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Comparative Study between Using Only Vaginal Misoprostol and Using Vaginal Misoprostol and Estradiol Cream for Induction of Labour: Randomized controlled trial

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Abstract

Objective: To evaluate the effectiveness of vaginal misoprostol versus vaginal misoprostol and estradiol cream for ripening of the very unfavorable cervix in patients requiring induction of labor to shorten induction delivery interval.

Methods: This study was a randomized controlled trial conducted on 120 women with unfavorable cervix during the period from April 2021 to October 2021. Patients were randomized into two equal groups as follows; ***Group I*** included 60 patients who were given only vaginal misoprostol 25 µg, and ***Group II*** included 60 patients in which women were given vaginal misoprostol 25 µg with vaginal estradiol 150 mg.

Results: Thirty-two patients (53.3%) in the misoprostol group and 38 patients (63.3%) in the estradiol group reached the active phase. According to the mode of delivery, 29 patients (48.3%) in the misoprostol and 24 patients (40%) in the estradiol group underwent cesarean section. The most common causes of CS were failed induction and fetal distress. With exception of the 1st minute Apgar score, no statistically significant difference in labor induction between both groups was reported.

Conclusion: We found that a combination between the misoprostol and estradiol does not achieve a significant difference in labor induction compared to vaginal misoprostol alone.

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Introduction

Induction of labor (IOA) is a common procedure that occurs in nearly 25% of term pregnancies.[1] IOL is an essential

vital intervention that reduces undesirable effects. Labor induction can decrease the frequency of stillbirths; reduce risks of infection, and lower cesarean section (CS) rates without increasing adverse pregnancy outcomes.[2]

Cervical preparation is one of the most substantial factors in the success of labor induction. Attempting induction with an unripe cervix is difficult and rarely successful. Inducing labor with an unripened cervix can result in induction failure or prolonged labor and childbirth with the use of instruments. This will contribute to low levels of satisfaction of delivery, and also to negative psychological and physical effects.[3]

While several methods of cervical ripening before induction have been proposed, prostaglandins are the current agents of choice.[4]

Misoprostol, a prostaglandin E1 analog has gained popularity as an IOL agent in recent years.[5] Misoprostol has some potential benefits over other prostaglandins. It is stable at room temperature, cheap, and can be given orally, vaginally, sublingually, and buccal. To this day, no unique dosage or administration method has been recorded without causing such side effects.[3]

Estradiol was proposed that acts synergistically with misoprostol vaginally and significantly hastens the process of cervical ripening, initiation of active labor, and vaginal delivery.[6]

The purpose of this study was to evaluate the effectiveness of vaginal misoprostol versus vaginal misoprostol and estradiol cream for ripening of the very unfavorable cervix in patients requiring induction of labor **aiming to initiation of active phase of labor for shortening induction delivery interval.**

Patients and Methods

Our study was registered on Clinical trial.gov.with the following number: NCT05306405. This study was a randomized controlled trial conducted on 120 women with unfavorable cervix during the period from **first April 2021 to 31th of October 2021 at Ain Shams University Maternity Hospital in Egypt**to compare the safety and effectiveness of vaginal misoprostol with combined vaginal misoprostol and estradiol for IOL in unfavorable cervix.

Eligible patients (according to our inclusion criteria which were female patients with gestational age from 36 - 41 weeks (**Gestational age was confirmed by sure last menstrual period of the patient or serial ultrasound if she did not have sure dating**) , with singleton living fetus < 4 k.gs**(confirmed by pregnancy ultrasound before induction of labor**) with cephalic presentation, had no labor pain, or**any amniotic fluid abnormalities (either oligohydramnios, DVP is less than 2 cm or polyhydramnios, DVP is more than 8 cm)** with Bishop score < 5), were randomly allocated to one of two treatment arms in a single-blind manner by the computer-generated system. While we excluded pregnant female patients who had multiple gestation, abnormal umbilical artery Doppler indices (**lost or reversed umbilical artery results**) or non-reassuring non-stress test (**e.g. FHR more than 160 b\m or less than 100 b\m**), fetal weight > 4 kgs, non-vertex presentation, intrauterine fetal death, and previous uterine surgery.

After taking informed written consent, the recruited patients were subjected to detailed history taking, through examination, including pelvic examination to demonstrate the presenting part and to assess cervical dilatation, effacement, consistency and station using Bishop score.[7] In addition, laboratory testing, including complete blood picture, Rh, Urine analysis was performed. Ultrasound was done trans-abdominally using MEDISON R5 Ultrasound

machine equipped with a 3.5 MHz Convex probe to evaluate the fetal biometry, placental site, fetal weight, and amount of liquor.

Patients were randomized into two equal groups as follows;***Group I*** **(control group)** included 60 patients who were given only vaginal misoprostol 25 µg (Vagiprost manufactured by ADWia pharmaceutical company), and ***Group II***included 60 patients in which women were given vaginal misoprostol 25 µg (Vagiprost) with vaginal estradiol 150 mg (Premarine cream manufactured by Aly and Aly pharmacy) every 1 gm of Premarine cream contain 150 mg Estradiol and the given dose was adjusted by a digital scale**.** Misoprostol was repeated every 4 h in both groups for maximum 5 doses[8]**,** reaching Bishop score > 8, rupture of membranes or occurrence of labor pain.The repeated doses, evaluation and labor were done by the supervisors and expert staff. Neither women nor the staff was known whether the woman under observation was assigned to only misoprostol or misoprostol with estradiol group.

Cervical evaluation was done using Bishop's score. A score < 5 was taken as unfavorable. End point of the study was initiation of active phase of 1st stage of labor which commence from 6 cm to full cervical dilatation.
Allocation Concealment Mechanism: using consecutive numbers on opaque sealed envelopes having a letter of "A" or "B" according to the sequence generated through the computer sequentially numbered opaque sealed envelope system with each envelope containing a letter corresponding to a number in the randomization list. Participating women will be allocated to each group according to the letter inside the envelope.

Ethical Considerations: The study was approved by
the ethics committee of the department of obstetrics andgynecology, faculty of medicine Ain Shams University. Informed written consent was taken from all participants before recruitment in the study, and after explaining the purpose and procedures of the study.

Sample size justification: Using PASS 11 program for sample size calculation, setting power at 80% and alpha error at 5%. Reviewing results from previous study[6] showed that time from initiation to active labour in misoprostol Versus misoprostol and estradiol groups was 15.33 $\pm$ 3.76 versus 12.97 $\pm$ 5.27. According to these findings sample size of at least 120 pregnant females (60/group) was needed.

Statistical methods: Data were collected, coded, revised, and entered into the Statistical Package for Social Science (Rstudio) version 2.3.2. The data were presented as numbers and percentages for the qualitative data, mean, standard deviations, and ranges for the quantitative data with parametric distribution and median with interquartile range (IQR) for the quantitative data with the non-parametric distribution. Shapiro test was used to verify the normality of distribution.The Chi-square test, Fisher exact test or Wilcoxon Mann-Whitney tests were used in the comparison between the two groups. P-value was considered significant as $P < 0.05$: Significant (S), and $P < 0.01$: Highly significant (HS).

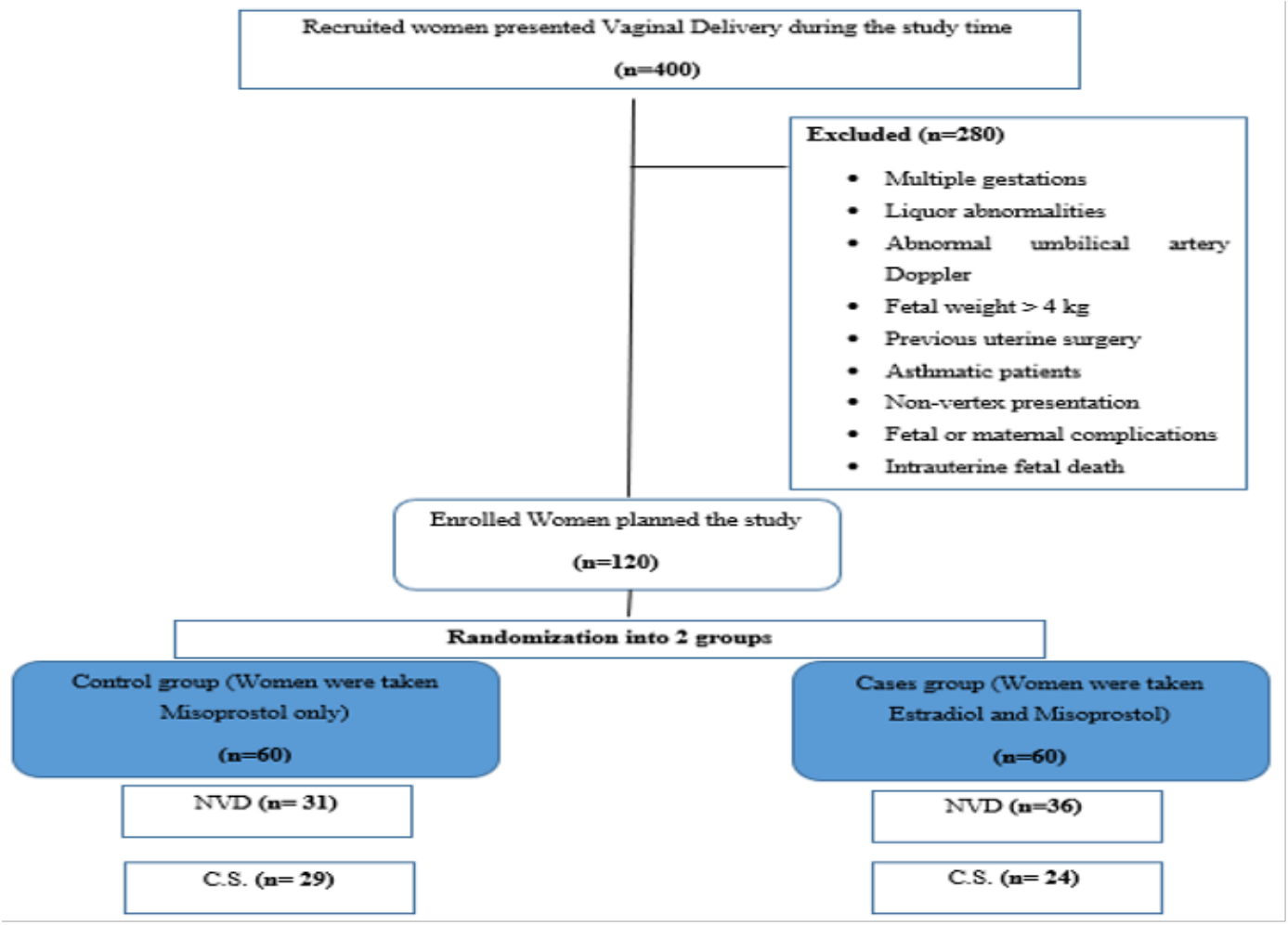

Figure (1): CONSORT Flow diagram showing the recruitment and handling of the study population during the study.

Results

Baseline characteristics were summarized in**Table (1).** No statistically significant differences were found between the two studied groups as regards age, parity, gestational age, abortion times, medical and surgical history.

The most common causes of induction were***decreased fetal kicks*** in 12 patients (20%) in the misoprostol group and 22 patients (36.7%) in the estradiol group, ***SEPT*** in 17 patients (28.3%) in misoprostol group and 15 patients (25%) in estradiol group while rupture of mem brane (***ROM***) in 11 patients (18.3%) in the misoprostol group and 13 patients (21.7%) in estradiol group. There was no statistically significant difference between the two groups at (p=0.151).

The minimum score in both groups was 3 while the maximum was 5 with mean ± SD (3.38± 0.56) in the misoprostol group and (3.28 ± 0.52) in the estradiol group. There was no statistically significant difference between the two groups according to Bishop's score at (p=0.06).

Maternal and fetal complications were presented in**Table (2).** No females had postpartum Hemorrhage and uterus rupture in both groups while two patients (3.3%) in the misoprostol group and only one patient (1.7%) showed hyper stimulation in the estradiol group. All patients in both groups showed no fetal hypoxia.

According to the mode of delivery, 29 patients (48.3%) in the misoprostol and 24 patients (40%) in the estradiol group underwent cesarean section with no statistically significant difference between the two groups according to the mode of

delivery. The most common causes of CS were failed induction and fetal distress. **(Table 3)**

The number of doses of misoprostol ranged between (1 – 3) doses with a mean ± SD of 2.19 ± 0.64 in the misoprostol group while ranged between (1 – 5) doses with a mean ± SD of 2.5 ± 0.83) in the estradiol group with no statistically significant difference at (p=0.201).

Among 32 patients in the active phase in the misoprostol group, there were 22 patients (68.8%) received oxytocin with a median time of 5.0 (4.0 - 6.0) hours while Among 38 patients in the active phase in the estradiol group, there were 25 patients (65.8%) received oxytocin with a median time of (5.0 (4.1 - 6.8). There was no statistically significant difference between the two groups and oxytocin intake and time of taking oxytocin at (p= 0.994, 0.315) respectively.

Patients who reach the active phase, the time needed to reach the active phase, and the induction delivery time in the active phase are illustrated in **Table 4**. Thirty-two patients (53.3%) in the misoprostol group and 38 patients (63.3%) in the estradiol group were in the active phase. Taking in our consideration that not all females who reached the active phase delivered by normal delivery. There was no statistically significant difference between both groups as regards the occurrence of the active phase, the time needed to enter the active phase, and induction of delivery time

Discussion

Labor induction should be used when the benefits of delivery outweigh the risks of continuing, for example, in the setting of maternal or fetal medical complications. These decisions should always be made in conjunction with the patient and their desires.[9] In the current study, the most common causes of labor induction were decreased fetal kicks, severe preeclampsia, and premature rupture of the membrane. There was no statistically significant difference between the two groups at (p=0.151).

Our findings as regards the cause of induction are consistent with***Walker et al.***'s who conducted a randomized, controlled trial involving primigravid women who were were randomly assigned to labor induction. They found the most common causes of IOL were post-term, preeclampsia, and premature rupture of the membrane.[10]

Misoprostol is prostaglandins that have been frequently used for cervical ripening and labor induction for many decades. Although we only find a few works in the literature linking misoprostol's cervical ripening effect to the presence or absence of estrogen, we believe that there is evidence to suggest a connection.[6][11]

Estrogen appears to be essential for cervical ripening to take place. Pregnant women with placental sulphatase deficiency (resulting in low circulating estrogens) do not show ripening of their cervix. The inflammatory cascade during the cervical ripening process involves leucocytes, and the presence of estrogen receptors on cervical leucocytes suggests that estrogen may directly regulate leucocyte function in the cervix. The local application of estrogen for the induction of labor has been tried, and estrogen does enhance cervical ripening. However, estrogens appear to be less effective than prostaglandins for the induction of labor and delivery, and there are insufficient data to draw any conclusions.[11]

In Norwegian university teaching hospital,***Oppegaard et al.*** performed a randomized, double-blind, placebo-controlled trial on 67 postmenopausal women to determine the effect of a combination of misoprostol and estradiol for preoperative cervical ripening in postmenopausal women. They concluded that one thousand micrograms of vaginal misoprostol, 12 hours prior to day-care hysteroscopy, after 14 days of pretreatment with vaginal estradiol, has a significant cervical ripening effect compared with placebo in postmenopausal women.[11]

Several studies[12][13] indicated that participants who were treated with misoprostol were suffering from gastrointestinal experiences, tachysystole, and hyperstimulation which was the result of misoprostol dosage.

On the contrary, in ***Dasgupta & Singh's study,*** there were no significant adverse effects seen with the use of vaginal 25 µg misoprostol on either fetus or mother in both protocols (misoprostol alone, misoprostol with estradiol)[6].

In the current study, no uterine rupture was recorded, but uterine hyperstimulation was reported in 3 patients (one patient in the estradiol group and 2 patients in the misoprostol group) which differed from ***Dasgupta & Singh,*** who reported no incidence of uterine hyperstimulation in their study.

As regards fetal complications in the current study, no fetal hypoxia was reported, but neonatal infections occurred in one patient in the misoprostol group. Meconium staining was higher in the misoprostol group than the estradiol group (21.7% vs 10%) with no significant difference between both groups as regards meconium staining (p=0.134). Six patients in the estradiol group and 10 patients in the misoprostol group were admitted to NICU with no statistically significant difference at (p=0.421). Although the 1st minute APGAR in the misoprostol group was significantly lower than the estradiol group (p=0.009*), the 5th minute APGAR was also lower in the misoprostol group than the estradiol group but with no statistically significant difference (p=136). Our findings regarding the fetal outcomes were in agreement with ***Dadashaliha et al.*** study[3].

In this study, although not statistically significant, the percentage of spontaneous labor in the misoprostol group (51.7%) was lower than the estradiol group (60%), and the CS in the misoprostol group was higher than the estradiol group (48.9% vs 40%, respectively). The causes of CS were failed induction and fetal distress with no statistically significant difference between both groups as regards causes of CS (p= 0.825, p= 0.63).

The rate of CS in our study was notably higher than in previous studies by ***Souizi et al.***, ***Dasgupta, and Roudsari et al.*** where the cesarean rate was 7%, 10%, and 10%, respectively[6][14][15]. Also, in ***Dadashaliha et al.'s*** study, the CS represented only 17% of patients who received vaginal misoprostol. The cesarean indications were failure to progress and meconium-stained liquor[3].

In this study, the mean ± SD of misoprostol doses in the estradiol group was higher than that in the misoprostol group (2.5 ± 0.83 versus 2.19 ± 0.64, respectively) with no statistically significant difference at (p=0.201).

In contrast to our results, on average, 4–5 doses of misoprostol were required in ***Dasgupta and Singh*** study for cervical ripening or initiation of active labor, however, the dose required in the combined group (vaginal misoprostol and vaginal estradiol) was significantly less than that in the misoprostol group (p = 0.017)[6].

Various studies have found induction delivery interval with vaginal misoprostol 16–20 h, which is in agreement with our study median (IQR) of 15.0 (12.5 - 18.6) in the misoprostol group and 16.8 (13.1 - 19.8) in the estradiol group[6][16]

In terms of oxytocin intake and time of taking oxytocin, no statistically significant difference between the two groups was found (p= 0.994, 0.315 respectively). Also, as regards the active phase, the time needed to enter the active phase, and the induction delivery time in the active phase, all were comparable in both groups with no statistically significant difference at (p= 0.355, 0.701, 0.519, respectively).

However, the findings of the current study do not support the previous research by ***Dasgupta & Singh.*** They reported significant differences between vaginal misoprostol versus vaginal misoprostol with estradiol for labor induction regarding induction initiation to cervical ripening interval, induction initiation to active labor initiation, and induction initiation

to delivery [Induction to cervical ripening (p = 0.017), the time required for cervical ripening (p = 0.042), the time required for starting of active labor (p = 0.017) and time required for delivery in vaginal delivery cases (p = 0.047)][6].

Another study that differs from our work was***Raksha et al. study.*** This was a randomized study conducted to compare the safety and effectiveness of vaginal misoprostol v/s combined vaginal misoprostol with estradiol for priming an unfavorable cervix. They found that time interval between the administration of the first dose to cervical ripening (p<0.001) and vaginal delivery (p<0.001), number of doses of misoprostol required for cervical ripening (p<0.001), the number of cases of failure of cervical ripening (p=0.009) were found to be lesser in the misoprostol and estradiol group when compared to the misoprostol only group. They concluded that estradiol acts synergistically with misoprostol vaginally and significantly hastens the process of cervical ripening, vaginal delivery and also decreases the number of doses of misoprostol required to achieve this[17]

Overall, our data suggested that a combination between vaginal misoprostol and vaginal estradiol does not achieve a significant difference in labor induction compared to vaginal misoprostol alone with exception of the 1st minute APGAR score. This was contradictory to the previous conclusion by ***Dasgupta & Singh and Raksha et al.*** Which proved that estradiol acts synergistically with misoprostol vaginally and significantly hastens the process of cervical ripening, initiation of active labor, and vaginal delivery[6][17]. Accordingly, further studies are required to validate the contradictory findings.

Conclusion

Although it was proposed that estradiol act synergistically with misoprostol in labor induction. This study was a randomized controlled trial to evaluate the effectiveness of vaginal misoprostol versus vaginal misoprostol and estradiol cream for ripening of the unfavorable cervix in patients requiring induction of labor. We found that although the spontaneous labor was more frequent in patients who received combined vaginal misoprostol and vaginal estradiol, however, this combination does not achieve a significant difference in labor induction regarding number of misoprostol doses, mode of delivery and time needed to enter the active phase compared to vaginal misoprostol alone with exception of the 1st minute Apgar score with no any significant results between fetal or maternal complications and use of combined vaginal misoprostol and vaginal estradiol**. We recommend** complementary studies to evaluate more than one method whether pharmacological or mechanical in labor induction to establish best model to be used safely in the clinical practice and validate the contradictory finding as regards the use of estradiol in labor induction.

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Table (1): Comparison between the two studied groups according to baseline characteristics

		Misoprostol group (N=60)	Estradiol group (N=60)	Test of significance
Age in years:				
	Range	19 – 36 years	19 – 45 years	**Mann-Whitney test**
	Mean ± SD	26.2 ± 5.1	27.7 ± 6.9	0.179
	Median (IQR)	25.5 (22.0 – 30.0)	25.0 (22.8 – 32.0)	
Age Category:				
	18-30	41 (68.3%)	42 (70.0%)	**Fisher test**
	30-40	19 (31.7%)	14 (23.3%)	0.092
	>40	0 (0.0%)	4 (6.7%)	
Parity:				
	Primipara	22 (36.7%)	29 (48.3%)	**Chi-square test**
	Multipara	38 (59.6%)	31 (51.7%)	0.268
Gestational age:				
	Range	36 – 41+ 2 weeks	36 – 42 weeks	**Mann-Whitney test**
	Mean ± SD	38.9 ± 1.5	38.8 ± 1.6	0.91
	Median (IQR)	38.9 (37.7 – 40.0)	39.0 (37.3 – 40.0)	
Abortion times:				
	Range	0 – 3 times	0 – 5 times	**Mann-Whitney test**
	Mean ± SD	0.3 ± 0.7	0.4 ± 1.0	0.576
	Median (IQR)	0.0 (0.0 – 0.0)	0.0 (0.0 – 1.0)	
Medical History:				
Hypertension:	Yes	6 (10.0%)	2 (3.3%)	0.439
Diabetes Mellitus:	Yes	2 (3.3%)	0 (0.0)	0.496
Other medical Comorbidity	ITP	2 (3.3%)	0 (0.0)	0.305
	RA	1 (1.7%)	0 (0.0)	
	SLE	1 (1.7%)	0 (0.0)	
	Thrombocytopenia	1 (1.7%)	1 (1.7%)	
Surgical History:				
	Appendectomy	2 (3.3%)	3 (5.0%)	**Fisher test**
	Cholecystectomy	0 (0.0)	1 (1.7%)	0.509
	Cystectomy	0 (0.0)	1 (1.7%)	
	Dand C	0 (0.0)	2 (3.3%)	
	Tonsillectomy	4 (6.7%)	5 (8.4%)	
	No	54 (90.0%)	48 (80.0%)	

Table (2): Comparison between the two studied groups according to Maternal Complications and fetal Outcome

		Misoprostol group (N=60)	Estradiol group (N=60)	Test of significance
Maternal Complications:				
Postpartum HE:	No	60 (100.0%)	60 (100%)	1
Uterus rupture:	No	60 (100.0%)	60 (100.0%)	1
Hyper stimulation	Yes	2 (3.3%)	1 (1.7%)	0.99
Fetal Outcome:				
Fetal hypoxia	No	60 (100.0%)	60 (100%)	1
Meconium Staining	Yes	13 (21.7%)	6 (10.0%)	0.134 ©
Neonatal Infection	Yes	1 (1.7%)	0 (0.0%)	0.99
1st minute APGAR	Mean ± SD	6.5 ± 1.0	6.9 ± 0.4	**0.009* β**
	Median (IQR)	7.0 (6.0 – 7.0)	7.0 (7.0 – 7.0)	
5th minute APGAR	Mean ± SD	8.7 ± 0.5	8.8 ± 0.4	0.136 β
	Median (IQR)	9.0 (8.0 – 9.0)	9.0 (9.0 – 9.0)	
NICU admission	Yes	10 (16.7%)	6 (10.0%)	0.421©

©: Chi-square test, β: Mann-whitney test.

Table (3): Comparison between the two studied groups according to Mode of Delivery

		Misoprostol group (N=60)	Estradiol group (N=60)	Test of significance
Mode of Delivery:				
	NVD	31 (51.7%)	36 (60.0%)	**Chi-square test**
	CS	29 (48.3%)	24 (40.0%)	0.359
Cause of C.S. Induction:				
Failed induction		14 (23.3%)	12 (20.0%)	0.825
Uterine hyperstimulation		2 (3.3%)	1 (1.7%)	1
Tach systole		1 (1.7%)	1 (1.7%)	1 0.631
Fetal distress		12 (20.0%)	9 (15.0%)	

Table (4): Comparison between the two studied groups according to Active phase:

		Misoprostol group (N=60)	Estradiol group (N=60)	Test of significance
Active phase:				
	No	28 (46.7%)	22 (36.7%)	**Chi-square test**
	Yes	32 (53.3%)	38 (63.3%)	0.355
Time needed to enter Active phase: (Hours)				
	Range	5.0 – 21.0 hours	6.5 – 20.5 hours	**Mann-Whitney test**
	Median (IQR)	13.5 (11.0 - 17.0)	14.5 (11.2 - 17.9)	0.701
Induction of Delivery Time: (Hours)				
	Range	6.5 – 23.0 hours	8.5 – 22.0 hours	**Mann-Whitney test**
	Median (IQR)	15.0 (12.5 - 18.6)	16.8 (13.1 - 19.8)	0.519

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