# Oral Misoprostol and Vaginal Isosorbide Mononitrate for Labor Induction

## *A Randomized Controlled Trial*

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**OBJECTIVE:** To estimate whether vaginal isosorbide mononitrate, added to oral misoprostol for cervical ripening and labor induction, shortens time to vaginal delivery.

**METHODS:** A prospective, randomized trial was conducted. Women scheduled for labor induction between 32 and 42 weeks and with unfavorable cervices (modified Bishop score 6 or lower) were randomized to receive oral misoprostol every 4 hours, up to four doses, with or without isosorbide mononitrate every 6 hours, up to two doses. A strict protocol was used, including timing of oxytocin use and amniotomy. Side effects were assessed 6 hours after study initiation. One hundred forty-two patients were required to detect a change in time to vaginal delivery of 4 hours ($\alpha$=.05 and $\beta$=.20). Data were analyzed by intent to treat. Student's *t*, chi square, Fisher's exact, and Mann–Whitney tests were used where appropriate with $P \leq .05$ deemed significant.

**RESULTS:** One hundred fifty-six women were randomized; three were excluded after randomization. Seventy-eight women received misoprostol, and 78 received misoprostol with isosorbide mononitrate. Demographic characteristics were similar between groups. The time to vaginal delivery was not reduced when isosorbide mononitrate was added to misoprostol. Cesarean delivery rates and contraction and fetal heart rate abnormalities were similar between groups. Side effects were also similar between groups, except that women given isosorbide mononitrate experienced headaches more often. Neonatal outcomes were similar between groups.

**CONCLUSION:** The addition of vaginal isosorbide mononitrate to oral misoprostol for cervical ripening and labor induction did not reduce time to vaginal delivery and was associated with a greater incidence of headache.

**CLINICAL TRIAL REGISTRATION:** ClinicalTrials.gov, www.clinicaltrials.gov, NCT00374621.

*(Obstet Gynecol 2010;116:121–6)*

**LEVEL OF EVIDENCE:** I

The practice of labor induction continues to rise in the United States, with 22.5% of all births in 2006 reported as a result of induction, a more than twofold increase since 1990.[1] Cervical ripening agents are routinely used in women with cervices that are unfavorable, which is often defined as a Bishop score of 6 or less.[2] Mechanical dilating agents such as Foley catheters and hygroscopic and osmotic dilators have been associated with decreased cesarean delivery rates when compared with oxytocin alone, but when compared with placebo or pharmacologic methods, there is insufficient evidence to indicate a reduction in time to delivery.[3] Placebo-controlled studies of pharmacologic ripening agents such as synthetic analogs of prostaglandin $E_1$ and prostaglandin $E_2$ have demonstrated reductions in time to delivery.[4,5] Misoprostol, a prostaglandin $E_1$ analog, has been widely used with safety and efficacy for cervical ripening and labor induction; routes of administration of misoprostol for this indication include vaginal, sublingual, and oral.[6] A stepwise oral misoprostol protocol (50 micrograms followed by 100 micrograms in each subsequent dose) was deemed safe and effective as vaginal administration in a recent randomized trial from our institution.[7]

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*Supported by the Division of Maternal–Fetal Medicine at Stanford University.*

*Presented at the Society for Maternal–Fetal Medicine Annual Meeting, January 26–31, 2009, San Diego, California.*

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***Financial Disclosure***
*The authors did not report any potential conflicts of interest.*


ISSN: 0029-7844/10

Isosorbide mononitrate is a nitric oxide donor and vasodilator used primarily for patients with angina pectoris.[8] The discovery that the expression of inducible nitric oxide synthase isoforms in the human cervix increases toward the end of pregnancy suggested a potential therapeutic role for nitric oxide donors in the cervical ripening process.[9]

Data regarding outpatient use of vaginal isosorbide mononitrate for cervical ripening are limited and conflicting. In the two existing trials, isosorbide mononitrate was used before scheduled labor induction. Twenty-two percent of women receiving isosorbide mononitrate presented in labor within 24 hours compared with 8% of women receiving placebo in one trial,[10] whereas another placebo-controlled trial failed to demonstrate a decreased time to delivery in women receiving isosorbide mononitrate.[11] When compared with vaginal misoprostol, inpatient use of isosorbide mononitrate resulted in a longer time to delivery but less frequent uterine tachysystole and hyperstimulation.[12] Only one randomized trial has examined whether adding a nitric oxide donor to a prostaglandin could reduce time to delivery during cervical ripening and labor induction; Nunes et al[13] demonstrated reduced time to delivery when vaginal glyceryl trinitrate and vaginal dinoprostone were compared with vaginal dinoprostone alone.

Inpatient labor induction, particularly with cervical ripening, can result in the need for a prolonged stay in labor and delivery. We sought to estimate whether the addition of vaginal isosorbide mononitrate to inpatient oral misoprostol reduces time to vaginal delivery.

## METHODS

We conducted a randomized controlled trial at Lucile Packard Children's Hospital at Stanford University. Women presenting for labor induction and with a modified Bishop score of 6 or lower were considered study candidates. Inclusion criteria were maternal age of 18 years or older, singleton gestation, gestational age between 32 and 42 weeks, cephalic presentation, and intact fetal membranes. Exclusion criteria were a history of cesarean delivery or other uterine surgery, dilation of 3 cm or greater, presence of a placenta previa or low-lying placenta, contraction frequency of three or greater in 10 minutes, nonreassuring fetal status, and significant systemic maternal disease other than preeclampsia or diabetes. Randomization was conducted through sequentially numbered opaque envelopes created from a random numbers table.

Women assigned to misoprostol alone received 50 micrograms misoprostol orally and then 100 micrograms every 4 hours up to four doses total until a modified Bishop score of 8 or higher was observed. Women assigned to misoprostol with isosorbide mononitrate received the same misoprostol dosing plus isosorbide mononitrate 40 mg vaginally every 6 hours up to two doses total until a modified Bishop score of at least 8 was observed. In both arms, if women with a modified Bishop score of less than 8 were contracting too frequently to receive a second dose of misoprostol (three or more contractions in 10 minutes), they were assessed 2 hours later and given misoprostol if administration criteria were met or given oxytocin if contractions remained too frequent. This option of delayed dosing of misoprostol existed only for potential second doses and coincided with the timing of an assessment for additional isosorbide mononitrate. Oxytocin was also indicated when a modified Bishop score of 8 or greater was observed or if spontaneous rupture of membranes occurred during the ripening process. Intravenous oxytocin was begun at 1 milliunits per minute 4 hours after the most recent misoprostol dose and was titrated in 1–2-milliunit increments every 20 minutes to achieve a contraction frequency up to five contractions every 10 minutes. Amniotomy was performed at 3–4-cm dilation or after at least 2 hours of oxytocin augmentation with cervical dilation of less than 3 cm. Maternal pulse and blood pressure were recorded during the ripening process to assess for the incidence of maternal hypotension or maternal heart rate changes; mean arterial pressures and pulse measurements were recorded every 15 minutes for the first hour of the induction process and then hourly during the first 4 hours of the ripening process. Hypotension was defined as mean arterial pressure 65 mm Hg or less, and tachycardia was defined as pulse 100 beats per minute or greater. Women were assessed for the presence of known potential side effects from misoprostol or isosorbide mononitrate by patient interview 6 hours after study initiation. All women underwent continuous electronic fetal heart rate monitoring and tocometry. All women were enrolled between September 2006 and December 2007.

The study was powered to detect the primary outcome of a change in time to vaginal delivery of 4 hours ($\alpha$=.05 and $\beta$=.20) assuming a baseline length of time to vaginal delivery of 19.3 hours and a standard deviation of 6.7 hours.[7] Based on these assumptions, we estimated that 46 women experiencing a vaginal delivery were necessary per arm. Further assuming conservatively a vaginal delivery rate of 65%, we estimated that at least 71 women per arm were required. Secondary outcomes included uterine tachysystole (more than five contractions in 10 min-

utes with or without fetal heart rate decelerations) and abnormal fetal heart rate patterns during the ripening process irrespective of contraction pattern. Mode of delivery and neonatal outcomes were also assessed.

Data were analyzed by intent to treat, and Student's *t*, chi square, Fisher's exact, and Mann–Whitney tests were used where appropriate with $P \leq .05$ deemed statistically significant. The Shapiro-Wilk test for normality for all of our length of labor metrics was used. The Stanford University Administrative Panels on Human Subjects in Medical Research provided approval for this study, and informed consent was obtained from each participant.

## RESULTS

Of 288 eligible women approached for the study, 156 consented and 132 declined enrollment. Seventy-eight women received misoprostol alone and 78 women received misoprostol with isosorbide mononitrate. Two women who received misoprostol with isosorbide mononitrate were discontinued from the study as a result of medical conditions that required further evaluation and treatment before delivery precluding continued labor induction; one was found to have severe thrombocytopenia and one had a previously undiagnosed cardiomyopathy. One additional woman randomized to misoprostol with isosorbide mononitrate requested removal from the study after inadvertently receiving both medications vaginally. Data were analyzed for 78 patients who received misoprostol and 75 women who received misoprostol with isosorbide mononitrate (Fig. 1).

Maternal demographic and obstetric characteristics were similar between groups with no difference in gestational age, modified Bishop score of 2 or less, proportion of women with a closed cervix at enrollment, or induction indication (Table 1). The primary outcome, median time to vaginal delivery, remained unchanged when isosorbide mononitrate was added to oral misoprostol (17.8 [13.1–21.8] hours for misoprostol alone compared with 18.8 [14.6–23.3] hours for misoprostol with isosorbide mononitrate, $P=.69$) (Table 2). Cesarean delivery rates and contraction and fetal heart rate abnormalities during cervical ripening were similar between groups (Table 2). There was no difference in the incidences of maternal tachycardia or maternal hypotension between groups within the first 4 hours (Table 3). Side effects 6 hours

**Table 1. Study Participant Characteristics**

| Characteristic | Misoprostol (n=78) | Misoprostol With IMN (n=75) | *P* |
|---|---|---|---|
| Maternal age (y) | 28.9±6.3 | 27.4±6.4 | .60 |
| Public assistance | 66 (84.6) | 66 (88.0) | .54 |
| Ethnicity | | | .39 |
| White | 15 (19.2) | 11 (14.7) | |
| Hispanic | 48 (61.5) | 51 (68.0) | |
| African American | 1 (1.3) | 2 (2.7) | |
| Asian | 6 (7.7) | 6 (8.0) | |
| Other | 8 (10.3) | 5 (6.7) | |
| Gestational age (wk) | 39.5±1.7 | 39.8±1.8 | .65 |
| Nulliparity | 43 (55.1) | 43 (57.3) | .78 |
| Bishop score 2 or less | 40 (51.3) | 32 (42.7) | .29 |
| Closed cervix | 31 (39.7) | 27 (36.0) | .63 |
| Induction indication | | | .31 |
| Postdates | 29 (37.2) | 35 (46.7) | |
| Preeclampsia | 21 (26.9) | 11 (14.7) | |
| Type 1 or 2 DM | 2 (2.6) | 1 (1.3) | |
| Gestational DM | 7 (9.0) | 9 (12.0) | |
| Oligohydramnios | 7 (9.0) | 9 (12.0) | |
| IUGR | 3 (3.8) | 3 (4.0) | |
| Other | 9 (11.5) | 7 (9.3) | |

IMN, isosorbide mononitrate; DM, diabetes mellitus; IUGR, intrauterine growth restriction.

Data are mean±standard deviation or n (%) unless otherwise specified.

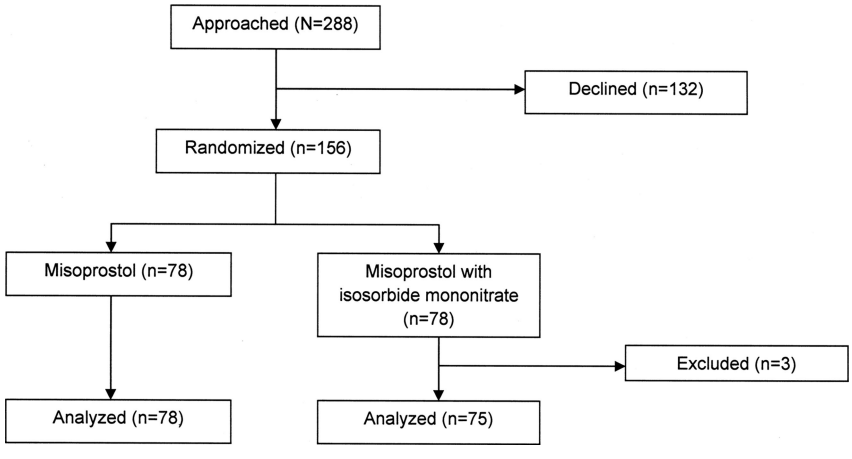


**Fig. 1.** Flow diagram of randomization.

*Collingham. Misoprostol and Isosorbide Mononitrate. Obstet Gynecol 2010.*

**Table 2. Obstetric Outcomes**

| Outcome | Misoprostol (n=78) | Misoprostol With IMN (n=75) | P |
|---|---|---|---|
| Time to vaginal delivery (h) | 17.8 (13.0–21.8) | 18.8 (14.6–23.3) | .69 |
| 37 wk or greater | 18.8 (13.6–22.5) | 20.1 (14.7–26.2) | .43 |
| Nulliparous | 20.3 (14.1–25.8) | 23.8 (18.8–26.4) | .14 |
| Time to delivery (h) | 19.6 (14.1–25.8) | 20.0 (14.7–26.4) | .68 |
| Delivery mode | | | .31 |
| SVD | 57 (73.1) | 49 (65.3) | |
| Assisted VD | 3 (3.8) | 4 (5.3) | |
| CD | 18 (23.1) | 22 (29.3) | |
| Tachysystole with or without decelerations | 8 (10.3) | 6 (8.0) | .34 |
| Tachysystole with decelerations | 1 (1.3) | 1 (1.3) | .67 |
| Fetal tachycardia | 5 (6.4) | 3 (4.0) | .48 |
| Variable decelerations | 21 (26.9) | 31 (41.3) | .06 |
| Prolonged decelerations | 2 (2.6) | 3 (4.0) | .36 |
| Epidural use | 71 (91) | 65 (87) | .39 |

IMN, isosorbide mononitrate; SVD, spontaneous vaginal delivery; VD, vaginal delivery; CD, cesarean delivery.
Data are median (25–75% interquartile range) or n (%) unless otherwise specified.

after initiation of cervical ripening were similar between groups with regard to nausea, diarrhea, flushing, palpitations, and dizziness. Headache, however, was reported by nearly 70% of women who received misoprostol with isosorbide mononitrate (69% compared with 15%, $P<.001$) with most women receiving analgesia for their headaches (Table 3). Neonatal outcomes, including birth weight, birth weight greater than 4,000 g, Apgar scores less than 7 at 1 and 5 minutes, meconium at the time of ruptured membranes, and neonatal intensive care unit admission, were similar between groups (Table 4).

**Table 3. Maternal Side Effects**

| Side Effect | Misoprostol (n=78) | Misoprostol With IMN (n=75) | P |
|---|---|---|---|
| Hypotension | 4 (5.1) | 8 (10.7) | .20 |
| Tachycardia | 15 (19.2) | 22 (29.3) | .15 |
| Headache | 12 (15.4) | 52 (69.3) | <.001 |
| Headache requiring analgesia | 4 (5.1) | 45 (60.0) | <.001 |
| Nausea | 8 (10.3) | 10 (12.8) | .56 |
| Diarrhea | 2 (2.7) | 1 (1.3) | .58 |
| Palpitations | 5 (6.4) | 3 (4.0) | .50 |
| Flushing | 10 (12.8) | 12 (16.0) | .58 |
| Dizziness | 6 (7.7) | 7 (9.3) | .72 |

IMN, isosorbide mononitrate.
Data are n (%) unless otherwise specified.

**Table 4. Neonatal Outcomes**

| Outcome | Misoprostol (n=78) | Misoprostol With IMN (n=75) | P |
|---|---|---|---|
| Birth weight (g) | 3,371±658 | 3,452±584 | .79 |
| Birth weight more than 4,000 g | 7 (9.0) | 14 (18.7) | .08 |
| Meconium | 8 (10.3) | 9 (12.0) | .82 |
| Apgar score less than 7 | | | |
| 1 min | 8 (10.3) | 4 (5.3) | .26 |
| 5 min | 1 (1.3) | 0 | .32 |
| NICU admission | 6 (7.7) | 8 (10.7) | .52 |

IMN, isosorbide mononitrate; NICU, neonatal intensive care unit.
Data are mean±standard deviation or n (%) unless otherwise specified.

## DISCUSSION

Investigational use of nitric oxide donors such as isosorbide mononitrate began in obstetrics with cervical ripening before first-trimester pregnancy termination. Early randomized trials showed that the use of vaginal nitric oxide donors resulted in less pressure required to dilate the cervix when compared with placebo.[14,15] Subsequent studies, however, failed to show a benefit when comparing nitric oxide donors with prostaglandins or with placebo for the same indication.[16–20] Additionally, the combination of vaginal isosorbide mononitrate to vaginal misoprostol in one trial failed to provide additional preoperative cervical ripening over vaginal misoprostol alone.[20]

In term gestations, vaginal isosorbide mononitrate for cervical ripening has shown effectiveness as judged by changes in Bishop score or cervical distensibility in randomized trials but with prolonged labor when compared with vaginal dinoprostone or vaginal misoprostol.[12,21,22] Nunes et al[13] found that length of induction to delivery was reduced from approximately 27 to 22 hours when inpatient administration of glyceryl trinitrate, a nitric oxide donor, was combined with vaginal prostaglandin dinoprostone. In contrast to the Nunes study, we did not show a benefit in the addition of vaginal isosorbide mononitrate to an oral misoprostol protocol for cervical ripening and labor induction in terms of reducing the length of time to vaginal delivery. We chose to use oral misoprostol to eliminate the potential for pharmacologic interaction between vaginal misoprostol and vaginal isosorbide mononitrate. The lack of synergy between oral misoprostol and vaginal isosorbide mononitrate may be a result of this choice. Recent basic science data

demonstrate splitting and disorganization of cervical collagen fibers in women receiving vaginal isosorbide mononitrate and in women receiving vaginal misoprostol before first-trimester abortion.[23] Studies of the effects of oral misoprostol on the cervical collagen network are unfortunately lacking, and a lack of tissue effect at the level of the cervix with the use of oral misoprostol may explain our negative findings. Although the literature on oral misoprostol is not as extensive as that of vaginal misoprostol, our approach is based on the results of a published randomized trial conducted at our institution comparing a stepwise oral misoprostol protocol (50 micrograms followed by 100 micrograms in each subsequent dose) with standard vaginal administration (25 micrograms). The results of this trial demonstrated that stepwise oral misoprostol was as effective as vaginal misoprostol for cervical ripening with a low incidence of tachysystole with fetal heart rate abnormalities, no increase in side effects, a high rate of patient satisfaction, and a lower cesarean delivery rate.[7] Based on the reported benefits of oral misoprostol and to eliminate potential pharmacologic interactions with dual vaginal administration, we proceeded with the current study design. Our lack of replication of the findings of Nunes et al may also be explained by our choice of specific nitric oxide donor and specific prostaglandin or our inclusion of multiparous women. Analysis of the data on nulliparous women only did not change the results (Table 2).

Nunes et al[13] saw an additional benefit to adding glyceryl trinitrate to dinoprostone; only 4% of women receiving both agents experienced tachysystole compared with 15% of women receiving dinoprostone alone. This finding seems plausible because nitric oxide has been shown to be a uterine relaxant in vitro.[24,25] We did not detect a reduction in our rate of tachysystole with the addition of isosorbide mononitrate to misoprostol, possibly secondary to our already low rates of contraction abnormalities in the arm receiving only misoprostol.

Both Ekerhovd et al[21] and Nicoll et al[26] showed statistically significant reductions in maternal blood pressure and increases in maternal pulse with isosorbide mononitrate use at term that were deemed clinically insignificant. We found no difference in the incidences of maternal tachycardia or hypotension between groups. We hypothesize that the difference in our hemodynamic results may be the result of our use of a prostaglandin in both groups, resulting in earlier labor symptoms and also a high rate of epidural use, masking any potential hemodynamic changes from isosorbide mononitrate. Similarly, Nunes et al[13] showed no significant maternal hemodynamic changes with their combination of a vaginal nitric oxide donor and vaginal prostaglandin.

Nearly 70% of women exposed to isosorbide mononitrate developed headaches, a comparable finding in other studies using isosorbide mononitrate for cervical ripening at term.[10,21,22] Additionally, we note that three of the women requiring analgesia for headache in the group receiving isosorbide mononitrate required a narcotic for control of their pain, whereas all patients receiving misoprostol alone required only acetaminophen. Although the incidence of self-reported headache is consistent with other studies, there is the potential for recall bias because women in this study were aware of the group to which they were randomized and had been informed of the risk of headache with isosorbide mononitrate before enrollment.

Our study was not placebo-controlled or blinded. Creation of a placebo tablet that appeared identical to isosorbide mononitrate was problematic, and the alternative of altering the isosorbide mononitrate tablets to appear identical to a placebo would incur the risk of uncertain vaginal absorption. We therefore used a strict ripening and induction protocol consisting of cervical examinations at established times in each group, oxytocin use at specific points and at a prescribed dose, and amniotomy at a set cervical dilation. We believe that the primary outcome of time to delivery was minimally affected by our lack of placebo or blinding. Although we appreciate that the intent-to-treat principle was not entirely achieved, we could not include data from a participant who requested removal from the study or data on length of labor from women who did not experience labor.

A recent meta-analysis of available data from trials using nitric oxide donors for cervical ripening before first-trimester surgical abortion concluded that nitric oxide donors are inferior to prostaglandins for this purpose and are associated with more side effects, especially headache.[27] Our data show that the addition of vaginal isosorbide mononitrate to oral misoprostol confers no reduction in time to delivery and results in a high incidence of headache, suggesting a similar limited role for isosorbide mononitrate in inpatient cervical ripening and labor induction.

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