A Comparison of Vaginal Misoprostol 800 μg Versus 400 μg in Early Pregnancy Failure: A Randomized Controlled Trial

Chalisa Prasartsakulchai MD*,
Yuen Tannirandorn MD*

** Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University*

Aim : *To compare the efficacy, side effects and patient satisfaction between 800 μg versus 400 μg intravaginal misoprostol for early pregnancy failure.*

Material and Method : *Women diagnosed as early pregnancy failure were randomly assigned to receive either 800 μg or 400 μg intravaginal misoprostol. The second dose was administered if there was no evidence of abortion in 24 h. The treatment failure was reffered to no complete abortion within 48 h. Dilatation and curettage was performed if the patients had heavy vaginal bleeding or evidence of incomplete abortion or no complete abortion.*

Results : *25 patients were randomized to receive 800 μg and 25 patients were to receive 400 μg misoprostol. Complete abortion was not significantly different between the 2 groups (72%, 76% respectively). Although median time to abortion in the 800 μg group was significantly shorter, the patients experienced more side effects especially fever which was significantly different (P = 0.04). In the 800 μg group, 2 patients had heavy vaginal bleeding and one patient developed endometritis. There was no significant difference in the patients' satisfaction between both groups.*

Conclusions : *400 μg of vaginal misoprostol are as effective as 800 μg in producing complete abortion in early pregnancy failure with less side effects and similar patient satisfaction.*

Keywords : *Early pregnancy failure, First trimester, Misoprostol, Pregnancy termination.*

J Med Assoc Thai 2004; 87(Suppl 3): S18-23

Early pregnancy failure is a common phenomenon that complicates 15 to 20% of all pregnancies[1]. There are several techniques for termination of early pregnancy failure. The majority of cases are currently treated by dilatation and curettage with many complications such as hemorrhage, infection, uterine adhesion, impaired future fertility, cervical trauma, uterine perforation and anesthetic error[2, 3].

Several studies have shown the same efficacy of medical treatment with either prostaglandin E1 or E2 compare to surgical treatment but less complications[4-6]. Misoprostol (Cytotec®), a synthetic prostaglandin E1 analogue had widely been used for medical abortion, cervical ripening before surgical abortion, labor induction and used for termination of pregnancy[5-7]. In many countries, intravaginal 800-1000 μg dose of misoprostol was recommended for termination of early pregnancy failure and they reported complete abortion rate of 60 to 88%[8-14] but they found many side effects such as nausea, vomiting, diarrhea, abdominal pain, chill and fever which were thought to be dose related. Lower dose might be decreasing these side effects with the same efficacy.

The purpose of this study was to compare the clinical efficacy of 2 doses of intravaginal misoprostol (800 μg versus 400 μg) for termination of early pregnancy failure and to compare the incidence of maternal side effects as well as maternal satisfaction between these 2 regimens.

Correspondence to : Prasartsakulchai C, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand. Phone: 0-2256-4824, Fax: 0-2256-4825, E-mail: ytannirandorn@hotmail.com

Material and Method

This randomized, controlled trial was conducted at the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand between June 2003 and September 2003.

The patients participated in this study were obtained from pregnant women who came to antenatal care clinic or gynecologic outpatient department with the problem of abdominal pain or abnormal uterine bleeding.

The inclusion criteria were all pregnant women with early pregnancy failure before 12 weeks of gestational age as determined by transvaginal ultrasound. Early pregnancy failure was defined as 1) an embryonic pole 5-14 mm with no embryonic cardiac activity, 2) an irregular intrauterine gestational sac with a mean sac diameter of $\geq$ 16 mm and no embryonic pole, and 3) abnormal growth on ultrasound image over or minimum of 7 days[4].

Exclusion criteria included 1) an inability to confirm pregnancy failure or intrauterine gestational sac location, 2) an inability or refusal of the patient to adhere to study follow-up requirements, 3) heavy vaginal bleeding (defined as soaking more than one heavy vaginal pad per hour for more than 2 h or more than one heavy pad per 30 min for more than 1 h, 4) anemia (defined as a hemoglobin concentration less than 10 mg/dl), 5) unstable vital signs, 6) maternal coagulopathy, 7) signs and symptoms of infection, 8) maternal history of asthma or cardiac disease, 9) known maternal allergy to prostaglandin or previous adverse reaction, and 10) open internal cervical os on speculum examination (as defined by allowing passage of a ring forceps). Written informed consent was obtained in all cases. This study was approved by the ethical committee of the faculty.

Before enrollment, all patients underwent transvaginal ultrasound (5 MHz transvaginal transducer, Aloka SSD-2000, Tokyo, Japan) to confirm fetal non-viability and initial laboratory evaluation included complete blood cell count, prothrombin time and partial thromboplastin time.

The patients fulfilled our criteria were offered 3 options, 1st option-expectant for complete abortion, 2nd option-immediate dilatation and curettage, and 3rd option-medical treatment by misiprostol.

Patients who chose medical treatment were subsequently randomized to receive either 800 μg misoprostol (four 200-μg tablets) regimen or 400 μg misoprostol (two 200-μg tablets) regimen by using random number tables.

The misoprostol tablets (Cytotec®, Searle Laboratories, New South Wale, Australia, 200 μg /tab) were dampened with 2-3 drops of normal saline and placed within the posterior vaginal fornix, then the patients remained in a semiprone position for at least 1 h. The second dose was placed at 24 h after initial dose if complete abortion had not occurred.

The treatment failure was defined as no evidence of complete abortion within 48 h. Dilatation and curettage was performed when 1) spontaneous abortion had not occurred after 48 h, 2) heavy vaginal bleeding, 3) incomplete abortion, 4) endometrial thickness more than 10 mm, evaluated by transvaginal ultrasound 6 h after the diagnosis of complete abortion, and 5) the patients' request upon dilatation and curettage. Incomplete abortion was defined as clinical findings of open cervical os with bleeding and retained conceptus or a sonographic finding of endometrial thickness more than 10 mm without midline echo. Complete abortion was defined as completely expulsion of conceptive products or pathological absence of conceptus after dilatation and curettage in patients with suspected incomplete abortion.

Vital signs were monitored every 4 h. Pain assessment was evaluated by 10 grades visual analogue scale. Acetaminophen 1000 mg (2 tablets) were given as analgesic treatment and supplement treatment was intramuscular Morphine 10 mg. Maternal side effects such as abdominal pain, fever defined as oral body temperature more than 38 c, diarrhea, nausea, vomiting and chill were recorded.

The primary outcome measure was complete abortion rate. The secondary outcome was patient side effects and satisfaction. Patient satisfaction was assessed by asking the patients to rate their degree of agreement with the following 2 statements: 1) I would recommend the treatment to a friend or family member with early pregnancy failure. 2) I would try the treatment again if I had another early pregnancy failure. The patients indicated their degree of agreement on a five-grading scale: strongly disagree, disagree, neutral, agree, or strongly agree.

From prior pilot study: In group 1 regimen (800 μg misoprostol) the outcome showed 80% of complete abortion and In group 2 regimen (400 μg misoprostol) the outcome showed 40% of complete abortion. So, the sample size obtained by calculation was 25 patients in each group ($\alpha = 0.05$, = 0.02).

Statistical analysis was performed with SPSS version 11 for Window XP (SPSS, Chicago, USA). Unpaired t-test was analyzed for continuous variables, Chi-square or Fisher exact test for categorical variables. Univariate analysis was used to define the prognostic variable. The descriptive data were shown in mean ± standard deviation. A p-value of < 0.05 was considered statistically significant.

Results

Fifty patients were enrolled this study. Twenty five patients were randomized to the group 1 regimen (800 μg misoprostol) and 25 patients were randomized to the group 2 regimen (400 μg misoprostol). The patient characteristics were similar between the 2 groups (Table 1).

Table 1. Patient demographic characteristics

	Misoprostol 800 μg (N =25)	Misoprostol 400 μg (N = 25)
Age, mean ± SD, years	29.8±7.6	33.3±4.5
Nulliparous, (%)	16 (64%)	11 (44%)
Previous abortion, (%)	7 (28%)	8 (32%)
Previous dilatation and curettage, (%)	2 (8%)	5 (20%)
Gestational age, mean ± SD, weeks	8.2±0.9	8.0±1.2
Hematrocrit, mean ± SD, volume percent	37.5±2.7	36.8±2.9
Type of pregnancy failure		
-Anembryonic pregnancy, (%)	10 (40%)	5 (20%)
-Embryonic death, (%)	15 (60%)	20 (80%)

Table 2 shows the outcomes of patients. Complete abortion rate (72% in group 1 versus 76% in group 2, p = 0.91), incomplete abortion rate (12% in group 1 versus 12% in group 2, p = 0.91), and rate of dilatation and curettage (32% in group 1 versus 32% in group 2, p = 1.00). No significant difference was found between the 2 groups. However, median time to abortion in the 800 μg group was significantly shorter than in the 400 μg group (9.0 hr versus 15.3 hr, respectively, p = 0.03). Thirteen patients (7 patients in the 800 μg group and 6 patients in the 400 μg group) failed to achieve complete abortion and underwent dilatation and curettage.

Univariate analysis of variance was used to evaluate the prognostic factors of the outcomes; such as maternal age, parity, previous cesarean section, previous abortion, previous dilatation and curettage, gestational age, body mass index, present of embryonic pole and mean crown-rump length. There was no significant variables demonstrated to influence the outcomes.

Table 3 shows the maternal side effects which were found to have no statistically significant difference between the 2 groups except for fever which was more frequent in the 800 μg group than in the 400 μg group (12 % versus 0%, p = 0.04). In the 800 μg group, 2 patients had heavy vaginal bleeding and required emergency dilation and curettage. One patient developed endometritis which responded to antibiotics. No patients had diarrhea or nausea & vomiting.

All patients completed the post treatment questionnaire for assessment of satisfaction. Overall, patient satisfaction with the treatment appeared to be high and there was no statistically significant

Table 2. Patient outcomes

	Misoprostol 800 μg (N =25)	Misoprostol 400 μg (N =25)	P value
Hospitalization, mean ± SD, days	3.24±1.30	2.96±0.79	0.36
Complete abortion, (%)	18 (72%)	19 (76%)	0.91
Incomplete abortion, (%)	3 (12%)	3 (12%)	
No abortion, (%)	4 (16%)	3 (12%)	
Dilatation and curettage, (%)	8 (32%)	8 (32%)	1.00
Median time to abortion,(range), h	9.0 (2.6-30.0)	15.3 (5.0-36.0)	0.03
Total dose, mean ± SD, g	922±320	512±184	0.75
Satisfaction, (%)			
Neutral	3 (12%)	4 (16%)	0.91
Agree	16 (64%)	15 (60%)	
Strong agree	6 (24%)	6 (24%)	

Table 3. Side effects

	Misoprostol 800μg (N =25)	Misoprostol 400μg (N =25)	P value
Pain scale, mean ± SD, scores	5.08±2.31	4.88±2.91	0.78
Pain scales ≥ 5 scores, (%)	12 (48%)	11 (44%)	1.00
Analgesic used, (%)	12 (48%)	12 (48%)	1.00
Acetaminophen, (%)	8 (32%)	3 (12%)	0.13
Morphine, (%)	5 (20%)	10 (40%)	
Diarrhea, (%)	0 (0%)	0 (0%)	1.00
Nausea and vomiting, (%)	0 (0%)	0 (0%)	1.00
Chill, (%)	3 (12%)	0 (0%)	0.23
Fever, (%)	7 (28%)	1 (4%)	0.04
Heavy vaginal bleeding, (%)	2 (8%)	0 (0%)	0.49
Infection needed intravenous antibiotic, (%)	1 (4%)	0 (0%)	1.00

difference between the 2 groups (Table 2). Forty three of 50 (86%) patients were satisfied or strongly satisfied. No one disagreed with the treatment.

Discussion

Obstetricians and Gynecologists have recently been challenged to rethink their approach to early pregnancy failure or miscarriage. Dilation and curettage has been traditionally used as the surgical method of treatment but uterine curettage is associated with 4 to10% rate of complication[1,2]. There have been several clinical trials that evaluated the efficacy of medical treatment for the evacuation of the first trimester uterus[4,8-14]. Misoprostol, a synthetic analogue of prostaglandin E1 has attracted attention as an effective and cost efficient agent for termination of pregnancy with minimal side effects and no serious complication[5,6]. Vaginal misoprostol is found to be more effective than oral misoprostol for uterine evacuation of early pregnancy failure[13]. Many studies have reported and recommended that vaginal dose of 400 to 1000 μg of misoprostol alone are effective in producing complete abortion in cases of early pregnancy failure up to 12 weeks of gestation in approximately 60 to 88%[8-14]. However the time interval for repeated doses are varied between studies and the side effects are thought to be doses dependent.

Muffley et al[4] performed a randomized trial which compared the efficacy of 800 μg of intravaginal misoprostol every 24 h up to a maximum of 3 doses versus surgical therapy (dilatation and curettage) for termination of pregnancy failure before 12 weeks of gestation. They found that the success rate of complete abortion in the misoprostol group was 60%. The mean expulsion time was 12.6 h and 48% of patients in the misoprostol group had nausea and diarrhea. Carbonell et al[11] reported the safety and efficacy of 1000 μg vaginal misoprostol self-administered every 24 h up to a maximum of 3 doses for early abortion. They found that complete abortion occurred in 93.0% of patients with the mean expulsion time of 8.1 h. However, the frequencies of nausea and diarrhea were high. Carbonell et al[12] studied the efficacy of 800 μg of intravaginal misoprostol every 24 h for a maximum of 3 doses for interrupting gestations of 10-12 weeks and found the success rate of complete abortion of 87% with the mean expulsion time of 6.6 h. Kovavisarach et al[8] investigated the effectiveness and side effects of intavaginal misoprostol 400 μg compared with a placebo for facilitating complete abortion in cases of blighted ovum with gestational age of up to 12 weeks. They found that complete abortion rate was significantly higher in the women receiving misoprostol (63%) compared with those receiving the placebo (18.5%). However, lower abdominal pain (74.1%) and fever (14.8%) were significantly higher in the misoprostol group than in the placebo group (22% and 0%, respectively).

Our study found that two vaginal doses of 400 μg of misoprostol were as effective as two vaginal doses of 800 μg of misoprostol in producing complete abortion (76% versus 72%, respectively) with the similar rate of the need for dilatation and curettage (32%). The median time to abortion in the 800 μg group was significantly shorter than in the 400 μg group (9.0 h versus 15.3 h). There may be an additional benefit of intravaginal misoprostol even if the treatment is not completely successful. All of the patients undergoing dilatation and curettage in both groups had a dilated cervix at the time of surgery, which intuitively should reduce the risk of perforation and cervical lacerations. In our study, we found no complication from dilatation

and curettage. Fever was the only side effect which was found to be significantly increased in the 800 μg group (28%). The treatment also appeared to be well tolerated. Forty eight percent of patients in both groups did not require analgesic drugs. There was no occurrence of serious complication.

In our study, we also assessed patient satisfaction as an outcome measure and we found that patient satisfaction (agree or strongly agree) in both groups was high (86%) with no statistically significant difference between the 2 groups. Cabezas[15] found a significantly greater percentage of women in the misoprostol group than in the surgical group who appeared to be highly satisfied with the procedure (68.5% versus 54.4%). Lee et al[16] also found that significantly more participants who experienced successful evacuation of the uterus with the misoprostol would choose the same method of treatment again.

In conclusion, our study demonstrated that intravaginal misoprostol is an effective method for termination of early pregnancy failure.Two vaginal doses of 400 μg of misoprostol administrated at 24 hour interval are as effective as two vaginal doses of 800 μg of misoprostol in producing complete abortion with less side effects and similar patient satisfaction.

References

1. Hemminki E. Treatment of miscarriage: current practice and rationale. Obstet Gynecol 1998: 91: 247-53.
2. Farrel RG, Stonington DT, Ridgeway RA. Incomplete and inevitable abortion: treatment by suction curettage in emergency department. Ann Emerg Med 1982; 11: 652-8.
3. Heisterberg L, Hebjorn S, Anderson LF, Petersen H. Sequelae of induced first trimester abortion: a prospective study assessing the role of postabortal pelvic inflammatory disease and prophylactic antibiotic. Am J Obstet Gynecol 1986; 155: 76-80.
4. Muffley PE, Stitely ML, Gherman RB. Early intrauterine pregnancy failure:a randomized trial of medical versus surgical treatment. Am J Obstet Gynecol 2002; 187: 321-6.
5. Blanchard K, Clark S, Winikoff B, Gaines G, Kabani G, Shannon C.Misoprostol for women's health: a review. Obstet Gynecol 2002; 99: 316-32.
6. Goldberg AB, Greenberg MB, Darney PD. Misoprostol and pregnancy. N Engl J Med 2001; 344: 38-47.
7. Herabutya Y, O-Prasertsawat P. Misoprostol in management missed abortion. Int J Gynaecol Obstet 1997; 56: 263-6.
8. Kovavisarach E, Sathapanachai U. Intravaginal 400 microgram misoprostol for pregnancy termination in cases of blighted ovum: a randomized controlled trial. Aust N Z J Obstet Gynaecol 2002; 42: 161-3.
9. Wood SL, Brain PH. Medical management of missed abortion: a randomized clinical trial. Obstet Gynecol 2002; 99: 563-6.
10. Ngai SW, Chan YM, Tang OS, Ho PC. Vaginal misoprostol as medical treatment for first trimester spontaneous miscarriage. Hum Reprod 2001; 16: 1493-6.
11. Carbonell JL, Rodriguez J, Aragon S. Vaginal misoprostol 1000 microgram for early abortion. Contraception 2001; 63: 131-6.
12. Carbonell JL, Varela L, Velazco A, Cabezas E, Tanda R, Sanchez C. Vaginal misoprostol for late first trimester abortion. Contraception 1998; 57: 329-33.
13. Creinin MD, Moyer R, Guido R. Misoprostol for medical evacuation of early pregnancy failure. Obstet Gynecol 1997; 89: 768-2.
14. Jain JK, Meckstroth KR, Mishell DR. Early pregnancy termination with intravaginally administered sodium chloride solution moistened misoprostol tablet. Am J Obstet Gynecol 1999; 181: 1386-91.
15. Cabezas E. Medical versus surgical abortion. Int J Gynecol Obstet 1999; 63: S141-46.
16. Lee DTS, Cheung LP, Haines CJ, Cahn KPM, Chung TKH. A comparison of the psychologic impact and client satisfaction of surgical treatment with medical treatment of spontaneous abortion: a randomized controlled trial. Am J Obstet Gynecol 2001; 185: 953-8.

การศึกษาเปรียบเทียบการใช้ยามิโสพรอสตอลขนาด 800 และ 400 ไมโครกรัม เหน็บทางช่องคลอดในการล้มเหลวของตั้งครรภ์ในระยะแรก

ชลิศา ประสาทสกุลชัย, เยื้อน ตันนิรันดร

วัตถุประสงค์ *: เพื่อศึกษาเปรียบเทียบประสิทธิผล, ผลข้างเคียง และความพึงพอใจ ในการใช้ยามิโสพรอสตอลขนาด 800 และ 400 ไมโครกรัมเหน็บทางช่องคลอดในการล้มเหลวของการตั้งครรภ์ในระยะแรก*

ขั้นตอน *: ผู้ป่วยที่ได้รับการวินิจฉัยเป็นการตั้งครรภ์ล้มเหลวในระยะแรกจะถูกสุ่มแบ่งเป็นกลุ่มแรก ขนาด 800 ไมโครกรัม และกลุ่มสองขนาด 400 ไมโครกรัม ยาจะถูกเหน็บซ้ำ ถ้าไม่พบการแท้งเกิดขึ้นในหลังเหน็บยา 24 ชั่วโมงและถ้าไม่พบการแท้งอย่างสมบูรณ์เกิดขึ้นใน 48 ชั่วโมงถือว่าการศึกษาล้มเหลว ผู้ป่วยจะได้รับการขูดมดลูก ถ้าไม่พบการแท้งเกิดขึ้น, มีเลือดออกจากช่องคลอดมากหรือ แท้งไม่ครบ*

ผลการศึกษา *: ผู้ป่วยกลุ่มละ 25 คน ไม่พบความแตกต่างในจำนวนผู้ป่วยที่เกิดการแท้งอย่างสมบูรณ์ (72% และ 76% ตามลำดับ P = 0.91) แม้ว่าในกลุ่ม 800 ไมโครกรัมจะใช้เวลาในการแท้งน้อยกว่าแต่ผลข้างเคียงโดยเฉพาะเรื่องไข้มากกว่า และไม่พบความแตกต่างอย่างมีนัยสำคัญในเรื่องของความพึงพอใจ*

สรุป *: ไม่พบความแตกต่างในประสิทธิผลของยามิโสพรอสตอลขนาด 400 และ 800 ไมโครกรัมเหน็บทางช่องคลอดในการเกิดการแท้งอย่างสมบูรณ์ทั้งที่ผลข้างเคียงในกลุ่ม400 ไมโครกรัมน้อยกว่าและความพึงพอใจของผู้ป่วยไม่ต่างกัน*