

# Use of Nitric Oxide Donor Isosorbide Mononitrate for Cervical Ripening at 41 Weeks' Gestation

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## Abstract

**Background:** The ideal agent for cervical ripening would induce adequate cervical ripening with minimal adverse effects to the mother and the fetus; the most favorable method for cervical ripening is not fully agreed till now; however, vaginal administration of isosorbide mononitrate (IMN) is considered a low-risk method of labor induction for post term. Our study was designed to assess the effect of IMN on cervical ripening and labor induction among 41 weeks pregnant women. **Objectives:** To assess the efficacy of the nitric oxide donor isosorbide mononitrate on cervical ripening at 41 weeks gestation. **Materials and Methods:** This study was conducted on 100 pregnant women recruited from the outpatient clinic fulfilling the inclusion criteria. Cases were divided into 2 groups. In first group 40 mg isosorbide mononitrate (IMN) tablet was applied vaginally in posterior fornix, and in second group placebo was applied vaginally in posterior fornix. Following up the cervical status after 24 hours of administration, the patient were asked about new symptoms especially headache, palpitation, dizziness or abdominal pain and the mode of delivery was assessed. **Results:** There was a significant improvement in the bishop score in the first group rather than the placebo group. No significant difference between the two groups was as regards the mode of delivery. **Conclusion:** IMN may be used for cervical preparation only before induction of labor in post term cases.

## Keywords

Cervical Ripening, Nitric Oxide Donor, IMN

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## 1. Introduction

Post term pregnancy refers to any pregnancy that extends after 42 weeks gestation or 294 days past the first day of the last menstrual period [1]. Post term may be in itself high risk. The placenta, which supplies the fetus with nutrients and oxygen from the mother starts aging and will eventually fail [2]. Miscalculation of last menstrual period (LMP) may be common cause of post term [3]. The use of ultrasound in early pregnancy for precise dating significantly reduces the number of post-term pregnancies compared to dating based on the LMP [4].

Post-mature baby is larger than average size baby, so it increases the incidence of cephalopelvic disproportion, shoulder dystocia, operative vaginal delivery [5], postpartum hemorrhage, caesarean sections rate [6] and meconium aspiration [7]. Fetal macrosomia increases incidence of birth injury [8], neonatal encephalopathy [9] and sudden infant death syndrome [10].

Once fetus is diagnosed post-mature, the mother should be offered additional monitoring as this can provide valuable clues that the fetus's health is being maintained. Compared with waiting indefinitely or waiting at least one week for labor to occur spontaneously, labor induction after 41 weeks of gestation is associated with fewer perinatal deaths [11].

Physiological cervical ripening is an active biochemical process; it has been described as an inflammatory process [12]. The Bishop Score is a common measure used to assess the cervical ripening [13]. Non-pharmacologic approaches to cervical ripening including herbal compounds, castor oil, hot baths, enemas, sexual intercourse, and breast stimulation till now have not proven efficient for cervical ripening or induction of labor [14]. Surgical methods for cervical ripening (stripping of the membranes, amniotomy, balloon catheter insertion in cervix), have been recommended for cervical ripening; however there are risks for this technique including infection, bleeding, accidental rupture of the membranes, and patient discomfort [15] [16].

With pharmacological cervical ripening, Prostaglandins E2 (Misoprostol) are the current method used for cervical ripening and labor induction [17]. But risks associated with its use include uterine hyperstimulation, nausea, vomiting, diarrhea, fever and accompanying FHR changes [18]. Uterine rupture in women with previous cesarean section limits its use to women who have a uterine scar [19]. There is insufficient information to support the use of mifepristone and relaxin for cervical ripening [20]. Oxytocin is the preferred pharmacologic agent for inducing labor when the cervix is favorable or ripe [21].

Nitric oxide (NO) is a small, highly reactive, free radical gas with a half-life time of a few seconds [22], expressed in three isoforms; all of these isoforms are present in various cells of the uterine cervix [23]. Cervical nitric oxide production is very low in post term pregnancy. Thus, it has been suggested that reduced cervical nitric oxide release may contribute to prolonged pregnancy [24]. In cervical ripening, immunological mediators play a crucial role in this process. NO is involved in the acute inflammatory response and amplifies the cytokine cascade stimulated during this response [25], via interactions either with prostaglandin biosynthesis or with lytic enzymes. It stimulates cyclooxygenase to increase the production of pro-inflammatory prostaglandins [26]. Its action is accomplished by effects on connective tissue and smooth muscle cells [27]. Isosorbide mononitrate (IMN) is a drug used principally in the treatment of angina pectoris. Vaginal administration IMN reduces the cervical resistance without inducing uterine hyperstimulation or abnormal fetal heart rate [28].

## 2. Patients and Methods

100 post term pregnant women at 41 weeks gestational age. All patients must fulfill the inclusion criteria; gestational age of 41 weeks, not in labor, cephalic presentation, singleton fetus, having a normal non-stress test and biophysical profile. patients with 3 pregnancy associated diseases as preeclampsia, placenta previa or unexplained vaginal bleeding during pregnancy, cardiac, pulmonary, renal or hepatic disease, history of severe persistent headache, polyhydramnios, placenta previa, probability of placenta abruption or any contraindication for induction of labor were excluded.

This study has been approved by national research ethics committee and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

## 3. Informed Consent

“Informed consent was obtained from all individual participants included in the study.”

At the first visit each woman will be subjected to: complete history taking, routine investigations: complete

blood picture, fasting blood sugar and complete urine analysis, general examination, obstetric examination (vaginal examination to assess the pelvis, Bishop score and the presenting part), obstetric ultrasonography, biophysical profile and Doppler to assess fetal wellbeing.

Cases divided into 2 groups, first group received 40 mg IMN tablet applied vaginally in posterior fornix, second group received placebo applied vaginally at the same site. Women were permitted to go home and instructed to come to the hospital immediately if they had any sign of dangerous symptoms (leakage of amniotic fluid, vaginal bleeding or decrease in fetal movements), otherwise they were asked to come back to the hospital after 24. The women were examined vaginally by the same physician to assess the cervical status, fetal monitoring and follow up the case till delivery.

## 4. Results

There was a significant difference between the IMN group and the controls with respect to the Bishop score (4.40 vs. 3.68,  $p = 0.031$ ) (Table 1), but there was no significant differences in the mode of delivery between the two groups (Table 2). The major side effect of IMN was headache, about 70% of cases complain from headache, which responded to a mild analgesia.

## 5. Discussion

Our study demonstrated that outpatient use of IMN has a significant effect in cervical ripening and Bishop Score after 24 hours of administration in posterior fornix. In our study 30 women (60%) in the IMN group in contrast to 10 women (20%) in the placebo group had positive cervical ripening after 24 hours ( $p = 0.001^*$ ). These results are consistent with previous studies that were done by Erling Ekerhovd in 2003 [28], Maria Bullarbo [29], and Rameez in 2007, which concluded that outpatient cervical ripening followed by labor induction with isosorbide

**Table 1.** Comparison between the two studied groups regarding the Bishop base score before and after 24 hours of administration.

	Study group	Control group
Bishop base score before administration		
Min. - Max.	0.0 - 6.0	0.0 - 6.0
Mean $\pm$ SD.	3.72 $\pm$ 1.29	3.60 $\pm$ 1.54
Median	4.0	3.0
p		0.471
Bishop score after administration		
Min. - Max.	0.0 - 7.0	0.0 - 7.0
Mean $\pm$ SD.	4.40 $\pm$ 1.81	3.68 $\pm$ 1.73
Median	5.0	3.0
p		0.031*

**Table 2.** Comparison between the two studied groups regarding the mode of delivery.

	Study group		Control group	
	No.	%	No.	%
Mode of delivery				
Normal vaginal delivery	32	64.0	26	52.0
C. S.	18	36.0	24	48.0
p				0.224

mononitrate seems to be an effective, safe and well tolerated procedure [30]. Another study done by Eddama *et al.* demonstrated that the proportion of women with an unripe cervix after 24 h of outpatient treatment was significantly lower in the IMN group as compared with the placebo group (64% vs. 77%,  $p = 0.02$ ) [31]. In our study there was a significant difference between the IMN group and the controls with respect to the Bishop score (4.40 vs. 3.68,  $p = 0.031^*$ ), which was consistent with Hamideh Yazdizadeh *et al.* in which there was a significant difference between the IMN group and the control group with respect to the Bishop score (4.92 vs. 4.03,  $p = 0.01$ ) [32]. In another study done by Kavita Agarwal *et al.*, the Bishop score was significantly improved 24 hours after initiation of the outpatient IMN treatment ( $p < 0.001$ ) and the needs for further cervical ripening and oxytocin infusion were less in the study than in the control group ( $p < 0.001$  and  $p = 0.008$ ) [33].

In this study there were no significant differences in the mode of delivery between the two groups, as 32 women treated with isosorbide mononitrate went into normal labor compared to 26 women in the placebo group ( $p > 0.05$ ); there were no significant differences as regard to normal labor. In Mohamed Furukan study it was reported that there was marked increase in the proportion establishing spontaneous labor (28% vs. 7.5%,  $p < 0.01$ ) and cervix was favorable for oxytocin infusion (40% vs. 9%,  $p < 0.001$ ) 2 days after therapy; in the same study the cesarean section rates were similar in both groups [30].

In our study there were no significant differences in cesarean delivery rate (36% vs. 48%,  $p > 0.05$ ), neonatal outcomes and Apgar score between the two groups, consistent with Sherif M. Habib *et al.* study [34].

The most common side effect in women treated with IMN was headache, experienced by 35 women (70%) compared to 4 women (8%) in placebo group ( $p < 0.05$ ); the intensity of headache was from mild to moderate headache. However Maria Bullarbo reported that higher incidence (88%) of women treated with isosorbide mononitrite was complained from headache compared to (4%) in placebo group [29].

So, vaginal administration of IMN reduces the cervical resistance and induces cervical ripening without inducing uterine hyperstimulation or abnormal fetal heart rate. So IMN can be used in outpatient clinic for cervical ripening with no need for admission or close fetal monitoring.

## Disclosure Statement

There is nothing to disclose.

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