Original Article

# Intravaginal Misoprostol for Cervical Ripening and Labor Induction in Nulliparous Women: A Double-blinded, Prospective Randomized Controlled Study

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## Abstract

**Background:** In China, no multicenter double-blinded prospective randomized controlled study on labor induction has been conducted till now. This study is to evaluate the efficacy and safety of intravaginal accurate 25-μg misoprostol tablets for cervical ripening and labor induction in term pregnancy in nulliparous women.

**Methods:** This was a double-blinded, prospective randomized controlled study including nulliparous women from 6 university hospitals across China. Subjects were randomized into misoprostol or placebo group with the sample size ratio set to 7:2. Intravaginal 25-μg misoprostol or placebo was applied at an interval of 4 h (repeated up to 3 times) for labor induction. Primary outcome measures were the incidence of cumulative Bishop score increases ≥3 within 12 h or vaginal delivery within 24 h. Safety assessments included the incidences of maternal morbidity and adverse fetal/neonatal outcomes.

**Results:** A total of 173 women for misoprostol group and 49 women for placebo were analyzed. The incidence of cumulative Bishop score increases ≥3 within 12 h or vaginal delivery within 24 h was higher in the misoprostol group than in the placebo (64.2% vs. 22.5%, relative risk [*RR*]: 2.9, 95% confidence interval [*CI*]: 1.4–6.0). The incidence of onset of labor within 24 h was significantly higher in the misoprostol group than in the placebo group (48.0% vs. 18.4%, *RR*: 2.6, 95% *CI*: 1.2–5.7); and the induction-onset of labor interval was significantly shorter in the misoprostol group ($P = 0.0003$). However, there were no significant differences in the median process time of vaginal labor (6.4 vs. 6.8 h; $P = 0.695$), incidence (39.3% vs. 49.0%, *RR*: 0.8, 95% *CI*: 0.4–1.5) and indications ($P = 0.683$) of cesarean section deliveries, and frequencies of maternal, fetal/neonatal adverse events between the groups.

**Conclusion:** Intravaginal misoprostol 25 μg every 4 h is efficacious and safe in labor induction and cervical ripening.

**Key words:** Cervical Ripening; Intravaginal; Labor Induction; Misoprostol; Placebo

## Introduction

Induction of labor is extensively used all over the world. Data from the World Health Organization (WHO) Global Survey on Maternal and Perinatal Health between 2004 and 2008 showed that 9.6% of all the deliveries involved labor induction. Among the countries surveyed, the incidence of labor induction of America was 11.4%, while that of China was only 6.4%.[1] In the United States, the incidence of labor

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induction increased significantly from 9.0% in 1989 to 18.4% in 1997, to over 23% in 2009.[2,3] In China, however, changes of nationwide data of the incidence of labor induction are still lacking.

On the other hand, increasing the incidence of the cesarean section has become a public health problem in China since the past 20 years.[4] Apart from the nonclinical factors that drive women and obstetricians to choose cesareans, failure of induce labor and lack of an effective medicine to induce labor in China, are two of the main clinical reasons for the increased rate.[5] Some women choose elective cesarean sections just because they are worried about an unsuccessful labor induction.

Prostaglandins (PGs) are widely used for cervical ripening and labor induction; according to the Chinese guideline for cervical ripening and labor induction in late pregnancy, dinoprostone and misoprostol are both recommended.[6,7] Vaginal prostaglandin E2 (PGE2) (dinoprostone) has been shown to increase the chance of vaginal delivery in 24 h compared with a placebo.[8] However, dinoprostone is costly and must be refrigerated or frozen during transportation and storage because of its thermal instability, which restricts its use in undeveloped regions in China.

Misoprostol is a synthetic PGE1 analog. Vaginal misoprostol has been shown to be associated with less use of epidural analgesia, more vaginal deliveries within 24 h, and more uterine hyperstimulation compared with vaginal PGE2.[9] Compared with dinoprostone, misoprostol is stable at the room temperature, which is more convenient for storage and administer;[10] moreover, its relatively inexpensive price makes it more acceptable. Although 25-μg misoprostol is recommended in the Chinese guidelines for labor induction, no tablets with an accurate 25-μg dose of misoprostol are currently available in China.

In this study, we conducted the first double-blinded, prospective randomized controlled clinical trial in China to evaluate the efficacy and safety of intravaginal misoprostol in cervical ripening and labor induction in term pregnancy in nulliparous women, by using a misoprostol tablet with 25-μg dosage. We hope our data from Chinese women can contribute to the world's database of using misoprostol as a labor inductor, and help to reduce the high incidence of cesarean section in this country.

## Methods

This double-blinded, prospective randomized controlled clinical study of misoprostol was conducted in 6 university hospitals across China from May 2012 to February 2013. The study was performed in accordance with the guidelines of the Declaration of Helsinki and was approved by the ethics committees of each hospital. All the investigators involved in the participant enrollment and subsequent follow-up have been trained and are certified to perform clinical trials according to the Good Clinical Practice issued by the China Food and Drug Administration. This clinical study was approved by the China Food and Drug Administration (No. 2011L00457) and has been registered on *www.clinicaltrials.gov* with clinicaltrials.gov identifier: NCT 01428037.

The 25-μg vaginal misoprostol tablets and placebo tablets with consistency in color, dosage, shape, smell, packaging, and tags were produced and freely provided by Guangzhou Regenex Pharmaceuticals Ltd., Guangzhou, China.

### Inclusive and exclusive criteria

Nulliparous women with a live singleton pregnancy who were eligible for induction labor were recruited in this study. All women provided informed consent prior to participation in the study. All subjects were aged 20 years or older; had a gestational age between 37 and 42 weeks, with head fetal presentation and intact amniotic membrane. All subjects were induced labor for the indications according to the Chinese guideline of cervical ripening and labor induction during the third trimester pregnancy (draft)[6] but demonstrated an unfavorable cervix (cervical Bishop score ≤6). Women were excluded if any of the following criteria was met: Placenta previa, placenta abruption, breech or transverse presentation, significant cephalopelvic disproportion, preeclampsia or eclampsia, suspected macrosomia, emergent fetal distress, fetal congenital malformation, and prior uterine surgical procedure history. Women with severe chronic diseases of the cardiac, pulmonary, hepatic, renal, hematopoietic, endocrine, or immune system; acute infection; cervical carcinoma; and contra-indications for the use of PG analogues (glaucoma, asthma, epilepsy, and allergy to PG) were also excluded.

### Sample size

The incidences of vaginal deliveries achieved within 24 h ranged from 61.3% to 75% for the misoprostol group and 0–10% for the placebo group; the Bishop scoring increases ≥3 in 12 h were about 50% for the misoprostol group and 25% for the placebo group.[9] We estimated the sample size according to the incidences of Bishop scoring changes, which needed more sample size than those of vaginal deliveries within 24 h did, at a two-sided alpha = 0.05 with 80% power. To determine as many adverse events of misoprostol as possible, the sample size ratio of the misoprostol: Placebo group was set to 3:1. Using PASS software, we determined the sample size of 41 for placebo, and 123 for misoprostol group. For consideration of the sample loss rate, we increased the sample size by 20% for the placebo group and 40% for the misoprostol group. Finally, a final total sample size of 225, with 175 patients receiving misoprostol and 50 receiving placebo (at a ratio of 7:2), was decided.

### Randomization and blinding

Participants were randomly assigned to the misoprostol or placebo group. Both participants and investigators were masked to group assignment, and data remained blinded to researchers until study enrollment was complete. Block randomization was used to provide balanced enrollment

among the hospitals. Randomized via a computerized randomization sequence, misoprostol: Placebo ratio was set to 7:2 in each block. A total of 25 blocks were distributed among the hospitals. In case of emergent unblinding, an envelope with a blinding code and the participant's group was distributed with the tablets to the investigators.

### Treatment

Tablets of 25-μg misoprostol or placebo were applied into the posterior fornix of the vagina at an interval of 4 h (repeated up to 3 times) for labor induction. The second and/or third doses were not administered to women who had three uterine contractions per 10 min sustained for 30–60 s each, spontaneous membrane rupture, uterine hyperstimulation, fetal heart rate abnormality, or who had previous undissolved tablets in the vagina. This protocol was based on the International Federation of Gynecology and Obstetrics (FIGO) misoprostol recommended dosages,[11] the WHO recommendations for induction of labor,[12] and the Cochrane review by Hofmeyr *et al*.[9] The Bishop scores were assessed each time the second or third tablet was going to be placed, and 12 h and 24 h apart from the first tablet if the labor was not completed. Labor inductions by amniotomy, intravenous drip of oxytocin, or vaginal dinoprostone were applied 24 h after the first tablet was provided, if the women (both the misoprostol and placebo groups) were still not in labor.

### Outcome measures

The primary outcome measure was the incidence of cumulative Bishop score increases ≥3 within 12 h or vaginal delivery achieved within 24 h. The secondary outcome measures included the incidence of onset of labor within 24 h, median induction-onset of labor interval, the incidence of women requiring oxytocin augmentation, and incidence and indications of cesarean section deliveries.

### Safety measures

Maternal safety measures included fever, nausea, vomiting or diarrhea, incidence of uterine hyperstimulation with or without fetal heart incidence changes, postpartum hemorrhage, precipitate delivery, genital tract laceration, instrument-assisted vaginal deliveries, uterine rupture, and amniotic fluid embolism, among others. Fetal and neonatal safety measures included fetal heart rate abnormality, meconium-stained amniotic liquor, and Apgar score <7 at 5 min. All adverse events were recorded from the time of the first dose of the study treatment until discharge from the hospital.

### Statistical analysis

The data were processed using SAS 9.13 software (SAS Institute, Cary, NC, USA), and two-sided $P < 0.05$ was considered significant. Continuous data are described as the mean ± standard deviation (SD) or median and quartile range, while categorical data are described as the frequency and percentage. Covariance analysis was used to control for center effects and to compare whether the effectiveness index at baseline was balanced. Dichotomous variables were compared between the groups using the Chi-square test or Fisher's exact test, and continuous variables were analyzed using the independent Student's *t*-test. The differences in the induction-onset of labor intervals were evaluated by log-rank test with Kaplan–Meier survival estimates.

## Results

A total of 225 women were randomized and treated with at least one tablet of misoprostol ($n = 175$) or placebo ($n = 50$). Of these, 3 women who withdrew consent were lost to follow-up. Therefore, 222 women with 173 for misoprostol group and 49 for placebo were included in full analysis set and analyzed for effective measurements. The flow chart is summarized in Figure 1. The two groups had no significant difference in the baseline demographic or the indications for labor induction [Table 1]. The indications for labor induction included: Over 41 weeks of gestation, maternal complications (gestational hypertension or gestational diabetes mellitus), nonreassuring fetal status (oligohydramnios or poor placental function), and informed choices. Among the 175 women recruited in the misoprostol group, 20, 83, and 72 women received one, two, and three doses of 25-μg misoprostol over an 8-h dosing period, respectively. All the 225 women were analyzed for the safety measurements.

### Primary outcomes

The incidence of cumulative Bishop score increases ≥3 within 12 h or vaginal delivery within 24 h in the misoprostol group was significantly higher than that in the placebo group (64.2% vs. 22.5%, relative risk [*RR*]: 2.9, 95% confidence interval [*CI*]: 1.4–6.0) [Table 2].

We also compared the incidence of cumulative Bishop score increases ≥3 within 12 h and the incidence of vaginal delivery within 24 h in the two groups separately, and found both of these incidences in the misoprostol group are higher than those in the placebo group [Table 2].

**Table 1: Baseline demographic and indications for labor induction of the participants**

| Indices | Misoprostol ($n = 173$) | Placebo ($n = 49$) |
|---|---|---|
| Age (years), mean (SD) | 28.3 (2.97) | 27.9 (3.21) |
| BMI (kg/m$^2$), mean (SD) | 27.3 (3.0) | 26.9 (2.6) |
| Gestation weeks, mean (SD) | 40.1 (0.87) | 40.1 (0.81) |
| Smoking, *n* (%) | 0 (0.00) | 0 (0.00) |
| Alcohol addiction, *n* (%) | 0 (0.00) | 0 (0.00) |
| Estimated fetal weight (kg), mean (SD) | 3.5 (0.25) | 3.5 (0.29) |
| Bishop score, mean (SD) | 3.5 (1.04) | 3.6 (0.95) |
| Indications for labor induction, % | | |
| Over 41 weeks of gestational | 68.7 | 71.5 |
| Maternal complications | 13.9 | 12.2 |
| Nonreassuring fetal status | 13.9 | 14.3 |
| Informed choices | 3.5 | 2.0 |

BMI: Body mass index.

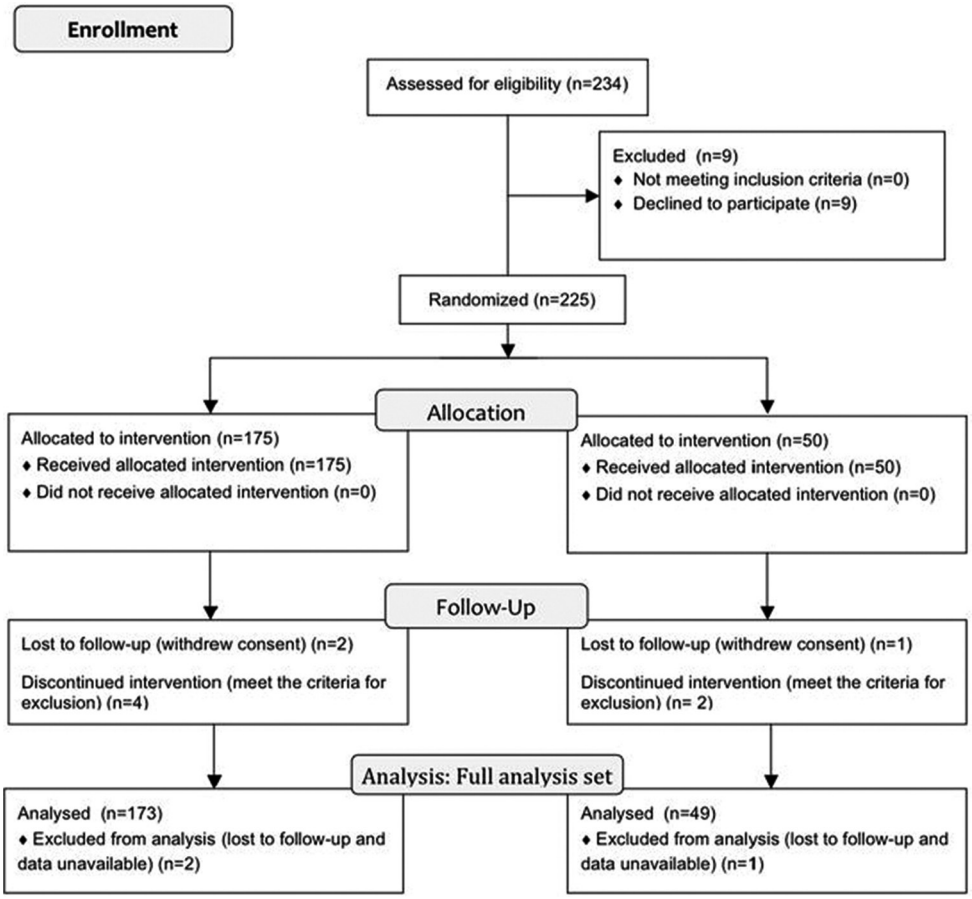


**Figure 1:** Flow chart of the women included in the study.

**Table 2: Comparison of the efficacy outcome measures between the misoprostol group and the placebo group**

| Items | Misoprostol ($n$ = 173) | Placebo ($n$ = 49) | Relative risk (95% *CI*) | *P* |
|---|---|---|---|---|
| Primary outcome measures | | | | |
| Incidence of cumulative Bishop score increases ≥3 within 12 h or vaginal delivery within 24 h ($n$ (%)) | 111 (64.2) | 11 (22.5) | 2.9 (1.4–6.0) | – |
| Incidence of cumulative Bishop score increases ≥3 within 12 h ($n$ (%)) | 85 (49.1) | 9 (18.4) | 2.7 (1.2–5.8) | |
| Incidence of vaginal delivery within 24 h ($n$ (%)) | 57 (33.0) | 5 (10.2) | 3.2 (1.2–8.6) | |
| Secondary outcome measures | | | | |
| Incidence of onset of labor within 24 h ($n$ (%)) | 83 (48.0) | 9 (18.4) | 2.6 (1.2–5.7) | |
| Median process time of vaginal labor, hours (median (Q1–Q3), $n$) | 6.4 (4.8–8.5) ($n$ = 105) | 6.8 (5.0–9.6) ($n$ = 25) | | 0.695 |
| Incidence of oxytocin augmentation requirement ($n$ (%)) | 44 (25.4) | 18 (36.7) | 0.7 (0.4–1.4) | – |
| Incidence of caesarean section deliveries ($n$ (%)) | 68 (39.3) | 24 (49.0) | 0.8 (0.4–1.5) | – |

*CI*: Confidence interval.

## Secondary outcomes

The incidence of onset of labor within 24 h in the misoprostol group was significantly higher than that of the placebo group (48.0% vs. 18.4%, *RR*: 2.6, 95% *CI*: 1.2–5.7) [Table 2].

The median induction-onset of labor intervals in both groups were not able to be calculated because the incidence of onset of labor in each group was <50%. However, when comparing the induction-onset of labor intervals between the two groups by log-rank test, we found the misoprostol group had significantly shorter induction-onset of labor intervals than the placebo group ($P$ = 0.0003) [Figure 2].

There was no significant difference in the median process time of vaginal labor (in hours, median [Q1–Q3]) between the two groups (6.4 [4.8–8.5] vs. 6.8 [5.0–9.6], $P$ = 0.695) [Table 2].

Although the incidence of oxytocin augmentation requirement in the misoprostol group tended to be lower than that of the placebo group, there was no significant difference

between the two groups (25.4% vs. 36.7%, *RR*: 0.7, 95% *CI*: 0.4–1.4) [Table 2].

Similarly, although the incidence of cesarean section deliveries in the misoprostol group tended to be lower than that of the placebo group, there was no significant difference between the two groups (39.3% vs. 49.0%, *RR*: 0.8, 95% *CI*: 0.4–1.5) [Table 2].

When comparing the indications for caesarean sections between the two groups, although there was a trend of more operations for suspected fetal distress and fewer for prolonged labor progress in the misoprostol group, this did not reach statistical significance ($P = 0.683$) [Table 3].

## Safety and tolerability

There were no significant differences in the incidences of any of the analyzed maternal and fetal adverse events between the two groups. There were no cases of precipitate delivery, uterine rupture, and amniotic embolism during the study, while uterine hyperstimulation with or without fetal heart rate abnormalities could be seen in both groups. Three postpartum hemorrhages were found in the misoprostol group, as compared to none in the placebo group, and the incidence of meconium-stained liquor tended to be higher in the misoprostol group; however, these data did not reach statistical significance [Table 4].

One woman in the misoprostol group received hysterectomy because of overwhelming postpartum hemorrhage. Eight hours after the third tablet of misoprostol was provided, this woman underwent a cesarean section, because her baby showed a frequent late deceleration in the latent period. During the section, this woman experienced a blood loss of over 5000 ml due to uterine atony, and her vital signs were unstable until she underwent the hysterectomy.

**Table 3: Comparison of indications for cesarean delivery in the misoprostol and placebo groups, *n* (%)**

| Factors | Misoprostol (*n* = 68) | Placebo (*n* = 24) | *P* |
|---|---|---|---|
| Suspected fetal distress | 32 (47.1) | 10 (41.7) | 0.683 |
| Prolonged labor | 20 (29.4) | 9 (37.5) | |
| Informed choice | 14 (20.6) | 4 (16.7) | |
| Others | 2 (2.9) | 1 (4.2) | |

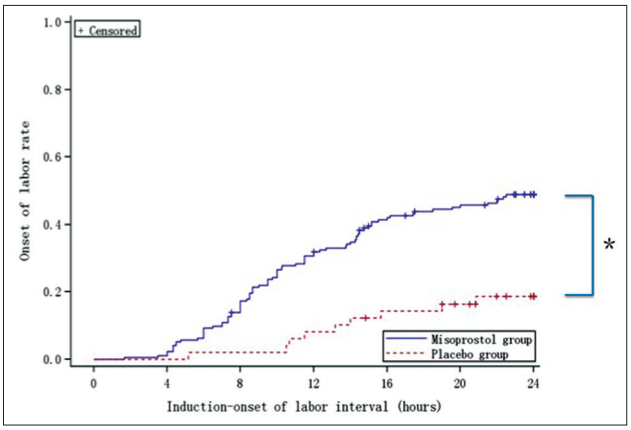


**Figure 2:** Kaplan–Meier survival estimates of the difference in the induction-onset of labor intervals between the misoprostol group ($n = 173$) and placebo group ($n = 49$). *Significant difference ($P = 0.0003$).

**Table 4: Comparison of the incidence of maternal and fetal adverse events in the misoprostol group and the placebo group, *n* (%)**

| Events | Misoprostol (*n* = 175) | Placebo (*n* = 50) | *P* |
|---|---|---|---|
| Any adverse events | 76 (43.4) | 16 (32.0) | 0.267 |
| Maternal adverse events | | | |
| Fever | 2 (1.1) | 0 (0.0) | >0.999 |
| Nausea or vomiting | 1 (0.6) | 0 (0.0) | >0.999 |
| Diarrhea | 1 (0.6) | 0 (0.0) | >0.999 |
| Constipation | 9 (5.1) | 0 (0.0) | 0.213 |
| Abnormal liver function | 8 (4.6) | 1 (2.0) | 0.688 |
| Anemia | 3 (1.7) | 1 (2.0) | >0.999 |
| Uterine hyperstimulation | 2 (1.1) | 1 (2.0) | 0.531 |
| Postpartum hemorrhage >500 ml* | 3 (1.7) | 0 (0.0) | >0.999 |
| Hysterectomy because of postpartum hemorrhage | 1 (0.6) | 0 (0.0) | >0.999 |
| Precipitate delivery | 0 (0.0) | 0 (0.0) | – |
| Perineal laceration | 19 (18.1) (*n* = 105) | 5 (20.0) (*n* = 25) | 0.780 |
| Instrument-assisted vaginal deliveries | 1 (1.0) (*n* = 105) | 1 (4.0) (*n* = 25) | 0.349 |
| Uterine rupture | 0 (0.0) | 0 (0.0) | – |
| Amniotic embolism | 0 (0.0) | 0 (0.0) | – |
| Fetal adverse events | | | |
| Fetal heart rate abnormality | 5 (2.9) | 2 (4.0) | 0.653 |
| Meconium – stained liquor | 37 (21.1) | 8 (16) | 0.423 |
| Apgar score <7 at 5 min | 1 (0.6) | 0 (0.0) | >0.999 |

*Includes the women who had a hysterectomy because of postpartum hemorrhage.

## Discussion

This study is the first double-blinded, prospective randomized controlled clinical trial evaluating the efficacy and safety of intravaginal misoprostol in cervical ripening and labor induction in term pregnancy in China. We found that, compared with the placebo, 25-μg intravaginal misoprostol significantly increased the incidence of cumulative Bishop score increases ≥3 within 12 h or vaginal delivery within 24 h from the start of labor induction, without significantly increasing the maternal and fetal complications and adverse events, which is consistent with other previous studies on the topic.[8] Our data also showed that 25-μg intravaginal misoprostol significantly increased the incidence of onset of labor within 24 h and reduced the induction-onset of labor interval when compared with a placebo, which is in agreement with previous reports.[13,14] Our findings suggested intravaginal misoprostol 25 μg is efficacious and safe in labor induction and cervical ripening in term pregnancy.

On the other hand, 25-μg intravaginal did not significantly reduce the median duration of vaginal labor. Further, when we compared the duration of each of the three periods of vaginal labor between the two groups, we similarly did not find any significant difference between the misoprostol and placebo groups (data not shown). This result differs from that of two other randomized controlled trials,[15,16] which reported a shorter duration of the latency period or active period in the misoprostol group. However, both of these previous studies lacked placebo controls, and may hence have an inherent performance and/or detection bias. Our double-blinded, prospective randomized controlled study suggested that 25-μg intravaginal misoprostol could only shorten the induction-onset of labor interval, but it does not have prolonged effects on the process of vaginal labor, as long as the labor starts.

Herein, although we found that the incidence of caesarean section deliveries in the misoprostol group tended to be lower than in the placebo group, no significant difference was found. Similarly, when analyzing the indication of cesarean section, although we found that there was a trend of more operations for fetal distress and fewer for prolonged labor progress in the misoprostol group, it did not reach statistical significance. In the previous studies about misoprostol use in labor induction, the rates of caesarean section in the misoprostol groups were inconsistent, although they tended to be reduced.[9] A recent network meta-analysis of labor induction with PGs found that intravaginal misoprostol (both tablets <50 μg and ≥50 μg) significantly reduced the cesarean section risk compared with placebo.[17] The insignificance of the difference of the cesarean section rate between the misoprostol and placebo groups in our study might be attributable to the limited numbers of patients recruited, and the effect of misoprostol on reducing the cesarean section rate should be further studied in the future.

In terms of the safety assessments, although there were no significant differences in the incidences of the adverse events/serious adverse events between the two groups, there were still some severe adverse events, including one case of hysterectomy due to overwhelming postpartum hemorrhage caused by uterine atony in the misoprostol group. In the previous studies of misoprostol in labor induction, neonatal and maternal mortality, and serious morbidity outcomes are often too rare or poorly reported. Our study suggests that, although the incidence of serious adverse events of intravaginal misoprostol insert for labor induction was low, clinicians should still be careful and be aware of the possible complications when using misoprostol for labor induction.

In our study, intravaginal 25-μg misoprostol applied every 4 h was found to be effective and safe. Our protocol was decided according to the FIGO Misoprostol Recommended Dosages, which changed to intravaginal 25-μg misoprostol every 6 h in 2012, after we had fixed our protocol. Until now, no study has been performed on the differences between 4-hourly and 6-hourly intravaginal misoprostol in labor induction, although both interval hours have been used in the clinical studies. Thus, more studies are needed to determine the optimal interval time for intravaginal misoprostol as a labor inducer.

Although this was a randomized, double-blinded, controlled study, several limitations exist. First, the inclusion and exclusion criteria may limit the generalizability of the data, particularly the stringent criterion of exclusion of any maternal or fetal compromise. Moreover, the solubility of the misoprostol tablets in the vagina, which might affect the onset time of the effectiveness of the tablets, was not recorded in this study.

In conclusion, our study suggested that 25-μg intravaginal misoprostol every 4 h is efficacious in labor induction and cervical ripening without significantly increasing the rates of maternal and fetal complications and adverse events. Further, 25-μg intravaginal misoprostol could reduce the induction-onset of labor interval, but did not show any effects on the process of vaginal labor. Clinicians should always be vigilant of the maternal and fetal complications when using misoprostol as a labor inducer. Herein, we provided data from the first double-blinded, prospective randomized controlled study on misoprostol for cervical ripening and labor induction in China. Our data from Chinese women can contribute to the world's database of using misoprostol as a labor inductor, and help to reduce the high incidence of cesarean section in this country.

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## Conflicts of interest

There are no conflicts of interest.

## References

1. WHO. Global Survey on Maternal and Perinatal Health. Global Survey Database Crude Tabulations. Geneva: World Health Organization; 2010. Available from: http://www.who.int/entity/reproductivehealth/topics/best_practices/globalsurveyoriginal/en/index.html. [Last revised on 2010 Aug, Last accessed on 2015 Sep 10].
2. Ventura SJ, Martin JA, Curtin SC, Mathews TJ. Births: Final data for 1997. Natl Vital Stat Rep 1999;47:1-96.
3. Martin JA, Hamilton BE, Ventura SJ, Osterman MJ, Kirmeyer S, Mathews TJ, *et al.* Births: Final data for 2009. Natl Vital Stat Rep 2011;60:1-70.
4. Feng XL, Wang Y, An L, Ronsmans C. Cesarean section in the People's Republic of China: Current perspectives. Int J Womens Health 2014;6:59-74.
5. Jin F, Sun Y, Liao Q. The discussion of induction and successful incidence of labor at term. Chin J Clin Obstet Gynecol 2009;4:248-51.
6. Obstetrics Subgroup, Chinese Society of Obstetrics and Gynecology, Chinese Medical Association. Guideline of cervical ripening and labor induction during the third trimester pregnancy (draft). Zhonghua Fu Chan Ke Za Zhi 2008;43:75-6.
7. Obstetrics Subgroup, Chinese Society of Obstetrics and Gynecology, Chinese Medical Association. Guideline of cervical ripening and labor induction during the third trimester pregnancy. Zhonghua Fu Chan Ke Za Zhi 2014;49:881-5.
8. Thomas J, Fairclough A, Kavanagh J, Kelly AJ. Vaginal prostaglandin (PGE2 and PGF2a) for induction of labour at term. Cochrane Database Syst Rev 2014;6:CD003101.
9. Hofmeyr GJ, Gülmezoglu AM, Pileggi C. Vaginal misoprostol for cervical ripening and induction of labour. Cochrane Database Syst Rev 2010;10:CD000941.
10. Crane JM, Butler B, Young DC, Hannah ME. Misoprostol compared with prostaglandin E2 for labour induction in women at term with intact membranes and unfavourable cervix: A systematic review. BJOG 2006;113:1366-76.
11. Misoprostol Recommended Dosages. International Federation of Gynecology and Obstetrics (FIGO); 2007. Available from: http://www.aogm.org.mo/assets/Uploads/aogm/Guidelines/FIGO/MisoprostolPoster2.pdf. [Last accessed on 2015 Sep 10].
12. WHO, Department of Reproductive Health and Research. WHO recommendations for induction of labour. Geneva: World Health Organization; 2011. Available from: http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241501156/en/ [Last accessed on 2015 Sep 10].
13. McKenna DS, Ester JB, Proffitt M, Waddell KR. Misoprostol outpatient cervical ripening without subsequent induction of labor: A randomized trial. Obstet Gynecol 2004;104:579-84.
14. Stitely ML, Browning J, Fowler M, Gendron RT, Gherman RB. Outpatient cervical ripening with intravaginal misoprostol. Obstet Gynecol 2000;96:684-8.
15. da Graça Krupa F, Cecatti JG, de Castro Surita FG, Milanez HM, Parpinelli MA. Misoprostol versus expectant management in premature rupture of membranes at term. BJOG 2005;112:1284-90.
16. Oboro VO, Tabowei TO. Outpatient misoprostol cervical ripening without subsequent induction of labor to prevent post-term pregnancy. Acta Obstet Gynecol Scand 2005;84:628-31.
17. Alfirevic Z, Keeney E, Dowswell T, Welton NJ, Dias S, Jones LV, *et al.* Labour induction with prostaglandins: A systematic review and network meta-analysis. BMJ 2015;350:h217.