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# Misoprostol in Labor Induction

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**Abstract**

The efficacy of a new dosing regimen of misoprostol, a recently introduced labor-inducing agent, was studied.

Fifty-eight patients received 50 μg of misoprostol intravaginally and the dose was repeated every 3 hours until uterine contractions begin. Those who had an adequate contraction pattern, defined as three contractions in 10 minutes, were not given the repeat dose. Oxytocin augmentation, but not further misoprostol doses, was used in patients with an inadequate contraction pattern. The maximum total daily dose was 200 μg.

The patients had the mean age of 28.9 ± 5.4, the mean gestational age of 211.8 ± 46.6 days, the mean gravidity of 2.5 ± 1.2, the mean parity of 0.9 ± 0.9 and the mean initial Bishop score of 1.6 ± 1.8. The mean required dose of misoprostol was 120.5 ± 54.7 μg and 10 of 58 patients required oxytocin augmentation. The mean induction of labor to delivery time was 701.5 ± 404.0 minutes. When 3 cases who gave birth with caesarean section were excluded, the interval was 708.4 ± 407.2 minutes. The mean 5th minute Apgar score of the newborns was 8.2 ± 2.5.

Two patients developed tachysystole after the second dose of misoprostol and were managed with vaginal irrigation and $O_2$ supplementation successfully. Slight nausea and vomiting in 2 patients were the other adverse reactions.

Our findings revealed that, 50 μg intravaginal misoprostol, combined with oxytocin augmentation when necessary, appears to be an effective and safe method of labor induction.

**Key words:** misoprostol, labor induction, cervical ripening

## Introduction

It is well-known that when the delivery is indicated, an unripe cervix can cause induction to fail.[1)] In this situation an increase in fetomaternal morbidity and mortality can be observed. Prostaglandins have been used for over 20 years to ripe the cervix and hence to decrease the rate of those adverse outcomes.[2)] The use of prostaglandins gives the advantage of stimulation of myometrial contractility as well. Though prostaglandin $E_2$ gels have been introduced into obstetrics initially, they have the disadvantage of being expensive and an unstable compound requiring refrigeration. Misoprostol, a synthetic prostaglandin $E_1$ ($PGE_1$) analogue, which was initially used in peptic ulcer treatment, is a promising agent in cervical ripening. Besides its beneficial effects in labor induction, it has been reported to cause less third stage blood loss when compared with oxy-

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tocin and ergometrine.[3] However, there is no agreement on its dosing regimens and route of application yet. This investigation was undertaken in an attempt to contribute to the discussion on its usage in labor induction.

## Materials and Methods

Fifty-eight patients, who were not in labor at the admission to Uludag University Medical Faculty, Department of Obstetrics and Gynaecology between January 1st; 1997 and June 30th; 1999 were included in the study. Inclusion criteria were: (1) singleton gestations, (2) cephalic presentation, (3) Bishop score ≤ 4 and (5) reactive nonstress test pattern. Exclusion criteria were: (1) abnormal fetal heart rate patterns, (2) malpresentation, (3) ultrasonographically estimated fetal weight > 4,000 or other evidence of cephalopelvic disproportion, (4) placenta previa or unexplained vaginal bleeding, (5) any contraindication to receiving prostaglandins, including history of asthma, glaucoma or preexisting cardiac or cardiovascular disease, (6) renal or hepatic dysfunction and (7) parity greater than 5.

The participants of this study were informed about the treatment and gave written consent. Fifty micrograms of misoprostol tablet was placed in the posterior vaginal fornix and the dose was repeated every 3 hours till the irregular or regular uterine contractions were achieved. Maximum daily dose was of 200 μg. Those who had an adequate contraction pattern, defined as three contractions in 10 minutes, were not given the repeat dose and the labor was followed up. Patients with inadequate contraction pattern at any misoprostol dose or no uterine contractions despite the total daily dose had been given, were decided to have i.v. oxytocin infusion starting with 4 mU/minute. Oxytocin dose was increased 4 mU/minute at 30 minute intervals till the achievement of adequate uterine contractions or to a maximum of 40 mU/minute.[4]

During these procedures excessive cervical manipulations were avoided to prevent the release of endogenous prostaglandins. Artificial rupture of the membranes was performed when the cervix is dilated 4 cm.

Continuous electronic fetal heart rate and uterine activity monitoring was performed with Sonicaid Team-System Central and fetal heart rate pattern was evaluated by Axis System 8002 software in each patient, by the application of the first misoprostol dose till delivery.

Tachysystole was defined as at least six contractions in 10 minutes for two consecutive 10 minute periods. Hypertonus was defined as a single contraction with a duration of at least 2 minutes. Hyperstimulation syndrome was defined as the presence of tachysystole or hypertonus associated with an abnormal fetal heart rate pattern.[3] When tachysystole and hypertonus developed, vagina was irrigated with 250 ml 0.9% NaCl and oxygen supplementation with nasal catheter in left lateral position was given.

## Results

Delivery indications of the patients are listed in Table 1. They had the mean age of 28.9 ± 5.4, the mean gestational age of 211.8 ± 46.6 days, the mean gravidity of 2.5 ± 1.2, the mean parity of 0.9 ± 0.9 and the mean initial Bishop score of 1.6 ± 1.8. The mean required dose of misoprostol was 120.5 ± 54.7 μg and 10 of 58 patients required oxytocin augmentation. The mean induction of labor to delivery time was 701.5 ± 404.0 minutes. When 3 cases who gave birth with caesarean sec-

**Table 1.** Delivery indications of the patients

| | *n* |
|---|---|
| Fetal anomaly | 10 |
| Isoimmunization | 3 |
| Premature rupture of the membranes | 7 |
| Intrauterine fetal death | 16 |
| Preeclampsia | 15 |
| Oligohydramnios | 7 |
| Total | 58 |

**Table 2.** Delivery parameters of the 3 caesarean section cases

| Case | GA (days) | Induction indication | Caesarean indication | DOI (hr) | TMD (μg) | Birth weight (g) | AS |
|---|---|---|---|---|---|---|---|
| I | 292 | Oligohydramnios | Acute fetal distress | 8 | 100 | 3,800 | 9 |
| II | 288 | Oligohydramnios | Acute fetal distress | — | 100 | 3,770 | 9 |
| III | 252 | Preeclampsia | Umbilical cord prolapsus | — | 100 | 3,000 | 9 |

GA: gestational age, DOI: duration of oxytocin infusion, TMD: total misoprostol dose, AS: 5th minute Apgar score

tion were excluded, the interval was 708.4 ± 407.2 minutes (Table 2). The mean 5th minute Apgar score of those newborns was 8.2 ± 2.5.

Two patients developed tachysystole 30 and 40 minutes after the second dose of misoprostol. Remnants of the dose were irrigated immediately from the vagina with concomitant oxygen supplementation. Uterine tachysystole was relieved completely within 30 minutes in both cases and there was no abnormality in fetal monitoring during that time. Slight nausea and vomiting were the other adverse reactions and aroused in 2 patients.

## Discussion

Misoprostol, a synthetic $PGE_1$ analogue has been used in peptic ulcer treatment as a cytoprotective agent. However, since Rabe *et al.* have emphasised the uterine contractile activity of misoprostol in 1987, many authors have concentrated on its primary usage in obstetrics.[5] In 1987, Mariani-Neto *et al.* in Brazil presented the first report of misoprostol usage in labor induction.[6] Because it was in tablet form and used orally in gastroenterology, initial route of application in obstetrics was per os, too. However intravaginal application was theoretically more advantageous than oral route, since the physician could have the chance to remove the unabsorbed tablets when any adverse reactions developed.

There are many studies about misoprostol usage vaginally. The literature review on misoprostol reveals the importance of dosing regimens. It seems that when each dose is decreased from 50 to 25 μg, even if the dose is repeated more frequently, both initiation of induction to delivery time (620–800 minutes vs 960–1405 minutes) and need for oxytocin due to arrest of dilation or inability to achieve adequate contractions (22–34 vs 42–46%) increase.[4,7–12] However no matter 25 or 50 μg in each dose is used, the mean amount of total dose requirement for delivery is almost 150–200 μg.[4,10–12]

There are many conflicting results about misoprostol induced abnormal uterine response. Though some authors have observed no tachysystole, hypertonus or hyperstimulation with 100 μg dose, which was given with 12 hr intervals to a maximum of 400 μg, most of the reports show that as the dose increases from 25 to 50 μg, incidence of tachysystole (3–17 vs 12–38%) and hyperstimulation (3–6 vs 9–11%) increase.[4,7–14] The common feature of those studies with high tachysystole and hyperstimulation rates, is the insistence on achievement of delivery by using misoprostol alone. In those studies , instead of combining the regimen with oxytocin, repeat doses of misoprostol have been given in patients with irregular uterine contractions. This fact reminds an accumulative effect of misoprostol, which provokes abnormal uterine activity. However it has been shown that, this abnormal activity could be rapidly reversed by tocolytics without apparent untoward intrapartum effects and no significant differences were noted in those patients in means of perinatal outcomes and mode of delivery.[14,15]

In this study, the patients received misoprostol intravaginally in the posterior fornix, hence the physician could have the chance to remove the remnants of the tablets in case of the uterine hyperresponsiveness. The dosing regimen was 50 μg and that amount was assumed to be the optimum dose neither to prolong the labor nor to increase the need for oxytocin.[4,7–12] Knowing that the terminal half-lives of misoprostol metabolites are 4.5 hours for a variety of animals, including human, the time interval between the doses in our study was 3 hours, which was assumed to prevent the accumulation of the drug while keeping the blood level of the agent above the minimally required level.[16] Maximum daily dose of misoprostol was 200 μg, which was the average dose required for delivery in many studies.[4,10–12] The important point in our study was that, the patients were not forced to achieve regular uterine contractions with misoprostol alone, but augmented with oxytocin when the contractions were irregular.

Though the rate of caesarean section has been reported within the range of 15.6–21.9% in the literature, our rate was 5.2% and all those patients were in the high risk group.[4,10,13] Tachysystole was seen in only 2 cases and resolved with irrigation. Uterine hyperresponsiveness (3.4%) was found to be less than the rates reported in the literature (9.4–38%).[4,10,13,14]

Misoprostol has been reported to be safe in terms of adverse drug reactions such as hemorrhage, febrile morbidity, diarrhea, nausea, and vomiting even with 200 μg doses.[17] Except slight nausea, vomiting and tachysystole, we did not experience any side effects due to misoprostol. Nausea and vomiting was not surely attributable to the drug and it would have been also due to labor itself.

Misoprostol was not only very well tolerated by the patients, it was also an economic method of labor induction. The mean dose of misoprostol

used in our patients costed almost 20–50 times less than the other prostaglandin derivatives would have cost.

Misoprostol seems to be a promising drug for labor induction. Possible advantages of misoprostol may be the cost effectiveness, ease of administration, well tolerability and most notably its dual action in cervical ripening and labor induction. However, future studies focusing on dosing regimens and route of application are needed.

## References


1. Bishop EH. Pelvic scoring for elective induction of labor. *Obstet Gynecol* 1964: 24: 266–268
2. Poulsen HK, Moller LK, Westergaard AG, Thomsen SG, Giersson RT, Arngrimsson R. Open randomised comparison of prostaglandin $E_2$ given by intracervical gel or vagitory for preinduction cervical ripening and induction of labor. *Acta Obstet Oynecol Scand* 1991; 70: 549–553
3. Diab KM, Ramy AR, Yehia MA. The use of rectal misoprostol as active pharmacological management of the third stage of labor. *J Obstet Gynaecol Res* 1999; 25: 327–332
4. Ramos LS, Kaunitz AM, Del Valle GO, Delke I, Schroeder PA, Briones DK. Labor induction with the prostaglandin $E_1$ methyl analogue misoprostol versus oxytocin: A randomised trial. *Obstet Gynecol* 1993; 81: 332–336
5. Rabe T, Basse H, Thuro H, Kiesel L, Runnebaum B. Effect of $PGE_1$ methyl analogue misoprostol on the pregnant uterus in the first trimester. *Geburtshilfe Frauenheilkd* 1987; 47: 324–331
6. Mariani-Neto C, Leao EJ, Baretto EM, Kenj G, De Aquino MM. Use of misoprostol for labor induction in stillbirth. *Rev Paul Med* 1987; 105: 325–328
7. Echeverria E, Rocha M. Estudio comparativo randomizado de induccion de parto con ocitocina y misoprostol en embarazos en vias de prolongacion. *Rev Chil Obstet Ginecol* 1995; 60: 108–111
8. Wing DA, Jones MM, Rahall A, Goodwin TM, Paul RH. A comparison of misoprostol and prostaglandin $E_2$ gel for preinduction cervical ripening and labor induction. *Am J Obstet Gynecol* 1995; 172: 1804–1810
9. Bugalho A, Bique C, Machungo F, Faaundes A. Induction of labor with intravaginal misoprostol in intrauterine fetal death. *Am J Obstet Gynecol* 1994; 171: 538–541
10. Wing DA, Rahall A, Jones MM, Goodwin TM, Paul RH. Misoprostol: An effective agent for cervical ripening and labor induction. *Am J Obstet Gynecol* 1995; 172: 1811–1816
11. Wing DA, Paul RH. A comparison of differing dosing regimens of vaginally administered misoprostol for preinduction cervical ripening and labor induction. *Am J Obstet Gynecol* 1996; 175: 158–164
12. Varaklis K, Gumina R, Stubblefield PG. Randomised controlled trial of vaginal misoprostol and intracervical prostaglandin $E_2$ gel for induction of labor at term. *Obstet Gynecol* 1995; 86: 541–544
13. Fletcher H, Mitchell S, Frederick J, Simeon D, Brown D. Intravaginal misoprostol versus dinoprostone as cervical ripening and labor-inducing agents. *Obstet Gynecol* 1994; 83: 244–247
14. Srisomboon J, Tongsong T, Tosiri V. Preinduction cervical ripening with intravaginal prostaglandin $E_1$ methyl analogue misoprostol A randomised controlled trial. *J Obstet Gynaecol Res* 1996; 22: 119–124
15. Herabutya Y, O-Prasertsawat P, Pokpirom J. A comparison of intravaginal misoprostol and intracervical prostaglandin $E_2$ gel for ripening of unfavorable cervix and labor induction. *J Obstet Gynaecol Res* 1997; 23: 369–374
16. Schoenhard G, Oppermann J, Kohn FE. Metabolism and pharmacokinetic studies of misoprostol. *Dig Dis Sci* 1985; 30: 126–131
17. Srisomboon J, Pongpisuttinun S. Efficacy of intracervical misoprostol in secondtrimester pregnancy termination: A comparison between live and dead fetuses. *J Obstet Gynaecol Res* 1998; 24: 1–5