



Comparison of Isosorbide Mononitrate Versus Misoprostol in Cervical Ripening at Term Before Induction of Labor: A Clinical Trial

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Abstract

Objectives: The aim of this study was to compare the effect of nitric oxide (Isosorbide mononitrate) versus misoprostol in cervix ripening and labor progression.

Methods: This study was a clinical trial. One hundred females with term pregnancies, referred for induction of labor with bishop score of six or less, were randomly allocated to receive either 40 mg Isosorbide Mononitrate (IMN) tablet vaginally or 25 μ g misoprostol vaginally every six hours for a maximum of three doses. P value of less than 0.05 was considered statistically significant.

Results: The bishop score decreased significantly due to increasing abortion numbers ($P = 0.04$; $r = -0.19$), yet this relationship in the two studied groups wasn't significant (P misoprostol = 0.67; $r = -0.06$, and P IMN = 0.57; $r = -0.05$). The mean primary bishop score was similar in the two groups ($P = 0.06$) yet the final score in the IMN group was significantly lower than the misoprostol group ($P = 0.001$). Also, Apgar score in the IMN group was significantly higher than the misoprostol group ($P = 0.02$). There was a significant difference between the side effects (meconium amniotic fluid, nausea, atony, abdominal pain and tachysystole) and medication group, while this was significantly lower in IMN than the misoprostol group ($P = 0.001$). P values of less than 0.05 were considered statistically significant.

Conclusions: Cervical ripening with IMN resulted in fewer adverse effects, and it was safer to use for cervical ripening. Therefore, it could be a good substitute for patients with a contraindication for misoprostol.

Keywords: Cervix, Misoprostol, Isosorbide Mononitrate, Bishop Score

1. Background

The final phase of pregnancy in human is commitment with contractions in the uterine that causes cervix ripening and leads the fetus to the delivery canal (1). The effect of prostaglandins (2-7) and Nitric Oxides (NO) (8, 9) on cervix ripening are known. Evaluation of the fundamental basis of NO donors like Isosorbide Mononitrate (IMN) and glyceryl trinitrate showed that IMN induces the cyclooxygenase enzymes in the cervix (5). Also, it induces variable configuration in supra-structure of cervix, like visible changes in its spontaneously rip procedures. Previous studies showed that the efficacy of NO in cervix ripening isn't like prostaglandin E2 (7, 9). Adding isosorbide mononitrate to dinoprostone or misoprostol did not increase the cervical ripening (8, 10-12).

The aim of this study was to compare between the ef-

ficacies of IMN versus misoprostol. Furthermore, this research evaluated the duration between prescription and delivery, amount of administered medicine in each group for cervix ripening, need for oxytocin for labor induction and probable side effects, in both therapeutic methods.

2. Methods

This study was a prospective clinical trial, double blind, randomization and pilot study that was done at Imam Reza hospital, Mashhad, Iran.

At first, the researchers registered this study on the RCT site with the following code: IRCT2017031233025N1. The researcher and analyst were unaware of the type of drug.

According to reference 4, this research considered 50 subjects in each group, thus, the present study was performed on 100 full term pregnant females (37 weeks or

more). They had the indication of ending pregnancy and did not use any methods for cervix ripening. The patients, who were 37 to 42 weeks pregnant, without underlying disease, without indication of vaginal misoprostol were entered in the study.

When the subjects had a bishop score equal to six or less, they were randomly allocated to one medication group by students of obstetrics and gynecology with A and B packet. A written consent form was obtained from all patients and ethics committee of Mashhad University of Medical Sciences confirmed the study protocol (code = 89886). The researchers recorded the demographic and pregnancy-related information and maternal medical history.

Electrocardiogram (ECG), heart physical examination, and blood pressure measurement was determined for all patients at the admission time. The bishop score was graded according to five criteria, including cervical dilation, effacement, consistency, and cervical and fetal station. According to a random table, the patients were allocated to two groups; in the misoprostol group, 25 µg of misoprostol tablets was administrated intra-vaginally every six hours for three doses. Prior to consumption, the bishop score was determined as well.

In the IMN group, 40 mg of IMN (two 20-mg tablets) was administrated intra-vaginally every six hours for three doses. All the patients in this group were under heart monitoring, till the end of delivery and for one hour afterwards. Moreover, in this group, up to three doses of IMN was used, if the cervix was not ripened.

In both groups, the bishop score was determined before each administration and mother's pulse and blood pressure was recorded. Therapeutic consumptions were stopped after consumption of three doses, whether or not the cervix was ripened.

Then the subjects were evaluated regarding the need for oxytocin induction and delivery course, kind of delivery, and neonatal Apgar on the first and fifth minute. During this period, all the probable therapeutic side effects were recorded. The exclusion criteria were considered as pregnancies below 37 weeks, bishop score of more than six, and using any other methods for cervix ripening. In addition, patients were excluded if they had any coagulation disorder, cardiovascular diseases, hypertension, adrenal diseases, corticosteroids therapy for any reason, cesarean history or any other womb surgery, and special problems related to pregnancy, such as severe pre-eclampsia.

2.1. Statistical Analysis

According to the study entitled "Randomized trial of isosorbide mononitrate versus misoprostol; for cervical ripening at term" conducted during year 2002, and the

mean bishop scores with a power of 80% and an alpha error of 5%, the sample size was calculated in each group as 35 people. Considering loss specimens, 50 subjects in each group were examined. This calculation was carried out using the two-sample t test method.

The SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA) was used for all statistical procedures. Data were expressed at mean ± SD. Differences in proportions were judged by χ^2 test and the t-test. A two-tailed P value of less than 0.05 was considered statistically significant.

3. Results

Hundreds of patients were entered in this study. The mean age of the participants was 25.11 ± 0.76 years old. There was a significant difference in the two therapeutic groups (24.34 ± 0.57 in Misoprostol and 25.88 ± 0.74 in Isosorbide patient; $P = 0.048$). The other demographic characteristics of the participants are shown in Table 1.

Table 1. Demographic Characteristics of the Studied Participants in Two Therapeutic Groups^a

Variables	Therapeutic Groups		P Value
	Misoprostol	Isosorbide	
Age	24.34 ± 0.57	25.88 ± 0.74	$P < 0.01$
Pregnancy			0.04
One	35 (70)	24 (48)	
More			
Two	13 (26)	15 (30)	
Three	1 (2)	5 (10)	
Four	1 (2)	2 (4)	
Five	0	4 (8)	
Abortion			0.01
-	48 (96)	39 (78)	
+	2 (4)	11 (22)	
Previous live birth			0.27
No	37 (74)	31 (48)	
Yes			
One	11 (22)	10 (30)	
Two	1 (2)	3 (10)	
Three	1 (2)	4 (6)	
Four	0	2 (6)	

^aValues are expressed as mean ± SD or No. (%).

According to LMP ($P = 0.92$) and sonography ($P = 0.31$), the mean parietal age wasn't significantly different among the two groups. Among the studied participants, 59 were having their first delivery (35 in the misoprostol; 24 in the

IMN group). Although the difference between first time labor (nulliparous) was seen in the primary analysis ($P = 0.04$), yet by removing this variable, as a confounding variable, this difference wasn't significant ($P = 0.06$).

In addition, the ratio of mothers without abortion in the misoprostol group (96%) was higher than IMN (78%) ($P = 0.01$). Furthermore, the bishop score decreased significantly due to increasing abortion numbers ($P = 0.04$; $r = -0.19$), yet this relationship in the two studied groups was not significant (misoprostol ($P = 0.67$; $r = -0.06$), IMN ($P = 0.57$; $r = -0.05$)).

Thirteen and 15 patients had one previous pregnancy in the misoprostol and IMN group, respectively, yet among them only 11 and 10 patients had a successful live birth delivery. The patients' previous gravity and parity history are summarized in Table 1. Comparison between the primary bishop score (at the admission time) and the final score is presented in Figures 1 and 2. The current analysis revealed that the mean primary bishop score was similar in the two groups ($P = 0.06$) yet the final score in the IMN group was significantly lower than the misoprostol group ($P = 0.04$). The relationship between the final bishop score and delivery numbers (Table 1) showed that there was a similar final bishop score in primipara females (8.17 ± 0.67) and multipara subjects (8.27 ± 0.54) that used misoprostol ($P = 0.65$; $r = 0.06$). While primipara females used IMN (7.04 ± 0.46), they had significantly lower bishop score than multiparas females (8.17 ± 0.67) ($P = 0.02$; $r = 0.30$). Ninety percent and 80% of mothers with misoprostol and IMN treatment, respectively, had similar scores in normal vaginal delivery ($P = 0.048$, Table 2). The most common cause of cesarean was failure to progress in 53.3% of cases in the two groups. The patients in the misoprostol group underwent cesarean due to prolonged labor, fetal distress, and meconium amniotic fluid.

The mean Apgar score showed that in the IMN group, it was significantly more than the misoprostol group, yet all were higher than seven and were normal and without any side effects. The mean duration of delivery of mothers in the IMN (18.60) group was significantly more than the misoprostol group ($P = 0.001$) (Table 2). Evaluation of the side effects showed that 15 cases (30%) in the misoprostol group (meconium amniotic fluid (4), nausea (4), atony (2), abdominal pain (1), tachysystole (1)) and two cases (4%) in the IMN (nausea and headache) group experienced side effects. There weren't significant differences between side effects and medication group, while this was significantly lower in IMN group ($P = 0.001$).

Table 2. Comparison of Variables in Two Therapeutic Groups

Variables	Therapeutic Groups		P Value
	Misoprostol	Isosorbide	
Apgar score > 7	50	50	-
Delivery time, mean \pm SD, h	16.67 \pm 1.69	18.60 \pm 2.75	< 0.01
Delivery			0.16
Vaginal	45 (90)	40 (80)	
Cesarean	5 (10)	10 (20)	
Need to induction*			< 0.01
Positive	5 (10)	38 (76)	
Negative	45 (90)	12 (24)	
Side effects			< 0.01
Positive	15 (30)	2 (4)	
Negative	35 (70)	48 (96)	

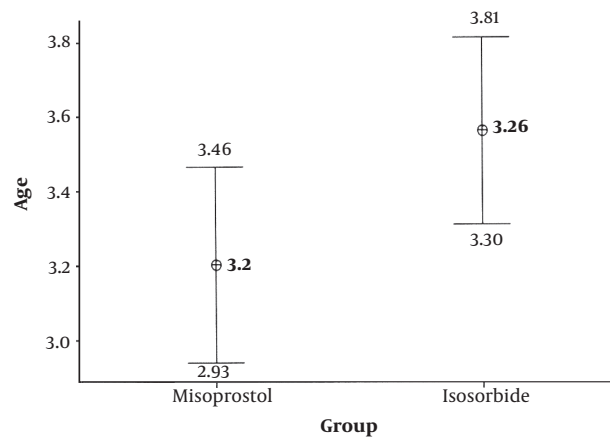


Figure 1. Comparison of bishop scores (admission time) in two studied groups ($P = 0.06$)

4. Discussion

The current results showed that there weren't significant differences among number of dosage therapy in the two studied groups. Chanrachakul et al. showed that IMN had lower side effects and efficacies with more needed oxytocin induction, compared with the misoprostol group (13), as the lower side effects of IMN were shown in the studis of Agawal et al. and Ei-Khayat et al. (14, 15). Also, in the current study, the authors found that side effects were more in the misoprostol group and the final bishop score was better with this therapy. The authors found that similar to the current study, the cesarean numbers weren't different in the two studied groups while the reasons were different (distocia and fetal distress in the IMN and misoprostol group, respectively) (8). However, in the current study,

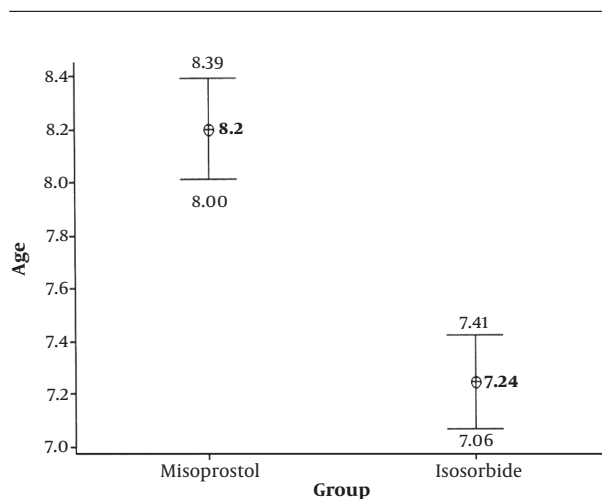


Figure 2. Comparison of final bishop scores in the two studied groups ($P < 0.001$)

the commonest reason for cesarean was failure to progress in the two groups. Evaluation of post term pregnant females (42 weeks) regarding IMN in the study of Bullarbo et al. showed that the commonest side effect was headache; however, no significant adverse effects were seen for mothers and the fetus (7). In addition, in the current study improvement of bishop score and any reasonable side effects (except headache and nausea) were presented for IMN administered subjects. Osman et al. evaluated prostaglandin E₂ (PGE₂) and IMN for cervix ripening before term delivery. They showed that PGE₂ had greater effects on bishop score variations than IMN and increased it more (16). The mean delivery duration (from beginning of treatment to delivery time) in IMN was longer than the PGE₂ group, as the study of Mizarchi et al. showed that PGE₂ was associated with a very high risk of cesarean delivery (17) and the other study demonstrated that IMNs were safe for cervical ripening (18). Furthermore, there weren't any severe side effects in the IMN group and mother's satisfaction level was higher in this group. However, the current study did not evaluate mother's satisfaction level yet found that misoprostol (from the prostaglandin family) significantly decreased the bishop score with shorter delivery duration. Chanrachakul et al. showed that using nitrates for cervix's ripening had lesser efficacies and side effects than PGE₂ (13). The current study did not evaluate the other therapies, yet regardless, cervix ripening and side effects like tachysystole in the misoprostol group was more than the IMN group.

Dawswell et al. evaluated different therapeutic and mechanical methods for cervix ripening. They found that there was not any adequate evidence for determining preferable and economic methods. However, the current

authors recommend that IMN is a safer method for cervix ripening due to its lesser side effects for the mother and fetus when compared with misoprostol (19).

Collingham et al. showed that NVD time was not shortened by IMN treatment. Also, cesarean numbers and abnormal FHR were the same between IMN and misoprostol groups (12). However, similar to the current study, they found that headache in the IMN group was more prevalent than the misoprostol group. Hofmer et al. evaluated the ISMO group ambulatory with the placebo group as control for cervical ripening. They found that duration between admission time to delivery and need to induction was lower in the Ismo group than the placebo (4). Moreover, similar to the current study, the tach systole prevalence was low, yet there weren't reasonable results regarding cesarean numbers and hyper-stimulation. However, in the current study, there were similar results in misoprostol and IMN about the cesarean, yet the authors did not observe hyper stimulation as a side effect.

In another study on cervical ripening and cephalic position pregnancy by IMN and placebo as control in nulliparous females, it was shown that IMN did not decrease delivery duration time and increased bishop score when compared with the placebo. Also, there weren't any differences in pain, emotional experience, and inclination to using this method for the next delivery (20). This study did not evaluate patient's inclination for the next delivery, while using IMN for cervix ripening showed that this 7% decrease led to reduction of 98.13£ for admission expenses (20). However, this study did not evaluate the overall admission expenses in the patients, yet due to cheaper expenses in the IMN compared with misoprostol (140.00 IR versus 30.000 IR for six pills) and its lesser side effects, this could be applied as a safe and cheap therapy.

4.1. Conclusion

In conclusion, IMN is an effective therapy for bishop score improvement, although in different studies, the cervix has shown variable responses to this therapy and it acts slower than prostaglandins, especially misoprostol. However, due to lesser side effects and economical expenses of IMN, it could be performed for cervical ripening of term pregnant females, thus, it could be recommended for future surveys in other countries as an appropriate ambulatory approach.

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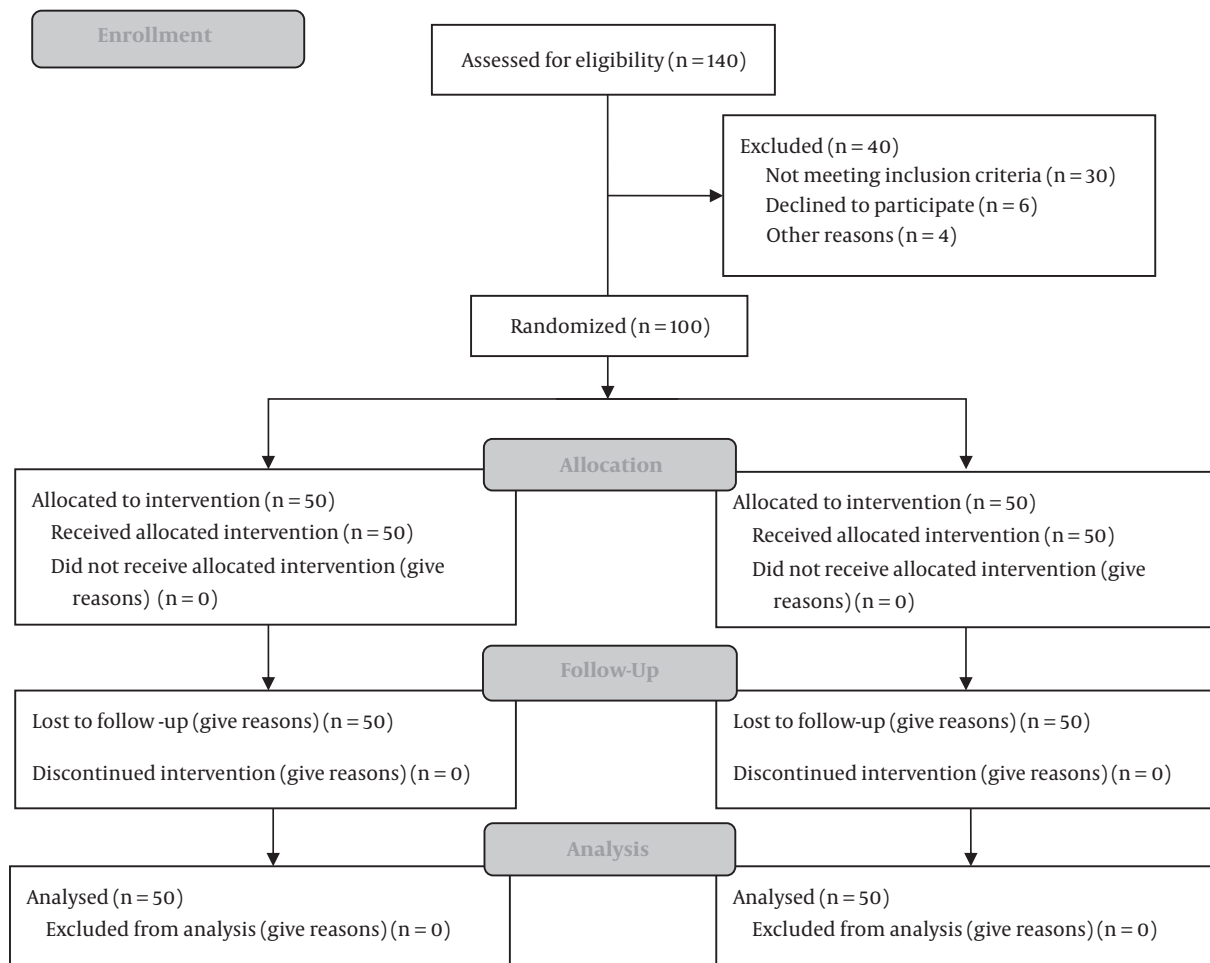


Figure 3. Study flowchart

Footnotes

Authors' Contribution: Conception and design by Marzieh Lotfalizade. Analysis and interpretation by Marzieh Lotfalizade. Data collection by Marzieh Lotfalizade, Nayereh Khadem Ghaebi, Vida Taghipour Bazargani, and Farideh Golhasani Keshtan. Writing of the article by Marzieh Lotfalizade, Nayereh Khadem Ghaebi. Critical revision of the article by Marzieh Lotfalizade and Nayereh Khadem Ghaebi. Final approval of the article by Marzieh Lotfalizade, Nayereh Khadem Ghaebi, Vida Taghipour Bazargani, and Farideh Golhasani Keshtan. Statistical analysis by Farideh Golhasani Keshtan. Overall responsibility by Nayereh Khadem Ghaebi.

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References

1. E. Riley L, R. Stark A. *American academy of pediatric and American college of obstetrics and gynecologists: guideline of parental care*. 6th ed. Washington; 2007.
2. Chan LY, Fu L, Leung TN, Wong SF, Lau TK. Obstetric outcomes after cervical ripening by multiple doses of vaginal prostaglandin E2. *Acta Obstet Gynecol Scand*. 2004;**83**(1):70–4. doi: [10.1111/j.1600-0412.2004.00356.x](https://doi.org/10.1111/j.1600-0412.2004.00356.x). [PubMed: [14678088](https://pubmed.ncbi.nlm.nih.gov/14678088/)].
3. Guinn DA, Davies JK, Jones RO, Sullivan L, Wolf D. Labor induction in women with an unfavorable Bishop score: randomized controlled trial of intrauterine Foley catheter with concurrent oxytocin infusion versus Foley catheter with extra-amniotic saline infusion with concurrent oxytocin infusion. *Am J Obstet Gynecol*. 2004;**191**(1):225–9. doi: [10.1016/j.ajog.2003.12.039](https://doi.org/10.1016/j.ajog.2003.12.039). [PubMed: [15295370](https://pubmed.ncbi.nlm.nih.gov/15295370/)].
4. Hofmeyr GJ, Gulmezoglu AM. Vaginal misoprostol for cervical ripening and induction of labour. *Cochrane Database Syst Rev*. 2003;(1):Cd000941. doi: [10.1002/14651858.cd000941](https://doi.org/10.1002/14651858.cd000941). [PubMed: [12535398](https://pubmed.ncbi.nlm.nih.gov/12535398/)].
5. Kelly AJ, Munson C, Minden L. Nitric oxide donors for cervical ripening and induction of labour. *Cochrane Database Syst Rev*.

- 2011;(6):Cd006901. doi: [10.1002/14651858.CD006901.pub2](https://doi.org/10.1002/14651858.CD006901.pub2). [PubMed: [21678363](https://pubmed.ncbi.nlm.nih.gov/21678363/)].
6. Ghosh A, Lattey KR, Kelly AJ. Nitric oxide donors for cervical ripening and induction of labour. *Cochrane Database Syst Rev*. 2016;**12**:Cd006901. doi: [10.1002/14651858.CD006901.pub3](https://doi.org/10.1002/14651858.CD006901.pub3). [PubMed: [27918616](https://pubmed.ncbi.nlm.nih.gov/27918616/)].
 7. Bullarbo M, Orrskog ME, Andersch B, Granstrom L, Norstrom A, Ekerhovd E. Outpatient vaginal administration of the nitric oxide donor isosorbide mononitrate for cervical ripening and labor induction postterm: a randomized controlled study. *Am J Obstet Gynecol*. 2007;**196**(1):500-5. doi: [10.1016/j.ajog.2006.08.034](https://doi.org/10.1016/j.ajog.2006.08.034). [PubMed: [17240231](https://pubmed.ncbi.nlm.nih.gov/17240231/)].
 8. Chanrachakul B, Herabutya Y, Punyavachira P. Randomized comparison of glyceryl trinitrate and prostaglandin E2 for cervical ripening at term. *Obstet Gynecol*. 2000;**96**(4):549-53. doi: [10.1097/00006250-200010000-00013](https://doi.org/10.1097/00006250-200010000-00013). [PubMed: [11004357](https://pubmed.ncbi.nlm.nih.gov/11004357/)].
 9. Promsonthi P, Preechapornprasert A, Chanrachakul B. Nitric oxide donors for cervical ripening in first-trimester surgical abortion. *Cochrane Database Syst Rev*. 2015. doi: [10.1002/14651858.CD007444.pub4](https://doi.org/10.1002/14651858.CD007444.pub4).
 10. Hatanaka AR, Moron AF, Auxiliadora de Aquino MM, de Souza E, de Silva Bussamra LC, Araujo Junior E, et al. Interruption of a study of cervical ripening with isosorbide mononitrate due to adverse effects. *Clin Exp Obstet Gynecol*. 2012;**39**(2):175-80. [PubMed: [22905458](https://pubmed.ncbi.nlm.nih.gov/22905458/)].
 11. Collingham J, Fuh K, Caughey A. randomized clinical trial of cervical ripening and labor induction using a misoprostol with or without intravaginal isosorbide mononitrate. In: 29th , editor. *Society for Maternal-Fetal Medicine (SMFM) 29th Annual Meeting*. 2009. 145 p.
 12. Collingham JP, Fuh KC, Caughey AB, Pullen KM, Lyell DJ, El-Sayed YY. Oral misoprostol and vaginal isosorbide mononitrate for labor induction: a randomized controlled trial. *Obstet Gynecol*. 2010;**116**(1):121-6. doi: [10.1097/AOG.0b013e3181e408f2](https://doi.org/10.1097/AOG.0b013e3181e408f2). [PubMed: [20567177](https://pubmed.ncbi.nlm.nih.gov/20567177/)].
 13. Chanrachakul B, Herabutya Y, Punyavachira P. Randomized trial of isosorbide mononitrate versus misoprostol for cervical ripening at term. *Int J Gynaecol Obstet*. 2002;**78**(2):139-45. doi: [10.1016/S0020-7292\(02\)00128-5](https://doi.org/10.1016/S0020-7292(02)00128-5). [PubMed: [12175715](https://pubmed.ncbi.nlm.nih.gov/12175715/)].
 14. Agarwal K, Batra A, Batra A, Aggarwal A. Randomized Comparison of Isosorbide Mononitrate and PGE2 Gel for Cervical Ripening at Term including High Risk Pregnancy. *Int J Reprod Med*. 2014;**2014**:147274. doi: [10.1155/2014/147274](https://doi.org/10.1155/2014/147274). [PubMed: [25763391](https://pubmed.ncbi.nlm.nih.gov/25763391/)]. [PubMed Central: [PMC4334047](https://pubmed.ncbi.nlm.nih.gov/PMC4334047/)].
 15. El-Khayat W, Alelaiw H, El-kateb A, Elsemary A. Comparing vaginal misoprostol versus Foley catheter plus vaginal isosorbide mononitrate for labor induction. *J Matern Fetal Neonatal Med*. 2016;**29**(3):487-92. doi: [10.3109/14767058.2015.1007036](https://doi.org/10.3109/14767058.2015.1007036). [PubMed: [25694257](https://pubmed.ncbi.nlm.nih.gov/25694257/)].
 16. Osman I, MacKenzie F, Norrie J, Murray HM, Greer IA, Norman JE. The "PRIM" study: a randomized comparison of prostaglandin E2 gel with the nitric oxide donor isosorbide mononitrate for cervical ripening before the induction of labor at term. *Am J Obstet Gynecol*. 2006;**194**(4):1012-21. doi: [10.1016/j.ajog.2005.10.812](https://doi.org/10.1016/j.ajog.2005.10.812). [PubMed: [16580290](https://pubmed.ncbi.nlm.nih.gov/16580290/)].
 17. Mizrachi Y, Levy M, Weiner E, Bar J, Barda G, Kovo M. Pregnancy outcomes after failed cervical ripening with prostaglandin E2 followed by Foley balloon catheter. *J Matern Fetal Neonatal Med*. 2016;**29**(19):3229-33. doi: [10.3109/14767058.2015.1121477](https://doi.org/10.3109/14767058.2015.1121477). [PubMed: [26572735](https://pubmed.ncbi.nlm.nih.gov/26572735/)].
 18. Dave A, Nigam P, Maru L. Isosorbide Mononitrate a Nitric Oxide Donor: A Study of Its Efficacy and Safety as an Agent for Cervical Ripening. *J Obstet Gynaecol India*. 2015;**65**(3):162-6. doi: [10.1007/s13224-014-0577-5](https://doi.org/10.1007/s13224-014-0577-5). [PubMed: [26085736](https://pubmed.ncbi.nlm.nih.gov/26085736/)]. [PubMed Central: [PMC4464556](https://pubmed.ncbi.nlm.nih.gov/PMC4464556/)].
 19. Dowswell T, Kelly AJ, Livio S, Norman JE, Alfirevic Z. Different methods for the induction of labour in outpatient settings. *Cochrane Database Syst Rev*. 2010;(8):Cd007701. doi: [10.1002/14651858.CD007701.pub2](https://doi.org/10.1002/14651858.CD007701.pub2). [PubMed: [20687092](https://pubmed.ncbi.nlm.nih.gov/20687092/)]. [PubMed Central: [PMC4241469](https://pubmed.ncbi.nlm.nih.gov/PMC4241469/)].
 20. Bollapragada SS, MacKenzie F, Norrie JD, Eddama O, Petrou S, Reid M, et al. Randomised placebo-controlled trial of outpatient (at home) cervical ripening with isosorbide mononitrate (IMN) prior to induction of labour-clinical trial with analyses of efficacy and acceptability. The IMOP study. *Bjog*. 2009;**116**(9):1185-95. doi: [10.1111/j.1471-0528.2009.02216.x](https://doi.org/10.1111/j.1471-0528.2009.02216.x). [PubMed: [19624440](https://pubmed.ncbi.nlm.nih.gov/19624440/)].