Comparison of two dosing regimens of vaginal misoprostol for labour induction: a randomised controlled trial

Doğum indüksiyonunda iki farklı vajinal misoprostol dozunun karşılaştırılması: rastgellenmiş kontrollü bir çalışma

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Abstract

Objective: To compare the clinical efficacy of two different dosing regimens of vaginal misoprostol for labour induction.

Material and methods: This is an open label randomised controlled trial of 100 eligible women with obstetrical or medical indications for labour induction at a secondary level care hospital on the west coast of India. Women were randomised to receive either a single 50 μg dose or multiple 25 μg doses (maximum of three doses) of misoprostol in the posterior vaginal fornix. The main outcome measure was induction to vaginal delivery interval.

Results: Mean induction delivery interval was 18.58±13.73 and 14.42±13.2 hours (P=0.73) in the 50 μg and 25 μg misoprostol group respectively. Delivery rate within 24 hours were 60% (30/50), in 50 μg group and 68% (34/50) in 25 μg group (P=0.53). The rates of caesarean section and operative vaginal delivery were similar in both groups. There was no significant difference in maternal side effects and neonatal outcome among regimens.

Conclusion: There was no statistically significant difference between the two regimens in terms of clinical efficacy.

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Key words: Misoprostol, induction of labour, low dose, single dose

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Özet

Amaç: Doğum indüksiyonunda iki farklı dozda vajinal misoprostol uygulamasının klinik etkinliğinin karşılaştırılması.

Gereç ve Yöntemler: Bu açık uçlu rastgellenmiş çalışma Hindistanın batı bölgesinde ikinci basamak hizmet veren bir hastanede, doğum indüksiyonu için obstetrik veya tıbbi bir endikasyonu olan 100 gebede yapıldı. Kadınlara vajinal yoldan tek doz 50mcg veya en fazla 3 doz 25 mcg misoprostol uygulandı. Çalışmanın temel araştırma sonucu indüksiyondan doğuma kadar geçen süre idi.

Bulgular: İndüksiyondan doğuma kadar geçen süre 50 ve 25 mcg gruplarında sırasıyla 18.58±13.73 ve 14.42±13.2 saatti (p=0.73). 24 saat içinde doğum hızı 50 mcg grubunda %60 (30/50) ve 25 mcg grubunda %68 idi (p=0.53). Her iki gruptaki sezaryen ve operatif doğum oranları benzerdi. Her iki gruptaki maternal ve neonatal sonuçlar benzerdi.

Sonuç: Klinik etkinlik açısından her iki doz rejimleri arasında istatistiksel olarak anlamlı bir fark yoktu.

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Anahtar kelimeler: Misoprostol, doğum indüksiyonu, düşük doz, tek doz

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Introduction

Situations arise in obstetrics where it becomes necessary to end a pregnancy in the interest of the mother or baby or both. There is a growing interest in the use of misoprostol, a prostaglandin E1 analogue for labour induction. A large body of data exists on misoprostol use in cervical ripening and labour induction. Vaginal application of misoprostol has been reported in over 9000 women worldwide and seems to have a safety profile similar to that of dinoprostone (1, 2). Insert full stop doses as high as 200 μg of misoprostol were used for labour induction in initial trials. Due to feto-maternal complications, the dose was titrated to 50 or 25 μg every two to six hours. There is a need to examine whether the reported increase in uterine hyperstimulation leading to a higher caesarean section rate and increased incidence of postpartum haemorrhage can be reduced with single dose or low dose regimens (3-6). The dosing interval is also a source of ongoing debate. Lower and less frequent doses cause fewer complications but result in longer insertion delivery interval (7). Although the use of lower dose (25 μg) vaginal misoprostol every 3 to 6 hours has been recommended (8, 9) the optimal dose and frequency of application is not firmly established. Hence the current trial was designed to compare the efficacy of vaginal administration of single 50 μg dose with multiple 25 μg doses of misoprostol for labour induction.

Methods

This is a randomised controlled trial conducted from October 2004 to November 2005 at the Dr TMA Pai Rotary Hospital (an

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associate hospital of Manipal University), Karkala, situated in west coast of India. The study was approved by the local institutional ethical committee. All eligible women with obstetrical or medical indication for labour induction were enrolled in the trial. The inclusion criteria included singleton pregnancy >37 weeks, cephalic presentation, Bishop score ≤5, amniotic fluid index ≥5, reactive fetal heart rate pattern, and intact or ruptured membranes. Women with prior uterine scars (previous caesarean section and myomectomy), para ≥3, multiple pregnancy, estimated fetal weight >4000 or <2000 grams, non reactive nonstress test, placenta previa, hypersensitivity to prostaglandins and severe asthma were excluded from the study.

Informed written consent was obtained from all participants. One hundred women admitted for labour induction were randomly allocated to receive either 25 or 50 μg misoprostol. Allocation of treatment was done by block randomisation. Blocks of ten were prepared using a random number table at the beginning of the trial. Allocation concealment was done using sealed sequentially numbered opaque envelopes. Randomisation was done by the doctor on emergency call before induction. The trial was not masked. A preinduction Bishop score was assessed and nonstress test performed. Women received either a single dose of 50 μg misoprostol (quartering 200 μg tablets, Cytolog, Zydus Alidac, India) or 25 μg misoprostol (quartering 100 μg tablets, Cytolog, Zydus Alidac, India) in the posterior fornix of the vagina. In the 25 μg group, the dose was repeated every six hours, until adequate uterine contractions (three contractions in 10 minutes) were established or cervical ripening was achieved. The maximum number of doses was limited to three in 24 hours. Electronic fetal heart rate monitoring was performed in all patients in active labour. Oxytocin augmentation and artificial rupture of membranes were performed when clinically indicated. Augmentation was delayed for six hours after administration of misoprostol. No epidural analgesia was used in our study.

A primary outcome measure was the interval from first dose of misoprostol to vaginal delivery. Secondary outcome variables included time interval from induction to onset of adequate uterine contractions, mode of delivery, indications for caesarean delivery, number of emergency caesareans performed for abnormal FHR pattern, number of doses of misoprostol used, oxytocin augmentation, incidence of adverse effects such as uterine contraction and FHR abnormalities (10). The uterine contraction abnormalities were classified as (11) a] uterine tachysystole was defined as six or more contractions in a 10-minute period for two consecutive 10-minute periods, b] uterine hypersystole / hypertonus was defined as a single contraction that lasted longer than 2 minutes, c] uterine hyperstimulation syndrome was defined as the presence of either tachysystole or hypertonus that resulted in a non reassuring FHR pattern (persistent decelerations, tachycardia or reduced short term variability). In case of uterine contraction abnormalities, the women were placed in the left lateral position, oxygen administration, subcutaneous terbutaline 0.25 mg and closely monitored until resolution of hyperstimulation.

Other secondary outcome variables were incidence of postpartum haemorrhage and neonatal outcome [birth weight, APGAR score at one and five minutes, incidence of meconium stained amniotic fluid, admission to neonatal intensive care unit (NICU)].

The women's satisfaction with induction of labour was also recorded, based on a simple scale of 0 to 100 and reported as percentage. Women were asked about overall satisfaction of intrapartum care 24 hours after delivery. The best satisfaction was scored as 100% and unsatisfied as zero. Women undelivered at 24 hours were considered as failed induction. Further action was taken based on existing departmental induction guidelines and the clinician's preferences as well as patient's wishes, i.e. repeat induction or oxytocin augmentation, non intervention for next 24 hours or delivered by caesarean after 48 hours as appropriate. Pre-trial sample size was not calculated due to feasibility of recruitment in a single centre during a limited period of course, as this trial was conducted as part of the requirement of a thesis for a two year course. Statistical analysis was performed using SPSS (version 11). Variables were analysed with chi-square test or Mann-Whitney's test and student t-test. The P value <0.05 was considered as significant. Intention to treat principle was utilised while analysing the data.

Results

One hundred and eight women were assessed for eligibility and hundred women were enrolled in the study. Two women did not meet the inclusion criteria and six women were not enrolled because they refused to participate. There was one incidence of protocol violation where one woman was inadvertently randomised to receive 50 μg misoprostol with initial Bishop score of ten which was an exclusion criteria. Data of this patient was also analysed as an intention to treat principle (Figure 1). After entering the trial no women were lost for follow up or opted out of the trial. All one hundred women enrolled were available for final analysis.

Maternal demographic characters and indications for induction were comparable in both regimens (Table 1). Mean induction delivery interval was 18.58±13.73 and 14.42±13.2 hours (P=0.73) in the 50 μg and 25 μg misoprostol groups respectively. The percentage of women delivering vaginally within 24 hours of induction were 68% (34/50), in the 25 μg group and 60% (30/50), in the 50 μg group RR= 0.88, 95% CI (0.66-1.19). The proportion of women delivering within twelve hours (30%, 15/50, vs. 32%, 16/50, p=1.00), and next 12 hours (38%, 19/50 vs. 28%, 14/50 p=0.39) of induction were similar among groups. A post hoc power analysis for primary outcome was 14%. There was no significant difference between groups regarding the onset of active labour (8.25±6.71 vs.11.92±10.15, p=0.3).

As highlighted in Table 2, there was no significant difference in the secondary outcome variables such as the use of oxytocin augmentation, uterine contraction abnormalities, abnormal cardiograph, modes of delivery and postpartum haemorrhage. The neonatal outcomes were comparable among groups. Potential adverse effects of misoprostol such as uterine rupture, nausea, vomiting, diarrhea and fever was not observed in the study population. However one primigravida in the 50 μg group died of severe atonic postpartum haemorrhage.

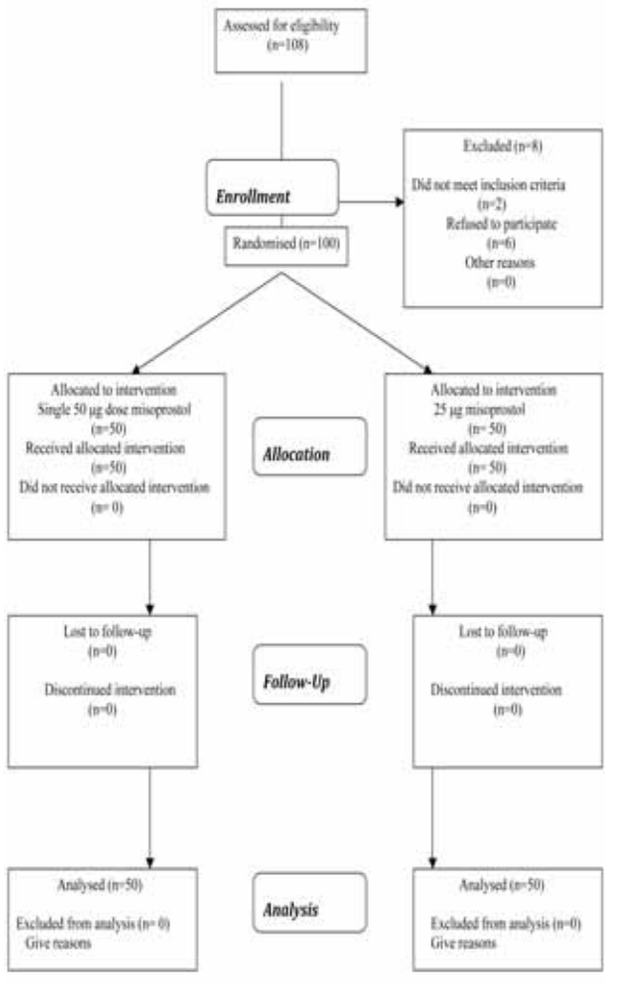

Figure 1. The consort E-flowchart for misoprostol trial

In the 25 μg group, the vaginal delivery rate with one dose was 34%, two doses 28% and three doses 6% (Table 3). Indications for caesarean section were comparable among groups (Table 4). Information on patient satisfaction was available in 48 women. Eighty eight percent, (22/25) of women in the 25 μg group and 100%, 23/23 of women in the 50 μg group had a satisfaction level of more than 50% (P=0.23).

Discussion

Although many trials used multiple doses of 50 μg misoprostol, the vast majority of women (50-87%) delivered with single dose (3, 12-16). Lokugamage et al (17) studied the efficacy of a single versus two dose regimen of 50 μg vaginal misoprostol for labour induction. Although the author concluded that the two dose regimen was more effective, the majority of patients in the two dose regimen 41/53 (77%) received only a single dose without pharmacological advantage of two doses. Hence the current trial looked at the role of single dose of 50 μg vaginal misoprostol in comparison with the currently recommended low dose regimens for labour induction.

In the current trial there was no statistically significant difference between the two misoprostol regimens in terms of clinical efficacy for labour induction. Although we found that the induction delivery interval was similar among the regimens, other investigators (3, 5, 6, 18-21) had demonstrated that it was shorter in the 50 μg group. In a meta-analysis comparing 25 and 50 μg misoprostol, the induction vaginal delivery interval was nearly five hours shorter in the 50 μg group (22). The proportion of women delivering within twelve hours and next 12 hours of induction were similar among the groups, which is consistent with other investigators (18, 20). However, more women delivered between 12-24 hours in the 25 μg group (27/49 vs 10/47, P<0.001) in one study (13) and fewer patients delivered vaginally in the 25 μg group in another study (19).

Table 1. Maternal demographic data

Variables	25 μg (N=50)	50 μg (N=50)	P value
Age (year + S.D)[a]	25.56±3.32	25.32±3.53	0.35
Parity[b]			
Nulliparous (n)	35 (70%)	37 (74%)	0.82
Multi (n)	15 (30%)	13 (26)	
Gestational age (weeks±S.D)[a]	39.36±1.06	39.42±1.03	0.08
BMI (kg/m^2±S.D)[a]	22.51±3.45	22.51±3.02	0.96
Initial Bishop score[a]	3.18±1.17	3±1.490.66	
Indication for labour induction[b]			
Past date	35 (70)	37 (74)	0.48
PROM	13 (26)	10 (20)	
Preeclampsia	1 (2)	3 (6)	
Patient's request	1 (2)	0 (0)	

[a]Student's t-test [b]Chi square test
PROM = premature rupture of membranes
BMI = body mass index
Data represented as mean±SD or number and percent

Table 2. Primary and secondary outcome variables

Outcome	25 μg (N=50) n %	50 μg (N=50) n %	P-value
Intrapartum variables			
Onset of active labour (h)[c]	8.25 + 6.71	11.92+10.15	0.3
Induction vaginal delivery interval[a]	14.42 + 13.2	18.58 + 13.73	0.73
< 12 h (n, %)[b]	15/50 (30)	16/50 (32)	0.19
12 - 24 h (n, %)[b]	19/50 (38)	14/50 (28)	
> 24 h (n, %)[b]	4/50 (8)	10/50 (20)	
Oxytocin augmentation[b]	11 (22)	14 (28)	0.64
Delivery method and fetal outcome			
Delivery[b]			
Spontaneous vaginal	36 (73.33)	38 (70)	0.88
Forceps	2 (6.7)	2 (3.33)	
Cesarean section	12 (20)	10 (26.7)	
APGAR score[b]			
1 minute (<7)	5 (3.3)	4 (10)	1.00
5 minute (<7)	0 (0)	0 (0)	
Meconium passage[b]	15 (30)	9 (18)	0.24
Birth weight (grams)[a]	3005 + 372	2940 + 503	0.73
NICU admissions[b]	7 (14)	8 (16)	1.00
Uterine contraction abnormalities[b]	2 (4)	3 (6)	
Uterine tachysystole	1 (2)	3 (10)	0.60
Hypertonus	0 (0)	0 (0)	
Uterine hyperstimulation syndrome	1 (2)	0 (0)	
Abnormal cardiotocograph[b]	8 (16)	4 (8)	0.35
Postpartum hemorrhage[b]	2 (4)	3 (6)	1.00
Atonic	0 (0)	1 (2)	
Traumatic	2 (4)	2 (4)	
Maternal death	1 (2)	0 (0)	

[a]Student's t-test, [b]Chi-square test, [c]Mann-Whitney U test

There was no difference in the overall caesarean delivery rates and caesarean rate for abnormal FHR pattern in the two groups. Has R et al. (18) reported an increase in caesarean section rate in the 50 μg group. However, Elhassan et al. (19) showed an increase in caesarean section rate in the 25 μg group. There was no significant difference in incidence of meconium passage among the groups with is consistent which other investigators (13, 18, 21). The reason for meconium passage is usually attributed to fetal hypoxemia as a result of excessive uterine contractions caused by a high dose of misoprostol. However, in the current series there was no significant difference in occurrence of uterine tachysystole among regimens, although some investigators have demonstrated an increased incidence of uterine contraction abnormalities in the 50 μg groups (3, 5, 18, 21). The high incidence of hyperstimulation in Dairo et al's (5) study is possibly due to higher doses (four doses) of misoprostol received by most women.

In the current series the incidence of traumatic postpartum haemorrhage was similar among groups. However, El-Sherbiny et al. (3) reported significantly increased incidence of atonic postpartum haemorrhage in the 50 μg group (9.78 vs 2.15% P<0.05). When looking at the data of traumatic postpartum haemorrhage, we cannot ignore the potential direct local effect of misoprostol on the genital tract (23). Further studies are needed to explore this concept to reduce side effects and to increase the safety profile. One maternal death in a 50 μg regimen cannot be directly attributable to misoprostol.

Body mass index (BMI) is an important maternal characteristic that can influence the dose response to vaginal misoprostol. Obese women might be expected to require higher doses or

Table 3. Induction delivery interval according to number of doses of misoprostol in 25 μg group

Induction delivery interval	Dose of misoprostol (25 μg)			
	Single dose	Two doses	Three doses	P value
≤ 24 h (n)	17	14	3	0.0022
> 24 h (n)	0	1	3	
Total	17	15	6	

Table 4. Indications for cesarean delivery

Indications[b]	25 μg (N=50)	50 μg (N=50)	P-value
Fetal distress	3	2	0.22
Non progress of labour	1	5	
Cervical dystocia	1	1	
Failed induction	1	0	
Abnormal FHR patterns	6	2	

[b]Chi-square test

more frequent applications, while women with a low BMI may require lower doses. Although mean BMI among groups were comparable in the current series, the overall mean BMI is much less (22 vs 32) in Indian women when compared with Western women (24).

The main strength of the study was that it was a prospective randomised controlled trial in which all the data of recruited participants could be analysed and both study groups received comparable care. However, the limitation associated with the current trial is small sample size which is prone to type II errors. Another limitation was that this trial was not masked and the outcome assessors were not blinded. Hence the possibility of inadvertent bias cannot be excluded. Although this trial is limited by the small number, it adds to the current body of literature available from different settings (rural), ethnicity and country. The safety of misoprostol cannot be established with this trial.

Induction of labour is a common obstetric intervention and the use of misoprostol as an induction agent is important due to its low cost and stability at room temperature. These additional advantages make it a suitable agent, particularly in under-resourced settings and tropical countries. Due to frequent electricity failure, it is not always possible to guarantee the potency of the widely used dinoprostone gel in developing countries. Moreover, the low dose misoprostol regimes were found to have similar efficacy to dinoprostone gel for labour induction (25).

In the Cochrane systematic review (1), vaginal misoprostol (25 μg three hourly or more), was found to be more effective than conventional methods of cervical ripening and labour induction. However, uterine hyperstimulation with fetal heart rate changes were increased. Thus, although misoprostol shows promise as a highly effective, inexpensive and convenient agent for labour induction, the lack of registration for this purpose is problematic in many countries.

Logistical problems like difficulty in cutting the tablet accurately and legal liabilities need to be addressed. In the light of available data and our findings, we suggest that clinical heterogeneity should be eliminated in future labour induction trials with vaginal misoprostol.

Conclusion

Our data indicates that there was no difference regarding the clinical efficacy between two labour induction regimens of vaginal misoprostol. However, large randomised trials on low dose and single dose regimes of misoprostol for labour induction are needed to get reliable data on the safety profile and rare events such as uterine rupture and maternal mortality.

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References

1. Hofmeyr GJ, Gulmezoglu AM. Vaginal misoprostol for cervical ripening and induction of labour. The Cochrane Database Syst Rev. 2003;CD000941. DOI:10.1002/14651858.CD000941.
2. Sanchez-Ramos L, Kaunitz AM. Misoprostol for cervical ripening and labour induction: a systematic review of the literature. Clin Obstet Gynecol 2000; 43: 475-88.
3. El-Sherbiny MT, El-Gharieb, Gewely HA. Vaginal misoprostol for induction of labour: 25 vs. 50 g dose regimen. Int J Gynecol Obstet 2001; 72: 25-30.
4. Sanchez-Ramos L, Kaunitz AM, Wears RL, Delke I, Gaudier FL. Misoprostol for cervical ripening and labour induction: a meta-analysis. Obstet Gynecol 1997; 89: 633-42.
5. Diro M, Adra A, Gilles JM, Nassar A, Rodriguez A, Salamat SM, Beydoun SN, O'Sullivan JM, Yasin SY, Burkett G. A double-blinded randomized trial of two dose regimens of misoprostol for cervical ripening and labour induction. J Matern Fetal Med 1999; 8: 114-8.
6. Srisomboon J, Singchai S. A comparison between 25 micrograms and 50 micrograms of intravaginal misoprostol for labour induction. J Med Assoc Thai 1998; 81: 779-83.
7. Wing DA, Paul RH. A comparison of differing dosing regimens of vaginally administered misoprostol for preinduction cervical ripening and labour induction. Am J Obstet Gynecol 1996; 175: 158-64.
8. ACOG committee opinion. New US Food and drug administration labeling of cytotec (misoprostol) use in pregnancy. Int J Gynecol Obstet 2003; 82: 137-8.
9. Weeks A, Alfirevic Z, Faundes A, Hofmeyr GJ, Safar P, Wing D. Misoprostol for induction of labour with a live fetus. Int J Gynecol Obstet 2007; 99(supp 2): S194-7.
10. International Federation of Gynecology and Obstetrics (FIGO). Guidelines for the use of fetal monitoring. Int J Gynecol Obstet 1987; 25: 159-67.
11. Curtis P, Evans S, Resnick J. Uterine hyperstimulation. The need for standard terminology. J Reprod Med 1987; 32: 91-5.
12. Meydanli MM, Çalışkan E, Haberal A. Prediction of adverse outcome associated with vaginal misoprostol for labour induction. Eur J Obstet Gynecol 2003; 110: 143-8.

13. Meydanli MM, Caliskan E, Burak F, Narin MA, Atmaca R. Labour induction post term with 25 micrograms vs. 50 micrograms of intravaginal misoprostol. Int J Gynecol Obstet 2003; 81: 249-55.
14. Krishnamma BS, Sundari A, Naidu IS. Evaluation of a new drug - Misoprostol for induction of labour. J Obstet Gynecol Ind 2002; 52: 64-6.
15. Sureka R, Lavanya R, Urala MS. Single dose misoprostol for induction of labour. Ob Gyn Today 2001; 6: 95-7.
16. Margulies M, Campos-Perez G, Voto LS. Misoprostol to induce labour [letter]. Lancet 1992; 339: 64.
17. Lokugamage AU, Forsyth SF, Sullivan KR, Refaey HE, Rodeck CH. Randomized trial in multiparous patients: investigating a single vs. two-dose regimen of intravaginal misoprostol for induction of labour. Acta Obstet Gynecol Scand 2003; 82: 138-42.
18. Has R, Batukan C, Ermis H, Cevher E, Araman A, Kilic G, Ibrahimoglu L. Comparison of 25 and 50 microgram vaginally administered misoprostol for preinduction of cervical ripening and labour induction. Gynecol Obstet Invest. 2002; 53: 16-21.
19. Elhassan EM, Mirghani, Adam I. Cervical ripening and labour induction with 25 μg vs. 50 μg of intravaginal misoprostol. Int J Gynecol Obstet 2005; 90: 234-5.
20. Farah LA, Sanchez-Ramos L, Rosa C, Del Valle GO, Gaudier FL, Delke I, et al. Randomized trial of two doses of the prostaglandin E1 analog misoprostol for labour induction. Am J Obstet Gynecol 1997; 177: 364-9.
21. Ding DC, Hsu TS, Su HY. Low dose intravaginal misoprostol for induction of labour at term. Int J Gynecol Obstet 2005; 90: 72-3.
22. Sanchez-Ramos, Kaunitz AM, Delke I. Labour induction with 25 versus 50 μg intravaginal misoprostol: A systematic review. Obstet Gynecol 2002; 99: 145-51.
23. Danielsson KG, 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: 275-80.
24. Wing DA, Tran S, Paul RH. Factors affecting the likelihood of successful induction after intravaginal misoprostol application for cervical ripening and labor induction. Am J Obstet Gynecol 2002; 186; 1237-40.
25. Gregson S, Waterstone M, Norman I, Murrells T. A randomised controlled trial comparing low dose vaginal misoprostol and dinoprostone vaginal gel for inducing labour at term. BJOG 2005; 112: 438-44.