

Misoprostol Efficacy in Second and Third Trimester Pregnancy Terminations

Yıldız Uyar, Sultan Buğday, Serçin Ordu, Yeşim Baytur

Celal Bayar Üniversitesi Tıp Fakültesi, Kadın Hastalıkları ve Doğum, Manisa

Abstract

Objective: Retrospective analysis and evaluating reliability and efficiency of misoprostol in 87 cases having pregnancy termination by using vaginal misoprostol between 12 and 35 weeks' gestation.

Methods: The present study was conducted at Celal Bayar University, Gynecology and Obstetrics Clinic, Perinatology unit between January 2006 and November 2008. A total of 87 cases at more than 12 weeks gestation, including 8 cases having uterine scars due to previous cesarean section and 79 cases having no previous uterine surgery, underwent pregnancy termination and were retrospectively analyzed. In all the cases, the induction agent administered was vaginal misoprostol. In cases having previous cesarean delivery, following the initial dose of 200 µg between 12-24 weeks' gestation and 100 µg at more than 24 weeks', misoprostol was administered 200 µg every 4 hours for a period of 24 hours until contractions started. In cases having no uterine scar, following the initial dose of 400 µg between 12-24 weeks' and 200 µg after 24 weeks', misoprostol was added 400 µg and 200 µg every 4 hours for a period of 24 hours, respectively. If needed, the same dose scheme was repeated after a 12 hours resting period and, in case of failure, an additional method was used.

Results: 53 cases (60.9%) were nulliparous and 34 cases (39.1%) were multiparous. 49 out of 87 (56%) cases were between 12 and 20 weeks' gestation, while 38 (44%) cases were at more than 20 weeks' gestation. The median induction-to-termination interval which was 28.5 h (1-137 h) for all the cases was 30.8 h in nulliparous cases and 24.8 h in multiparous cases, and no statistically significant difference was detected ($p=0.32$). In 16 cases duration of pregnancy termination was over 48 h. In 10 cases (11.5%) pregnancy termination was achieved by using an additional method. Compared to the cases having no uterine scar, additional methods were used significantly more in cases having previous cesarean delivery (25% versus 10%; $p=0.000$). 2 cases developed complications (23%): fever and hemorrhage in one case and hemorrhage in one case. 1 case underwent cesarean section due to hemorrhage. No uterine rupture was observed in the cases.

Conclusion: Using vaginal misoprostol is a fairly safe, efficient and non-invasive method in second and third trimester pregnancy termination. However, studies with wider series are needed to assess reliability of using misoprostol in cases with uterine scarring.

Keywords: Misoprostol, Termination of pregnancy, Induction, Second and third trimester.

İkinci ve üçüncü trimestr gebelik sonlandırmalarında misoprostol etkinliği

Amaç: 12-35. gebelik haftaları arasında vajinal misoprostol kullanılarak sonlandırma yapılan 87 olgunun retrospektif analizi ve 2. ve 3. trimestr gebelik sonlandırmalarında misoprostol kullanımının güvenilirlik ve etkinliğinin değerlendirilmesi

Yöntem: Bu çalışmaya Ocak 2006 ve Kasım 2008 tarihleri arasında Celal Bayar Üniversitesi Kadın Hastalıkları ve Doğum Kliniği Perinatoloji polikliniğine başvuran ve 12 haftanın üzerinde gebeliği sonlandırılan toplam 87 olgu dahil edildi. Sezaryan nedeniyle uterus ta skarı olan 8 olgu ve geçirilmiş uterus cerrahisi olmayan 79 olgunun retrospektif analizi yapıldı. Tüm olgulara indüksiyon ajanı olarak vajinal misoprostol uygulandı. Sezaryan geçirmiş olgularda kontraksiyonlar başlayana kadar 12-24. haftalar arasında 200 µg, 24. haftadan sonra 100 µg misoprostol başlangıç dozunu takiben her 4 saatte bir 200 µg eklenerek 24 saat bitimine kadar devam edildi. Uterusta skarı olmayan olgularda ise 12-24. haftalar arasında 400 µg başlangıç dozu sonrası her 4 saatte bir 400 µg, 24. hafta

dan sonra 200 µg başlangıç dozunu takiben her 4 saatte bir 200 µg uygulandı. 24 saat bitiminde kontraksiyonların başlamaması durumunda 12 saatlik dinlenme periyodunu takiben aynı doz şeması tekrarlandı, gerekirse başka bir yöntem de eklendi.

Bulgular: 53 vaka (%60.9) nullipar, 34 vaka (%39.1) multipardı. 49 (%56) olgu 12-20. gebelik haftaları arasında, 38 (%44) olgu 20. gebelik haftasının üstündeydi. İndüksiyon başlangıcı ile gebeliğin sonlanması arasında geçen ortalama süre tüm vakalar için 28.5 saat (1-137 saat), nulliplarlarda 30.8 saat, multiparlarda ise 24.8 saat idi, istatistiksel anlamlı farklılık saptanmadı ($p=0.32$). 16 vakada (%18) gebeliğin sonlanma süresi 48 saatin üstündeydi. 10 vakada (%11.5) sonlandırmanın tamamlanması için ek bir yöntem kullanımı gerekti. Sezaryan geçirmiş olgularda ek yöntem kullanımı uterusu skarı olmayan olgulara göre anlamlı yüksekti (sırasıyla % 25, % 10; $p=0.000$). 1 olguda ateş ve kanama, 1 olguda ise kanama olmak üzere 2 olguda komplikasyon gelişti (%2.3), her 2 olguda nullipardı. Kanama nedeniyle 1 olguya sezaryan sekişyo yapıldı. Uterus rüptürü hiçbir vakada görülmedi.

Sonuç: Vaginal misoprostol kullanımı ikinci ve üçüncü trimester gebelik terminasyonu için oldukça etkili, güvenli ve non-invaziv bir yöntemdir. Ancak uterusu skarı olan olgular için güvenilirliği açısından daha geniş serili çalışmalar gereklidir.

Anahtar Sözcükler: Misoprostol, Gebelik terminasyonu, İndüksiyon, İkinci ve üçüncü trimester.

Introduction

In recent years, prostaglandins and its analogs have been widely used for medical abortion in obstetrics practice. Today, increasing antenatal diagnosis of fetal malformations with prenatal ultrasonography and serum screening tests¹ and labor induction in 15% of all pregnancies² increase use of prostaglandin for this purpose. Also, increasing number of cesarean deliveries³ and pregnancy termination due to medical indications increase use of prostaglandin analogs in patients with a history of previous cesarean. Pregnancy termination by using prostaglandins and its analogs provide a safe alternative to surgical termination.⁴ Misoprostol is a synthetic prostaglandin E1 analog used in prophylaxis and treatment of gastroduodenal ulcers, and its usage in pregnancy is contraindicated due to its uterotonic effect.⁵ Basic aims in the second and third-trimester pregnancy terminations are achieving a safe, effective, inexpensive and fast termination with minimum adverse effects. Owing to these, using misoprostol for induction is very common although it is not licensed in many countries.⁶ Misoprostol is a cheap drug that does not require special transfer and storage conditions as other prostaglandin analogs used previously.

It can be administered orally and causes less gastrointestinal adverse effects. Recently, it has been used to induce labor in live term fetuses too.⁷ However, more uterine tachysystole⁸ and uterine rupture when administered vaginally in the second trimester pregnancy terminations in women having a history of cesarean section⁹ prevent elimination of concerns about this drug. Although there are increasing number of publications demonstrating that misoprostol is safe in the second trimester pregnancy termination in cases having uterine lower segment transverse incision,¹⁰ real incidence of uterine rupture is not known. In this retrospective study, our aim was to evaluate the safety and efficacy of using intravaginal misoprostol in inducing of the second and third trimester pregnancy terminations.

Methods

In the present study, retrospective analysis were performed on 87 cases whose pregnancies were terminated by vaginal misoprostol at more than 12 weeks gestation due to maternal or fetal indications at Celal Bayar University Gynecology and Obstetrics Clinic Perinatology Unit between January 2006 and November

2008. Parity, gestation week, obstetric history, presence of uterine scar, requirement of additional method, indications, induction-to-termination interval and delivery complications were recorded for all the cases. After getting the approval of Celal Bayar University, Medical Faculty, Perinatology Committee for termination of pregnancies, all the patients were informed on the issue that misoprostol is not licensed for pregnancy terminations and asked to sign an informed consent form that includes detailed information on complications.

Vaginal misoprostol protocol to be used for termination was determined according to the gestational week and presence of uterine scar. 1x200 µg misoprostol was placed in the posterior vaginal fornix in pregnancies having uterine scar due to previous cesarean section while 2x200 µg misoprostol was used in cases having no uterine scar at less than 24 weeks gestation. During the first 24 hours following the initial dose, vaginal misoprostol administration at initial dose was repeated every 4 hours until uterine contractions started. Before misoprostol administration at more than 24 weeks gestation in pregnancies with live fetuses, fetocide was performed by intracardiac lethal dose potassium chloride administration under ultrasonographic guidance. Then, 1x100 µg and 1x200 µg vaginal misoprostol was started in cases having uterine scar and cases without uterine scar, respectively. When contractions did not start, 1x200 µg misoprostol was administered every 4 hours. If contractions did not start at the end of the first 24 hours, dose scheme appropriate to the characteristics of the cases in both groups were repeated the same way after a 12 hours rest period. When

pregnancy termination was not completed after 48 hours following the initial misoprostol administration, an additional method was used. Additional methods included using oxytocin, foley catheter in cervical channel and traction or termination of pregnancy by cesarean section. Epidural analgesia was used for pain management when requested by the cases.

Following vaginal misoprostol administration, vital signs and adverse effects observed in the cases were recorded every 4 hours. In cases having fever was equal to or more than 38.5 C, 1 gr paracetamol and, if needed, cold compress were used. When required, 10 mg metoclopramide or 50 mg cyclizine were administered as antiemetic agents every 8 hours. While induction-to-termination interval was defined as the time that elapsed from the initial misoprostol administration until fetal expulsion, the need to use an additional method for termination was defined as failure of misoprostol. 1 hour was allowed for placenta removal after fetal expulsion. Patient was examined carefully by ultrasonography to see whether complete removal of fetus and placenta was achieved. When incomplete termination was suspected or findings of rest placenta were present, surgical evacuation of the uterus was planned, and all the cases were followed for bleeding control at delivery service for 2 hours. All women were called for controls 1 month after termination.

All the data obtained from the cases were evaluated using SPSS (15.0 for Windows) program. In statistical evaluations Mann-Whitney U test was used for continuous variables and chi-square test was used for categorical vari-

Table 1. Characteristics of the study group.

	Nulliparous (n=53)	Multiparous (n=34)	Total (n=87)
Mean maternal age (\pmSD)	25.33 (\pm 4.62)	31.16 (\pm 5.1)	27.6 (\pm 5.5)
Gestational age at termination (\pmSD)	18.77 (\pm 5.34)	20.81 (\pm 6.83)	19.74 (\pm 5.65)
Pregnancy ?24 weeks' gestation (%)	14 (26.4)	18 (53)	32/87 (37)

Table 2. Indications for termination.

Indication	n	(%)
Trisomy 21	3	(3.5)
Chromosomal abnormalities other than trisomy 21	2	(2.3)
IUMF	10	(11.5)
Anhydramnios	9	(10.3)
Maternal disease	3	(3.5)
Other congenital abnormalities	53	(60.8)
Hydrops fetalis	4	(4.6)
Teratogen	1	(1.2)
Twin-to-twin transfusion syndrome	2	(2.3)

ables. $P < 0.05$ was considered as statistically significant.

Results

In this study, results obtained from 87 women having termination between 12 and 35 weeks' gestation in a 3 years period were analyzed. Table 1 shows the characteristics of the women who underwent vaginal misoprostol induced termination at the second and third trimesters and Table 2 shows termination indications.

53 cases (60.9%) were nulliparous and 34 cases (39.1%) were multiparous. While no significant difference was observed between nulliparous and multiparous cases with respect to induction-to-termination interval ($p=0.32$), required total misoprostol dose was significantly higher in nulliparous women ($p=0.019$). Treatment results are given in Table 3. In 49% of

the cases, termination was achieved in the first 24 hours. While the ratio of nulliparous women terminating within 24 hours after misoprostol administration was 52%, the ratio of multiparous women terminating within 24 hours was 44%. Pregnancy was terminated within 36 hours in 63% of the cases while termination was achieved within 48 hours in 70% of the cases. All the terminations were completed in 4 days. Only in one case, termination was not achieved despite using an additional method to misoprostol induction, and cesarean section was used for delivery. In the said case having in utero mort fetus at 17 weeks' gestation, termination was tried to be achieved vaginally using other also additional methods due to bleeding, but upon failure, cesarean decision was taken after 55 hours.

In 90.8% of the cases ($n=79$), there was no uterine surgery history while 9.2% had previous

Table 3. Treatment results of women having termination by misoprostol during the second and third trimester.

	Mean dose of misoprostol (μ g)	Mean induction-to-abortion time (hours)
Nulliparous (n=53)	1200 (\pm 802.6)	30.8 (\pm 21.6)
Multiparous (n=34)	800 (\pm 702.2)	24.8 (\pm 28.35)
Total (n=87)	1035 (\pm 783.44)	28.5 (\pm 24.32)
P	0.019	0.32

Table 4. Complication rates and abort intervals in pregnant women having an abortion between 12 and 24 and > 24 weeks' gestation.

	12-24 weeks' gestation (n=55)	>24 weeks' gestation (n=32)
Mean induction-to-abortion interval (hours) (\pmSD)	27.7 (\pm 24.6)	31.3 (\pm 24.6)
Misoprostol failure (%)	1 (%1.8)	0
Fever (%)	1 (%1.8)	0
Hemorrhage (%)	1 (%1.8)	0
Using additional method (%)	8 (%14.5)	2 (%6.3)

cesarean section. 3 cases out of those having previous cesarean section were at more than 24 weeks' gestation. Additional methods were required in 11.5% (n=10) of all the cases. 7 of the cases requiring additional methods were nulliparous, 3 were multiparous and there were two previous cesarean section cases among them. Both of these 2 cases having previous cesarean section and in whom additional methods were used for pregnancy termination were at more than 24 weeks' gestation; and foley catheter was inserted in cervical channel in 1 of them being at 28 weeks' gestation. The other case was at 34 weeks' gestation and her pregnancy was terminated using oxytocin additionally. Additional method was used when termination was not achieved when 48 hours elapsed after vaginal misoprostol administration and beginning of induction. Only in one case, additional method was used before 24 hours due to bleeding and oxytocin was added for termination in this case. Surgical evacuation

of uterus due to placental retention was needed in none of the cases.

Mean induction-to-termination interval was 31.3 hours in cases at more than 24 weeks' gestation while the said interval was 27.7 hours in those at less than 24 weeks' gestation; and there was no significant difference ($p=0.62$). In 2 cases at more than 24 weeks' gestation, termination was achieved by using an additional method; however no complications developed in these cases. Among all patients, complications after induction by misoprostol were observed in 2 cases. One case had hemorrhage while the other had both fever and hemorrhage. Both of these cases were at less than 24 weeks' gestation and nulliparous. Pregnancy was terminated by cesarean section in one of these cases while oxytocin was used for termination in the other case. Table 4 shows a comparison of cases at more than 24 weeks' and less than 24 weeks' gestation with regard to induction-to-termination intervals and complication rates.

Discussion

Misoprostol has been widely used in induction of pregnancy terminations during the second and third trimesters.⁶ However, there exist a great range of variation in its administration route, frequency and dose. Misoprostol providing a noninvasive regimen for termination of pregnancy offers many advantages such as oral, rectal, sublingual or vaginal administration, low cost, stability at room temperature; and different doses of misoprostol have been shown to be effective.¹¹ However, effective minimum dose, either orally or vaginally, for labor induction or pregnancy termination with minimum adverse effects both for fetus and mother in case of presence of a live fetus should be evaluated in further studies.^{7,12} There exist no standard regimen scheme neither for induction of labor in the third trimester nor for pregnancy termination in the second and third trimesters.

Pregnancies were terminated by vaginal misoprostol induction in 88.5% of our cases; however, in 11.5% of the cases an additional method was required along with misoprostol. Chawdhary et al.¹³ compared mifepristone oral followed by vaginal misoprostol (RU 486) with misoprostol alone for pregnancy terminations during first trimester and found that mifepristone oral followed by vaginal misoprostol provides a better success rate with fewer complications. They reported a success rate of 94% with combined mifepristone and vaginal misoprostol and 86% with only vaginal misoprostol. However, they stated that misoprostol alone was not as successful as combined regimen due to some limitations of their study. In a retrospective analysis of 252 cases, Mazouni et al.¹⁴ showed a 99.2% success by combined vaginal misoprostol and mifepristone administration in

pregnancy terminations at more than 15 weeks' gestation. In a study where they used a combination of misoprostol and mifepristone, Tang et al.¹⁵ showed that sublingual administration was more effective than oral administration. In another study where they used only misoprostol,¹⁶ they reported a success rate of 95% in vaginal administration and 91% success rate in sublingual administration after 48 hours. Similarly, in a retrospective study, Goh et al.¹⁷ achieved termination of pregnancy at between 12 and 24 weeks' gestation by vaginal misoprostol with later addition of mifepristone, if required, and reported that termination was completed 97.9% and 99.5% after 24 and 36 hours from the beginning of termination respectively. Mifepristone is an antagonist of progesterone receptor and it has been shown that using mifepristone before analogue in second trimester pregnancy terminations with prostaglandin analogue decreases the time that elapses from the initial administration of prostaglandin until fetus expulsion.¹⁸ This antigestagen sensitizes the pregnant uterus to exogenous prostaglandin. However, misoprostol is more commonly used in developing countries as it is cheap and requires no special storage conditions compared to mifepristone which is an expensive and requires special storage conditions. Bhattacharjee et al.¹⁹ compared sublingual and vaginal administration of misoprostol in second trimester pregnancy terminations and found that both of the methods were equally effective. The failure rate was 9.42% after 48 hours in vaginal administration, which is consistent with the results (9.5%) of Wong et al.²⁰ but higher than the rate (5%) reported by Tang et al.¹⁶ While misoprostol was initially administered orally, today vaginal administration is preferred. Pharmacokinetic studies showing that systemic bioavailability of vaginally

administered misoprostol is three times higher than that of misoprostol administered orally supports its vaginal administration.²¹ Behrashi et al.²² compared oral and vaginal misoprostol administration in second trimester pregnancy terminations and found that vaginal administration of misoprostol resulted in a higher success rate with no significant differences in induction to delivery time and complications rates between vaginal and oral administration. By vaginal administration of misoprostol, in our study, we obtained a success rate of 85% in pregnancies at less than 24 weeks and 93.7% in those at more than 24 weeks, which makes a total success rate of 88.5%. In our study, termination was achieved within 48 hours in 70% of the cases. Except one case, all the pregnancies were terminated in 96 hours. Our results are not as high as those of the clinic studies reporting very high success rates; however, when compared to that of Tang et al.,¹⁶ we used lower doses of misoprostol and observed fewer complications. Tang et al.¹⁶ found that incidence of fever increased significantly in vaginal administration and there existed no significant difference between sublingual and vaginal administration with respect to other complications. They reported that this could have resulted from the higher bioavailability of repeated vaginal misoprostol. As a result, Tang et al. stated that vaginal misoprostol should be the first choice but sublingual administration could be used as an alternative. In our study, we observed fever in 1 case and hemorrhage in 2 cases. Compared to multiparous women, the total misoprostol dose used for termination was significantly higher in nulliparous women and although there was no statistically significant difference with respect to mean induction-to-termination interval between nulliparous and multiparous

women, it was longer in nulliparous women. These results are consistent with the results of the previous studies reporting a difference between responses of nulliparous and multiparous women to induction agents.^{17,23} Goh et al.¹⁷ stated that this could be resulted from the difference between cervical compliances of two groups. Goh et al. reported that, compared to nulliparous women, surgical evacuation of uterus was twice more in multiparous women and stated that the same result had been obtained in some previous studies too. Goh et al. completed termination surgically if bleeding was more than 500 ml during fetus or placenta removal. Bartley et al.²⁴ stated that more efficient establishment of pregnancy in multiparous women might cause this. 37% of our cases were at more than 24 weeks' gestation, and mean induction-to-termination interval was moderately longer in these cases. Mozouni et al.¹⁴ showed in their analysis that when terminations were achieved by misoprostol and mifepristone, pregnancies at more than 24 weeks' gestation were associated with longer induction interval and higher morbidity. However, with respect to morbidity in pregnancies at more than 24 weeks' gestation, results of our study differ from that of Mazouni et al. 8 of the 10 cases requiring additional method for termination were at less than 24 weeks' gestation and similarly 2 cases having complications were at less than 24 weeks' gestation too. However, compared to our study, Mazouni et al.¹⁴ studied significantly more cases in their analysis.

Today, clinicians do not use a standard protocol in using misoprostol for pregnancy terminations. There is no consensus with respect to the administration way, dose and frequency

as there is a few number of well planned randomized controlled trials on this subject. It has been found that vaginal administration is more effective than oral administration, possibly because of accumulation at plasma levels and causes less gastrointestinal complications.^{21,25} However, there is a variability in the absorption of vaginally administered misoprostol among different individuals. For this reason, sublingual administration is favored; there may be variability in the absorption among different individuals but it has been reported that it reaches high serum peak concentrations by rapid absorption.²⁶ Tang et al.¹⁶ reported in their study that patients prefer sublingual administration.

In pregnancies at more than 12 weeks' gestation, pregnancy terminations are carried out by medical methods rather than surgical procedures. Morbidity is lower in termination achieved by medical methods,⁴ and genetic analysis of fetus is possible. Adverse effects of prostaglandins are related mainly dose. However, various administration methods, dose schemes and intervals related to misoprostol make it hard to compare data. In our study, complications were observed in only 2 cases and both of these cases were nulliparous. Requirement of higher misoprostol dose in nulliparous women may lead to this result. Sanches-Ramos et al.^{9,27} showed in a study and meta-analysis that use of misoprostol increases risk of tachysystole and hyperstimulation without causing negative perinatal outcomes. Dodd et al.⁶ found that use of misoprostol causes adverse effects at a low rate in the second and third trimester pregnancies; however, they showed that data were not sufficient to evaluate rare but life threatening complications such as uterine rupture. It has been drawn attention to

the fact that history of cesarean section is not a contraindication for using misoprostol but there exist an increased risk of uterine rupture regardless of the gestational week.⁸ In a retrospective analysis of 91 cases, Aslan et al.²⁸ showed that induction of delivery with misoprostol causes a two fold increased risk of uterine rupture in women with previous cesarean section and they stated that one should be careful with respect to maternal reliability.

In our study we obtained a success rate of 88.5% by misoprostol in second and third trimesters pregnancies and termination was achieved by using an additional method in 11.5% of the cases. Among those where an additional method was used, in only one case, we had to terminate pregnancy by cesarean section due to hemorrhage. Our complication rate (2.3%) was rather low. With respect to failure of misoprostol, although some of which report lower rates,¹⁶ our results are in consistency with many studies in the literature.^{19,20,22} Taking these data into consideration, we can say that misoprostol is highly effective and reliable in second and third trimester pregnancy terminations.

Although number of cases with a history of cesarean section is low in our study, no complications related to misoprostol were observed in these cases. Additional methods were used two times more in terminating pregnancies of cases having history of cesarean section but these additional methods did not increase the risk of complications.

Conclusion

For standard usage of misoprostol in the future, detecting optimal dose and optimal administration method should be the most important concern of the studies. Thus, evalua-

tion of rare complications such as uterine rupture would be more objective and satisfactory. Once optimal dose and intervals are detected, further studies involving larger samples and multiple centers are required.

References

1. Taipale P, Ammala M, Salonen R, Hiilesmaa V. Two-stage ultrasonography in screening for fetal anomalies at 13–14 and 18–22 weeks of gestation. *Acta Obstet Gynecol Scand* 2004; 83: 1141–6.
2. Choy-Hee L, Raynor BD. Misoprostol induction of labor among women with a history of cesarean delivery. *Am J Obstet Gynecol* 2001; 184: 1115–7.
3. Kozak LJ, Weeks JD. US trends in obstetric procedures. 1990–2000. *Birth* 2002; 29: 157–61.
4. Karim SM, Filshie GM. Therapeutic abortion using PGF α 2. *Lancet* 1970; 1: 157–9.
5. Collins PW. Misoprostol: discovery, development, and clinical applications. *Med Res Rev* 1990; 10: 149–72.
6. Dodd JM, Crowther CA. Misoprostol versus cervagem for the induction of labour to terminate pregnancy in the second and third trimester: a systematic review. *Eur J Obstet Gynecol Reprod Biol* 2006; 1: 125: 3–8.
7. Hofmeyr GJ, Gulmezoglu AM. Vaginal misoprostol for cervical ripening and induction of labour. *Cochrane Database Syst Rev* 2003;(1): CD000941.
8. Berghahn L, Christensen D, Droste S. Uterine rupture during second trimester abortion associated with misoprostol. *Obstet Gynecol* 2001; 98: 976–7.
9. Sanches-Ramos L, Kaunitz AM, Wears RL, Delke I, Gaudier FL. Misoprostol for cervical ripening and labor induction: a meta-analysis. *Obstet Gynecol* 1997; 89: 633–42.
10. Pongsatha S, Tongsong T. Misoprostol for second trimester termination of pregnancies with prior low transverse cesarean section. *Int J Gynecol Obstet* 2003; 80: 61–2.
11. Bartley J, Baird DT. A randomised study of misoprostol and gemeprost in combination with mifepristone for induction of abortion in the second trimester of pregnancy. *Br J Obstet Gynaecol* 2002; 109: 1290–4.
12. Alfievic Z, Weeks A. Oral misoprostol for induction of labour. *Cochrane Database Syst Rev* 2006 19; (2): CD001338.
13. Chawdhary R, Rana A, Pradhan N. Mifepristone plus vaginal misoprostol vs vaginal misoprostol alone for medical abortion in gestation 63 days or less in Nepalese women: a quasi-randomized controlled trial. *J Obstet Gynaecol Res* 2009; 35: 78–85.
14. Mazouni C, Provencal M, Porcu G, Guidicelli B, Heckenroth H, Gamarre M et al. Termination of pregnancy in patients with previous cesarean section. *Contraception* 2006; 73(3): 244–8.
15. Tang OS, Chan CC, Kan AS, Ho PC. A prospective randomized comparison of sublingual and oral misoprostol when combined with mifepristone for medical abortion at 12–20 weeks gestation. *Hum Reprod* 2005; 20: 3062–6.
16. Tang OS, Lau WN, Chan CC, Ho PC. A prospective randomised comparison of sublingual and vaginal misoprostol in second trimester termination of pregnancy. *BJOG* 2004; 111: 1001–5.
17. Goh SE, Thong KJ. Induction of second trimester abortion (12–20 weeks) with mifepristone and misoprostol: a review of 386 consecutive cases. *Contraception* 2006; 73: 516–9.
18. Urquhart DR, Templeton AA. The use of mifepristone prior to prostaglandin-induced mid-trimester abortion. *Hum Reprod* 1990; 5: 883–6.
19. Bhattacharjee N, Saha SP, Ghoshroy SC, Bhowmik S, Barui G. A randomised comparative study on sublingual versus vaginal administration of misoprostol for termination of pregnancy between 13 to 20 weeks. *Aust N Z J Obstet Gynaecol* 2008; 48(2): 165–71.
20. Wong KS, Ngai CS, Yeo EL, Tang LC, Ho PC. A comparison of two regimens of intravaginal misoprostol for termination of second trimester pregnancy: a randomized comparative trial. *Hum Reprod* 2000; 15(3): 709–12.
21. Ziemann M, Fong SK, Benowitz NL, Banskter D, Darney PD. Absorption kinetics of misoprostol with oral or vaginal administration. *Obstet Gynecol* 1997; 90: 88–92.
22. Behrashi M, Mahdian M. Vaginal versus oral misoprostol for second-trimester pregnancy termination: a randomized trial. *Pak J Biol Sci* 2008; 11: 2505–8.
23. Thong KJ, Baird DT. Induction of second trimester abortion with mifepristone and gemeprost. *Br J Obstet Gynaecol* 1993; 100: 758–61.
24. Bartley J, Tong S, Everington D, Baird DT. Parity is a major determinant of success rate in medical abortion: a retrospective analysis of 3161 consecutive cases of

- early medical abortion treated with reduced doses of mifepristone and vaginal gemeprost. *Contraception* 2000; 62: 297-303.
25. Ho PC, Ngai SW, Liu KL, Wong GC, Lee SW. Vaginal misoprostol compared with oral misoprostol in termination of second-trimester pregnancy. *Obstet Gynecol* 1997; 90: 735-8.
26. Tang OS, Schweer H, Seyberth HW, Lee SW, Ho PC. Pharmacokinetics of different routes of administration of misoprostol. Pharmacokinetics of different routes of administration of misoprostol. *Hum Reprod* 2002; 17: 332-6.
27. Sanches-Ramos L, Kaunitz AM. Misoprostol for cervical ripening and labor induction: a systematic review of the literature. *Clin Obstet Gynecol* 2000; 43: 475-88.
28. Aslan H, Unlu E, Agar M, Ceylan Y. Uterine rupture associated with misoprostol labor induction in women with previous cesarean delivery. *Eur J Obstet Gynecol Reprod Biol* 2004 15; 113: 45-8.