Scholars LITERATURE

Journal of Womens Health Care and Management

Research Article

DOI: https://doi.org/10.47275/2692-0948-147
Volume 4 Issue 3

The Effect of Adding Vaginal Evening Primrose Oil to Misoprostol During induced abortion; A Randomized Controlled Trial

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Abstract

Background: Missed abortion, significant birth defects, and some women's decision not to carry a pregnancy to term are all reasons for mid-trimester pregnancy termination. The aim of this work was to assess evening primrose oil's (EPO) effect on the duration of induction of abortion.

Methods: This prospective registered, randomized controlled study included 144 women in their missed abortion singleton mid-trimester of pregnancy (14 - 28 weeks). The assignment was random to one of two equal groups. Group I: received 200 mcg Misoprostol and EPO. Group II: received Misoprostol only. The induction to onset of cervical dilatation time was the primary outcome.

Results: Temperature was insignificantly different in all times of measurements except at 48 h, it was significantly lower in group I compared to group II. Pulse was significantly lower in group I compared to group II at all times of measurements. Pain was insignificantly different at all times of measurements between both groups except at 8 (h), 24 (h) and 48 (h), it was in group I significantly lower than group II.

Conclusion: In women with second trimester missed abortion, vaginal administration of EPO with misoprostol had no additional significant effect on duration of induction of delivery, duration to cervical dilatation, maternal satisfaction, vaginal bleeding, fetal expulsion, and surgical removal of placenta.

Keywords: Evening primrose oil, Misoprostol, Second trimester missed, Miscarriage

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Citation: Metwally SR, El Nashar EM, Khalifa MA (2023) The Effect of Adding Vaginal Evening Primrose Oil to Misoprostol During induced abortion; A Randomized Controlled Trial. J Womens Health Care Manage, Volume 4:3. 147. DOI: https://doi.org/10.47275/2692-0948-147

Received: October 27, 2023; **Accepted:** November 23, 2023; **Published:** November 29, 2023

Introduction

Pregnancy termination is an important matter that is fraught with complicated and emotional issues [1]. The mid-trimester is the most frequent period to terminate a pregnancy, with two-thirds of all significant problems that are related to abortion occurring during this period [2, 3]. The decision not to continue a pregnancy, significant birth defects and missed abortion are all reasons to terminate pregnancy during mid-trimester [4, 5].

Medications appear to be a viable option for pregnancy termination during mid-trimester [6]. Mifepristone and misoprostol are a successful combination (rate of success is about 97 - 99% within 24 h) [7]. However, in economically challenged nations, these treatments are no longer inexpensive or available. Furthermore, it is not without problems, particularly in the case of a scared uterus [8].

The evening primrose plant seeds (*Oenothera biennis*) are the precursor of EPO. It's high in essential fatty acids like omega-6 and unsaturated fatty acids, such as linoleic and gamma—1 linolenic acid [9]. Its therapeutic benefits are due mostly to its omega-6 essential fatty acids, which can induce the generation of cytokines and prostaglandins in an indirect manner [9]. Thus, EPO can be used for cervical ripening by theory [10]. There are not enough randomized clinical trials (RCTs) on the effects EPO has on pregnancy and labor induction [9, 11]. There have been no previous studies on its usage in cervical ripening prior to the termination of a pregnancy in the second trimester.

The aim of this work was to assess EPO effect on the duration of induction of abortion in women with second trimester missed abortion.

Methodology

Patients registration

This prospective registered (ClinicalTrials.gov ID: NCT02714699), randomized controlled study was executed at Women Health Hospital in Assiut after approval from Ethical Committee and obtaining informed written consent.

Participants were recruited from emergency unit who aged above 18 years, nullipara or previous vaginal delivery only and were in missed abortion singleton mid-trimester of pregnancy (14 - 28 weeks), with Bishop score ≤5. Exclusion criteria included previous cesarean sections, women with heavy bleeding, amniorrhexis, multiple gestations,

evidence of placenta low implantation by ultrasound (US) and uterine infection (proved either clinically or laboratory).

Assignments of participants were random to one of two groups based on a table of random numbers generated by computer and serially numbered closed opaque envelopes were used for allocation concealment. Group I: include 72 women received 200 mcg misoprostol and EPO. Group II: include 72 women received misoprostol only.

All participants included in this study were subjected to complete medical history including gestational age and detailed obstetric history. clinical examination included two-dimensional trans-abdominal ultrasound (2D TAS) to assess the placental site, amniotic fluid volume and gestational age.

Vaginal examination was carried out every 6 h to insert the medications and assess the bishop score. Every 4 h, blood pressure, pulse and body temperature were measured, and for pain VAS was assessed. For pain management, Ketorolac 30 mg were administered intravenously (IV) when needed. All participants were given 2 gm of 1st generation cephalosporin intravenously (IV) to prevent uterine infection. When cervical dilatation of 4 cm occurred, 10 IU oxytocin in 500 ml glucose was added every 6 h at the rate of 30 miu per minute till complete expulsion occurred. Voluntary delivery of placenta, membranes and cord was permitted after expulsion of the fetus. In case of a hemorrhage or no spontaneous expulsion for 4 h, surgical placental excision under general anesthesia was provided.

After the termination of pregnancy, women were observed for no less than 6 h. to rule out the presence of placental remnants, an US examination was conducted before discharge. Anti-D vaccine was given to non-sensitized Rh-negative women.

The induction to onset of cervical dilatation time was the primary outcome. The secondary outcomes included the rate of successful expulsion, the rate of vaginal bleeding, the rate of surgical removal of the placenta, the associated pain (measured by visual analogue scale VAS) and maternal satisfaction (measured by visual analogue like scale from 0 - 100).

Sample size justification

The sample size was determined considering our main outcome as a guide (induction to expulsion time). Rahimi-Sharbaf et al., indicated that the mean time from induction to complete abortion with misoprostol is 927.77 ± 459 min [12]. According to this assumption, the addition of EPO may reduce this time by approximately 20% so the two-sided chi-square (χ^2) test with α of 0.05 a total sample size of at least 144 participants was supposed to have 90% power to detect the difference in the time between both groups considering a lost to follow up rate of 10%.

Statistical analysis

SPSS software, version 21, was used to analyze all the data. The Chi-square test was used to compare categorical data in both groups, while the student t-test was used to analyze continuous variables. The Shapiro-Wilks test was used to determine the normality of the various pain scores for statistical analysis. P-value <0.05 was considered a significant value.

Results

In terms of age, body mass index, residence, occupation, parity, gravidity, and medical disorders (hypertension, DM, and others) and Gestational age, there was no statistically significant difference between groups (Table 1). The temperature was insignificantly different in all times of measurements except at 48 h, it was significantly lower in group I than group II. (p = 0.018) (Table 2). Pulse was significantly lower in group I than group II at all times of measurements. (p = 0.006, 0.013, 0.043, 0.015, 0.003, 0.002, 0.004, and <0.001, respectively) (Table 3). Pain score was insignificantly different at all times of

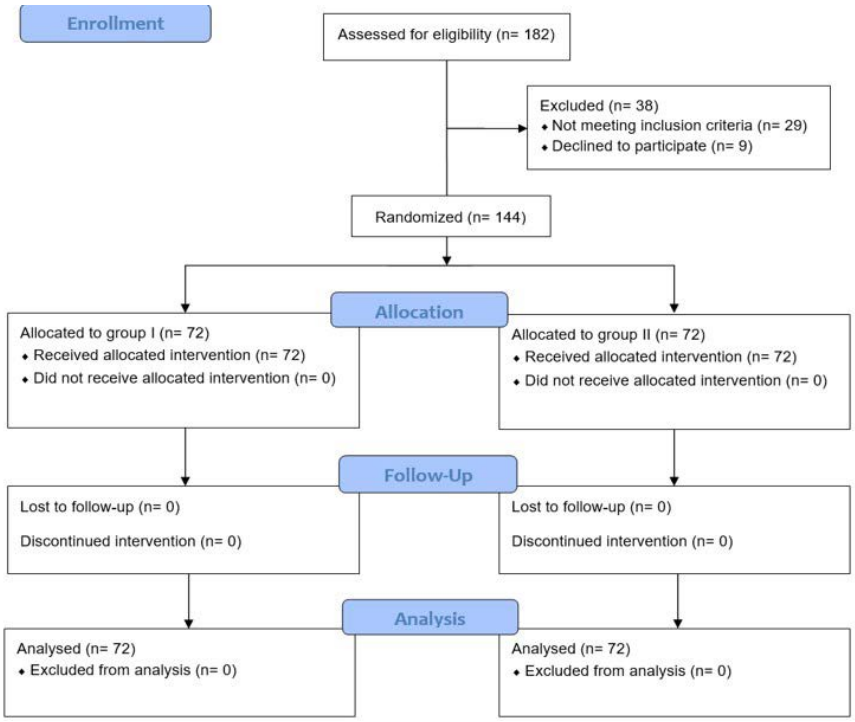

Figure 1: Participants' CONSORT flow diagram throughout stages of the trial.

Table 1: Patients' demography and characteristics in both groups.

		Group I (n = 72)	Group II (n = 72)	p-value
Age (years)	**Mean ± SD**	28.32 ± 6.48	29.94 ± 6.74	0.142
	Range	17 - 45	18 - 44	
BMI (kg/m²)	**Mean ± SD**	30.64 ± 4.33	30.49 ± 3.44	0.815
	Range	22 - 37	22 - 38	
Residence	**Urban**	31 (43.06%)	29 (40.28%)	0.737
	Rural	41 (56.94%)	43 (59.72%)	
Occupation	**Yes**	17 (23.61%)	10 (13.89%)	0.137
Parity	**Median**	3	2	0.196
	Range	0 - 5	0 - 5	
Gravidity	**Median**	4	4	0.961
	Range	1 - 8	1 - 7	
Medical diseases	**Hypertension**	6 (8.33%)	5 (6.94%)	0.756
	DM	8 (11.1%)	7 (9.72%)	0.787
	Others	3 (4.17%)	1 (1.39%)	0.314
Gestational age (weeks)	**Mean ± SD**	19.97 ± 3.12	20.60 ± 3.70	0.275
	Range	14 - 26	17 - 27	

Table 2: Temperature (°C) in both groups.

	Group I (n = 72)		Group II (n = 72)		p-value
	Mean	**± SD**	**Mean**	**± SD**	
0	37.21	0.47	37.23	0.38	0.724
4 (h)	37.18	0.29	37.09	1.25	0.534
8 (h)	37.17	0.40	37.25	0.47	0.257
12 (h)	37.23	0.28	37.33	0.49	0.138
16 (h)	37.24	0.24	37.29	0.28	0.311
20 (h)	37.33	0.26	37.32	0.26	0.842
24 (h)	37.22	0.26	37.30	0.28	0.208
28 (h)	37.26	0.25	37.35	0.26	0.118
32 (h)	37.32	0.25	37.42	0.19	0.129
36 (h)	37.29	0.30	37.41	0.16	0.130
40 (h)	37.47	0.32	37.51	0.17	0.704
44 (h)	37.44	0.30	37.48	0.30	0.785
48 (h)	37.36	0.31	37.64	0.20	**0.018***

Table 3: Pulse in both groups.

	Group I (n = 72)		Group II (n = 72)		p-value
	Mean	**± SD**	**Mean**	**± SD**	
0	81.38	7.18	84.52	7.00	**0.006***
4 (h)	83.03	7.57	85.94	6.91	**0.013***
8 (h)	84.06	8.06	86.42	6.67	**0.043***
12 (h)	83.61	7.52	86.63	6.80	**0.015***
16 (h)	83.82	7.92	87.64	6.50	**0.003***
20 (h)	86.03	6.53	89.25	5.61	**0.003***
24 (h)	86.17	7.26	90.68	5.42	**0.002***
28 (h)	88.36	7.19	92.30	3.83	**0.004***
32 (h)	87.03	8.05	95.37	4.19	**<0.001***
36 (h)	89.14	7.80	94.71	5.38	**<0.001***
40 (h)	87.90	6.40	97.50	5.54	**<0.001***
44 (h)	88.00	6.61	98.73	6.08	**<0.001***
48 (h)	87.78	6.59	101.82	6.10	**<0.001***

measurements between both groups except at 8 (h), 24 (h) and 48 (h), it was significantly lower in group I than group II (p = 0.003, 0.009, and 0.005, respectively) (Table 4). Duration to cervical dilatation, maternal satisfaction, vaginal bleeding, fetal expulsion, and surgical removal of placenta were insignificantly different at all time measurements between both groups (Table 5).

Discussion

Among the causes for mid-trimester termination of pregnancy are missed abortions, serious fetal deformities, and the desire of women who do not wish to keep a pregnancy and will usually seek termination of pregnancy [13]. For a mid-trimester abortion, medical treatment looks to be a possible alternative. Mifepristone and misoprostol in combination is a highly effective option (with a success rate of 97 - 99% in just 24 h) [14]. In developing countries, these medications are no longer unaffordable or unavailable. Furthermore, it is not without risks, particularly if the uterus is scared [15].

Table 4: Pain score in both groups.

	Group I (n = 72)		Group II (n = 72)		p-value
	Mean	**± SD**	**Mean**	**± SD**	
0	2.08	1.42	2.34	1.42	0.220
4 (h)	3.50	1.79	3.80	1.45	0.145
8 (h)	4.24	1.73	4.89	1.53	**0.003***
12 (h)	5.57	1.67	5.33	1.77	0.561
16 (h)	5.81	1.73	6.04	2.01	0.342
20 (h)	6.40	1.62	6.78	2.32	0.141
24 (h)	6.17	1.45	7.00	3.25	**0.009***
28 (h)	6.71	1.50	7.20	4.07	0.362
32 (h)	6.97	1.33	7.72	5.59	0.423
36 (h)	7.43	1.43	8.08	6.66	0.926
40 (h)	7.29	1.42	8.70	7.55	0.130
44 (h)	7.38	0.96	9.22	9.64	0.125
48 (h)	7.40	1.07	9.94	10.54	**0.005***

Table 5: Outcome in both groups.

		Group I (n = 72)	Group II (n = 72)	p-value
Duration to cervical dilatation (h)	**Mean ± SD**	31.46 ± 11.94	28.63 ± 12.27	0.163
	Range	13 - 60	10 - 60	
Maternal satisfaction	**Mean ± SD**	73.40 ± 10.31	76.53 ± 9.52	0.061
	Range	50 - 90	50 - 95	
Vaginal bleeding	**Yes**	15 (20.83%)	9 (12.50%)	0.182
Fetal expulsion	**Yes**	62 (86.11%)	60 (83.33%)	0.646
Surgical removal of placenta	**Yes**	21 (29.17%)	12 (16.67%)	0.075

EPO's medicinal benefits are mostly due to its omega-6 essential fatty acids, which can indirectly regulate prostaglandin and cytokine production. As a result, EPO might potentially be utilized to accelerate cervical ripening [16]. This study evaluated the effect of EPO on the duration of induction of delivery in women with second trimester missed abortion. According to our knowledge there are not enough RCTs on the effects of EPO on pregnancy and labor induction. No previous trials in its use in cervical ripening before termination of second trimester pregnancy.

The effect of EPO and misoprostol on cervical ripening/dilatation were compared by Nouri et al. [17]. In this double-blind RCT study women with no history of normal vaginal delivery and menopausal women (ages: 20 - 75 years) were recruited. Participants who were dilatation, hysteroscopy, and curettage candidates were divided into two groups at random. In the first group, two capsules of 200 μg misoprostol (N = 84) while in the second group two capsules of 500 mg EPO (N = 81) were inserted into the posterior fornix two hours prior to surgery. They agreed with current study and stated that the study groups' demographic data, cesarean sections, history of pregnancies, and normal vaginal deliveries were similar (p > 0.05).

EPO's effects on the length of pregnancy and labor were studied by Kalati et al. [16]. The research was carried out as a placebo-controlled randomized, triple-blind trial on women with a gestational age of 40

weeks with low-risk nulliparous and a Bishop score below 4. In EPO group, EPO 1000 mg capsules were administered, twice daily, for seven days. Placebo was administered in a similar frequency in the control group. Overall, 80 women finished the study (40 in each group). They stated no significant differences among the groups compared to the baseline data in an agreement with the current study.

Regarding temperature, it was insignificantly different in all times of measurements except at 48 h, it was significantly lower in group I in comparison to group II. Pulse, at all times of measurement, was significantly lower in group I in comparison to group II.

Bahmani et al. [18] compared the efficacy of EPO vaginal capsule and misoprostol on cervical ripening of nulliparous women. This one-blind randomized study was performed in Sanandaj Be`sat Hospital on 130 women with post term pregnancy. Participants were randomly allocated into either intervention or control group. A combination of 500 mg EPO vaginal capsule and 25 μg of sublingual misoprostol were administered to the intervention group while a placebo-vaginal capsule and 25 μg of sublingual misoprostol were administered to the control group. They agreed with the present study and indicated no significant difference in vital signs of blood pressure among the groups ($p = 0.6$), pulse ($p = 0.16$), breathing ($p = 0.15$), and temperature ($p = 0.10$).

Regarding pain, it was insignificantly different at all times of measurements between both groups except at 8 (h), 24 (h) and 48 (h), it was significantly lower in group I in comparison to group II.

Nouri et al. [17] agreed with current study and stated that the adverse effects included 2 cases of diarrhea, 1 case of fever and 3 cases of severe abdominal pain, all in misoprostol group compared to no adverse effects in the EPO group ($p = 0.029$).

Regarding gestational age, duration to cervical dilatation, maternal satisfaction, vaginal bleeding, fetal expulsion, and surgical removal of placenta, they were insignificantly different at all-time measurements between both groups.

Bahmani et al. [18] disagreed with current study and stated that the intervention group had significantly higher mean bishop score compared to the control group ($p < 0.05$). This might be due to different sample size and study methodology in comparison with current study. There were no significant differences among the groups regarding fetal heart rate in an agreement with the current study ($p = 0.57$). As regards uterine contractions, the mean and standard deviation was 3.45 ± 0.72 in the intervention group compared to 3.39 ± 0.87 in the control group, which was of no statistical significance ($p = 0.67$).

Kalati et al. [16] agreed with current study and stated significant differences between groups in Bishop score. There also were no significant differences between groups regarding the duration of different stages of labor. In the case group, the mean interval between the beginning of the study and delivery was 4.39 ± 1 days compared to 4.45 ± 1.84 days in control group. The amount of bleeding after delivery was not significantly different between the groups.

Diansuy and Aguilar [19] determined the efficacy of EPO gel capsule as a cervical ripening during labor induction on term singleton pregnant women. The main aim was to assess the change in Bishop score after the EPO capsules had been administered. A quasi-experimental cross-sectional investigation from May to July 2016 was carried out. They included labor induction women with an intact amniotic sac, a Bishop score ≤ 4 and a biophysical profile score of 8/8 or 10/10. They disagreed with current study and stated statistically significant change in Bishop score from baseline to 4 h after insertion of EPO capsules ($p = 0.001$). While 11 patients (85%) showed improvement in Bishop score after 4 h, 4 (31%) of them had a change in Bishop score (≥ 4) which is clinically significant. Specifically, there were statistically significant changes in the effacement ($p = 0.006$), dilatation ($p = 0.027$), and consistency ($p = 0.002$). These results might be due to different methodology and drug doses.

In a two-arm randomized controlled trial Tanchoco and Aguilar [20] evaluated the feasibility of cervical dilatation to permit insertion of a 10 - 11 mm Hegar's dilator with intravaginal EPO versus intracervical laminaria prior to surgical hysteroscopy. The laminaria group received intracervical laminaria 12 h prior to the operation. The EPO group received six soft gel capsules 6 h prior followed by 4 soft gel capsules 1 h before the operation. A 5-point Likert scale was used to assess the ease of dilatation and patient acceptance. Initial cervical dilation and time to attain Hegar's10 mm have been documented. Both compounds were shown to be efficient in dilating the cervix. When compared to the laminaria group, cervical dilatation was smoother and took less time in the EPO group. Furthermore, the simplicity of administration made EPO more acceptable and convenient.

Conclusion

In women with second trimester missed abortion, vaginal administration of EPO with misoprostol had no significant additional effect on duration of induction of delivery, duration to cervical dilatation, maternal satisfaction, vaginal bleeding, fetal expulsion, and surgical removal of placenta. However, evening primrose oil decreased the associated side effects of misoprostol like fever, tachycardia, and pain intensity.

Acknowledgements

None.

Conflict of Interest

None.

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