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**Original Research Article**

# A comparative study to determine the effectiveness of oral mifepristone and vaginal isosorbide mononitrate as cervical ripening agents for induction of labor in pregnant women with gestational age 28 to 34 weeks

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## ABSTRACT

**Background:** The process of inducing labor is definitely one of the most commonly done obstetric procedures worldwide. An unfavourable cervix is a major reason for unsuccessful induction. Cervix must be softened. IOL should only be performed when there is an obvious medical need and advantages are greater than risks.
**Methods:** The present study was conducted at the Department of Obstetrics and Gynaecology, MGM Medical College, Indore from February 2023 to January 2024.One hundred pregnant women of gestational age 28 to 34 weeks, who had a valid indication for termination of pregnancy, were included in the study after valid consent and randomised into two groups. Oral Mifepristone was used in one group and vaginal isosorbide mononitrate IMN in the other. Modified Bishops Score was subsequently assessed and compared.
**Results:** In the study, indications for termination were hypertensive disorders of pregnancy, IUFD, anhydramnios, severe oligohydramnios and PPROM. Mean±SD of Bishop score before and after IMN were 1.84±1.23 and 4.40±1.34, whereas for Mifepristone 1.42±1.42 and 4.92±1.68, respectively. Mean cervical ripening to delivery time in IMN group was 30.04±3.37 hours; while in mifepristone group, it was 28.50±3.48 hours. Most patients delivered vaginally in both the groups (IMN group 88%; mifepristone group 94%). Both Mifepristone and IMN were generally well-tolerated by participants.
**Conclusions:** This study provides evidence supporting the effectiveness of both drugs as cervical ripening agents.

**Keywords:** Cervical ripening, Oral mifepristone, Vaginal isosorbide mononitrate IMN, Induction of labor IOL

## INTRODUCTION

The process of inducing labor is definitely one of the most commonly done obstetric procedures worldwide. IOL is considered when it is believed that the results for the baby, the mother, or both are more favourable than with waiting for labor to start on its own.[1] Since IOL is associated with the risk of uterine stimulation leading to foetal distress and uterine rupture, it should be carried out in facilities where maternal and foetal wellbeing can be monitored and caesarean section can be performed.[2]

An unfavourable cervix is a major reason for unsuccessful induction. To address this issue, the cervix must be softened. Cervical ripening occurs due to a sequence of intricate biochemical reactions that culminate in the restructuring and readjustment of collagen molecules. The cervix becomes thinner, softer, more relaxed, and wider due to uterine contractions, enabling easy passage of the

fetal part during labor. The Bishop score is the most commonly used scoring system for evaluating the cervix.[3]

Mifepristone possesses antiglucocorticoid and antiprogesterone characteristics as a steroidal compound. It enhances contractions of the uterus, leading to thinning and widening of the cervix to end the pregnancy.

Nitric oxide donors have been studied in different clinical uses, such as preparing the cervix for delivery. Using isosorbide mononitrate IMN as the second dose, increasing the dosage, or using dinitrate gel preparation can lead to improved outcomes without the typical side effects associated with prostaglandins.[4]

This study aims to evaluate the efficacy of oral Mifepristone versus vaginal IMN for cervical ripening in pregnant women between 28- and 34-weeks' gestation.

## METHODS

### *Study centre*

MGM Medical College and MTH hospital, Indore.

### *Study design*

Randomised control trial (simple randomisation).

### *Study duration*

12 months from the date of approval of study topic

### *Study of population*

28-to-34-week pregnant women.

Randomization to be done for allotment of cases in both the groups (simple randomisation)

CTRI registration number: CTRI/2023/06/053401

### *Sample size calculation*

Sample size is calculated by using G-power software version 3.1.9.4 with two-sided alpha set at 5% and power set at 80%. Minimum calculated sample size is 46 in each group. So minimum total sample size is 92 in both groups.

### *Sample size*

Total number of participants in the study -100, 50 in each group.

### *Selection criteria*

Patients were selected based on the following selection criteria.

### *Inclusion criteria*

All 28-to-34-week pregnant females who need induction of labor for obstetric and maternal indications.

Bishop score <4

Those giving consent.

### *Exclusion criteria*

Contraindication to vaginal birth, hypersensitivity to mifepristone and IMN, contraindications to mifepristone and IMN, those not giving consent.

### *Study procedure*

Pregnant women meeting the inclusion criteria who visit the Obstetrics and Gynaecology outpatient department at MGMMC and M.T.H. hospital Indore are included in the study after obtaining informed consent. A total of 100 women are included in the study. All participants were provided with a patient information sheet and were allowed to ask questions about the study and their participation.

Data regarding sociodemographic profile collected, detailed clinical history taken and clinical examination including per abdominal and per vaginal examination done. Modified Bishops' score assessed in all the patients and documented.

Patients randomly allocated into groups (Group A and B).

Group A received an initial 40 mg dose of isosorbide mononitrate in the posterior vaginal fornix, followed by the same dose again after 6 hours.

The Bishop Score evaluated 12 hours post the first application.

In group B, Tab Mifepristone 200mg single dose administered orally. Modified Bishop score assessed at the end of 12 hours.

Then, T. misoprostol given sublingually for induction of labor in both groups according to period of gestation and intensity of uterine contractions assessed.

The effectiveness of IMN and Mifepristone as Cervical Ripening Agents was assessed based on:

Improvement in Bishops' score; duration between administration of cervical ripening agent and delivery; Failed induction-after 2 doses of misoprostol 3hr apart.

## RESULTS

A total of 100 pregnant women participated in the study.

50 (50%) patients were in Group 1; and 50 (50%) were in Group 2.

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50 (50%) patients were in Group 1; and 50 (50%) were in Group 2.

The indications for induction of labor between the two groups include anhydramnios,IUFD, PPROM,severe oligohydramnios, antepartum eclampsia and severe pre-eclampsia.

In the IMN group, the mean preripening Bishop Score was 1.84±1.23; and the mean post ripening Bishop score was 4.40±1.34. The difference was found to be statistically significant (P=0.001). The mean difference of Bishop score was 2.56.

In Mifepristone group, the mean pre ripening Bishop Score was 1.42±1.42; and the mean post ripening Bishop score was 4.92±1.68. The difference was found to be statistically significant (P=0.001). The mean difference of Bishop score was 3.50.

The mean Bishop score post ripening was significantly high than the mean pre ripening Bishop score in both the groups.

**Table 1: Comparison of indications for induction of labour between the two groups (n=100).**

| Indications | Groups | | Z test, P value |
|---|---|---|---|
| | Group 1 | Group 2 | |
| **Anhdyramnios** | 4 (8.0%) | 5 (10.0%) | 0.726, NS |
| **IUFD** | 12 (24.0%) | 12 (24.0%) | 1.000, NS |
| **PPROM** | 8 (16.0%) | 7 (14.0%) | 0.779, NS |
| **Severe oligohydramnios** | 3 (6.0%) | 3 (6.0%) | 1.000, NS |
| **Hypertensive disorders of pregnancy** | 23 (46%) | 23 (46%) | 1.000, NS |
| **Antepartum eclampsia** | 3 (6.0%) | 2 (4.0%) | 0.645, NS |
| **Severe pre-eclampsia** | 20 (40.0%) | 21 (42.0%) | 0.841, NS |

Z test for two sample proportion applied. P value <0.05 was considered as statistically significant; NS: non-significant

**Table 2: Comparison of pre ripening Bishop score with post ripening Bishop score (n=100).**

| Group 1 | Bishop score (Mean±SD) | 't' value, df' | P value |
|---|---|---|---|
| **Preripening** | 1.84±1.23 | -23.012, df=49 | 0.001 |
| **Post ripening** | 4.40±1.34 | | |
| Group 2 | | | |
| **Preripening** | 1.42±1.42 | -27.920, df=49 | 0.001* |
| **Post ripening** | 4.92±1.68 | | |

Paired 't' test applied. *P value=0.001, Significant.

**Table 3: Time interval between cervical ripening to delivery (n=100).**

| | Cervical ripening to delivery time (Mean±SD) | 't' value, df' | P value |
|---|---|---|---|
| **Group-1** | 30.04±3.37 | 2.249, df=98 | 0.027* |
| **Group-2** | 28.50±3.48 | | |

Unpaired 't' test applied. *P value=0.027, Significant

**Table 4: Comparison of mode of delivery between two groups (n=100).**

| Mode of delivery | Groups | |
|---|---|---|
| | Group 1 | Group 2 |
| **LSCS** | 06 (12.0%) | 03 (6.0%) |
| **Vaginal delivery** | 44 (88.0%) | 47 (94.0%) |
| **Total** | 50 (100.0%) | 50 (100.0%) |

Pearson Chi-square test applied. Chi-square value=6.099, df=4, P value=0.192, Not significant

**Table 5: Comparison of maternal side effects between the two groups (n=100).**

| Side effects | Groups | | Z test, P value |
|---|---|---|---|
| | Group 1 | Group 2 | |
| **None** | 23 (46.0%) | 32 (64.0%) | 0.070, NS |
| **Headache** | 11 (22.0%) | 3 (6.0%) | 0.02* |
| **Fever** | 6 (12.0%) | 0 (0.0%) | 0.011* |
| **Dizziness** | 5 (10.0%) | 0 (0.0%) | 0.022* |
| **Nausea** | 4 (8.0%) | 6 (12.0%) | 0.502, NS |
| **Vomiting** | 3 (6.0%) | 4 (8.0%) | 0.696, NS |
| **Diarrhea** | 0 (0.0%) | 2 (4.0%) | 0.152, NS |
| **Palpitations** | 0 (0.0%) | 6 (12.0%) | 0.011* |

Z test for two sample proportion applied. *P value <0.05 was considered as statistically significant; NS: non-significant.

The mean cervical ripening to delivery time in Group-1 was 30.04±3.37 hours; while in Group-2, it was 28.50±3.48 hours. The mean cervical ripening to delivery time was significantly lower in the mifepristone group compared to the IMN group.

In IMN group, 6 (12%) patients underwent LSCS; while 44 (88%) patients underwent vaginal delivery. In mifepristone, 3 (6%) patients underwent LSCS; 47 (94%) patients underwent vaginal delivery.

The incidence of headache, fever, dizziness were significantly higher in the IMN group, while the incidence of palpitations was significantly higher in the Mifepristone group, and nausea, vomiting and diarrhea incidence was comparable between the two groups.

In comparing special newborn care unit (SNCU) admission and stillbirth rates between the 2 groups, the data reveals striking similarities. Both groups, each comprising 50 cases, showed identical proportions for SNCU admission, with 76.0% of neonates from both Group 1 and Group 2 requiring SNCU care. This was largely because of prematurity and indications like apnea of prematurity, respiratory distress, low birth weight and IUGR.

## DISCUSSION

The procedure of induction of labor has been the most widely used clinical procedure. In about 20% of pregnancies, labor is induced for a variety of reasons. In this study, vaginal IMN, in a formulation which is cost-effective and widely available, was compared with oral Mifepristone.

A total of 100 pregnant women of gestational age 28 to 34 weeks participated in the study. They were divided into 2 comparable groups, with 50 participants in each group. In group A vaginal IMN was given while in group B oral Mifepristone was given for cervical ripening.

The mean age of patients in Group-1 was 26.38±3.68 years; and in Group-2, it was 25.46±3.63 years. Both groups were comparable with respect to age of the patients.

### *Indications for induction of labor*

Both Group 1 and Group 2 had 24.0% of patients with IUFD (Intra Uterine Fetal Demise) and 46% patients in both the groups had hypertensive disorders of pregnancy like antepartum eclampsia and severe pre-eclampsia, necessitating preterm induction of labor. The incidence of severe oligohydramnios was 6.0% in both Group 1 and Group 2. Group 1 had a rate of 16.0% while Group 2 had 14.0% for PPROM. The incidence of anhydramnios was 8.0% in Group 1 and 10.0% in Group 2, with no statistically significant difference observed.

In Dixit MS et al study, comparing IMN and prostaglandin E2 for cervical ripening, the most frequent reason for induction was postdatism (80% in IMN group and 77% in PGE2 group), followed by mild preeclampsia. (20% within the IMN group and 23% within the PGE2 group).[6]

Dave et al identified several reasons for induction such as overdue pregnancies, restricted fetal growth, fetal demise, high blood pressure conditions, diabetes, and low amniotic fluid levels.[7]

At our centre, prostaglandins like Dinoprostone (PGE2) and misoprostol (PGE1) are common agents used for cervical ripening and induction of labor in postdated pregnancies. However, additional methods are required for cervical ripening in 28 to 34 weeks pregnancies.

In order to assess the effectiveness of cervical ripening agents [IMN and mifepristone] in preterm pregnancies, in our study, we have included pregnant women between 28 to 34 weeks gestation that required induction of labor because of indications like IUFD, hypertensive disorders of pregnancy like eclampsia and severe pre-eclampsia, anhydramnios severe oligohydramnios and PPROM.

### *Improvement in modified Bishops score*

The primary outcome of this study was the effectiveness in cervical ripening, assessed using the modified Bishops score. Our results indicate that both mifepristone and IMN were effective in achieving cervical ripening, as evidenced

by significant increases in Bishop scores from baseline in both treatment groups.

In the IMN group, the mean pre ripening Bishop Score was 1.84±1.23; and the mean post ripening Bishop score was 4.40±1.34. The mean difference of Bishop score was 2.56. The difference was found to be statistically significant.

In the mifepristone group, the mean pre ripening Bishop Score was 1.42±1.42; and the mean post ripening Bishop score was 4.92±1.68. The mean difference of Bishop score was 3.50. The difference was found to be statistically significant.

Mifepristone demonstrated a greater increase in the modified Bishops score compared to IMN.

This finding aligns with the research conducted by Li L, Gao W, and Chen S at Beijing Tian Tan Hospital, Capital University of Medicine, on inducing labor in term women using mifepristone and misoprostol.[9] In the study, it was found that women who were administered mifepristone had a cervical length that was 1-3 cm shorter and a Bishop score that was 4-5 higher compared to their pre-treatment measurements.

Likewise, in the study by Priyanka et al, there was a significant statistically improvement in the mean Bishop's score after 24 hours when using Mifepristone. This increase in score suggests withdrawal of progesterone indirectly.[5]

The mean cervical ripening to delivery time in Group-1 was 30.04±3.37 hours; while in Group-2, it was 28.50±3.48 hours. The time interval was found to be significantly lower in the Mifepristone group compared to IMN group.

In Priyanka et al study, in primigravidae, the average time from induction to delivery using mifepristone in postdated pregnancies was 47.57 hours.[5] Similar results were reported by Wing et al.[10]

In the Agrawal et al study, time from treatment initiation to delivery and labour delivery interval was significantly shorter in PGE2 group compared to IMN group ($P<0.001$).[12] Osman et al also found time from initiation of treatment to delivery interval significantly shorter in PGE2 group, 26.9 hours versus 39.7 hours in IMN group.[8]

The relatively shorter ripening to delivery interval in our study may be because of the use of misoprostol for induction of labor after cervical ripening.

Comparison of mode of delivery between the 2 groups

The rate of caesarean section was slightly lower (6%) in the Mifepristone group compared to the IMN group (12%). In the IMN group, 88% patients delivered vaginally whereas in the Mifepristone group 94% patients delivered vaginally. However, the difference was not statistically significant.

This result is comparative with the study conducted by Priyanka et al, using Mifepristone, 90% patients delivered vaginally, 10% underwent emergency LSCS.[5] More spontaneous vaginal deliveries and less incidence of LSCS and less instrumental deliveries were noted by Fathima et al.[11]

Similarly, Hapangama and Neilson stated that women who received mifepristone were at a lower risk of having a caesarean section due to labor induction failure (RR 1.43, 95% CI 0.20–0.80) and were less likely to require oxytocin for augmentation (RR 0.80, 95% CI 0.66–0.97).[13]

***Comparison of maternal side effects between the 2 groups***

Maternal side effects, such as of headache, fever and dizziness were reported more frequently in the IMN group, whereas mifepristone was associated with a higher incidence of palpitations. The incidence of nausea, vomiting and diarrhea were comparable between the two groups.

***Neonatal outcome***

Both groups, each comprising 50 cases, showed identical proportions for SNCU admission, with 76.0% of neonates from both Group 1 and Group 2 requiring SNCU care. This was largely because of prematurity and indications like apnea of prematurity, respiratory distress, low birth weight and IUGR.

24.0% of neonates in each group (12 cases in each group) were induced because of intrauterine fetal demise, hence in these patients the neonatal outcomes were stillbirth.

## CONCLUSION

The present study aimed to evaluate and compare the effectiveness of oral Mifepristone and vaginal Isosorbide Mononitrate (IMN) as cervical ripening agents for induction of labor in pregnant women between 28 to 34 weeks of gestation. This study concludes that Mifepristone is a better cervical ripening agent compared to IMN. This study provides evidence supporting the effectiveness of both oral mifepristone and vaginal Isosorbide Mononitrate as cervical ripening agents. Mifepristone has shown promise in facilitating cervical ripening in pregnant females. It modulates progesterone receptors and induces changes in cervical tissue that result in cervical ripening. By inhibiting the effect of progesterone, Mifepristone increases the release of endogenous prostaglandins, leading to cervical softening, effacement and dilatation. It has demonstrated a greater increase in the Modified Bishops score and a shorter cervical ripening to delivery

time compared to IMN. Nevertheless, further research involving a larger sample size is needed, particularly in the 28-to-34-week gestation period, in order to demonstrate its effectiveness as a preferred method for cervical ripening. IMN is an appealing substitute because it doesn't have significant side effects for mothers and no side effects for fetuses. It leads to relaxation of smooth muscles by elevating cGMP levels in muscle cells. The time from induction to delivery decreases after administering IMN along with inducing agents. It is also economically advantageous compared to other agents for cervical ripening, particularly prostaglandins which are frequently utilized. Due to its affordable price, IMN could be beneficial, particularly in settings with limited resources, particularly for women who cannot use other medications or women with allergies. If prostaglandins are used in combination with a lower dose, it may result in cost savings and a reduction in prostaglandin-related side effects. Further research is needed to determine the effectiveness of using IMN in pregnancies between 28 and 34 weeks in order to support its regular use.

Individual patient characteristics and preferences should guide the choice of cervical ripening agents.

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