

# Sublingual versus Vaginal Misoprostol for the Induction of Labor at Term: A Randomized, Triple-Blind, Placebo-Controlled Clinical Trial

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## What's Known

- There are several fetal and maternal indications for the termination of a pregnancy, but no completely safe and ideal method is known yet.
- Misoprostol stimulates myometrial contractions, is effective and inexpensive, and has no significant effects on lungs or vessels.
- The ideal dose and routes of the administration of misoprostol for the induction of a live-term fetus have yet to be confirmed.
- Although the FDA has not approved misoprostol for labor induction yet, it has been used successfully in several clinical trials.

## What's New

- In the present study, meconium-stained amniotic fluid was detected 3 times more frequently in the sublingual group (P=0.03).
- Uterine hyperstimulation, late FHR decelerations during labor, and Cesarean deliveries were observed almost twice more frequently in the sublingual group — albeit not statistically. Additionally, final maternal and neonatal outcomes were almost similar.
- The sublingual method had a greater uterotonic potency than did the vaginal route.
- Vaginal administration seemed to be safer than did the sublingual route for a live-term pregnancy.

## Abstract

**Background:** We sought to compare the effectiveness and safety of sublingual versus vaginal misoprostol for the termination of pregnancy with a live full-term fetus.

**Methods:** This randomized, triple-blind, placebo-controlled clinical trial was performed on 200 primiparous women with normal, singleton, full-term pregnancies candidated for the induction of labor. Sublingual and vaginal tablets containing misoprostol (25 mcg) or placebo in similar shapes were administered every 4 hours until the Bishop score reached above 8. Maternal and neonatal complications and outcomes were compared.

**Results:** There were 100 parturient women in each group. The mean maternal age, gestational age, and Bishop score at the commencement of misoprostol had no statistical differences between the sublingual and vaginal groups. The mean time interval between misoprostol commencement and delivery was 497.10±291.49 and 511.67±08.46 minutes for the sublingual and vaginal groups, correspondingly. Twenty-two women had Cesarean deliveries in the sublingual group versus 14 in the vaginal group. Meconium-stained amniotic fluid was seen in 12 women in the sublingual group and 4 in the vaginal group (P=0.03). Late fetal heart rate deceleration was observed in 8 women in the sublingual group and 4 in the vaginal group (P=0.22). The mean neonatal birth weight, blood gas value at birth, Apgar score, and length of admission time in the neonatal intensive care unit were not different between the 2 groups.

**Conclusion:** Sublingual and vaginal misoprostol had similar effectiveness; however, meconium-stained liquor was observed considerably more frequently with sublingual misoprostol than with vaginal misoprostol.

**Trial Registration Number:** IRCT201402096541N3

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**Keywords:** • Induced labor • Misoprostol • Pregnancy • Sublingual administration • Vaginal absorption

## Introduction

The artificial termination of a pregnancy with a live full-term fetus is indicated when the risks of its continuation outweigh those of its termination. There are several fetal and maternal indications for the termination of a pregnancy such as prolonged gestation, intrauterine fetal growth restriction, antiphospholipid syndrome,

premature or prolonged rupture of membranes, preeclampsia, chorioamnionitis, abruption, maternal hypertension or diabetes, and fetal death.<sup>1</sup> Several methods have been used for the induction of labor and termination of pregnancy with different degrees of safety and success, and many investigations have been performed on this topic. Nonetheless, a consensus has yet to emerge about the most appropriate method for all women.

Misoprostol is a prostaglandin E1 methyl ester and is used orally for the prevention or treatment of peptic ulcer.<sup>2</sup> Oral misoprostol with a rapid absorption is de-esterified to active misoprostol acid in the liver rapidly. Misoprostol acid has a half-life of between 20 and 40 minutes and is excreted in the urine. Misoprostol stimulates myometrial contractions in a pregnant uterus by selectively binding to EP2/EP3 prostanoid receptors.<sup>3</sup> In 1992, misoprostol was first reported for the termination of a pregnancy with a live fetus.<sup>4</sup>

Misoprostol is inexpensive and effective and can be stored at room temperature. In contrast to other prostaglandins, misoprostol has no significant effect on the lungs or vessels and can be safely used in patients with asthma. The Food and Drug Administration (FDA) has not approved misoprostol for labor induction or cervical ripening yet, but this medication has been used successfully in several clinical trials. The ideal dose and routes of the administration of misoprostol for the induction of labor at full term are still a matter of controversy. The National Institute for Health and Clinical Excellence (NICE) released a clinical guideline in 2008 and restricted the use of misoprostol only to clinical trials and termination of pregnancies with a dead fetus.<sup>5</sup> However, the American College of Obstetricians and Gynecologists (ACOG) supported its usage in 2009 for women who did not have a previous Cesarean delivery or a major uterine surgery.<sup>6</sup>

The present investigation was designed as a triple-blind study to compare the effectiveness and safety of sublingual versus vaginal misoprostol for the induction of labor in women with a live full-term fetus.

## Patients and Methods

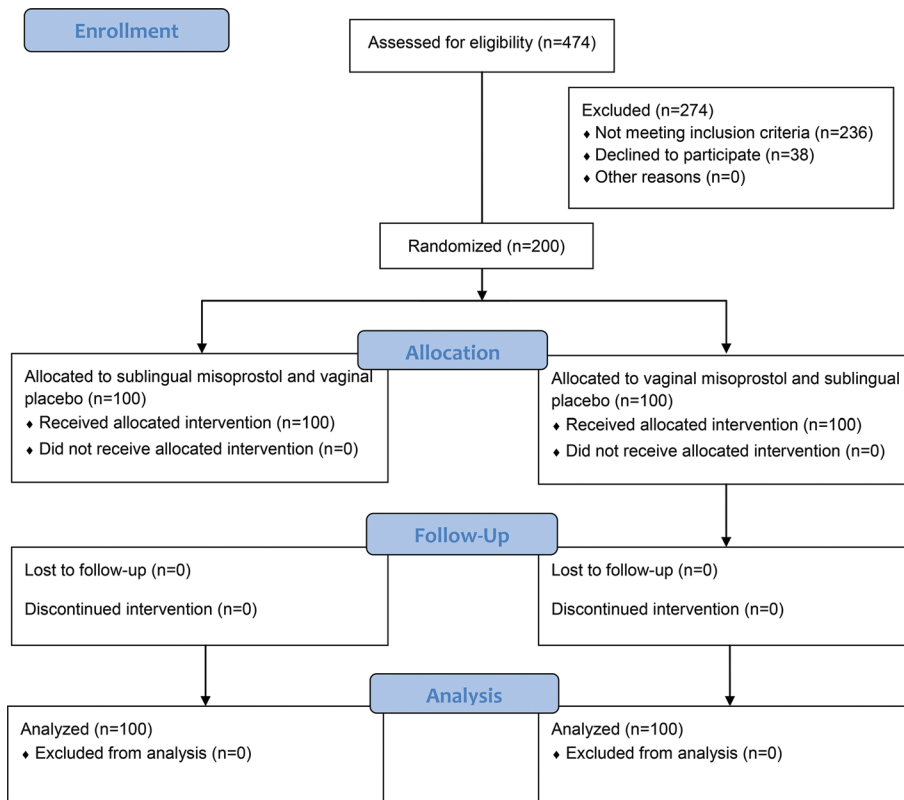
This randomized, triple-blind, placebo-controlled clinical trial was performed in Hafez Hospital and Hazrat-e-Zeinab Hospital (affiliated to Shiraz University of Medical Sciences) from 2009 to 2011. From 474 pregnant women initially assessed for eligibility, 236 women were excluded because they did not meet the inclusion

criteria and 38 women declined to participate. Finally, 200 women in their third trimester of pregnancy with obstetric or medical indications for the induction of labor were enrolled for randomization in this study. The participants' CONSORT flow diagram is depicted in Figure 1.

The inclusion criteria were comprised of first singleton pregnancy, minimum gestational age of 37 weeks, cephalic presentation, having a live fetus, estimated fetal weight <4000 grams, and the Bishop score <7. The exclusion criteria comprised hypersensitivity to prostaglandins, previous uterine scar, fetal congenital malformations, intrauterine growth restriction, non-reassuring fetal heart rate, gestational age <37 weeks, oligohydramnios (amniotic fluid index <5 cm), placenta previa, abnormal fetal presentation, and minimum Bishop score =8. Additionally, women with diabetes, hypertension, hyperthyroidism, or epilepsy were all excluded from the study.

Sublingual and vaginal tablets of misoprostol (25 mcg) (Cytotec, Searle Pharmaceuticals, High Wycombe, Bucks, U.K.) and placebos in similar shapes were specifically prepared for the study by the pharmaceuticals division of Shiraz University of Medical Sciences. Two hundred medication packages were prepared and coded as *A* or *B*. All the packages contained 2 similar plastic bags; one of them contained sublingual tablets and the other bag contained vaginal suppositories. Every patient received 1 medication package coded as *A* or *B* via the simple randomization technique. In each package, only one of the plastic bags contained misoprostol and the other one was a similarly shaped placebo. Both types of preparations were used for every woman who entered the study. Only the pharmacist knew which bag contained the active form of medication. The placebo tablets were composed of inactive ingredients including microcrystalline cellulose (Avicel), lactose, corn starch, and magnesium stearate.

The application of the medications was repeated every 4 hours until the cervical Bishop score advanced to more than 8. Before the administration of the next dose, vaginal examination was performed and the Bishop score and uterine contractions were reassessed. If the Bishop score was <8 and the uterine contractions occurred fewer than 3 times in 10 minutes, another dosage was used. A maximum dose of 150 mcg of misoprostol (6 doses) was planned. If active labor still had not been achieved, oxytocin was commenced 6 hours after the last dose of misoprostol. Close observation of the mother and continuous fetal heart monitoring were



**Figure 1:** Participants' CONSORT flow diagram.

performed for the whole study population. The data were collected and entered in Statistical Package for the Social Sciences, version 15 (SPSS, Chicago, IL., U.S.A.), using the codes prepared by the pharmaceuticals division. The independent-samples *t*-test was used for the analysis of equality of means, and the categorical variables were analyzed using the chi-square test. A  $P < 0.05$  was considered significant. The statistician was also blinded to the codes. The codes were broken after the finalization of the statistical analyses. The researcher, the patients, and the statistician were blinded to the nature of the medications prescribed.

Uterine hyperstimulation was considered a side effect of the induction of labor. Uterine hyperstimulation was defined as the occurrence of excessive uterine activity, associated with a non-reassuring fetal heart rate, with more than 5 contractions in 10 minutes.<sup>1,2</sup> The time interval from the first dose of misoprostol to delivery, number of misoprostol doses, uterine hyperstimulation, need for oxytocin augmentation, meconium-stained amniotic fluid, method of delivery, indications for abdominal delivery, neonatal birth weight, Apgar score and cord blood gas analysis, neonatal intensive care unit (NICU) admission, and outcome were compared between the 2 groups.

The institutional Review Board of Shiraz

University of Medical Sciences approved the study. All the women signed an informed consent form. This trial was registered in The Iranian Registry of Clinical Trials (IRCT201402096541N3).

## Results

The study population comprised 200 women: 100 received sublingual misoprostol and vaginal placebo, while the others took vaginal misoprostol and sublingual placebo. All the women were primiparous, and there were no significant differences between the groups regarding maternal age or gestational age and the Bishop score at the beginning of the study. These data are presented in Table 1.

The spontaneous rupture of the amniotic membrane at the time of admission and prolonged duration of pregnancy were the main indications for the induction of labor in the current study. The side effects of the medications such as nausea and vomiting were almost the same in the 2 groups. The mean time interval between medication commencement and delivery was shorter in the sublingual group, without statistical significance. Meconium-stained amniotic fluid was detected 3 times more frequently in the sublingual group ( $P = 0.03$ ). Uterine hyperstimulation and Cesarean delivery

**Table 1:** Maternal characteristics, complications, and outcomes in the study patients, who received sublingual and vaginal misoprostol

| Variable   | A- sublingual misoprostol | B- vaginal misoprostol | P value |
|--|---------------------------|------------------------|---------|
| Maternal age (year)  | 25.94±4.21                | 26.59±4.63             | 0.30    |
| Gestational age (day)  | 284.86±6.50               | 284.36±7.69            | 0.62    |
| Gestational age>280 days   | 24 (24%)                  | 27 (27%)               | 0.62    |
| Labor pain on admission  | 52 (52%)                  | 48 (48%)               | 0.57    |
| Amniorrhexis on admission  | 52 (52%)                  | 48 (48%)               | 0.57    |
| Bishop score at misoprostol commencement                           | 4.84±1.50                 | 4.78±1.54              | 0.78    |
| Nausea   | 4 (4%)                    | 5 (5%)                 | 0.50    |
| Vomiting   | 2 (2%)                    | 5 (5%)                 | 0.44    |
| Uterine hyperstimulation with non-reassuring FHR                   | 13 (13%)                  | 7 (7%)                 | 0.15    |
| Mean time interval between starting misoprostol and delivery (min) | 497.10±291.49             | 511.67±308.46          | 0.73    |
| Normal vaginal delivery  | 78 (78%)                  | 86 (86%)               | 0.14    |
| Cesarean delivery  | 22 (22%)                  | 14 (14%)               | 0.14    |
| Indications for cesarean   |                           |                        |         |
| Fetal distress   | 13 (13%)                  | 7 (7%)                 | 0.15    |
| Vaginal bleeding   | 4 (4%)                    | 6 (6%)                 | 0.51    |
| Meconium-stained liquor and non-reassuring FHR                     | 12 (12%)                  | 4 (4%)                 | 0.03    |

The data are presented as number (%) or mean±SD. FHR: Fetal heart rate

were observed almost twice more frequently in the sublingual group, but the values were not statistically significant. The neonatal outcomes and complications are presented in Table 2.

The mean neonatal birth weight and the mean neonatal blood gas values were not different between the 2 groups. Late deceleration in fetal heart rate during labor was observed twice more frequently, with a higher frequency of NICU admissions, in the sublingual group; however, these values were not statistically significant.

None of the women needed to receive the sixth dose of misoprostol because they all reached a Bishop score >8. Only 4 women in the sublingual and 7 in the vaginal group needed to take the fifth dose of misoprostol. Oxytocin was not administered for any woman. All the mothers and neonates were discharged in good condition from the hospital.

## Discussion

Labor induction has had an increasing trend:<sup>7,8</sup> from 9.5% in 1990 and 19.4% in 1998 to 22.1% in 2004. There are several maternal or fetal indications for the induction of labor in modern obstetrics. Nonetheless, the induction of labor requires careful clinical judgment considering the benefits and risks to the mother and the prognosis for the survival and outcome of the neonate. Although the advances in the management of newborns in the NICU may have influenced the decisions to opt for the advantages of delivery despite the continuation of a very high-risk pregnancy, what constitutes

the best and safest method of labor induction for mother and fetus is still a matter of debate. For years, obstetricians have drawn upon such various methods for the induction of labor as membrane sweeping, amniotomy, extra-amniotic Foley catheter insertion, extra-amniotic saline infusion, castor oil consumption, intravenous oxytocin, vaginal prostaglandin E2, vaginal prostaglandin F2α, misoprostol, and even acupuncture, all with different success rates and probable complications.<sup>2</sup>

Several investigations have concluded that misoprostol confers higher vaginal delivery rates and lower Cesarean delivery rates than do other prostaglandins, oxytocin, or placebos.<sup>9,2</sup> The strong ripening effect of misoprostol on the cervix can be explained by its direct effect that initiates physiological uterine contractions. It has been reported that the vaginal application of misoprostol has higher efficacy with a longer duration of elevated plasma levels and 3 times more bioavailability than does the oral route by the elimination of the hepatic or gastrointestinal effect.<sup>10</sup>

The administration of high doses of misoprostol (i.e. 400 to 600 mcg) may induce side effects such as shivering, nausea, vomiting, hyperthermia, and diarrhea. These side effects are, however, less common with doses of 25 to 50 mcg, used for the induction of a term pregnancy.<sup>11</sup> In the present study, nausea and vomiting were experienced by only a few women, the majority of whom were in the vaginal group. Nevertheless, the difference was not statistically significant between the groups.

**Table 2:** Fetal and neonatal complications, blood gas values, and outcomes in the study groups, who received sublingual and vaginal misoprostol

| Variable  | A- sublingual misoprostol | B- vaginal misoprostol | P value |
|---|---------------------------|------------------------|---------|
| Late fetal heart rate deceleration during induction               | 8 (8%)                    | 4 (4%)                 | 0.22    |
| Neonatal birth weight (g)   | 3287.70±268.79            | 3291.50±257.42         | 0.91    |
| Neonatal PH   | 7.33±0.07                 | 7.32±0.07              | 0.67    |
| Neonatal PO <sub>2</sub>  | 40.69±10.29               | 40.29±12.16            | 0.80    |
| Neonatal PCO <sub>2</sub>   | 39.43±4.98                | 38.56±6.19             | 0.27    |
| Neonatal HCO <sub>3</sub>   | 22.11±4.66                | 22.04±4.79             | 0.91    |
| Neonatal base excess  | -1.46±6.50                | -0.56±6.46             | 0.32    |
| Apgar score at 1 min <7   | 14 (14%)                  | 10 (10%)               | 0.38    |
| Apgar score at 5 min <7   | 1 (1%)                    | 2 (2%)                 | 0.56    |
| Neonatal sex (male)   | 51 (51%)                  | 54 (54%)               | 0.67    |
| NICU admission  | 11 (11%)                  | 7 (7%)                 | 0.32    |
| Meconium as indication for NICU admission                         | 8 (8%)                    | 3 (3%)                 | 0.21    |
| Respiratory distress as indication for NICU admission             | 3 (3%)                    | 5 (5%)                 | 0.72    |
| Length of neonatal residency in NICU for the admitted group (day) | 6.54±1.29                 | 6.00±2.00              | 0.49    |

The data are presented as number (%) or mean±SD. NICU: Neonatal intensive care unit

Pharmacokinetic studies on the different routes of the administration of misoprostol have demonstrated that sublingual misoprostol acid reaches a higher serum peak concentration with a shorter time-to-peak concentration than does vaginal misoprostol acid.<sup>12</sup> The plasma concentration of misoprostol reaches a peak at 27.5±18 minutes after oral, 26±11.5 minutes after sublingual, and 80±37 minutes after vaginal application.<sup>11-13</sup> In 2002, the first report on the sublingual administration of misoprostol for labor induction was published.<sup>14</sup>

In the present study, to recruit parturients of very similar condition, we selected only women with Bishop scores <7. The mean Bishop score was 4.84±1.50 and 4.78±1.54 in the sublingual group and the vaginal group, respectively. Considering the fact that the main goal of using medications for the induction of labor was the ripening of an unfavorable cervix.

In standard definitions, tachysystole is defined when more than 5 contractions occur in 10 minutes, hypertonus when a contraction lasts for more than 120 seconds, and hyperstimulation when excessive uterine activity with a non-reassuring fetal heart rate presents.<sup>1</sup> In the current study, uterine hyperstimulation was detected to be almost twice more frequent in the sublingual group, and also the number of the women who needed Cesarean section for fetal distress was higher in the sublingual group than in the vaginal group, which is in agreement with the results of a study by Feitosa et al.<sup>13</sup> In both studies, however, the values were not statistically significant. A systematic review based on 5 randomized clinical trials found that the risk of uterine tachysystole with sublingual

misoprostol, compared to the vaginal route, was increased.<sup>14</sup>

Late fetal heart rate deceleration and meconium-stained amniotic fluid were also seen more frequently in the sublingual group in the current study. Given that diarrhea is one of the adverse effects of misoprostol insofar as it occurs in more than 10% of the persons who take the drug in high oral dosages, we wonder whether misoprostol induces meconium passage via a direct effect on the fetal bowel smooth muscles or whether it is a real sign of fetal distress and hypoxia. All the neonates in our study had acceptable blood gas analyses at birth and good outcomes.

In the present study, the induction of labor was successful in both groups of sublingual and vaginal misoprostol and no woman needed oxytocin augmentation. However, induction failed in 13 to 15% of the women in the study by Feitosa et al.<sup>13</sup> In both studies, 25 mcg of misoprostol was used, but the difference in the success rates may have been created by the frequency of administration (every 4 hours in our study vs. every 6 hours in the previous study).

There are 2 published studies comparing 25 and 50 mcg of vaginal and sublingual misoprostol every 6 hours: Both reported equal effectiveness and safety.<sup>15,16</sup> Misoprostol with minimum doses of 25 mcg administered orally, vaginally, sublingually, or buccally was compared to prostaglandin E<sub>2</sub> in a systematic review, which concluded that misoprostol, compared to prostaglandin E<sub>2</sub>, was associated with increased risks of tachysystole and hyperstimulation, high rates of vaginal delivery within 24 hours, low rates of oxytocin use, and increased meconium

staining.<sup>17</sup> In the present study, the women in the sublingual group needed shorter time intervals between admission and delivery, and only 4 women needed the fifth dose of medication versus 7 in the vaginal group. These findings, albeit not statistically significant, are all in favor of the great uterotonic potency of the sublingual method of administration compared to the vaginal route.

A systematic review performed to compare sublingual and vaginal misoprostol for the induction of labor at term concluded that both methods were comparable and that the sublingual route had no additional clinical advantage.<sup>14</sup> Still, logically sublingual misoprostol, by comparison with vaginal misoprostol, has the advantage of easy administration. Two studies compared patient satisfaction between sublingual and vaginal misoprostol and concluded that the sublingual method was associated with higher patient satisfaction.<sup>16,18</sup>

First and foremost among the limitations of the present study is its small sample size, which precludes exact conclusions. Also, we did not compare fever and hyperthermia, as a common complication of misoprostol, between the 2 groups. Another drawback of note is that we could not evaluate patient satisfaction due to the special design of the study and the simultaneous administration of both routes of the medication and the placebo.

Previous research has shown that misoprostol has the potential to prevent or treat postpartum hemorrhage: This finding merits due attention, should be considered and used on special occasions when lives are at risk.<sup>19</sup>

We believe that misoprostol is a very effective and potent drug and that it may have complications similar to those associated with other uterotonic medications. The administration of misoprostol in small dosages will reduce the unwanted effects. However, the experience with misoprostol is still limited for pregnancies with a live full-term fetus and more precise randomized clinical trials are needed, especially in the case of a scarified uterus. The Federation of International Gynecologists and Obstetricians (FIGO) suggests a half dose of misoprostol for women with a previous Cesarean section.<sup>20-22</sup> However, there are still many questions and uncertainties surrounding the administration of misoprostol for those who have previous uterine scars.

## Conclusion

In the present study, sublingual and vaginal misoprostol showed similar effectiveness for

the termination of pregnancies with a live full-term fetus. Meconium-stained liquor was considerably frequent after the administration of sublingual misoprostol compared to the vaginal route. However, the final maternal and neonatal outcomes were almost similar without any statistically significant differences.

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**Conflict of Interest:** None declared.

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