



# Letrozole Combined with Misoprostol versus Misoprostol Alone in the Management of Patients with First Trimester Delayed Miscarriages: Our Experience

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## Abstract

**Backgrounds & Objectives:** Miscarriage is the most common complication of pregnancy. Misoprostol (Miso), a synthetic analogue of prostaglandin E1, has an uterotonic effect and it can stimulate myometrial contraction and cause cervical ripening and dilatation. Letrozole (LTZ), non-steroidal reversible aromatase inhibitor acting by suppressing the peripheral conversion of androgen to estrogen which is important in the maintenance of pregnancy. Our aim was to compare the success rate & safety of LTZ combined with Miso to Miso alone in the management of first trimester delayed miscarriages (FTDM) up to 12 weeks gestation.

**Patients & Methods:** 126 patients of 20-38 years old were enrolled in a hospital based clinical trial and allocated into 2 groups. LTZ/Miso group (n=64) given LE, 2.5 mg every 8 hrs./ 3 days followed by per-vaginal (PV) Miso 800 µg on 4<sup>th</sup> day and Miso group (n=62) received only PV Miso 800 mcg and repeated if necessary. All patients were with Hb > 10g/dL. Exclusion criteria: medical conditions contradicted with induction of abortion. Vital signs, any side effects including PV bleeding were recorded. US done 7 days post misoprostol to monitor outcomes. Evacuation carried out if medical management failed. Data analysis by using SPSS version for windows, P-value significant if < 0.05.

**Results:** 4 patients from LTZ/Miso group & 6 from Miso group lost in follow-up and were excluded. The remaining in both groups completed the study and analyzed. Complete miscarriage rate in LTZ/Miso group (48/60, 80%) was significantly higher than that of Miso group (29/56, 51.8%) (P<0.001). The mean of induction-to-miscarriage time in LTZ/Miso group was significantly shorter than the Miso group (P<0.003). Time from admission to discharge in LTZ/Miso group was significantly shorter than those in Miso group (P<0.05). Indication for curettage in LTZ/Miso group was significantly less than Miso group (P=0.004) Surgical evacuation was performed either because of failure of medical termination or severe bleeding. No major side effects were recorded in both groups.

**Conclusion:** Combination of LTZ with Miso was associated with a higher complete miscarriage and lower surgical evacuation rates, decreasing the interval between induction and expulsion of conception products in women with FTDM, and without major complications.

**Keywords:** Letrozole; Misoprostol; First trimester delayed miscarriage

**Abbreviations:** SD: Standard Deviation; FTDM: First Trimester Delayed Miscarriage; NICE: National Institute for Health and Care Excellence; SPSS: Statistical Program for Social Science.

## Introduction

(FTDM) is one type of miscarriages which defined as a failure to expel of an embryonic gestation and embryonic or fetal death that occurring in 10-20% of clinically recognized pregnancies [1-3]. With around 95% success rates, surgical evacuation is regarded as the standard treatment for such cases, which had been widely performed all over the world in the past 50 years [4]. However, the costs of surgery as well as the complications associated with surgery and anesthesia are major concerns, in addition to the increased risk of infection, bleeding and decreased fertility caused by intrauterine adhesions. Some studies have thus suggested that expectant or medical management might be more suitable instead of surgical evacuations [5,6]. Expectant management has been reported with unpredictable success rate ranging from 25-76% [7-9]. Waiting for spontaneous expulsion of the products of conception would waste much time, during which women may suffer uncertainty and anxiety in addition to the risks of emergency surgical treatment, bleeding and blood transfusions [7,10].

Miso by itself is used for the medical management of miscarriage as an alternative to surgery [11-14]. Miso is a synthetic analogue of naturally occurring prostaglandin E1 which induces abortion by stimulating the myometrium and cause cervical ripening and dilatation [15]. Compared with other type of prostaglandins, it has the advantage of feasibility, simple and easy administration, low price, stability at room temperature, and fewer side effects [16,17]. The range of reported success rate of induction of abortion with misoprostol is quite different in several studies (between 37% and 86%) depending on the regimen, route of administration, and dosage used [14]. A single dose of 800 mcg of Miso by vaginal or oral route for FTDM was recommended by National Institute for Health and Care Excellence (NICE) [18]. However some studies reported that, a lower dose or different routes of Miso misoprostol may be equally effective [19,20]. Miso has also been used in combination with other medication such as Mifepristone to increase the success rate of up to 95% [21-24]. The widespread use of mifepristone is limited by the fact that it is

expensive, and is not available in many countries [15,25,26] so, a cheaper and easily available alternative such as LTZ has been studied.

LTZ is a non-steroidal, third generation aromatase inhibitor. It reversibly and competitively binds with the iron in cytochrome P450 and prevents the production of estrogen by the enzyme aromatase which is secreted from the placenta, ovarian granulosa cells, and other tissues, such as fat, muscle, brain and breast tissue [27]. LTZ is widely used in the treatment of hormonally-responsive breast cancer after surgery [28,29]. And other gynecological conditions which are hormonal dependent such as management of subfertility, endometriosis and uterine fibroids in combination with Cabergoline [30]. It has been shown that the use of LTZ combined with vaginal misoprostol was more effective than misoprostol alone in termination of pregnancy [31,35,36,37].

Previous studies explored the mechanism of LTZ in medical abortion. One study concluded that, the expression of progesterone and estrogen receptor transcripts and estrogen receptor-alpha protein were all suppressed by LTZ in the placentas of women receiving LTZ; however, their study only examined second trimester terminations and not terminations in the first trimester of pregnancy [38]. Another study evaluated the effect of LTZ-induced estradiol suppression on the reduction of progesterone receptor expression and apoptosis in the first trimester pregnancies and found no difference in the expression of progesterone receptors and apoptotic markers in decidual tissue after pretreatment with LTZ for 7 days before first trimester abortion [39]. Also, another study measured the effect of LTZ on uterine artery Doppler indices prior to surgical termination of first trimester pregnancy and found significant decreases in both pulsatility and resistance index in the LTZ group, which suggests that blood flow changes might play a role in the mechanism of action of LTZ [41]. However, recent study has shown that LTZ has no effect on uterine contractions [42]. In our study, we aimed to compare the success rate (The rate of complete miscarriage) & safety of LTZ combined with Miso versus Miso alone for medical termination of FTDM.

## Patients and Methods

A hospital based clinical trial was conducted at Obstetrics & Gynecology departments, Al-Amal hospital & Misurata Medical Centre, during a period of 15 months from first

January 2017 to 31<sup>st</sup> March 2018. Patients were recruited from outpatient antenatal clinics with inclusion criteria: gestation age up to 12 weeks based on LMP with no fetal cardiac activity diagnosed by ultrasound scan, age between 20-38 years old, pre-treatment hemoglobin concentration (Hb)  $\geq 10$  gr/dL with no coagulopathy, agreement by the woman to undergo surgical termination if treatment fails; willing and able to participate after the study had been explained; Exclusion criteria: presence of fibroid or uterine anomalies, having intrauterine device, coagulopathy, and any other medical conditions contradicted with induction of abortion. A detailed medical history was taken and physical examination was performed including local examination to assess the cervix, investigations were performed including complete blood count, blood group and Rh typing, screening for thrombophilia. A total of 126 patients with FTDM were randomly divided into 2 groups; (LTZ/Miso group) in which 64 patients received LTZ 2.5mg every 8 hours for three days followed by vaginal Miso 800mcg on 4<sup>th</sup> day which is the day of admission and (Miso group) in which 62 patients were admitted to receive only Miso tablet of 800 mcg given as a single PV dose.

Patients stayed in the hospital after the administration of Miso for 4 hours. Time of expulsion of product of conceptions, side effects if any including (nausea, vomiting, diarrhea, headache, fever, skin rash or abdominal pain) and PV bleeding were recorded. They were discharged after the 4-hrs observation period if the PV bleeding was not heavy and abdominal pain was not severe. A follow-up visit was arranged on day 7 during which a transvaginal ultrasound was performed and blood sample was taken for Hb level. Patients who did not abort till 7 days were considered failure to induce complete miscarriage and surgical evacuation was performed under general anesthesia. Surgical evacuation was performed at any time over the 7 days follow up period if there was heavy bleeding. If no surgical evacuation was necessary over the 7 days, the outcome of treatment was labeled as complete miscarriage.

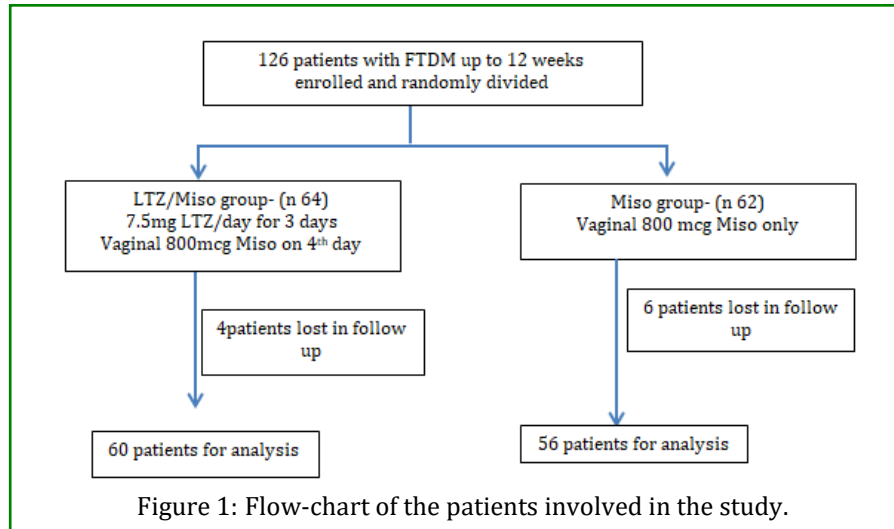
The main treatment outcome evaluated was the success rate of this protocol, represented by patients achieving a complete miscarriage with the medical treatment and the induction-to-miscarriage time in each group. Also the presence of side effects was analyzed.

## Statistical Analysis

Data were analyzed using the Statistical Program for Social Science (SPSS) version 20.0. Quantitative data were expressed as mean $\pm$ standard deviation (SD). Qualitative data were expressed as frequency and percentage. Independent t-test of significance was used to compare 2 means. Chi-square ( $\chi^2$ ) test was used to compare proportions of 2 qualitative parameters. Probability (p-value):  $p>0.05$  was considered insignificant,  $p\leq 0.05$  was considered significant, and  $p<0.001$  was considered highly significant.

## Results

A total of 126 patients diagnosed with FTDM met the inclusion criteria and were elected to enroll on this study. During follow up period, 4 patients in LTZ/ Miso group, and 6 patients in Miso group did not return for the follow-up visit and were excluded. Finally, 60 patients in LTZ/Miso group and 56 patients in Miso group completed the study and analyzed (Figure 1). The mean age of patients in the LTZ/ Miso group and Miso group was  $28.3\pm 3.4$  and  $29.8\pm 4.5$  years respectively. Mean GA was  $9.2 \pm 3.4$  and  $10.9\pm 1.8$  respectively. The number of previous miscarriages was 21 (35%) and 18 (32.14%) respectively which showed no significant difference between the groups. The rate of recurrent miscarriages was high in both groups; the difference was not significant (Table 1). The rate of complete abortion was (48/60, 80%) in LTZ/Miso group and (29/56, 51.8%) in Miso group, the differences was statistically significant ( $P < 0.0001$ ) (Figure 2). Surgical treatment was performed in the remaining (39/126, 30.95%), representing the total failure of medical treatment. The mean duration time from Miso administration to expulsion of product of conception (induction-to-miscarriage time) was shorter ( $6.1\pm 1.6$  hrs) in LTZ/Miso group compared with ( $9.4\pm 2.2$  hrs) in Miso group. The difference was also statistically significant ( $<0.003$ ) (Table 2). The mean hemoglobin before treatment was (10.90 g/d, ranging 9-11g/d) and (10.82 g/dl ranging 9-12) in LTZ/Miso group and Miso group respectively, the difference was not significant ( $P=0.654$ ). After treatment, the mean hemoglobin was (10.40 g/d, ranging 9-11g/d) and (10.24 g/dl ranging 8.5-11.10) in LTZ/Miso group and Miso group respectively, the difference was not significant ( $P=0.428$ ).

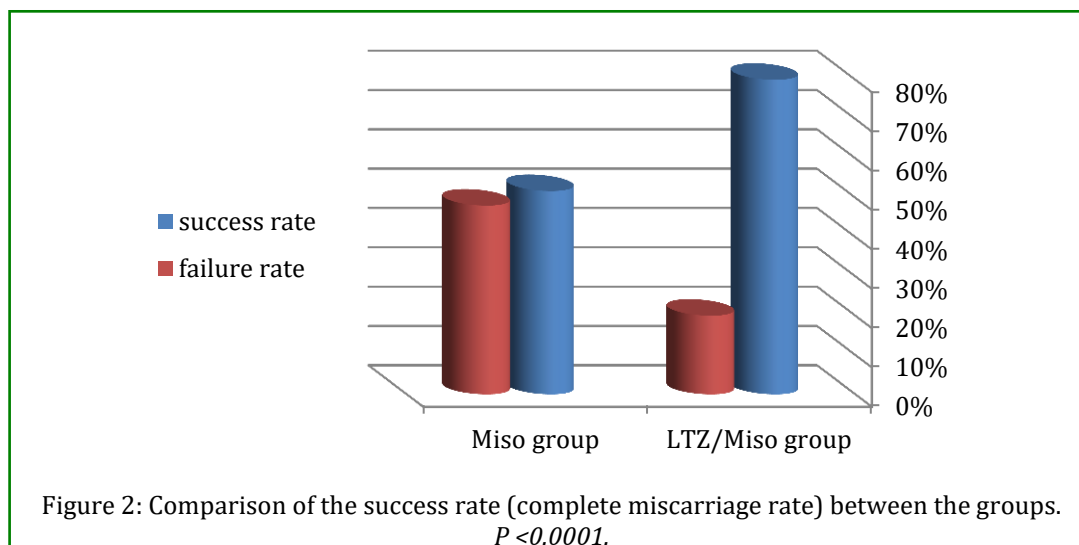


Variables	LTZ/Miso group (n=60)	Miso group (n=56)	P value
Age (years)	28.3±3.4	29.8±4.5	0.14
BMI	23.4±1	22.9±2	0.09
Gestational age (weeks)	9.2 ± 3.4	10.9±1.8	0.17
Gravidity			
1	14 (23.3%)	10 (17.8%)	
2	13 (22.6%)	8 (14.2%)	
≥3	32 (53.3%)	33 (58.9%)	
Previous miscarriage	21 (35.0%)	18 (32.1%)	

Table 1: Comparison of demographic data.

The recorded side effects after LTZ/Miso treatment were Nausea & vomiting (16.7%), abdominal pain (10.0%), fever (8.3%) and sever bleeding needing evacuation (6.7%), and diarrhea (5%) whereas after Miso only administration, sever bleeding needing

evacuation(14.3%), nausea & vomiting (10.7%), abdominal pain (7.1%), fever (7.1%) and diarrhea (3.6%). The difference between groups was not significant; almost all side effects subside on follow up visit (Table 2).



P value	Group A LTZ/Miso	Group B Miso	Variables
Induction to miscarriage time (h)	6.1±1.6	9.4±2.2	<0.003
Side effects	28 (46.6%)	24 (42.8%)	>0.05
• Nausea & vomiting	10 (16.7%)	6 (10.7%)	
• Abdominal pain	6 (10.0%)	4 (7.1%)	
• Diarrhea	3 (5.00%)	2 (3.6%)	
• Fever	5 (8.30%)	4 (7.1%)	
Sever bleeding needing evacuation	4 (6.70%)	8 (14.3%)	

Table 2: Comparison of induction-to-miscarriage interval and side effects of medication.

## Discussion

The present study is aimed to assess the effects of sequential LTZ/Miso protocol compared with Miso alone for the induction of FTDM. Based on our observations, there was a higher rate of complete miscarriages in the group received LTZ/Miso (80%) compared to the Miso group (51.8%) which was statistically highly significant. The induction-to-miscarriage time was significantly shorter in LTZ/Miso group compared to the Miso group. Previous studies also reported a significant difference in favour of the LTZ/Miso group. In Lee et al. study, after use of LTZ (10 mg for 3 days) combined with a single dose of vaginal Miso (800mcg), complete abortion rate was 93% up to 49 days gestation [31]. A study by Torky HA et al. who used LTZ 10 mg twice daily for 3 days followed by 800mcg administered vaginally, showed a complete miscarriage rate of 78% compared to 39% in group received placebo prior to Miso administration [34]. Another study explored the regimen of sublingual Miso following pretreatment with LTZ 10 mg for 3 days in women with gestational age less than 17 weeks and showed a complete abortion rate of 76.7% [33]. In a pilot study, by Yeung et al. tested a longer protocol of 7-days course of LTZ followed by vaginal Miso and showed a very high complete abortion rate about 95% [39]. Javanmanesh F et al. found a significantly higher rate of complete abortions (78.3%) in those who received 10mg daily Letrozole for 3 days followed by oral Misoprostol with mean induction- abortion interval of 22.61±7.721 hours [40].

A possible explanations for the different results could be the different treatment regimens and differences in gestational age, in addition, differences in studied populations, genetic diversity and distribution of receptors, PH of the vagina, drug manufacturers were confounding factors that must be considered. However like previous studies, LTZ/Miso combination is more effective than Miso alone or with placebo. Our study also showed that the mean induction-to-miscarriage time in LTZ/Miso group was significantly shorter than the time in

Miso group (6.1±1.6 hrs). Our result was within the range of time reported by other studies, after the addition of LTZ pretreatment of Miso [31,38,39,29].

Regarding the side effects, the regimen used was well tolerated with no major side effects and was comparable between the groups. Our study was similar to some previous studies that show similar side effects [43]. The proportion of women who complained of nausea, vomiting and abdominal pain was higher in LTZ/Miso group and that may be related to the use of two medications. In addition, the proportion of women with severe bleeding who needed surgical evacuation was lower in the LTZ group, none of the women had a marked drop in hemoglobin level or required blood transfusion. Based on the success of management of first trimester delayed miscarriages, Letrozole might be considered as medical treatment of ectopic pregnancy as estradiol suppression facilitate the abortion process and leads to cease development of this condition.

## Conflicts Of Interest

The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

## Financial Disclosure

The authors declare that this study has received no financial support.

## Conclusion

Our results showed that a 3-day course of Letrozole (2.5mg every 8hrs) followed by vaginal Misoprostol 800 mcg on the 4<sup>th</sup> day was associated with a higher complete miscarriage rate and decreased the interval between induction and expulsion in women with FTDM. However, further studies using different regimens and different indications may be warranted.

## Author Contributions

**AME**-designed the study, data collection, conducted the clinical work and writing manuscript. **FME**- conducted the literature search, statistical analyses/interpretation, and critical review. All authors approved the final manuscript.

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