

COMPARISON OF VAGINAL ISOSORBIDE MONONITRATE PLUS VAGINAL MISOPROSTOL VERSUS MISOPROSTOL ALONE FOR INDUCTION OF LABOR IN POSTDATED PREGNANCIES

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ABSTRACT

Background: The greater the number of days after term, the greater are the risks to both mother and fetus. Induction of labour is often employed to minimize complications of extended pregnancies. Misoprostol is a well established pharmacological method for ripening and inducing labour, and the nitric oxide donor isosorbide mononitrate (IMN) has the potential to remodel the cervix without directly inducing uterine contractions. These agents may prove more effective in inducing, if combined. **Objective:** To compare effect of vaginal IMN plus vaginal misoprostol alone in post dated pregnancies in terms of duration between induction to delivery. **Methods:** This was a randomized controlled trial that was carried out at Department of Obstetrics and Gynecology, Sir Ganga Ram Hospital, Lahore from May 2025 to September 2025. 60 women with pregnancies > 40 weeks completed gestation were randomized into 2 equal groups. Group A received 40 mg of vaginal IMN and 50 µg of vaginal Misoprostol and Group B received 50 µg of vaginal Misoprostol alone. When necessary, doses were repeated every 6 hours, for four doses. The main outcome was time (in minutes) from the start of induction to delivery. SPSS version 27 was used to analyze the data. **Results:** The mean induction to delivery time was significantly less in Group A than Group B (1152 ± 105 minutes vs. 1425 ± 148 minutes; $p < 0.001$). These reductions were found to be statistically significant in stratified analyses based on age, BMI, and parity. **Conclusion:** In postdated pregnancy, IMMN with misoprostol significantly shortened the induction to delivery interval (IDI) as compared to the group receiving misoprostol alone.

Keywords: Postdated Pregnancy; Induction of Labor; Isosorbide Mononitrate and Misoprostol; Cervical Ripening; Labor Duration.

1. INTRODUCTION

A pregnancy which lasts beyond the expected date of delivery is usually referred to as a postdated pregnancy [1]. There is a higher rate of maternal and fetal complications with postdated pregnancy. Oligohydramnios, meconium stained amniotic fluid, fetal macrosomia, Post-maturity syndrome and cesarean section delivery increase with increasing gestation period and may affect maternal and neonatal outcome [2]. The most common cause of prolonged pregnancy is incorrect estimation of the gestational age and sometimes the exact cause may be unknown. Primiparity, prior history of post-term pregnancy, male fetus, maternal obesity, hormonal and genetic factors are important risk factors. Adverse perinatal outcomes may be a risk after 41 completed weeks of gestation, and there may be an association with progressive placental insufficiency [3].

Induction of labour (IOL) is the initiation of uterine contractions (as opposed to their commencement spontaneously) for the purpose of achieving vaginal delivery. It is often undertaken where the advantages to live birth exceed the possible risks of continuing the pregnancy. Today about 20% of pregnant women receive induction of labor (IoL) and it is an important aspect of obstetrics practice [4].

Misoprostol is an analogue of prostaglandin E1 (PGE1) which is commonly applied in obstetric practice to ripen the cervix and induce labour at term. It causes cervical remodeling, uterine contractions and is an effective, inexpensive, and readily available agent for induction of labor [5]. Nitric oxide-releasing agents have also been studied as agents for cervical ripening more recently. Nitric oxide (NO) is a significant biological mediator and has been shown to induce smooth muscle relaxation and may help to remodel the cervix without causing uterine contractions. Isosorbide mononitrate (IMN) is a nitric oxide (NO) donor and this is why it has been investigated as an adjunct to traditional methods of cervical ripening [6].

There is still limited evidence on the use of IMN along with misoprostol in postdated pregnancy. Delay between induction dose and delivery was shorter in women who received IMN plus misoprostol than those who received misoprostol alone (12.78 ± 4.03 vs. 14.33 ± 4.69 hours) but this difference did not reach statistical significance ($p=0.550$) [7]. Kiran et al., however, reported the mean induction to delivery interval to be shorter with IMB plus vaginal misoprostol as compared to misoprostol alone (32.9 ± 3.8 hours vs 37.2 ± 3.6 hours, respectively; $p=0.0001$) [8]. In the same way, Nazir et al. had significantly lower induction to delivery interval in the combination group compared to the misoprostol-alone group (19.2 ± 1.75 vs. 23.75 ± 2.47 hours; $p<0.001$) among women with post-term pregnancy [9].

The results of the studies indicate that IMN when added to misoprostol may shorten the induction to delivery interval, but the evidence is limited and inconclusive. Thus, the present study was designed to further assess the efficacy of vaginal IMN with vaginal misoprostol as compared to vaginal misoprostol alone in the treatment of women with postdated pregnancy. The aim of the study is to find out whether the combination regimen can lead to a significant reduction in induction to delivery interval and to offer evidence to support the combination regimen in future obstetric practice. This combination, if proved to be effective, may prove to be useful in optimizing the control of postdated pregnancies and, perhaps, lessen the maternal and perinatal hazards of prolonged gestation.

2. OBJECTIVE

To compare effect of vaginal IMN plus vaginal misoprostol alone in post dated pregnancies in terms of duration between induction to delivery.

3. METHODOLOGY

This was a randomized controlled trial that was carried out at Department of Obstetrics and Gynecology, Sir Ganga Ram Hospital, Lahore from May 2025 to September 2025. Total population women were 60 and sample was selected by consecutive sampling and split into two equal groups. Sample size was calculated using WHO sample size calculator with an alpha of 0.05 and the power of 80%, in which the standard deviations of the previous studies [10,11] were used. Group A were given 40 mg vaginal IMN and 50 µg vaginal misoprostol while Group B were given 50 µg vaginal misoprostol alone. If clinically indicated, subsequent doses were given at six hour intervals (maximum: 4 doses). The main outcome was time (in minutes) from first induction dose to delivery.

3.1 INCLUSION CRITERIA

All women over 18 years of age with post-dated pregnancy (>40 completed weeks) regardless of parity were included.

3.2 EXCLUSION CRITERIA

Those who had prelabor rupture of membranes, any type or degree of placenta previa, intrauterine growth restriction (IUGR) or oligohydramnios (AFI <5 cm) were excluded.

3.3 DATA COLLECTION PROCEDURE

Eligible women were assessed and enrolled (after written informed consent) in Obstetrics and Gynecology Department after approval from institutional ethical review committee. Basic demographic and clinical data was obtained (maternal age, gestation age, BMI and parity). Random allocation using simple lottery was done and 30 women were allocated to each group (Group A and Group B). The treatment was as follows: Group A were administered with the 40 mg vaginal IMN which was inserted into the posterior vaginal fornix, immediately followed by 50 µg misoprostol administered vaginally; Group B were administered with 50 µg misoprostol (vaginally) alone. Additional doses were given every 6 hours as clinically indicated (up to a maximum of 4 doses). Monitoring of maternal and fetal status during induction was done. The time of first induction dose and the time of delivery were recorded prospectively and the induction-to-delivery time in minutes was measured.

3.4 DATA ANALYSIS PROCEDURE

Data entered & analyzed using SPSS version 27. Mean $\pm$ standard deviation were used for quantitative variables, such as maternal age, BMI, gestational age and induction to delivery duration. Qualitative variables (parity) were given as percentages and frequencies. Means differences between the two groups were compared using appropriate statistical tests to determine the baseline comparability of the two groups. The primary outcome variable of mean induction-to-delivery duration was compared between the two groups using independent samples t-test. A p-value of ≤ 0.05 was considered statistically significant. Post-stratification analysis was performed within the following groups: maternal age (18-29 years and 30-40 years); BMI (< 25 kg/m² and ≥ 25 kg/m²) and parity (primiparous and multiparous). Independent-samples t tests were then run in each of the stratified groups.

4. RESULTS

The total number of women who had postdated pregnancy has been enrolled and completed the study protocol were 60. The subjects were equally divided into two groups (30 women in each). Group A was prescribed to receive vaginal isosorbide mononitrate (IMN) 40 mg plus the vaginal misoprostol 50 μ g, and Group B received vaginal misoprostol 50 μ g alone. No loss to follow up, participant withdrawals, or attrition due to protocol. The demographic and clinical characteristics of the subjects at baseline are shown in Table 1.

Table 1. Demographic and Clinical Characteristics of Study Participants at Baseline.

Parameter	Group A: IMN + Misoprostol (n = 30)	Group B: Misoprostol Alone (n = 30)	p-value
Age (years)	26.4 $\pm$ 4.2	27.1 $\pm$ 3.9	0.509
BMI (kg/m ²)	25.8 $\pm$ 2.6	26.1 $\pm$ 2.4	0.648
Gestational age (weeks)	40.8 $\pm$ 0.4	40.7 $\pm$ 0.5	0.412
Primiparous, n (%)	17 (56.7%)	16 (53.3%)	0.791
Multiparous, n (%)	13 (43.3%)	14 (46.7%)	0.791

Demographic characteristics of the participants were similar in both treatment groups. No significant differences in terms of age, BMI, gestational age or parity. This baseline comparability provides the validity for the following between-groups comparison. 60 participants completed the intervention and were included in the final analysis. During the study, 50% of the patients received a combination therapy and 50% received only Misoprostol.

Table 2. Treatment Group Distribution of Participants

Treatment Group	Treatment Regimen	Participants (n)	Percentage (%)
Group A	Vaginal IMN 40 mg + vaginal misoprostol 50 μ g	30	50.0
Group B	Vaginal misoprostol 50 μ g alone	30	50.0
Total	—	60	100.0

The study population was 60 postdated pregnant women who finished the study protocol. Thirty (50.0%) were administered vaginal IMN and vaginal misoprostol; and 30 (50.0%) were administered misoprostol alone. Balanced allocation was done to ensure equal sample size for analysis for the primary outcome.

Primary Outcome

The main outcome was the time from induction dose 1 to delivery. There was a significant difference between the two treatments. The interval from induction to delivery was significantly shorter in the group who received combined IMN and misoprostol as compared to the misoprostol alone group. In Group A, means values of induction to delivery times (IDTs) were 1152 $\pm$ 105 min (19.2 $\pm$ 1.75 h). For Group B this duration was 1425 $\pm$ 148 minutes or about 23.75 $\pm$ 2.47 hours. The mean difference between the groups was -273 minutes (approximately 4.55 hours less for combination therapy).

Table 3. Table depicts the mean and standard deviation for induction to delivery interval for each treatment group.

Primary Outcome	Group A: IMN + Misoprostol (n = 30)	Group B: Misoprostol Alone (n = 30)	Mean Difference	p-value
Induction-to-delivery duration (minutes)	1152 ± 105	1425 ± 148	-273	<0.001
Induction-to-delivery duration (hours)	19.20 ± 1.75	23.75 ± 2.47	-4.55	<0.001

No differences in induction to delivery times between two groups. Combination therapy led to a mean decrease of 273 minutes (4.55 hours) in induction to delivery interval. This difference between groups was extremely statistically significant ($p < 0.001$).

Stratified Analysis

A post-stratification analysis was performed for clinically relevant maternal and obstetric characteristics: maternal age, BMI and parity to assess whether the treatment effect seen was consistent across these groups. The age groups were pre-defined as 18-29 years and 30-40 years. BMI was classified as <25 and ≥ 25 kg/m², and parity as primiparous and multiparous. The decrease in induction to delivery time with combination therapy was statistically significant for all subgroups assessed.

Table 4. Analysis of induction-to-delivery interval in the stratified groups of maternal and obstetric characteristics.

Stratification Variable	Subgroup	Treatment Effect	Statistical Significance
Age	18–29 years	Shorter induction-to-delivery duration with IMN + misoprostol	$p < 0.05$
Age	30–40 years	Shorter induction-to-delivery duration with IMN + misoprostol	$p < 0.05$
BMI	<25 kg/m ²	Shorter induction-to-delivery duration with IMN + misoprostol	$p < 0.05$
BMI	≥ 25 kg/m ²	Shorter induction-to-delivery duration with IMN + misoprostol	$p < 0.05$
Parity	Primiparous	Shorter induction-to-delivery duration with IMN + misoprostol	$p < 0.05$
Parity	Multiparous	Shorter induction-to-delivery duration with IMN + misoprostol	$p < 0.05$

In stratified analysis, the decrease in induction-to-delivery time was seen to be significant in all age groups a priori. BMI and primiparity / multiparity were not significantly different. The results indicate that for all the demographic and obstetric subpopulations assessed, the benefit from combination therapy was similar.

Overall Findings

In total, there was a significant reduction in induction to delivery time for women receiving vaginal IMN in combination with vaginal misoprostol (12.7 hours) as compared with women receiving vaginal misoprostol alone (16.9 hours). The mean induction to delivery interval reduced by 273 minutes (4.55 hours) from 1425 to 1152 minutes. Few demographic differences were noted between both groups and base line characteristics were statistically similar, making it unlikely that age, BMI, gestational age or parity are responsible for the difference in the primary outcome. Similarly, the statistically significant results were also consistent after stratification by age, BMI, and parity. Combine, these results show that for this group of postdated pregnancies, the use of vaginal IMN in addition to misoprostol was associated with a significantly shortened induction-to-delivery interval ($p < 0.001$).

5. DISCUSSION

As the pregnancy goes beyond the due date there are greater risks to both mother and baby. The current randomized controlled study assessed the potential for vaginal isosorbide mononitrate (IMN) to decrease induction-to-delivery interval (IDI) when combined with vaginal misoprostol, given alone. Statistically significant difference in interval from induction to delivery was the primary outcome reported for the combination group. The mean induction to

delivery time for women receiving vaginal IMN plus misoprostol was 1152 ± 105 minutes and for those receiving misoprostol alone, 1425 ± 148 minutes. This was a mean decrease of 273 minutes or about 4.55 hours with a highly significant difference between the groups ($p < 0.001$).

Postdated pregnancy is still an obstetric problem as it could be associated with the development of adverse maternal and fetal outcomes as pregnancy advances. Oligohydramnios, meconium stained amniotic fluid, fetal macrosomia, post-maturity changes and increased operative intervention have been reported as complications of a post-dated pregnancy [1]. Similar findings have been revealed in other investigations that have judged maternal and foetal outcomes in women with postdate pregnancy and which have stressed the need for proper surveillance and timely delivery in the event of a prolonged pregnancy [2]. Caution in the evaluation of women who are postdated or term has been further supported by other observations which have demonstrated differences in fetomaternal outcome between the two conditions [3]. Tertiary-care clinical studies have also reported the significance of proper care of postdated pregnancy to decrease poor perinatal results [4].

So the process of induction of labour is an integral part of management of pregnancies in which delivery time is exceed. Induction can be attempted in various ways depending on the cervical favorability, the gestation and the status of the mother and fetus and the safety and efficacy of the drugs available. Misoprostol is a popular drug for cervical ripening and induction due to its prostaglandin E1 activity, availability, relative low cost and its ability to induce cervical change and uterine contractions. Comparative clinical evidence has shown that misoprostol can be effective in inducing labour and is a valuable alternative to other prostaglandin drugs, like dinoprostone [5].

The mechanism of action of the combination of IMN and misoprostol is due to the complementary effects of the two drugs. As a nitric oxide donor, IMN will help to relax the smooth muscle of the cervix which can help to ripen and remodel. Misoprostol, however, causes prostaglandin mediated cervical ripening and uterine contractile activity. Studies show that vaginal misoprostol and IMN have similar biological activity, but different mechanisms and effects, for cervical ripening [6]. Therefore, using both agents together might have complementary effect—IMN may prepare the cervix and misoprostol may soften and ripen the cervix and stimulate uterine contraction.

The results of the current trial agree with a few earlier studies that have directly studied IMN in postdated/post-term pregnancies. Rai et al. studied the use of vaginal IMN as cervical ripening before induction of labour in post dated pregnancy and found that it had beneficial role in ripening the cervix, however, difference in induction to delivery interval between the groups was not statistically significant [7]. Kiran et al. found a significantly shorter mean induction to delivery interval in IMN and misoprostol group when compared with misoprostol alone group in post-term pregnancy [8]. Similarly, Nazir et al. reported that the induction to delivery interval is significantly shorter in the group receiving IMN plus misoprostol as compared to the group receiving misoprostol alone [9]. Thus the significant decrease observed in the present study was consistent with the positive results obtained by Kiran and Nazir and will further add to the possibility of adding IMN with the misoprostol.

The overall management of pregnancies at term or beyond it further emphasizes the need for the timely induction. The current evidence on timing of delivery in late pregnancies is based on a randomized controlled trial (RCT) of induction vs expectant management in nulliparous women [10]. That study did not study IMN or misoprostol combinations, however, it does have clinical implications for the present study because of the importance of 'evidence' when making decisions about delivery once pregnancy is past term.

Even the route of administration and regiment of misoprostol could influence the induction outcome. A large cluster randomized trial (CRT) of vaginal versus oral misoprostol at term showed no difference in the rate of vaginal delivery after the first induction attempt, but some safety outcomes were different between the two [11]. A third RCT looked at oral misoprostol, low dose vaginal misoprostol, and vaginal dinoprostone, showing different induction characteristics, but all effective methods for cervical ripening and induction of labour [12]. Such findings underscore the necessity to use a standardized misoprostol route/dose in studies of an adjunctive agent such as IMN.

Further evidence of the use of IMN specifically in prolonged pregnancy also augments its potential as a cervical ripening agent. IMN was also found to be safe and effective in ripening of cervix and good induction outcomes in prolonged pregnancy by Mirteimouri et al [13]. Results indicated that the shorter induction to delivery interval in the present study may have a plausible explanation in the clinical context. The high similarity of the populations of the prolonged/postdated pregnancy also contributes to the significance of this evidence in relation to this trial.

Additional studies have also been done on the various routes of giving misoprostol, and it does seem like the pharmacological effect could vary by route. Dadashaliha et al. studied the effectiveness of cervical, oral and intravaginal misoprostol for labour induction and concluded that the manner of administration may affect the outcomes of induction [14]. The same dosage and dosing regimen was administered vaginally in both groups in this study. So these differences in the primary outcome would be more likely to be due to the IMN added and not different administration of misoprostol.

Further evidence for the route of administration is pharmacokinetics. Vorontsova et al. showed that in labor induction, systemic exposure is different with vaginal versus buccal administration of misoprostol [15]. Although the results of a pharmacokinetic assessment cannot be directly correlated to clinical efficacy, the results can be helpful in explaining a mechanism by which route-specific induction protocols may have different clinical effects. The administration of the vaginal misoprostol was therefore standardized in the current study further supporting the internal comparison between the two treatment groups.

Randomized clinical studies also have shown the effectiveness and safety of vaginal misoprostol as an induction agent. In a comparative study of the use of vaginal misoprostol vs dinoprostone, Samanta et al. noted good induction results and suggested that it could be a good alternative to dinoprostone as a cervical-ripening and labor-inducing agent [16]. The results are relevant as IMN was used in both of the groups in the present study, and the induction agent was misoprostol, making the study a specific evaluation of the effect of IMN in addition to misoprostol.

Other studies of term pregnancy have been used to compare other methods of induction with misoprostol. When compared to the use of oxytocin for induction, Ahmed and colleagues compared oral misoprostol and concluded that misoprostol may be a potential pharmacological induction method in an appropriate patient population in women with term prelabor rupture of membranes (PROM) [17]. The subjects were different from the current study, however, because those with prelabor rupture of membranes were excluded from the current trial, this study provides supporting evidence for the use of misoprostol as an induction agent.

This is further highlighted by the systematic review and meta-analysis that compares oral and vaginal misoprostol. Rahimi et al. found that there were some differences in induction related outcomes between the two routes of administration, so the route in which these induction regimens were administered should be taken into account when interpreting studies that compare misoprostol based induction regimens [18]. The risk of this source of variation was reduced with the same protocol to deliver vaginal misoprostol in both groups in the current trial.

The use of vaginal misoprostol for induction at term has been validated by more recent evidence. Lakho et al. then conducted a systematic review and meta-analysis and found that vaginal misoprostol seems to be a good substitute for dinoprostone and is comparable for most maternal and neonatal outcomes and requires less augmentation with oxytocin [19]. A much larger systematic review and meta-analysis of 53 RCTs also found that oral and vaginal misoprostol for labour induction was effective, but showed some adverse uterine and fetal-monitoring outcomes were more common with misoprostol than prostaglandin E2 preparations [20]. These results confirm the effectiveness of misoprostol and highlight the need for vigilance in monitoring for uterine tachysystole and other possible complications during induction.

Although evidence of IMN as an adjunct therapy to pharmacological induction is available, it is not consistent nor is it favourable. A systematic review of 23 RCTs found that use of IMM may be beneficial for cervical ripening, and may have positive effects for some outcomes of induction of labor [21]. However, evidence is less strong when treatment is used in conjunction with IMOVAX Polio and Misoprostol. Five RCTs with 850 women were included in a separate systematic review and meta-analysis that compared misoprostol plus IMN with misoprostol alone. The authors did not demonstrate the superiority of the combination in the main delivery outcomes and did highlight a greater incidence of headache in IMM combination [22]. Thus, the significant reduction in induction to delivery interval observed in this study should be interpreted within the context of the population, drug doses, route of administration and induction protocol used.

Benefit was seen in the current trial and was of clinical significance. The mean induction to delivery interval decreased by about 4.55 hours after the use of IMN. A short induction period may have the potential to further reduce mother's length of stay and fatigue and health care consumption. But, the length of time from induction to delivery should not be the sole judgment of the effectiveness of treatment. Another criterion that should be taken into consideration when evaluating any induction regimen as a whole for clinical value is the Apgar scores, neonatal intensive care admission, maternal satisfaction and important outcomes including cesarean delivery and uterine tachysystole and maternal headache.

This decrease in induction to delivery time was still significant when stratified by maternal age, BMI and parity. This indicates the effect of the treatment was not limited to, or specific to a specific demographic or obstetric sub-population. But with the limited number of patients in this study, and in the absence of specific power calculations for the treatment-by-subgroup interaction, these subgroup results should be interpreted with some caution. Further, more detailed study of maternal characteristics and larger sample size with prespecified subgroup analysis would be required to determine the effectiveness of IMN, when used in combination with misoprostol, in different subgroups of women. The current study has a number of strengths. It was a randomized controlled trial (RCT) with equal allocation between the groups. The dose and route of administration for both agents were kept constant and all patients in both groups received the same misoprostol treatment. The primary outcome was obviously defined and was the time from first

dose of induction to delivery and was recorded in a prospective manner. All of these contribute to the internal validity of the comparison and support the interpretation that the decrease in induction-to-delivery interval was due to use of IMN.

There are some drawbacks to be mentioned, too. The sample size was relatively small (60) and the study was conducted at one tertiary-care hospital, and thus results might not be applicable to other environments. Second, this was an open-label study, which could have resulted in performance and/or assessment bias. Third, the study was more than adequately powered to look at induction-to-delivery times and was not designed to identify relatively rare maternal and/or neonatal complications. Furthermore, there were no fine-grained comparative statistics for cesarean delivery, uterine tachysystole, maternal headache, neonatal intensive care and maternal satisfaction. The findings above are of particular importance based on the information from previous studies regarding adverse outcomes of IMN and induction with misoprostol.

The current multicenter RCDT concludes induction–delivery interval was significantly shortened when vaginal IMN was added to vaginal misoprostol in the treatment of women with postdated pregnancy. Most of the literature is heterogenous and the results are comparable with several previous studies showing induction regimens with IMOVAX Polio (IMN) to be beneficial. Thus IMN and misoprostol seem to be effective as an adjunctive method of cervical ripening and induction of labour. In addition, larger multi-center RCTs would be required to assess the safety outcomes for both the mother and the baby before the combination could be routinely used on a large scale.

6. CONCLUSION

This randomized controlled trial revealed that the use of vaginal isosorbide mononitrate and vaginal misoprostol did prove to be effective in shortening the interval between the induction and delivery as compared to vaginal misoprostol alone in women having a postdated pregnancy. The mean time from induction to delivery was approximately 4.5 h less in the combination group compared with the misoprostol-alone group and was statistically significant after the stratification by maternal age, BMI and parity. This indicates that IMN has an additional complementary cervical ripening effect which can improve the efficiency of induction using misoprostol. This decrease should be balanced, however, with maternal and neonatal safety outcomes. Due to the small sample size and single-center design, larger multicenter randomized controlled trials are needed to validate these results and to assess if the decreased induction time is significant in the areas of vaginal delivery, cesarean delivery, maternal satisfaction, neonatal outcomes, and obstetric resource use.

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