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Late second trimester fetal death termination with one previous cesarean section; Combination of Intra-vaginal PGE2 and PGE1 analogue: A randomized study

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ABSTRACT

Aims: The aim of this work is to evaluate the effect of combining dinoprostone and misoprostol as a method of medical termination of pregnancy in patients with late 2nd trimester IUFD. Methods: This is a randomized clinical trial. 150 participants with past history of one transverse LSCS and late 2nd trimester IUFD were admitted for medical termination of pregnancy.They were divided into 3 groups, the first one received intra-vaginal misoprostol 50 µgm (4 doses with 6 hours interval), the second one received intra-vaginal dinoprostone 3 mg (4 doses with 6 hours interval) and the third one received a combination of both drugs intra-vaginally (2 doses of dinoprostone 3 mg followed by 2 doses of misoprostol 50µgm with 6 hours interval) and the clinical response to the three regimens was evaluated. Results: Dinoprostone followed by misoprostol showed statistically significant difference when compared to misoprostol and dinoprostone as regard response to induction, induction-contraction interval, induction-expulsion interval and the final outcome of termination of pregnancy. Conclusion: Using dinoprostone followed by misoprostol is more effective than using any of the two drugs separately as a method of pregnancy termination in patients with late 2nd trimester IUFD and past history of one LSCS.

Keywords: Dinoprostone, Misoprostol, Second trimester termination of pregnancy, Uterine scar

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INTRODUCTION

Termination of pregnancy (TOP) remains one of the most common procedures in obstetrics and gynecology, with an estimated 50 million induced abortions each year worldwide. TOP is performed either by surgical evacuation or medically by prostaglandins. In general, these are misoprostol, gemeprost and dinoprostone, which are widely used and which have been proved to be safe and efficient for cervical ripening, induction of labor and termination of pregnancy [1].

Misoprostol is a PGE_1 analogue available in a tablet form that is stable at room temperature and inexpensive

[2]. Two common routes of misoprostol administration are vaginal and sublingual; but they have different pharmacokinetics and effectiveness [3]. The vaginal route has few side effects such as nausea, vomiting, hyperpyrexia and diarrhea [4].

The FIGO recommendation for second trimester IUFD termination with vaginal misoprostol is adjusted according to gestational age: at 18–26 weeks; 100 μgm every 6 hours to a maximum of 4 doses" and the doses should be reduced in women with previous cesarean section [5]. Misoprostol for 2nd trimester termination appears safe among women with one prior low transverse cesarean section, as it is associated with the risk of uterine rupture 0.4%, hysterectomy 0% and blood transfusion 0.2% [6, 7]. A high rate of vaginal delivery was achieved at low doses of misoprostol, with a short induction-to-delivery interval [8].

Misoprostol and dinoprostone are safe and effective drugs for cervical ripening and labor induction but misoprostol is more cost effective and stable at room temperature and induction to delivery time was significantly less with it but more side effects were seen. Required doses were less with dinoprostone. Failure of induction was more with dinoprostone and fetal distress was more with misoprostol. These findings suggest that misoprostol is safe, effective and less expensive drug for cervical ripening and induction of labor [9]. Dinoprostone has been the agent of choice for preinduction cervical ripening for several years. However, it has several disadvantages: it is expensive and it requires continuous refrigeration [10].

The aim of this work is to evaluate the effect of combining dinoprostone and misoprostol as a method of medical termination of pregnancy in late 2nd trimester IUFD patients.

MATERIALS AND METHODS

This randomized clinical trial was carried out in Obstetrics and Gynecology department of faculty of medicine, Zagazig University. One hundred and fifty participants with past history of one lower segment transverse cesarean section (LSCS) admitted to Maternity Hospital in the period between October 2015 and July 2017 with late 2nd trimester IUFD for termination of pregnancy. The study protocol was approved by the Institutional Research Ethical Committee. All patients included were fully counseled about the nature of the study, as well as potential side effects. An informed written consent was obtained from all participants. Inclusion criteria: one previous transverse LSCS (from C.S. report), singleton pregnancy, IUFD between 20 to 28 weeks and pre-induction Bishop Score was < 6 [11]. Exclusion criteria: polyhydramnios, multiple pregnancy, low lying placenta, coagulation disorders, chorioamnionitis, and congenital müllerian duct anomalies. Patients with history of allergy to misoprostol or dinoprostone, uncontrolled hypertension, hepatic disorders, previous uterine surgery like myomectomy, hysterotomy, uterine rupture repair or uterine perforation during D&C and previous upper segment cesarean section were also excluded.

In this study, 150 participants with late 2nd trimester IUFD and previous one transverse LSCS were admitted for termination of pregnancy.

Participants were classified into three groups, each 50 patients using a computer generated randomization table. Group (1); included 50 women who received intra-vaginal misoprostol 50 μgm every 6 hours for a maximum 4 doses. Group (2); included 50 women who received intra-vaginal dinoprostone 3 mg every 6 hours for a maximum 4 doses. Group (3); included 50 women who received 2 doses of dinoprostone 3 mg intra-vaginally (6 hours apart) followed after 6 hours by 2 doses of misoprostol 50 μgm intra-vaginally (6 hours apart). Seven patients were excluded from the study, so 143 patients were included in the final analysis as shown in Figure 1.

Each patient was fully assessed by complete history taking, examination and baseline investigations (full blood count, kidney function tests, liver function tests, coagulation profile, random blood glucose, urine analysis) and ultrasound report were reviewed. Assessment of the uterine cervix including; effacement, dilatation, consistency and position as well as the station of the presenting part was done to obtain the Bishop score [11]. The participants were examined regularly at 6, 12, 18 and 24 hours after taking the medication to evaluate the change in the Bishop score. Vital signs were monitored every two hours. Women were asked to report to the residents and nurses when they had uterine contractions, pain, or abnormal symptoms such as headache, shivering, dizziness, fainting, and gastrointestinal symptoms.

In all patients, once efficient uterine contractions were established, no further prostaglandin was administered. With the onset of uterine contractions, all patients were monitored carefully for signs of uterine scar dehiscence or rupture.

Indications to start oxytocin infusion were: (1) inefficient uterine contractions with Bishops score > 6 after 6 hours from the last dose of medication for maximum 6 hours duration. Oxytocin infusion was started at 2 mU/min and increased in incremental doses of 1–2 mU/min at 15–30 min intervals as needed to achieve efficient uterine contractions (3 to 4 contractions per 10 minutes) [12]. In the presence of failure of uterine response to prostaglandin administration, inefficient uterine contraction with Bishop score < 6 or signs of uterine scar dehiscence or rupture; hysterotomy was done.

Placental expulsion was expected within 30 minutes following fetal delivery. If 30 minutes have passed and the placenta not delivered, 30 units oxytocin infusion was administered over 4 hours. If the placenta was not delivered after oxytocin infusion or there is excessive vaginal bleeding, manual or surgical removal of the placenta was performed under general anesthesia.

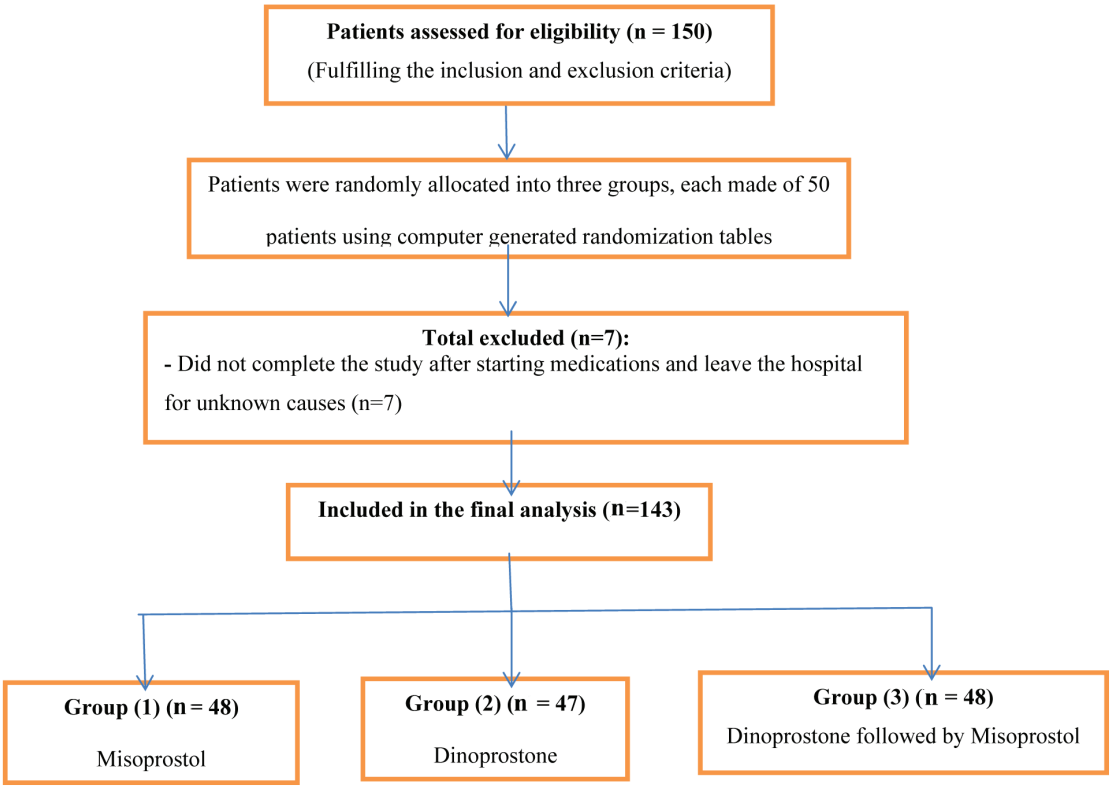

Figure 1: Flow chart of participants.

Transvaginal ultrasound was performed to all patients to ensure complete expulsion of the placenta and empty uterine cavity.

The primary outcome measures were evaluation of response to induction; either success of induction (establishment of uterine contractions {efficient or inefficient} within 24 hours of prostaglandin administration) or failure of induction (diagnosed by absence of uterine contractions), induction-contraction interval {the duration between the 1st dose administered and the onset of efficient uterine contractions (hours)}, induction-expulsion interval {the duration between the 1st dose administered and the fetal expulsion (hours)} and the final outcome (either complete expulsion was confirmed by TVS or incomplete expulsion which need evacuation). The secondary outcomes were evaluation of side effects and complications associated with the termination method.

Statistical analysis

Data was tabulated and analyzed using SPSS version 20 for data processing. Data was expressed as frequency and percentage for qualitative variables and mean ± standard deviation (SD) for quantitative one. Analysis of variance (One way ANOVA test), and Chi square test were used for comparison between the studied groups. P-value < 0.05 is considered significant and p-value > 0.05 is considered non-significant.

RESULTS

There were no significant differences between the three studied groups as regard maternal age, parity, gravidity, gestational age at the time of termination, body mass index (BMI) and pre-induction Bishop score as shown in Table 1.

As regard response to induction, group 3 {Dinoprostone followed by Misoprostol} showed statistically significant difference when compared to group 1 {Misoprostol}; (p-value = 0.049) and group 2 {Dinoprostone}; (p-value = 0.046), with more response to induction in group 3. There was failure of response in 6 cases in group 1, 6 cases in group 2 and 1 case in group 3, where hysterotomy was done as shown in Table 2 and Figure 2.

Efficient uterine contractions occurred in 46 cases of group 3, 40 cases of group 2 and 41 cases of group 1 as shown in Figure 2. As regard induction-contraction interval for cases with efficient uterine contractions, group 3 showed statistically significant difference when compared to group 1 (p-value = 0.043) and group 2 (p-value = 0.037), with shorter induction-contraction interval in group 3 as shown in Table 3. Inefficient uterine contractions occurred in one case of group 3 and one case of group 2 with Bishop score > 6 which required oxytocin augmentation with complete expulsion occurred (those two cases were not included in the table of final outcome). One case of group 1 showed inefficient uterine contraction with Bishop Score < 6, to whom hysterotomy was performed as shown in Figure 2.

As regard induction-expulsion interval, group 3 showed statistically significant difference when compared to group 1 (p-value = 0.02) and group 2 (p-value = 0.02), with shorter induction-expulsion interval in group 3 as shown in Table 4. One case in group 3, 3 cases in group 2 and 1 case in group 1 with efficient uterine contractions experienced imminent uterine rupture and hysterotomy was performed as shown in Figure 2.

Table 1: Maternal and pregnancy characteristics of the study groups

Women's characteristics	Group 1 (N = 48)	Group 2 (N = 47)	Group 3 (N = 48)	p-value
Maternal age (years)	28.5+1.4	28.6+1.3	28.9+1.1	0.28
Parity	3+0.9	2.8+0.7	2.7+0.6	0.14
Gravidity	4.5+1.4	4.2+1.3	4+1.3	0.19
G.A. (weeks)	24.7+1.2	24.6+1.3	24.2+1.1	0.1
BMI (Kg/m^2)	25.7+3.9	24.9+4.7	26.1+2.6	0.3
Pre-induction Bishop Score	4.1+1	4.2+1.1	4.5+1.2	0.19

BMI: Body mass index; G.A.: Gestational age

Table 2: Response to induction after prostaglandins administration

Response	Group 3 (N = 48)	Group 1 (N = 48)	Group 3 (N = 48)	Group 2 (N = 47)
Success	47 (97.9%)	42 (87.5%)	47 (97.9%)	41 (87.2%)
Failure	1 (2.1%)	6 (12.5%)	1 (2.1%)	6 (12.8%)
p-value	0.049*		0.046*	

* Statistically significant difference

Table 3: Induction - contraction interval

Time interval	Group 3 (N =46)	Group 1 (N = 41)	Group 3 (N = 46)	Group 2 (N = 40)
< 12 hours	3 (6.5%)	5 (12.2%)	3 (6.5%)	5 (12.5%)
12–24 hours	41 (89.2%)	28 (68.3%)	41 (89.2%)	27 (67.5%)
>24 hours	2 (4.3%) 8 (19.5%)		2 (4.3%) 8 (20%)	
p-value	0.043*		0.037*	

• Induction-contraction interval (hours): Means that the duration between the 1st dose administered and the onset of efficient uterine contractions.
* Statistically significant difference

Table 4: Induction-expulsion interval

Time interval	Group 3 (N = 45)	Group 1 (N= 40)	Group 3 (N = 45)	Group 2 (N = 37)
< 12 hours	3 (6.7%)	4 (10%)	3 (6.7%)	4 (10.8%)
12–24 hours	40 (88.9%)	26 (65%)	40 (88.9%)	24 (64.9%)
>24 hours	2 (4.4%)	10 (25%)	2 (4.4%)	9 (24.3%)
p-value	0.02*		0.02*	

Induction - expulsion interval (hours): Means that the duration between the 1st dose administered and the fetal expulsion.
* Statistically significant difference

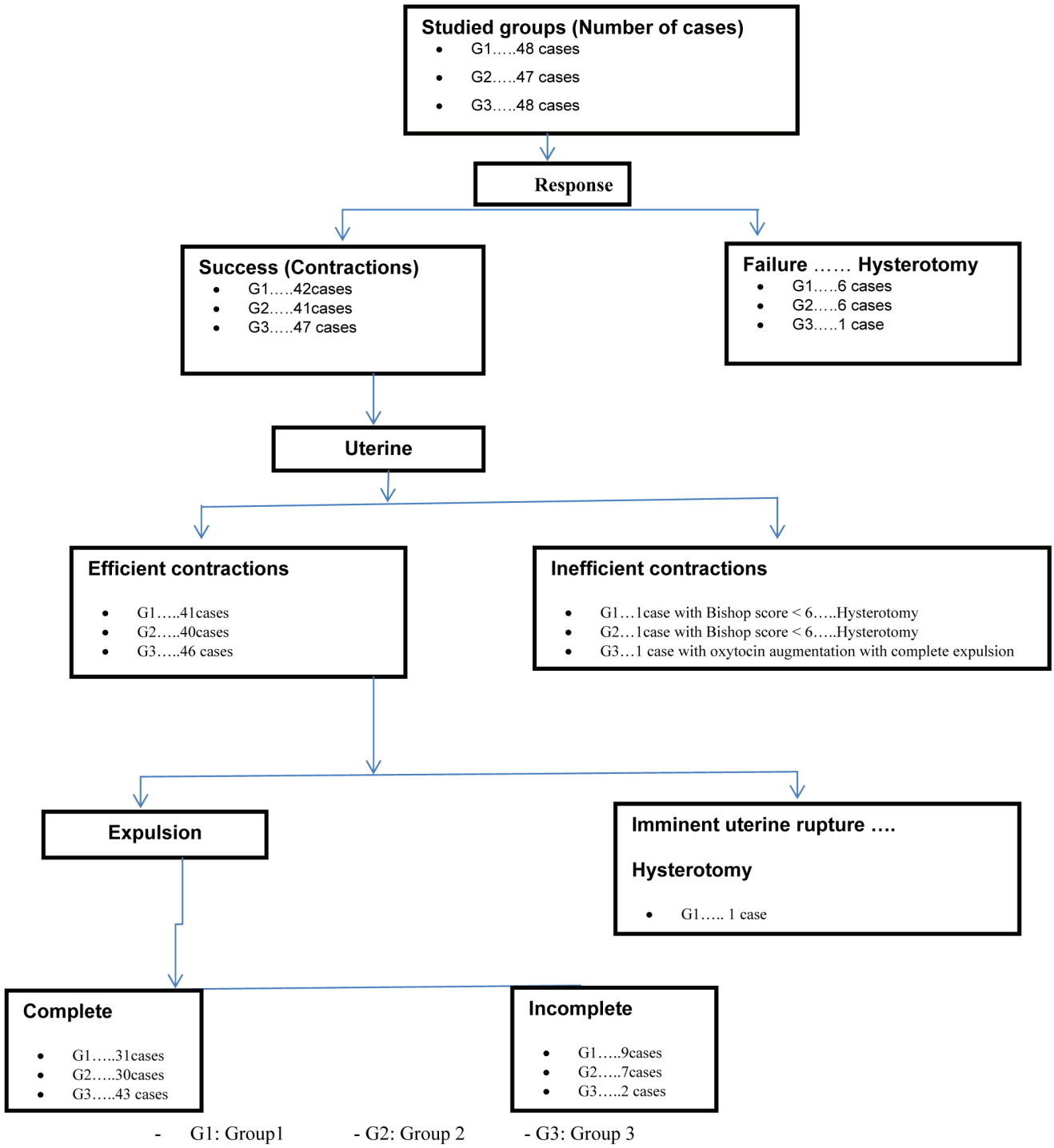

Figure 2: Diagram showing the results of the study.

Table 5: Final outcome of termination of pregnancy

Pattern of expulsion	Group 3 (N= 45)	Group 1 (N= 40)	Group 3 (N= 45)	Group 2 (N=37)
Complete expulsion	43 (95.6%)	31 (77.5%)	43 (95.6%)	30 (81.1%)
Incomplete expulsion	2 (4.4%)	9 (22.5%)	2 (4.4%)	7 (18.9%)
p-value	0.01*		0.04*	

* Statistically significant difference

As regard the final outcome, group 3 showed statistically significant difference when compared to group 1 (p-value = 0.01) and group 2 (p-value = 0.04), with more patients experienced complete expulsion in group 3 as shown in Table 5 and (Figure 2).

Hysterotomy was performed due to failed induction, imminent rupture uterus or inefficient uterine contractions with Bishop score < 6 as shown in Table 6 and Figure 2. Also; as regard hysterotomy, group 3 showed statistically significant difference when compared to group 1 (p-value = 0.045) and group 2 (p-value = 0.022), with less patients performed hysterotomy in group 3 as shown in Table 6. Table 7 showed various side effects and complications associated with termination of pregnancy in different groups.

DISCUSSION

This study compared the efficacy and safety of misoprostol and dinoprostone in the late 2nd trimester IUFD termination.

As regard response to induction, group 3 (Dinoprostone followed by Misoprostol) showed statistically significant difference when compared to group 1 (Misoprostol) and group 2 (Dinoprostone), with more response to induction in group 3. There was failure of response in 6 cases in group 1, 6 cases in group 2 and 1 case in group 3, to whom hysterotomy was performed. The success of induction was 97.9% in group 3, 87.2% in group 2 and 87.5% in group 1. In a study by Bhattacharjee et al., 2007, women with previous cesarean section needing 2nd trimester termination was given 200µg misoprostol vaginally between 21 to 26 weeks. The success rate of termination was 70 % with no reported scar rupture [13]. In a study by Munir et al., 2014, the overall success rate of 2nd trimester termination for three methods including oral misoprostol, extra amniotic PGF2α and intra-cervical Foley's catheter traction in women having previous cesarean section was 61.3% without any scar rupture. Misoprostol is safe and more efficacious than PGF2α and intra-cervical Foley's catheter traction for 2nd trimester pregnancy termination in women with previous cesarean section when used in doses of 200µg every 6 hours by oral route [14].

As regard induction-expulsion interval, group 3 showed statistically significant difference when compared to group 1 and group 2, with shorter induction-expulsion interval in group 3. In group 3, expulsion occurred in 95.6% in the period within 24 hours and 4.4 % of cases after 24 hours. In misoprostol group, 75% of cases expulsion was occurred in first 24 hours and 25% of cases after 24 hours. In dinoprostone group, expulsion was occurred in 75.7% of cases within 24 hours and 24.3% of cases after 24 hours. In a study by Khooshideh., 2007, performed a comparison between misoprostol and dinoprostone for termination of 2nd trimester pregnancy. In group 1 misoprostol 400 µgm was inserted vaginally and repeated every 12 hours (not to exceed 4 doses), unless labor was initiated and maintained regularly. In group 2 patients received dinoprostone gel 0.5 mg vaginally. If uterine contractions were not started, oxytocin infusion was beginning 3 hours after the last dose. The time interval

Table 6: Hysterotomy as regard indications and percentage between different studied groups

Indications of hysterotomy	Group (3) (N=48)	Group (1) (N=48)	Group (3) (N=48)	Group (2) (N=47)
Yes	2 (4.2%)	8 (16.7%)	2 (4.2%)	9 (19.1%)
• **Failed induction**	1	6	1	6
• **Imminent rupture uterus**	1	1	1	3
• **Inefficient uterine contractions with Bishop score < 6**	0	1	0	0
No	46 (95.8%)	40 (83.3%)	46(95.8%)	38 (80.9%)
p-value	0.045*		0.022*	

* Statistically significant difference

Table 7: Side effects and complications associated with termination of pregnancy

Side effects and complications	Group 1 (N= 48)	Group 2 (N= 47)	Group 3 (N= 48)
Blood loss > 500 ml	2 (4.2%)	3 (6.4%)	1 (2.1%)
Blood transfusion	1 (2.1%)	2 (4.3%)	1 (2.1%)
Shivering and chills	13 (27.1%)	1 (2.1%)	5 (10.4%)
Headache	2 (4.2%)	8 (17%)	6 (12.5%)
GIT symptoms	7(14.6%)	12(25.5%)	9 (18.75%)
Fever	9 (18.75%)	2 (4.3%)	7 (14.6%)

between 1st dose to delivery was 13.2 hours for vaginal misoprostol and 15.1 hours for vaginal dinoprostone group and there were no significant differences between two groups. All cases aborted within 24 hours. No major complications were seen in both groups. Also there was no significant difference in amount of blood loss, operative removal of the placenta. The mean dose of oxytocin used in dinoprostone group was higher than the other group (p = 0.01) [15].

In a study by Biswas, 2015, compared the efficacy, safety and tolerance of vaginal misoprostol (100 μg 4-hourly) with dinoprostone gel (0.5 mg 6-hourly) for induction of labor in the late intrauterine fetal death. The induction-to-delivery interval was significantly shorter with the misoprostol (8.13 ± 1.62 hours vs. 14.32 ± 2.46 hours; p <0.001). The total dose of misoprostol was significantly lower than the group pretreated with dinoprostone gel (1.78 ± 0.80 vs. 3.50 ± 1.12; p <0.001). The induction-expulsion interval with misoprostol group was 15 hours and 21 hours in dinoprostone group [16].

In a study by Huma et al., 2016 compared intravaginal misoprostol with dinoprostone for termination of 2nd trimester pregnancy. The average induction-abortion interval in the misoprostol group was 15.05 hours and successful abortion was achieved in 80% whereas in dinoprostone group 48% aborted in the same time interval (15.05 hours). The rate of incomplete abortion requiring evacuation and curettage was 20% in misoprostol group and 52% in dinoprostone group. In misoprostol group frequently observed side effects were rigors (24%), fever (14%), abdominal pain (40%) [17].

As regard final outcome of termination of pregnancy, group 3 showed statistically significant difference when compared to group 1 and group 2, with high incidence of the complete expulsion in group 3. In a study by Tharihalli and Bhat., 2017, they used vaginal misoprostol 50 μg at 6 hours interval. The average induction to delivery interval was 14.68 hours. All women delivered within 40 hours of administration of first dose of misoprostol with 47%, 86% and 100% delivered within 12 hours, 24 hours and 40 hours respectively [18]. Nagaria et al., 2007, found that misoprostol was safe and an effective agent for cervical ripening. Moreover, they found it a convenient way of inducing abortion in 2nd trimester of pregnancy. It is also noted that misoprostol was successfully used in patients with previous uterine scar [4]. In another study, the authors concluded that there was an increased rate of uterine rupture with misoprostol use compared to dinoprostone in women with previous cesarean delivery [3].

The benefits obtained from combining both drugs in sequential manner (dinoprostone and misoprostol) in the same patient may be: (1) Their synergistic effect in inducing uterine contractions and producing cervical ripening; (2) Occurrence of smooth physiological uterine contractions with also physiological softening of the cervix made this regimen unique in inducing uterine contraction with the least failure rate, less cases of imminent uterine rupture, less cases of inefficient uterine contractions and less risk of hysterotomy (3) Using just two doses from each drug helped to reduce the side effects and complications.

CONCLUSION

Dinoprostone improves cervical ripening, while misoprostol initiates uterine contractions with cervical ripening that is associated with complete expulsion and low incidence of scar rupture. Using dinoprostone followed by misoprostol is more effective than using any of the two drugs separately as a method of pregnancy termination in patients with late 2nd trimester IUFD and past history of one LSCS. Dinoprostone improving cervical ripening and misoprostol initiate uterine contractions with cervical ripening which associated with complete expulsion and low incidence of scar rupture. More studies need to be done in this regard to confirm or exclude our results which need increasing sample size.

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Author Contributions

Mohamed Lotfy Mohamed El-sayed – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Mostafa Abdo Ahmed – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Ibrahim Abdel Gafor – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Mohamed El bakery Lashin – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None

Consent Statement

Written informed consent was obtained from the patient for publication of this study.

Conflict of Interest

Authors declare no conflict of interest.