Journal of Clinical and Nursing Research, 2022, Volume 6, Issue 2
http://ojs.bbwpublisher.com/index.php/JCNR
ISSN Online: 2208-3693
ISSN Print: 2208-3685

A Comparative Study on the Effects of Vaginal Misoprostol and Vaginal Misoprostol Plus Estradiol on Labor Induction

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Abstract: *Background:* Cervical ripening is an important factor in predicting successful labor induction. In an unfavorable cervix, ripening should be done before induction. In this study, the effect of misoprostol and that of misoprostol plus estradiol on cervical ripening were compared. *Methods:* This randomized, double-blinded study included a total of 190 pregnant women who were identified for pregnancy termination due to maternal or fetal cause at 37 weeks with Bishop score of less than 4. The patients were assessed between April 2015 to April 2016 in two university hospitals at northeast Iran (Omol-Banin Hospital and Emam Reza Hospital, Mashhad). The patients who met the inclusion criteria were randomly assigned to two groups: the intervention group (Group A), who received 25 micrograms of vaginal misoprostol plus 50 micrograms of estradiol, and the control group (Group B), who received 25 micrograms of vaginal misoprostol only. Misoprostol was administered at 4-hour intervals until cervical ripening (Bishop score ≥ 8) or upon initiation of active phase in both the groups. The maximum dosage of misoprostol was three doses, whereas estradiol was administered only once. *Results:* In this study, the main causes of pregnancy termination were ROM and post-term. There was no significant statistical difference in the Bishop score between the two groups ($P = 0.13$). In addition, no significant difference was observed in the duration of time for cervical ripening (Bishop ≥ 8) between the two groups ($P = 0.7$). The duration between drug administration to the initiation of active phase and also from active phase to delivery showed no significant differences between the two groups ($P = 0.49$ and 0.24, respectively). There was also no significant difference in the delivery route (operative vaginal delivery or Cesarean section) ($P = 0.2$ and $P = 0.91$, respectively). *Conclusion:* From this study, the use of misoprostol plus estradiol did not improve cervical ripening or decrease the induction time. Further studies are recommended to investigate complementary results.

Keywords: Misoprostol; Estradiol valerate; Labor induction

Online publication: February 18, 2022

1. Introduction

Labor induction refers to the methods used to stimulate uterine contraction before the spontaneous onset of labor. Labor induction is recommended in cases where labor is more beneficial for the mother or fetus rather than continued pregnancy. Labor induction is one of the most common obstetric measures. Women's

and midwives' associations around the world, such as ACOG (American College of Obstetricians and Gynecologists) and NICE (National Institute for Health and Care Excellence), have issued clear and precise guidelines on this issue [1-3]. Chorioamnionitis, severe preeclampsia, post-term pregnancy, gestational hypertension, and different types of maternal medical disorders are the potential causes for labor induction. Cervical ripening is a physiological state that begins at the end of pregnancy and is completed at the start of labor. The condition of the cervix at the onset of labor induction is a predictor of its success. Bishop score is a quantitative measurement system for determining the position of the cervix and its degree of readiness before labor induction. A Bishop score equal to or less than 6 indicates an unfavorable cervix, while a score over 8 represents a favorable cervix and an appropriate response to labor induction [4]. If the cervix is unfavorable, it should be first prepared and then labor induction performed, in order to increase the probability of vaginal delivery. There are several ways to prepare a cervix before labor induction, which includes pharmaceutical and mechanical methods. One of the pharmacological methods is the use of prostaglandins, which have been widely used to optimize the cervix [5]. Prostaglandins can dissolve collagen bundles and increase the content of cervical fluid, resulting in improved cervical response to contractions caused by oxytocin. Also, these medications can precipitate uterine contraction and the initiation of labor [6]. One of the most commonly used prostaglandins is misoprostol, which is used in the form of vaginal or oral doses ranging from 25 to 50 µg at intervals of 4 to 6 hours to prepare the cervix [7,8]. Misoprostol is a synthetic analogue of prostaglandin E1 that can be stored at room temperature and is inexpensive. The possibility of oral administration of this drug due to the rupture of membrane, in which at least vaginal examination should be performed, has distinguished misoprostol from other pharmaceutical methods.

With the constant buildup of estrogen in the mother's circulation at the end of pregnancy, a hypothesis has been raised that this could be the initiator of labor. Numerous studies have been done to prove this effect [9]. Estradiol increases the incidence of oxytocin and cyclooxygenase-2 receptors as well as contributes to cervical readiness. In addition to that, estradiol has an overlapping effect with prostaglandins. Reversing the estrogen to progesterone ratio at the end of pregnancy has led to an increase in prostaglandin production, triggering a cascade that affects the onset of labor [10].

Attempts have been made to use estradiol by administrating estradiol gel via extra-amniotic approach, vaginal approach, intra-cervical approach, or intramuscular injection, which can improve the condition of the cervix without causing any stimulant effect on the uterus [11,12].

Since the effect of the simultaneous use of prostaglandin and estradiol on cervical ripening and labor induction has not been studied in literatures, this study was designed to evaluate the effect of this simultaneous administration and compare it with the administration of misoprostol alone in cervical preparation.

2. Methods and materials

2.1. Study design

This study is a randomized, double-blinded clinical trial performed in Mashhad University of Medical Sciences between April 2015 to May 2017. The study protocol was approved by the Institutional Review Board of Mashhad University of Medical Sciences. The registration code in the IRCT (Iranian Registry of Clinical Trials) system is IRCT2014120920264N1. This study included 190 pregnant women at gestational week greater than 36 weeks with indication of pregnancy termination due to maternal or fetal cause. Upon obtaining their informed written consent, the mothers who met the inclusion criteria were randomly assigned to two groups: an intervention group (25 µg of vaginal misoprostol plus 50 µg of estradiol) and a control group (25 micrograms of vaginal misoprostol only).

2.2. Participants

The inclusion criteria were as follows: singleton pregnancy with vortex presentation, absence of contraindications for vaginal delivery, no indication for emergency delivery, no known liver or kidney diseases, and no contraindications for using misoprostol, such as coagulation disorders, asthma, or glaucoma. The exclusion criteria were as follows: distress resulted in Cesarean section before cervical ripening and incomplete checklist.

2.3. Randomization and blinding

In terms of randomization, a computer randomized assignment list was prepared and given to an individual independent of the study to assign numbers to envelopes based on that list and put pills into those envelopes. This individual was also given the envelopes' coding to be able to break the codes in case of unwanted complications and determine the grouping of the mothers. Trained midwives were assigned to open the envelope for each mother, respectively, and the vaginal drug delivery was performed by them. None of the examiners, specialists, or mothers were aware of the grouping; only those midwives who prescribed the drug at the time of admission were aware of the patients' grouping, who, of course, did not play any other role in subsequent evaluations.

2.4. Instrument

Cervical evaluation was performed to evaluate cervical favorability based on the Bishop score (**Table 1**).

The Bishop score is a quantitative measurement system to determine the position of the cervix and its degree of readiness before labor induction, of which a score of less than or equal to 6 indicates an undesirable cervix, whereas a score more than 8 indicates a favorable cervix or a cervix with appropriate response to induction.

Table 1. Bishop scoring system

Cervical position	Cervical consistency	Station (-3 to +3)	Cervical effacement (%)	Dilation (cm)	Score
Posterior	Firm	-3	30%	0	0
Medial	Medium	-2	40-50%	1-2	1
Anterior	Soft	-1	60-70%	3-4	2
-	-	+1 and +2	More than 80%	More than 5	3

2.5. Intervention

Upon admission, the patients in the intervention group received 25 µg of misoprostol (Cytotec®, Pfizer) plus 50 µg of estradiol (Vagifem®, Novo Nordisk) and those in the control group received 25 µg of misoprostol alone. After the initial administration, misoprostol was repeated every 4 hours for both the groups until the Bishop score was greater than 7 or the active phase of labor began. Both misoprostol and estradiol were inserted into the vagina. Experienced midwives responsible for the pregnant mothers in the maternity ward placed these drugs in the posterior cul de sac.

The patients were then monitored until delivery. The interval between cervical ripening and the onset of the active phase of labor, the interval between the onset of medication delivery and the method of delivery (Cesarean or normal delivery), as well as the complications during delivery, including onset of postpartum hemorrhage, meconium-stained amniotic fluid, the Apgar score at 1 minute and 5 minutes, as well as the admission of neonate into NICU were recorded.

2.6. Outcome

The primary outcomes of the study included the duration from the first dose of drug administration to the onset of active phase or a Bishop score over 7, and the duration from the first dose of the drug to delivery.

The secondary outcomes were the amount of misoprostol doses, the frequency of Cesarean section, the frequency of instrumental delivery, the occurrence of fetal distress, the occurrence of maternal complications in the form of postpartum hemorrhage requiring blood transfusion, fetal Apgar score, and NICU admission.

2.7. Sample size

The sample size was calculated based on the findings of a study conducted by Dasgupta in 2012 [13], which reported that the mean values of induction initiation to delivery interval were 12.97 ± 5.27 in the intervention group and 15.33 ± 3.76 in the control group. Considering $\alpha = 0.05$ and $\beta = 0.2$, the sample size was calculated equal to 88 in each group with the aid of the formula for comparing the two means, and in view of probable loss of samples, the sample size was considered as 95 patients in each group.

2.8. Statistical analysis

The data were analyzed using Statistical Package for Social Sciences (SPSS) Version 23 (IBM, Inc, Chicago, IL, USA). Kolmogorov-Smirnov test was used to evaluate the normal distribution of data. In the case of a normal distribution of data, independent t-test was used to compare the quantitative variables between the two groups; otherwise, Mann-Whitney U test was used.

Fischer's exact test was used to compare qualitative variables. $P = 0.05$ was considered statistically significant in the calculations.

3. Results

This is a double-blinded, randomized, clinical trial involving 190 pregnant women with indication of pregnancy termination. The women were randomly assigned to two groups, with 95 in each group. In the intervention group (Group A), four were excluded from the study due to incomplete checklists (**Figure 1**).

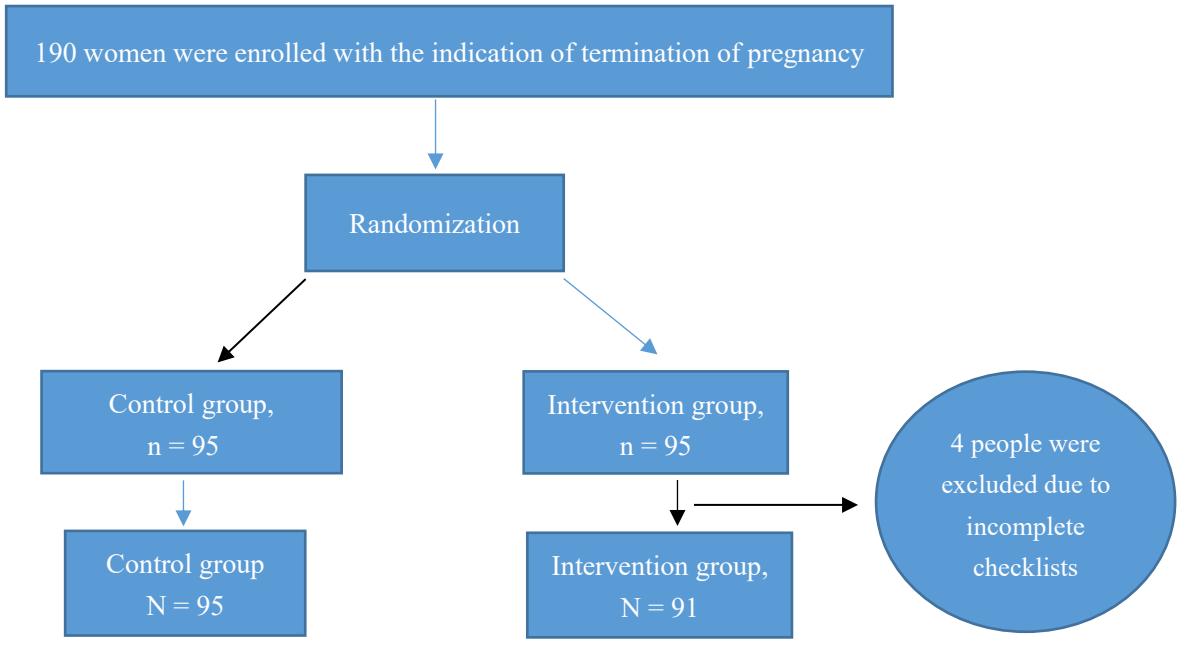

Figure 1. A CONSORT diagram of the current study

The women in the intervention group were similar in terms of personal characteristics, such as age, number of previous pregnancies, abortion history, and smoking (**Table 2**).

The mean gestational age of the women in the intervention group was 39.31 ± 4.14 and that of the control group was 39.16 ± 1.5 (P = 0.66).

The Bishop score in the intervention group was 2.23 ± 2.1 and that of the control group was 2.46 ± 1.18 (P = 0.33). There was no statistically significant difference between both the groups.

Table 2. Demographic characteristics of the studied groups

Variable	Intervention group	Control group	*P* value
Age*	27.11 ± 5.9	26.66 ± 5.4	0.67
Nulliparity[α]	48 (53.3)	50 (54.3)	0.89
Abortion history[α]	13 (14.3)	15 (15.8)	0.77
Smoking[α]	0	1 (1.1)	0.32

Note: *Independent t-test; [α]Fisher's exact test [Frequency (percentage)].

Table 3 shows the indications of pregnancy termination and their distribution in both the groups. No significant difference was observed between the two groups. The common causes of pregnancy termination in both groups were post-term pregnancy and preterm rupture of membrane.

Table 3. Indication of pregnancy termination

Indication of pregnancy termination	Misoprostol	Misoprostol plus estradiol	*P* value
0.39	25 (27.5)	21 (22.1)	Post-term
0.60	58 (63.7)	64 (67.4)	PROM

In this study, the interval between drug administration and cervical ripening (Bishop score ≥ 8) of the intervention group was 4 hours (2 to 5 hours) and that of the control group was also 4 hours (2 to 8 hours), which was not statistically significant (P = 0.7). The interval between drug administration and the onset of the active phase of labor of the intervention group was 5 hours (2.5 to 8.5 hours) and that of the control group was 5.5 hours (3 to 10 hours), which was also not statistically significant (P = 0.24). Moreover, for the intervention group, the duration from drug prescription until delivery was 8 hours (4.5 to 14 hours), while that of the control group was also 8 hours (5 to 14) hours (P = 0.49), none of which differed significantly.

For the intervention group, the median dose of 25 µg misoprostol to ripen the cervix was one dose (1 to 3 doses) and that of the control group was also one dose (1 to 2 doses) (P = 0.42).

Out of 91 women in the intervention group, 11 underwent Cesarean section, whereas 4 underwent instrumental delivery. Of 95 women in the control group, 12 underwent Cesarean delivery, whereas only 1 had vacuum-assisted delivery. There was no significant difference between the two groups in terms of the delivery method (Cesarean section or instrumental delivery) (P = 0.91 and P = 0.2).

There were four cases of fetal distress in the intervention group and 7 in the control group (P = 0.38). According to **Table 4**, the fetal outcomes in both the groups did not have any significant difference.

Table 4. Fetal outcomes

	Intervention	Control	*P*
Apgar score below 5 in the first minute	1	1	0.38
Apgar score below 7 in 5 minutes	2	1	
Meconium-stained amniotic fluid	7	3	0.21
NICU admission	5	4	0.74

Maternal complications were in the form of postpartum hemorrhage requiring blood transfusion, in which there was a case from the intervention group and another from the control group ($P = 0.99$).

4. Discussion

About 20% of pregnancies require labor induction for the termination of pregnancy. The indications are such as postdate pregnancy, rupture of membrane without the initiation of contractions, and gestational hypertension. In this study, the main reasons for the termination of pregnancy were preterm rupture of membrane and postpartum pregnancy, which is consistent with Dasgupta's study [13].

The hypothesis that high estradiol and low progesterone in mammals result in cervical ripening [14] was confirmed in a study on rats [9]. In that study, it was shown that eosinophilic infiltration and collagen modification for cervical ripening are caused by several hormones, including estradiol and relaxin [9]. However, this hypothesis was rejected in a study by Konopka and other researchers [10], in which the association between the reduction of progesterone and the efficacy of dinoprostone has not been established; in addition, the estradiol levels were not significantly different in the group that responded to the induction with dinoprostone with the group that did not respond. In this current study, the administration of misoprostol plus estradiol did not improve the Bishop score, neither did it reduce the duration from the induction of labor to delivery.

Various studies have indicated that the misoprostol administration and delivery interval is between 16 to 20 hours [15-17], but in this current study, the interval was between 4.5 and 14 hours. This could be attributed to the greater Bishop score at the onset of labor induction.

This study found that misoprostol administration at 4-hour intervals is not associated with increased mortality, perinatal morbidity, and adverse maternal complications, which is consistent with another study by Maurice and other researchers [18]. In that study, misoprostol was administered at 2-hour intervals, without any associations with increased mortality, perinatal morbidity, and adverse maternal complications. In a study conducted by Yue and other researchers, it has been shown that the use of estradiol valerate helps to facilitate IUD removal, with lesser need for cervical dilation by curettage [19]. Concerning that, in order to facilitate cervical dilation in non-pregnant women and even after menopause, prostaglandin, and in particular, misoprostol, has been used in studies and for meta-analysis [20,21], in which it was mentioned that misoprostol facilitates the opening of the cervix in hysteroscopy for women after menopause. As of today, several studies on the concomitant administration of misoprostol and estradiol in preparing the cervix in term pregnancies have been conducted. In a study carried out by Dasgupta on two groups of 45 term women, it was found that 25 μg of misoprostol plus estradiol can improve the cervical preparation for labor, initiate the active phase of labor, and significantly increase vaginal delivery [13], but in this current study, none of the above had improved. One of the possible reasons for the difference between the results can be the role and effect of racial differences in the response of the cervical connective tissue to the drug compound used for cervical ripening.

Another possible theory to justify the difference between the results of this study with those of previous studies is that estradiol may improve the effect of misoprostol on cervical ripening up to a certain serum

level, but with higher levels, it may not have any effect in promoting cervical ripening. Therefore, one of the suggestions for further studies is to measure the level of estradiol before drug administration.

Other than that, the difference in the drug combination used in this study with Dasgupta's study may have contributed to the difference in results as Dasgupta's study did not mention the type of pill used and the manufacturer.

In another similar study by Rokasha in 2013, the results were similar to those of Dasgupta's study in terms of accelerated cervical preparation, increased vaginal delivery, and reduced dose required for misoprostol [22].

Another study that compared the effect of estrogen and placebo gel on cervical preparation and on improving the Bishop score in 44 pregnant women concluded that estrogen cream alone is not effective in improving the Bishop score and has no difference with a placebo. Similarly, in this study, the administration of misoprostol plus estradiol failed to improve the Bishop score compared to misoprostol alone [23].

One of the strengths of this study is the large number of samples compared to similar studies. One of its limitations is that it would be better to study patients with the same complaint and similar gravity for the purpose of homogeneity between the groups.

5. Conclusion

Considering this study and its larger number samples compared to similar studies (95 in each group), it can be concluded that the administration of estradiol plus prostaglandin does not improve the response to cervical preparation or shorten the duration of delivery.

Disclosure statement

The authors declare no conflict of interest.

References

[1] James DK, Steer PJ, Weiner CP, et al., 2014, High Risk Pregnancy: Management Options. Elsevier Saunders, 1145-1148.

[2] Wing DA, Tran S, Paul RH, 2002, Factors Affecting the Likelihood of Successful Induction After Intravaginal Misoprostol Application for Cervical Ripening and Labor Induction. Am J Obstet Gynecol, 186(6): 1237-1240; discussion 1240-1243.

[3] Andersson S, Minjarez D, Yost NP, et al., 2008, Estrogen and Progesterone Metabolism in the Cervix during Pregnancy and Parturition, 93(6): 2366-2374.

[4] Laughon SK, Zhang J, Troendle J, 2011, Using a Simplified Bishop Score to Predict Vaginal Delivery. Obstetrics & Gynecology, 117(4): 805-811.

[5] Cunningham FG, Leveno KJ, Bloom SL, et al., 2018, Obstetrics, 25th Edition, MC Graw Hill, New York, 523-532.

[6] Alfirevic Z, Aflaifel N, Weeks A, 2014, Oral Misoprostol for Induction of Labour. Cochrane Database Syst Rev, 2014(6): CD001338.

[7] Mazhar SB, Imran R, Alam K, 2003, Trial of Extra Amniotic Saline Infusion with Oxytocin Versus Prostaglandin E2 Pessary for Induction of Labor. J Coll Physicians Surg Pak, 13: 317-320.

[8] Nizard J, Cromi A, Molendijk H, et al., 2005, Neonatal Outcome Following Prolonged Umbilical Cord Prolapse in Preterm Premature Rupture of Membranes. BJOG, 112(6): 833-836.

[9] Luque EH, Muñoz de Toro MM, Ramos JG, et al., 1998, Role of Relaxin and Estrogen in the Control of Eosinophilic Invasion and Collagen Remodeling in Rat Cervical Tissue at Term. Biol Reprod, 59(4): 795-800.

[10] Konopka CK, Morais EN, Naidon D, et al., 2013, Maternal Serum Progesterone, Estradiol and Estriol Levels in Successful Dinoprostone-Induced Labor. Braz J Med Biol Res, 46(1): 91-97.

[11] Gordon AJ, Calder AA, 1977, Oestradiol Applied Locally to Ripen the Unfavourable Cervix. Lancet, 2(8052-8053): 1319-1321.

[12] Magann EF, Perry KG Jr, Dockery JR Jr, et al., 1995, Cervical Ripening Before Medical Induction of Labor: A Comparison of Prostaglandin E2, Estradiol, and Oxytocin. Am J Obstet Gynecol, 172(6): 1702-1706; discussion 1704-1708.

[13] Dasgupta E, Singh G, 2012, Vaginal Misoprostol Vs Vaginal Misoprostol with Estradiol for Labor Induction: A Prospective Double Blind Study. J Obstet Gynaecol India, 62(1): 47-51. DOI: 10.1007/s13224-012-0156-6

[14] Fritz MA, Speroff L, 2011, Clinical Gynecologic Endocrinology and Infertility, 8th Edition, Lippincot Williams and Wilkins, Philadelphia, 322-323.

[15] Roztocil A, Pilka A, Jelinek J, et al., 1998, A Comparison of Three Preinduction Cervical Priming Methods: Prostaglandins E2 Gel, Dilapan S Rods and Estradiol Gel. Ceska Gynecol, 63(1): 3–9.

[16] Quinn MA, Murphy AJ, Kuhn RJP, et al., 2005, A Double Blind Trial of Extra-Amniotic Oestriol and PGF2a Gels in Cervical Ripening. BJOG, 88(6): 644-649.

[17] Hall R, Gardea M, Harlass F, 2002, Oral Versus Vaginal Misoprostol for Labor Induction. Obstet Gynecol, 99(6): 1044-1048.

[18] Morris M, Bolnga JW, Verave O, et al., 2017, Safety and Effectiveness of Oral Misoprostol for Induction of Labour in a Resource-Limited Setting: A Dose Escalation Study. BMC Pregnancy and Childbirth, 17(1): 298.

[19] Yue H, Ye NH, Li CJ, et al., 2010, Clinical Observation on the Efficacy of Intrauterine Device Removal in Postmenopausal Women by Methyl Carboprost. Chinese Journal of Misdiagnosis, 10: 4381.

[20] Gkrozou F, Koliopoulos G, Vrekoussis T, et al., 2011, A Systematic Review and Meta-Analysis of Randomized Studies Comparing Misoprostol Versus Placebo for Cervical Ripening Prior to Hysteroscopy. Eur J Obstet Gynecol Reprod Biol, 158(1): 17-23.

[21] Selk A, Kroft J, 2011, Misoprostol in Operative Hysteroscopy: A Systematic Review and Meta-Analysis. Obstet Gynecol, 118(4): 941-949.

[22] Raksha M, Rao AA, Kamath A, et al., 2013, Induction of Labor in Unfavourable Cervix: Vaginal Misoprostol Versus Vaginal Misoprostol with Estradiol. Int J Pharm Biomed Res, 4(4): 202-205.

[23] Larmon JE, Magann EF, Dickerson GA, et al., 2002, Outpatient Cervical Ripening with Prostaglandin E2 and Estradiol. J Matern Fetal Neonatal Med, 11(2): 113-117.