400 µg Oral and Vaginal Misoprostol Comparison Before Manual Vacuum Aspiration for Voluntary Termination of Pregnancy Before 10 Weeks Gestation

10 Haftalıktan Önceki İstemli Gebelik Sonlandırılmasında Kullanılan Manuel Vakum Aspirasyonundan Önce 400 µg Oral ve Vaginal Misoprostolün Karşılaştırılması

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ÖZET

Amaç: Bu çalışmanın amacı 10 haftadan küçük gebeliklerin terminasyonu için kullanılan cerrahi evakuasyonun 3 ve 6 saat öncesi kullanılan 400 µg oral ve vaginal misoprostolün etkinliği ve tolerabilitesinin karşılaştırılması

Gereç ve Yöntemler: Kliniğimizde en sık kullanılan 4 misoprostol rejiminin kullanıldığı 210 hasta retrospektif olarak değerlendirildi; Evakuasyondan 3 saat önce oral 400 µg (O3), 6 saat önce oral 400 µg (O6), 3 saat önce ovaginal 400 µg (V3), 6 saat önce vaginal 400 µg (V6).

Bulgular: Dozajına, kullanım yoluna ve zamanlamasına bakılmaksızın misoprostolün servikal dilatasyon üzerine belirgin etkisi vardır. Dilatasyon ihtiyacı kontrol grubuna kıyasla tüm misoprostol gruplarında belirgin olarak azdır. Diğer dört gruba kıyasla kontrol grubunda %5.8 oranla aşırı miktarda kan kaybı izlenmiştir. Postoperatif inceleme, hematocrit düşüşü, endometrial kalınlık ve analjezik ihtiyacı tüm gruplarda benzer bulunmuştur. Preoperatif VAS skorları O6 ve V6 gruplarında yüksekti. En sık görünen yan etki bulantı olup, özellikle oral (O3, O6) gruplarda belirgindi.

Sonuç: Analiz 10 haftalık ve öncesi gebeliğin istemli sonlandırılmasından 3 saat önce alınan 400 µg vaginal misoprostolün ideal kullanım yolu ve dozajı olarak göstermektedir.

Anahtar kelimeler: Misoprostol; planlanmamış gebelik

ABSTRACT

Aim: The aim of the present study was to compare the effectiveness and tolerability of 400 µg oral and 400 µg vaginal misoprostol administered 3 or 6 hours before surgical evacuation for termination of pregnancy before 10 weeks of gestation

Material and Method: A total of 210 patients with mostly used four regimens in our department; oral 400 µg misoprostol 3 hours before evacuation (O3), oral 400 µg misoprostol 6 hours before evacuation (O6), vaginal 400 µg misoprostol 3 hours before evacuation (V3), vaginal 400 µg misoprostol 6 hours before evacuation (V6) were retrospectively analyzed.

Results: Misoprostol administration regardless to dosage, route and timing had significant effect on cervical dilatation. Dilatation requirement was significantly low in all misoprostol groups compared with control. 5.8% of subjects in control group had abundant blood loss significantly higher than other four groups. Postoperative evaluation showed that hematocrite decrease, endometrial thickness measurement and postoperative analgesic usage were similar in all groups. Preoperative VAS scores were higher in O6 and V6 groups. The most frequent side effect was nausea and it was especialy seen in oral (O3,O6) groups.

Conclusion: The analyze showed that 400 µg vaginal misoprostol taken 3 hours before vacuum aspiration for voluntary termination of pregnancy before 10weeks gestation seems as an ideal route and dosage.

Key words: Misoprostol; unplanned pregnancy;

AIM

Each year 46 million pregnancies are terminated voluntarily. Nearly 60% of these terminations carried out under safe conditions and the remaining are "unsafe abortions". At the second half of the twentieth century, dilatation and curettage (D & C) was the most common method for safe termination of early pregnancy until 1960s when the vacuum aspiration gained greater acceptance and has become the standard of care (1,2).

Misoprostol (15-deoxy-16-hydroxy-16-methyl prostaglandin E1) is a synthetic prostaglandin E1 analogue. It was developed by Searle in 1973 for the treatment and prevention of peptic ulcer due to its inhibition of gastric acid secretion and its various mucosa-protective properties (3). Besides this action on the digestive tract, misoprostol is also a strong stimulator of uterine contractility, cervical ripening and dilatation (4). Misoprostol like agents, that have great importance for successful vacuum aspiration, seems to be needed for minimizing the risks related with inadequate cervical dilatation such as incomplete evacuation of the uterine cavity and excessive bleeding due to retained products and damage to the cervix in the form of cervical lacerations or cervical stenosis and incompetence with possible negative impacts on future pregnancies (5).

As a cervix-ripening agent, misoprostol has demonstrated usefulness by both oral and vaginal routes in a dose of 400 µg, as self-administered or as administered by a physician. The oral route mostly caused more side effects than the vaginal route. However there is no consensus about the timing of administration (6-8).

The aim of the present study was to compare the effectiveness and tolerability of 400 µg oral and 400 µg vaginal misoprostol administered 3 or 6 hours before surgical evacuation for termination of pregnancy before 10 weeks of gestation.

MATERIAL AND METHOD

A total of 312 patients complied with gestational age of up to 84 days of amenorrhea were retrospectively analyzed. The patients with systemic disease, history of cervical minor or major operations (electrocautery, conization, cervical cerclage, etc.), active genital infection, bleeding or spotting during the current pregnancy or threatened or missed abortion, multiple pregnancy and basal cervical dilatation greater than 4 mm were excluded from the study.

A total of 210 patients with mostly used four regimens in our department; oral 400 µg misoprostol 3 hours before evacuation, oral 400 µg misoprostol 6 hours before evacuation, vaginal 400 µg misoprostol 3 hours before evacuation and vaginal 400 µg misoprostol 6 hours before evacuation are retrospectively analyzed. Also 42 women without any medication are taken as the control group.

Four different protocols used in the department were assessed retrospectively.

Group 1, oral misoprostol (O3) 400 µg 3 hours before vacuum aspiration (n =48);

Group 2, oral misoprostol (O6) 400 µg 6 hours before vacuum aspiration (n =54);

Group 3, vaginal misoprostol (V3) 400 µg 3 hours before vacuum aspiration (n =56);

Group 4, vaginal misoprostol (V6) 400 µg 6 hours before vacuum aspiration (n =52);

Group 5, control without any medication (n =42);

All the patients were taken for manual vacuum aspiration (MVA) with Karman suction curette under general anesthesia. After the aspiration had ended, the uterine cavity was carefully checked with a curette. All uterine aspirations were performed with the assistance of direct abdominal ultrasound.

RESULTS

Table 1 shows baseline characteristics. The mean age of women was about 30-35 years, with mean gestational week of 6-7weeks. The four study groups and the control group were similar in terms of demographic variables, gestational age in weeks at the time of surgical evacuation and obstetric history, (gravidity, parity, and number of primiparous and multiparous patients) (Table 1).

Table 1. Baseline characteristics of the groups

	Age (years) (mean)	Gravidity (mean)	Parity (mean)	D&C (mean)	Vaginal birth (mean)	Caeserean Section (mean)	Gestational week (mean)
O3 (n=48)	31,62	2,62	1,06	0,44	0,62	0,44	6,06
O6 (n=54)	33,62	3,38	1,5	0,62	0,88	0,62	6,38
V3 (n=56)	35,21	3,07	1,43	1,36	0,93	0,50	6,43
V6 (n=52)	30,67	2,92	0,96	0,25	0,63	0,33	6,42
Control (n=42)	31,35	2,68	1	0,40	0,45	0,55	6,20

Operative outcome measures

In the operation room; the postmedication cervical dilatation before termination, duration of the procedure and intraoperative bleeding, need for dilatation were evaluated.

Before termination in the operating room, the size of the largest Hegar's dilator that could be passed into the cervical os without resistance was recorded as the cervical dilation achieved by medication. The mean dilatation recorded for all groups were 4.06, 5.25, 5.93, 6.07 and 2.95 respectively. Misoprostol administration regardless to dosage, route and timing had significant effect on cervical dilatation (Table 2).

The need for dilatation was also assessed in all groups. 62.5% of O3 group, 62.9% of O6 group, 67.8% of V3 group and 63.4% of V6 group didn't need any intraoperative dilatation before evacuation. On the other side 73.9% patients without medication needed dilatation. Dilatation requirement was significantly low in all misoprostol groups compared with control, but no difference was found between the misoprostol groups (Table 2).

Surgical time was measured immediately from the speculum inserted after the general anesthesia had been administered until the speculum had been removed at the end of the procedure. The surgical timings were 9.56, 9.38, 9.00, 9.00 and 10.85 minutes in groups 1-5 respectively. The time spent for evacuation was less in group 1, 2, 3, 4 then group 5 but was not significant (Table 2). The surgical termination was unsuccessful in two of the control group subjects. The surgeon was unable to pass the Carmen cannula from the cervical os in both patients.

Intraoperative blood loss was subjectively measured by the surgeon as scarce, usual or abundant (Table 3). All misoprostol groups had similar results for intraoperative blood loss. 5.8% of subjects in control group had abundant blood loss significantly higher then other four groups.

Postoperative outcome measures

Postoperatively subjects were assessed 2 hours and 7 days after the surgical procedure. None of the subjects had serious postoperative complications. The vital signs were evaluated for 2 hours and all the patients were discharged 2 hours after the procedure. In the 7th day postoperative examination, the hematocrite levels, endometrial thickness and postoperative analgesic requirement were examined.

Preoperative hematocrite levels of the five groups were (O3:36.6% O6:34.3% V3:36.3% V6:34.5% Control:

Table 2. Preoperative outcome measures

	Cervical dilatation achieved by medication (mean)*	No Need for Dilatation	Duration of the procedure (mean) (in minutes)
O3 (n=48)	4,06	62,5% n=30	9,56
O6 (n=54)	5,25	62.9% n:34	9,38
V3 (n=56)	5,93	67.8% n:38	9,00
V6 (n=52)	6,07	63.4% n=33	9,00
Control (n=42)	2,95¶	26.1% n=11	10,85

***** The size of the largest Hegar's dilator that could be passed into the cervical os without resistance was recorded as the cervical dilation

¶ P<0.05 Control group compared with study groups

Table 3. Intraoperative blood loss

	Scarce	Usual	Abundant
O3 (n=48)	50%	50%	0%
O6 (n=54)	53.7%	46.3%	0%
V3 (n=56)	64.9%	33.9%	0.02%
V6 (n=52)	67.3%	32.7%	0%
Control (n=42)	59.5%	35.7%	5.8%¶

¶ P<0.05 Control group compared with study groups

36.4%) similar, and did not changed postoperatively at the seventh day (O3:36.1% O6:33.5% V3:35.7% V6:34% Control:35.6%). When postoperative follow-ups were evaluated, the number of days of spotting or bleeding after vacuum aspiration showed no difference between the groups (O3:4.1, O6:4.6, V3:4.3, V6:3.4, Control:5.1, in days).

Seven days after evacuation, mean endometrial thickness measured by transvaginal ultrasonography (General electric Loqic 200) in the misoprostol groups were similar to eachother and control group. (O3;3.31mm, O6;4.75mm, V3;3.79mm, V6;4.25, Control;4.55mm). Postoperative analgesic requirement which was assessed by the number of pills used during this period was similar for all groups.

Complications, side effects and pain scores

The pain scores and side effects of the medication just before the surgical procedure were analyzed. The degrees of the pain of the subjects were tested by VAS (visual analogue scale) which was a horizontal line, 10cm in length. The subjects marked on the line, the point that they felt, representing their pain perception of the current state. The pain score was determined by measuring in centimeters from the left hand end of the line to the point that the patient marked. The pain VAS scores were measured before evacuation, 2 hours after evacuation and seven days after evacuation.

The mean VAS score before evacuation were statistically high in O6 (4,38) and V6 (4,33) groups. O3 (1,88) and V3 (1,86) groups' VAS scores were slightly higher then the control (0,92) but not statistically significant. The VAS scores at the 2nd hour and 7th day were also assessed and no difference was found (Table 5).

The side effects evaluated preoperatively were shown in Table 5. The mostly seen side effect of misoprostol was nausea. The other mostly seen side effects were; vomiting, fever and diarrhea. Nausea was significantly higher in oral groups rather then vaginal and control groups. Nearly 1/3 of the subjects in oral groups experienced nausea without vomiting. Vomiting, fever and diarrhea was similar in all groups.

The presence of vaginal bleeding before the surgical procedure was also assessed. The bleeding was seen in 25%, %25.9, 30.3%, 51.9% and 0.02% of subjects in group1-5 respectively. It was significantly high in V6 group then control and other study groups (Table 6)

DISCUSSION

There are many different protocols used for first

Table 4. Postoperative measures

	Preoperative Hematocrit	Postoperative Hematocrit	Days with spotting or bleeding (mean)	7th day endometrial thickness (mean) (in mm)	The number of analgesic pills used (mean)
O3 (n=48)	36.6%	36.1%	4.1	3.31	1.88
O6 (n=54)	34.3%	33.5%	4.6	4.75	2.50
V3 (n=56)	36.3%	35.7%	4.3	3.79	1.36
V6 (n=52)	34.5%	34.0%	3.4	4.25	1.00
Control (n=42)	36.4%	35.6%	5.1	4.55	2.35

Table 5. Side effects after misoprostol administration

	VAS score (Preoperative)	VAS score (2nd hour)	VAS score (7th day)
O3 (n=48)	1,88	2,50	2,38
O6 (n=54)	4,38¶	2,38	2,12
V3 (n=56)	1,86	2,00	1,93
V6 (n=52)	4,33¶	2,50	2,33
Control (n=42)	0,92	2,70	2,42

¶ P<0.05

Table 6. Side effects after misoprostol administration

	Nausea	Vomiting	Fever	Diarrhea	Presence of bleeding
O3 (n=48)	64.58% n=31¶	6.25% n=3	2.08% n=1	2.08% n=1	25% n=12
O6 (n=54)	64.81% n=35¶	5.55% n=3	4.16% n=2	1.85% n=1	25.9% n=14
V3 (n=56)	33.92% n=19	3.57% n=2	1.78% n=1	0% n=0	30.3% n=17
V6 (n=52)	40.38% n=21	7.69% n=4	0% n=0	0% n=0	51.9% n=27 ¶
Control (n=42)	19.04% n=8	4.76% n=2	0% n=0	2.38% n=1	0.02% n=1

¶ P<0.05

trimester pregnancy termination. Especially in developing countries, since the educated trained staff number is not enough, some non-surgical abortion techniques are provided as well. These medical techniques usually include mifepristone followed by prostaglandin analogue. But for many countries like Turkey, since mifepristone is not available, surgery still seems to be the first choice for voluntary termination. In this retrospective analyze we tried to find answer for three simple questions. Should misoprostol be given as a premedication before manual vacuum aspiration (MVA) with Karman suction curette under general anesthesia for pregnancy termination before 10 weeks of gestation? If yes, what should be the route of administration and when should be the ideal timing?

In the study we assessed two different routes (oral and vaginal) and two different timing (3 and 6 hour before procedure) and compared with a control group without any medication. Zieman et al.(9) performed the first pharmacokinetic study comparing the oral and vaginal routes of administration in 1997.They found out that the area under the plasmaconcentration-versus-time curve (AUC) which represents the bioavailability of misoprostol after vaginal administration was significantly greater than that following oral administration.

Postmedication cervical dilatation before termination & Need for dilatation & Preoperative bleeding

As we focused on the preoperative parameter analyze, in the analyze it's obvious that regardless to timing, vaginal administration of misoprostol have greater effect on cervical dilatation. But the average dilatation for both vaginal and oral routes was lower then previously reported studies (10-12) but similar to one reported from Spain (13). Also the evacuation with prior vaginal premedication needed less dilatation. Both the oral and vaginal group needed statistically significant less dilatation then the control group (14).

Decreasing the need for cervical dilatation has the potential to decrease the number of uterine perforations that may complicate up to 2% of the first trimester surgical abortions (15) On the other hand, most of the uterine perforations are clinically unnoticed without causing serious complications and the incidence may be as low as 0.12% in the experienced hands of senior surgeons.

The strong actions of vaginal groups on cervix uteri brought out an unwanted problem. 51.9% of V6 group subjects had bleedings preoperatively which was higher then the oral and control group. This is an important side effect of the medication that may decrease the patients' compliance to the procedure and the comfort of the subjects.

Intraoperative bleeding & Duration of the procedure

Intraoperative blood loss was less in the vaginal groups but statistically there were no difference between the five groups, however it's not measured but the staff's observations were considered. The loss was reported similar in recent studies, too (13).

Duration of the procedure did not differ between the groups, and it was longer to what has been reported by others (5) However, the terminations in our study were all done by second year trainees which may explain the long duration of the procedure (16,17).

Vas score

Regarding pain scores as assessed using the VAS, O3, V3 and control groups were nearly same prior to evacuation (Table 5). O6 and V6 groups had significantly higher scores preoperatively. Two hours and seven days after evacuation, pain scores were comparable for all the misoprostol and control groups. The total number of analgesic pills used between evacuation and the seventh day were high in O6 and control groups (O3:1.88, O6:2.50, V3:1.36, V6:1.00, Control:2.35).

The hematocrite levels & Mean endometrial thickness

Preoperative hematocrite levels of the groups were changed minimally and similarly in all groups without any significant differences. Also we evaluated the number of days of bleeding or spotting after the procedure, showing no significant differences between any groups. Prior

medication did not significantly effect the bleeding postoperatively as previously shown in other researches (5).

In the present study, the mean thickness of endometrial line was evaluated 7 days after evacuation finding no differences between the groups. As previously analyzed postoperative thickness is an important indicator for a successful termination procedure (18-20).

Although the endometrial line was thinner in O3 and V3 groups, all groups had lines lower than 5mm that indicated a successful termination without any rest tissue.

Complications and Side Effects

There were many conflicting results for side effects of misoprostol used at the first trimester. Except the nausea the side effects of misoprostol was minimal in our study. The oral group had higher incidence of nausea compared with the vaginal and control groups. We found no difference between oral, vaginal and control group when compared the other side effects like, vomiting, fever and diarrhea. Previously many other researches proved the higher gastrointestinal side effects after oral route (21-26).

The overall bioavailability is higher with vaginal misoprostol, but peak plasma concentration is higher with oral than with vaginal route and it is believed that this high peak plasma concentration may be the cause of the increased systemic adverse effects (27).

As a conclusion, the study showed that 400 µg vaginal misoprostol taken 3 hours before vacuum aspiration for voluntary termination of pregnancy before 10weeks gestation seems as an ideal route and dosage by decreasing the need for cervical dilatation with higher cervical dilatation levels with fewer side effects. Vaginal misoprostol given 6 hours before the procedure have high preoperative bleeding ratio and pain scores which limits its' usage.

REFERENCES

1. WHO-World Health Organization. Unsafe abortion-Global and regional estimates of the incidence of unsafe abortion and associated mortality in 2000. 4th edition. WHO; 2004. 82pp. Available in: http://www.who.int/reproductive-health/publications/unsafe_abortion_estimates _04/estimates.pdf.
2. Goldberg AB, Dean G, Kang MS, Youssof S, Darney PD. Manual versus electric vacuum aspiration for early first-trimester abortion: a controlled study of complication rates. Obstet Gynecol 2004;103:101–7.
3. Watkinson G, Hopkins A, Akbar FA. The therapeutic efficacy of misoprostol in peptic ulcer disease. Postgrad Med J 1998;64:60–77.
4. Gemzell KD, Marions L, Rodriguez A, Spur BW, Wong PYK, Bygdeman M. Comparison between oral and vaginal administration of misoprostol on uterine contractility. Obstet Gynecol 1999;93:275–280.
5. Cakir L, Dilbaz B , Caliskan E, Dede F. S, Dilbaz S, Haberal A. Comparison of oral and vaginal misoprostol for cervical ripening before manual vacuum aspiration of first trimester pregnancy under local anesthesia: a randomized placebo-controlled study. Contraception 2005;71:337–342
6. Carbonell JLL,Velazco A, RodriguezY, Tanda R, Sanchez C, Barambio S, et al. Oral versus vaginal misoprostol for cervical priming in first trimester abortion. A randomized trial. Eur J Contracept Reprod Health Care 2001;6:134–40.
7. Oppergaard K, Abdelnoor M, Nesheim BI, Jerve F, Eskild A. The use of oral misoprostol for pre-abortion cervical priming: a randomised controlled trial of 400 versus 200 µg in first trimester pregnancies. BJOG 2004;111:154–159.
8. Hamoda H, Ashok P, Flett GMM, Templeton A. A randomized controlled comparison of sublingual and vaginal administration of misoprostol for cervical priming before first-trimester surgical abortion. Am J Obstet Gynecol 2004;190:55–59.
9. Zieman M, Fong SK, Benowitz NL, Bansketer D, Darney PD. Absorption kinetics of misoprostol with oral or vaginal administration. Obstet Gynecol 1997;90:88–92.
10. Hamoda H, Ashok P, Flett GMM, Templeton A. A randomized controlled comparison of sublingual and vaginal administration of misoprostol for cervical priming before first-trimester surgical abortion. Am J Obstet Gynecol 2004;190:55–59.
11. MacIssac L, Grossman D, Balisteri E, Darney P. A randomized controlled trial of laminaria, oral misoprostol, and vaginal misoprostol before abortion. Obstet Gynecol 1999;93:766–770.
12. Taner ZM, Nas T, Bor P, Güner H, Yıldırım M. Yasal Tahliye Öncesi Servikal Dilatasyonu Sağlamak ve Kolaylaştırmak Amacı ile Misoprostol Kullanımı. Turkiye Klinikleri J Gynecol Obst 1997;7(3):159-162
13. Esteve JL, Marı´ JM, Valero F, Llorente M, Salvador I, Varela I, et al. Sublingual versus vaginal misoprostol (400 Ag) for cervical priming in first-trimester abortion: a randomized trial Contraception 74 (2006) 328–333
14. Ashok PW, Hamoda H, Nathani F, Flett GM, Templeton A.Randomized controlled study comparing oral and vaginal misoprostol for cervical priming prior to surgical termination of pregnancy. Br J Obstet Gynaecol 2003;110:1057–1061.
15. Kaali SG, Szigetvari IA, Bartfai GS. The frequency and management of uterine perforations during first trimester abortions. Am J Obstet Gynecol 1989;161: 406–408.

16. MacIssac L, Grossman D, Balisteri E, Darney P. A randomized controlled trial of laminaria, oral misoprostol, and vaginal misoprostol before abortion. Obstet Gynecol 1999;93:766–770.
17. Aronsson A, Helstrfm L, Gemzell-Danielsson K. Sublingual compared with oral misoprostol for cervical dilation prior to uterine aspiration: a randomized comparison. Contraception 2004;69: 165–169.
18. Salakos N, Iavazzo C, Bakalianou K, Gregoriou O, Paltoglou G, Kalmantis K, et al. Misoprostol use as a method of medical abortion. Clin Exp Obstet Gynecol 2008;35:130–132 .
19. Robledo C, Zhang J, Troendle J, Barnhart K, Creinin MD, Westhoff C, et al. Clinical indicators for success of misoprostol treatment after early pregnancy failure. Int JGynecol Obstet 2007;99:46–51.
20. Reeves MF, Lohr PA, Harwood BJ, Creinin MD. Ultrasonographic endometrial thickness after medical and surgical management of early pregnancy failure. Obstet Gynecol 2008;111:106–112.
21. Tang SO, Chung HP The pharmacokinetics and different regimens of misoprostol in early first-trimester medical abortion Contraception 2006; 74:26–30.
22. Ashok PW, Hamoda H, Nathani F, Flett GM, Templeton A. Randomized controlled study comparing oral and vaginal misoprostol for cervical priming prior to surgical termination of pregnancy. Br J Obstet Gynaecol 2003;110:1057–1061.
23. Kulier R, Gulmezoglu A, Hofmeyr G, Cheng L, Campana A. Medical methods for first trimester miscarriage. Cochrane Database Syst Rev 2004;2: CD002855.
24. Pang MW, Lee TS, Chung TK. Incomplete miscarriage: a randomized controlled trial comparing oral with vaginal misoprostol for medical evacuation. Hum Reprod 2001;16: 2283–2287.
25. Helena von Hertzen, Gilda Piaggio, Nguyen Thi My Huong, Effi cacy of two intervals and two routes of administration of misoprostol for termination of early pregnancy: a randomised controlled equivalence trial Lancet 2007;369:1938–1946
26. Von Hertzen H, Honkanen H, Piaggio G, Bartfai G,Erdenetungalag R, Gemzell Danielsson K, et al. WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion I: Efficacy. BJOG 2003;110:808–818.
27. Zieman M, Fong SK, Benowitz NL, Banskter D, Darney PD. Absorption kinetics of misoprostol with oral or vaginal administration. Obstet Gynecol 1997;90:88–92.