (Table 2). In their prospective comparison study of second-trimester pregnancy termination using 200 μg vaginal misoprostol administered every 12 hours, Srisomboon and Pongpisuttinun [5] also demonstrated significantly high efficacy for misoprostol in cases of fetal demise compared with live-fetus pregnancy. This may be the result of increased endogenous production of prostaglandins following the removal of an inhibitory effect of prostaglandin E_2 in the amniotic fluid that exists with a live fetus [7].

We found that the presence of preterm premature rupture of membranes was another significant independent factor influencing the AI and that it perfectly predicted successful delivery within 12 hours (Tables 2 and 3). It has been postulated that the production and release of prostaglandins and the increase of oxytocin when the fetal membranes are ruptured result in shorter labor [8]. This may explain the role of preterm premature rupture of membranes in our study.

The AI of women with prior cesarean delivery was shorter than those without by the log-rank test; nonetheless, we did not find that the presence of prior cesarean delivery was an independent factor with the Cox proportional-hazards model, thus the significant log-rank test finding may be merely due to the significant correlation between prior cesarean delivery and parity (Spearman's rho = 0.29, $p = 0.003$).

All of six of our patients with prior cesarean delivery had uneventful deliveries, and the presence of a prior uterine scar had no impact on the AI. Herabutya et al [9] also reported that the abortion interval did not differ between the prior cesarean delivery group and the control group. Despite the fact that uterine rupture did not occur in any of our cases, there is always an inherent risk of uterine rupture in women with prior cesarean delivery undergoing second-trimester misoprostol abortion [10–15]. Goyal [10] reported that the risk of uterine rupture in women with prior cesarean delivery was 0.28% [95% confidence interval (CI) 0.08–1.00%] and the risk of uterine rupture in women without prior cesarean delivery was 0.04% (95% CI 0.01–0.20%). Berghella et al [11] also reported an incidence of uterine rupture of 0.4% (95% CI 0.08–1.67%) in women

Table 3
Univariate and multivariate logistic regression analyses for predicting failing induction within 12 hours ($n = 101$) in second trimester termination using misoprostol ($n = 101$).

Variables	Univariate analysis			Multivariate analysis[a]		
	Odds ratio	95% CI	p	Odds ratio	95% CI	p
Maternal age (y)	1.05	0.99–1.10	0.09	—	—	—
Body mass index (kg/m^2)	1.05	0.96–1.15	0.28	—	—	—
Parity	1.68	1.03–2.75	0.04	2.12	1.16–3.88	0.01
Gestational age (wk)	0.96	0.81–1.14	0.65	—	—	—
The presence of IUFD	4.82	1.37–17.0	0.01	—	—	—
The presence of PPROM	NA	NA	NA	NA	NA	NA
The presence of fetal anomaly	0.45	0.17–1.18	0.10	—	—	—
Male fetus	3.45	0.88–13.5	0.08	—	—	—
Birth body weight (g)	0.995	0.990–1.000	0.04	0.992	0.986–0.998	0.01
Vaginal dose (200 μg = 0, 400 μg = 1)	1.53	0.68–3.44	0.30	—	—	—

NA = not assessable because the presence of PPROM ($n = 5$) perfectly predicts successful induction within 12 hours.
CI = confidence interval; IUFD = intrauterine fetal demise; PPROM = preterm premature rupture of membranes.
[a] By the backward stepwise method until all the remaining values are $p < 0.05$.

with one prior low transverse cesarean delivery. Therefore, despite the authors' conclusion that second-trimester misoprostol abortion for women with a prior cesarean delivery appears safe [10,11], we should not ignore the probable higher risk of uterine rupture in women with a scarred uterus. Thus, appropriate counseling about the risk of uterine rupture should be given prior to second-trimester misoprostol abortion, especially for women with a scarred uterus; and women with a scarred uterus should receive lower doses of misoprostol and be instructed not to double the dose if there is no initial response [16].

Many studies have been conducted to investigate the optimal route and dosage of misoprostol administration. Given the considerable variation in reported outcomes and the regimen of misoprostol adopted, no consensus has been reached. Dickinson and Evans [17] found that the use of 400 μg vaginal misoprostol every 6 hours was 1.9-fold more likely to result in delivery within 24 hours compared with oral administration (400 μg orally every 3 hours; rate of delivery 86% vs. 45%). Tang et al [18] introduced a prospective randomized controlled trial comparing two regimens (400 μg sublingual or vaginal misoprostol every 3 hours for a maximum of five doses); vaginal misoprostol was found to result in a higher success rate than sublingual misoprostol at 24 hours but a similar abortion rate at 48 hours. Wong et al [19] suggested that a 3-hour regimen provides a significantly shorter AI and a higher percentage of successful abortions within 48 hours than the 6-hour interval group. In balancing the efficacy and side effects for the termination of second trimester pregnancy, the WHO recommended the use of vaginal or sublingual misoprostol at 3-hour intervals; however, no specific dosing recommendations are endorsed due to a lack of clinical studies [20]. The Society of Family Planning also reported that the misoprostol doses of 400 μg are generally superior to 200 μg or less, and dosing every 3 hours is superior to less frequent dosing [21].

The combination of mifepristone and misoprostol is only approved for early first trimester termination in Taiwan. It is worth mentioning that recent studies showed that this combined regimen is the most effective and fastest for second trimester abortion [21,22]. Nonetheless, where mifepristone is unavailable or affordable, misoprostol alone has also been shown to be effective for second trimester abortion, although the efficacy is lower than the combined regimen [21,22].

Dickinson and Doherty [4] showed that younger maternal age and increasing gestational age were associated with a longer AI in a consecutive case series involving 1066 women. In our study, advanced maternal age appeared to have a shorter AI in the univariate analysis (HR = 1.03, $p = 0.03$), but its significance diminished after adjusting for other confounding factors. There was no association between gestational age and the AI (HR = 1.04, $p = 0.33$); nonetheless, we found that increasing body weight at birth, which is highly correlated to increasing gestational age (Spearman's rho = 0.81, $p < 0.001$), was associated with failed delivery within 12 hours (Table 3). Additionally, a higher priming vaginal dose (400 μg) did not appear to significantly reduce the AI (HR = 1.32, $p = 0.17$). However, the aforementioned differences between other authors' studies and our own may be due to our limited sample size.

The limitations of the present study include its limited sample size and retrospective nature. Nonetheless, given the substantial variation in the outcomes and regimens used in the existing literature, our experience suggested that oral misoprostol at 6-hour intervals following a priming vaginal dose is effective and safe for second trimester pregnancy termination.

In conclusion, higher parity, intrauterine fetal demise and the preterm premature rupture of membranes were associated with a shorter abortion interval. The regimen of 200 μg oral misoprostol at 6-hour intervals following a 200 μg or 400 μg priming vaginal dose is feasible and efficacious for second trimester pregnancy termination. These results are valuable to physicians when counseling women who request second trimester pregnancy termination.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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