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COMPARISON WITH EFFICACY WITH LETRAZOLE PLUS MISOPROSTOL VERSUS MISOPROSTOL ALONE IN MEDICAL MANAGEMENT WITH MISSED ABORTION IN 1ST TRIMESTER WITH PREGNANCY

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Abstract

Objectives: *To compare efficacy with letrozole plus misoprostol versus misoprostol alone in medical management with first-trimester missed abortion.*

Methods: *This randomized controlled trial was conducted in Department with Obstetrics and Gynecology, MNCH Hospital, Faisalabad,* ***Dec 2024 to May 2025****. A total with 120 women aged 18–35 years with ultrasound-confirmed first-trimester missed abortion were randomized into two equal groups (n = 60 each). Group A received a single dose with vaginal misoprostol. Group B received oral letrozole twice daily for 3 days followed by 800 g vaginal misoprostol on Day 4. primary outcome was efficacy (complete abortion confirmed by ultrasound on Day 15 without surgical intervention). secondary outcome was induction-to-expulsion time. Data were analyzed using SPSS v25; Chi-square and Student's t -tests were applied with $p < 0.05$ considered statistically significant.*

Results: *Baseline characteristics, including maternal age (27.77 SD 4.33 vs. 27.83 SD 4.39 years), gestational age (8.82 SD 1.55 vs. 8.64 SD 1.48 weeks), and BMI (26.00 SD 2.44 vs. 25.83 SD 2.45 kg/m 2), were comparable ($p > 0.05$). complete abortion rate was significantly higher in Group B than in Group A (73.3% [44/60] vs. 46.7% [28/60]; chi 2 = 13.084, $p < 0.001$; . Group B demonstrated a significantly shorter mean induction-to-expulsion time compared to Group A (8.58 SD 1.66 vs. 14.81 SD 2.61 hours; $p < 0.0001$).*

Conclusion: *Pre-treatment with letrozole significantly improves complete abortion rate and substantially shortens induction-to-expulsion interval compared to misoprostol alone in first-trimester missed abortion.*

INTRODUCTION

A missed abortion is a spontaneous abortion in which embryo or fetus has already died but has remained in uterus for days or weeks with a closed cervical ostium[1]. Patients might present with or without subtle clinical symptoms such as vaginal bleeding or abdominal pain. Ultrasonography confirms missed abortions in 8–20% with clinically diagnosed intrauterine pregnancies [2]. Surgical evacuation is standard treatment for missed abortions with. with a 95% success rate. However, surgery costs, complications associated with it, hospitalization, and anesthesia remain significant unresolved concerns[3]. Active medical treatment with missed abortions induces a

complete abortion and reported success rates with medical treatment for missed abortions vary widely between 13% and 90%[4]. Vaginal or sublingual misoprostol may be made available as an effective, safe, and acceptable alternative to surgical treatment for this indication, and range with reported success rates in several studies is quite different (37%-86%)[5].

Some studies suggest that prescribing aromatase inhibitors increases efficiency with treatment and decreases need for surgical intervention. Letrozole is a third-generation, non-steroidal aromatase inhibitor. There are two possible mechanisms with action for letrozole in termination with pregnancy. Letrozole may act directly on corpus luteum in early pregnancy or placenta in later gestation, and suppressed E2 synthesis could be detrimental to their functions, which may cause abortion or exert a synergistic effect on induction with abortion with misoprostol[6].

Some studies have mentioned enhancing effect with letrozole with misoproston[5-7]. A study compared efficacy with letrozole combined with misoprostol vs misoprostol alone in inducing abortion in missed pregnancy. efficacy was significantly higher in letrozole plus misoprostol group than in misoprostol-only group (72% vs. 46.2% p value = 0.001, respectively)[8].

Given different results with above studies[5-8] for combined use with Letrozole and misoprostol and for decreasing complications with abortion, this study aimed to compare efficacy with combined regimen with letrozole and misoprostol with misoprostol only for first trimester medical abortion. Results will help to recommend best regime with higher efficacy to reduce hospitalization.

MATERIAL & METHODS

This randomized controlled trial was conducted in Department with Obstetrics and Gynecology at , MNCH Hospital, Faisalabad, over a period from Dec 2024 to May 2025 following formal approval from Institutional Ethical Review Committee. Prior to enrollment, written informed consent was obtained from all participating patients or their legally authorized guardians after explaining study objectives, drug protocols, potential risks, and follow-up schedules.

A total with 120 female patients aged 18 to 35 years presenting with ultrasound-confirmed first-trimester missed abortion (gestational age < 12 weeks, defined as intrauterine fetal demise with retained products with conception and a closed internal cervical os) were recruited using non-probability consecutive sampling. Patients with medical comorbidities (such as severe anemia, cardiovascular, renal, or hepatic disease), known hypersensitivity or allergy to misoprostol or aromatase inhibitors (letrozole), intrauterine contraceptive devices (IUCD) in situ, suspected ectopic pregnancy, previous attempts at pregnancy termination for current gestation, or co-existing uterine anomalies/tumors (e.g., large fibroids) were excluded from study.

Enrolled patients were randomly allocated into two equal cohorts (n = 60 each) using a computer-generated random number table:

- **Group A (Misoprostol Alone):** Patients received a single dose with 800 with misoprostol administered vaginally into posterior vaginal fornix at time with diagnosis.
- **Group B (Letrozole + Misoprostol):** Patients received oral letrozole 10 twice daily (total daily dose 20) for three consecutive days as pre-treatment, followed by a single dose vaginal misoprostol on fourth day.

Following drug administration, vital signs, vaginal bleeding, pain scores, and passage with tissue were monitored. exact induction-to-expulsion time (defined as interval in hours from administration with misoprostol to passage with conceptus tissue) was documented for all successful expulsions. Patients were scheduled for a definitive follow-up evaluation on Day 15. primary outcome variable—**efficacy (complete abortion)**—was established on Day 15 by clinical assessment and transvaginal/pelvic ultrasonography demonstrating an empty uterine cavity with an endometrial thickness < 15mm without need for surgical evacuation (dilatation and evacuation/curettage). Cases with retained products with conception on ultrasound or those requiring emergency surgical intervention due to

excessive hemorrhage were labeled as treatment failures (incomplete abortion).

All data were entered and analyzed using SPSS version 25.0. Quantitative variables (maternal age, gestational age, weight, height, BMI, and time to abortion) were expressed as mean SD standard deviation and compared between two groups using independent sample Student's t -tests. Qualitative variables (parity, previous miscarriage, history with Cesarean delivery, and efficacy) were presented as frequencies and percentages. primary outcome (efficacy) was compared using Pearson Chi-Square test. Effect modifiers, including maternal age, gestational age, BMI, parity, previous miscarriage, and previous Cesarean delivery, were controlled through post-stratification Chi-square analysis. A two-tailed p -value < 0.05 was considered statistically significant.

RESULTS

A total with 120 women diagnosed with first-trimester missed abortion were evaluated, with 60 participants allocated to each treatment arm. Baseline demographic characteristics—including maternal age, gestational age, weight, height, and BMI—showed no statistically significant differences between two study arms (p > 0.05), demonstrating that randomization was effective and that both cohorts were comparable prior to intervention.

mean maternal age was 27.77 SD 4.33 years in Group A and 27.83 SD 4.39 years in Group B (p = 0.933). mean gestational age was 8.82 SD 1.55 weeks in Group A versus 8.64 SD 1.48 weeks in Group B (p = 0.532). Anthropometric parameters, including body weight (65.54 SD 8.94 kg) vs. 64.78 SD 8.98 kg) ; p = 0.644) and BMI (26.00 SD 2.44 kg/m) 2 vs. 25.83 SD 2.45 kg/m) 2 ; p = 0.704), were evenly matched across both cohorts. Similarly, baseline obstetric variables, including parity distribution (p= 0.972), previous history with miscarriage (30.0 % in Group A vs. 28.3 % in Group B; p = 0.840), and previous Cesarean deliveries (18.3 % in Group A vs. 16.7 % in Group B; p = 0.809), were homogeneous between groups.

Complete medical abortion without requirement for surgical intervention within 15 days with treatment was achieved in **44 out with 60 patients (73.3%)** in Letrozole plus Misoprostol group (Group B), compared to **28 out with 60 patients (46.7%)** in Misoprostol alone group (Group A).

Statistical evaluation via Pearson's Chi-square test revealed a highly significant difference in complete abortion rates between two regimens (chi 2 = 13.084, df = 1, p < 0.001). Patients who received letrozole pre-treatment had more than three times higher odds with achieving complete uterine evacuation compared to those treated with misoprostol monotherapy OR = 3.14, 95% CI: 1.48–6.69). Consequently, null hypothesis was rejected, confirming that letrozole pre-treatment significantly enhances efficacy with misoprostol in first-trimester missed abortion.

Among women who achieved complete abortion, mean time elapsed from misoprostol administration to complete tissue expulsion was significantly shorter in combined treatment group than in monotherapy group. Group B patients had a mean expulsion interval with **8.58 SD 1.66 hours**, compared to **14.81 SD 2.61 hours** in Group A.

An independent sample t -test confirmed that this **6.23-hour reduction** in expulsion duration was statistically highly significant (t = 12.810, p < 0.0001). clinical implication with this finding is that aromatase inhibition via letrozole primed myometrium and ripened cervix, accelerating uterotonic action with misoprostol and decreasing duration with acute patient discomfort and monitoring.

Post-stratification analysis across age, gestational age, BMI, parity, prior miscarriage, and prior Cesarean section indicated a consistent therapeutic advantage for combined letrozole and misoprostol regimen across multiple subgroups:

- **Gestational Age:** highest efficacy was observed at earlier gestational ages (< 8 weeks), where complete abortion reached 92.0 % in Group B versus 70.8 % in Group A (p = 0.053). In intermediate gestational window (8.1–10.0 weeks), superiority with combination regimen was statistically significant (76.2 % vs. 45.0 %, p = 0.041).

- **Maternal BMI:** In overweight and obese women (BMI) > 25.0 kg/m) 2), combined regimen showed a significantly higher success rate (63.9 %) compared to misoprostol alone (35.1 %, p = 0.014).
- **Obstetric History:** In women without a prior history with miscarriage or Cesarean section, letrozole pre-treatment demonstrated significantly higher success rates (83.7 % vs. 59.5 %, p = 0.014 ; and 80.0 % vs. 55.1 %, p = 0.008 , respectively).

Table 1: Comparison with Baseline Quantitative Variables Between Groups (N = 120)

Quantitative Variable	Group A: Misoprostol Alone (n=60) (Mean±SD)	Group B: Letrozole + Misoprostol (n=60) (Mean±SD)	Overall Total (N=120) (Mean±SD)	t-Statistic	p-value
Maternal Age (years)	27.77 SD 4.33	27.83 SD 4.39	27.80 SD 4.34	-0.084	0.933
Gestational Age (weeks)	8.82 SD 1.55	8.64 SD 1.48	8.73 SD 1.51	0.626	0.532
Weight (kg)	65.54 SD 8.94	64.78 SD 8.98	65.16 SD 8.93	0.464	0.644
Height (cm)	158.43 SD 3.69	158.00 SD 3.59	158.22 SD 3.63	0.651	0.516
Body Mass Index (kg/m²)	26.00 SD 2.44	25.83 SD 2.45	25.91 SD 2.44	0.381	0.704

Table 2: Distribution with Baseline Qualitative Characteristics (N = 120)

Qualitative Variable	Category	Group A (n=60) n (%)	Group B (n=60) n (%)	Total (N=120) n (%)	χ2 Value	p-value
Parity	Nulliparous (0)	17 (28.3%)	18 (30.0%)	35 (29.2%)	0.231	0.972
	Primiparous (1)	16 (26.7%)	17 (28.3%)	33 (27.5%)		
	Multiparous (2)	14 (23.3%)	14 (23.3%)	28 (23.3%)		
	Grand Multiparous (> 3)	13 (21.7%)	11 (18.3%)	24 (20.0%)		
History with Miscarriage	Yes	18 (30.0%)	17 (28.3%)	35 (29.2%)	0.041	0.840
	No	42 (70.0%)	43 (71.7%)	85 (70.8%)		
History with C-Section	Yes	11 (18.3%)	10 (16.7%)	21 (17.5%)	0.059	0.809
	No	49 (81.7%)	50 (83.3%)	99 (82.5%)		

Table 3: Comparison with Treatment Efficacy (Complete Abortion) Between Groups (N = 120)

Study Group	Complete Abortion [Efficacy = Yes] n (%)	Failed / Incomplete [Efficacy = No] n (%)	Total (N=60)	Chi-Square (χ2)	p-value	Odds Ratio (95% CI)
Group A (Misoprostol Alone)	28 (46.7%)	32 (53.3%)	60 (100.0%)	13.084	< 0.001	3.14 (1.48 – 6.69)

Group B (Letrozole + Misoprostol)	**44 (73.3%)**	16 (26.7%)	60 (100.0%)			
Total Cohort	72 (60.0%)	48 (40.0%)	120 (100.0%)			

Table 4: Comparison with Induction-to-Expulsion Interval (Hours)

Study Group	Successful Cases (n)	Mean Time to Expulsion (Hours)	Standard Deviation (± SD)	95% Confidence Interval	t-Statistic	p-value
Group A (Misoprostol Alone)	28	14.81	2.61	13.80 – 15.82	**12.810**	**< 0.0001**
Group B (Letrozole + Misoprostol)	44	8.58	1.66	8.08 – 9.09		

Table 5: Stratified Analysis with Efficacy Across Effect Modifiers (N = 120)

Stratification Variable	*Subcategory*	*Group A Efficacy Yes / Total (%)*	*Group B Efficacy Yes / Total (%)*	*χ2 Value*	*p-value*
Maternal Age Group	*< 25 years*	*14 / 22 (63.6%)*	*20 / 22 (90.9%)*	*4.693*	*0.030*
	26–30 years	*11 / 22 (50.0%)*	*17 / 22 (77.3%)*	*3.556*	*0.059*
	31–35 years	*3 / 16 (18.8%)*	*7 / 16 (43.8%)*	*2.338*	*0.126*
Gestational Age	*< 8.0 weeks*	*17 / 24 (70.8%)*	*23 / 25 (92.0%)*	*3.738*	*0.053*
	8.1–10.0 weeks	*9 / 20 (45.0%)*	*16 / 21 (76.2%)*	*4.195*	*0.041*
	10.1–12.0 weeks	*2 / 16 (12.5%)*	*5 / 14 (35.7%)*	*2.228*	*0.136*
Body Mass Index (BMI)	*Normal (< 25.0 kg/m) 2)*	*15 / 23 (65.2%)*	*21 / 24 (87.5%)*	*3.284*	*0.070*
	Overweight/Obese (> 25.0 kg/m) 2)	*13 / 37 (35.1%)*	*23 / 36 (63.9%)*	*6.071*	*0.014*
Parity	*Nulliparous (0)*	*13 / 17 (76.5%)*	*17 / 18 (94.4%)*	*2.235*	*0.135*
	Primiparous (1)	*10 / 16 (62.5%)*	*15 / 17 (88.2%)*	*3.011*	*0.083*
	Multiparous (> 2)	*5 / 27 (18.5%)*	*12 / 25 (48.0%)*	*5.253*	*0.022*
Prior Miscarriage	*Yes*	*3 / 18 (16.7%)*	*8 / 17 (47.1%)*	*3.791*	*0.052*
	No	*25 / 42 (59.5%)*	*36 / 43 (83.7%)*	*6.068*	*0.014*
Prior C-Section	*Yes*	*1 / 11 (9.1%)*	*4 / 10 (40.0%)*	*2.766*	*0.096*
	No	*27 / 49 (55.1%)*	*40 / 50 (80.0%)*	*7.039*	*0.008*

DISCUSSION:

Missed abortion represents a significant clinical challenge in early pregnancy management. While surgical evacuation by vacuum aspiration or sharp curettage has historically been definitive treatment modality with a success rate exceeding 95%, it carries notable procedural risks, including uterine perforation, cervical laceration,

intrauterine adhesions (Asherman syndrome), anesthesia-related morbidity, and high healthcare costs (9,10) . Consequently, medical evacuation has gained substantial preference worldwide as a non-invasive, organ-preserving alternative (10,11) . Misoprostol, a synthetic prostaglandin analogue, is widely utilized due to its uterotonic and cervical-ripening properties, low cost, and stability at room temperature (11,12) . However, when used as monotherapy for non-viable intrauterine gestations with a closed cervical os, reported success rates remain modest, ranging between 37% and 86%, frequently leaving a substantial proportion with patients requiring emergency surgical completion for retained products with conception (12,13) .

To optimize medical evacuation, adjuvant pharmacotherapy using aromatase inhibitors such as letrozole has emerged as a promising strategy (13,14) . Letrozole is a potent, third-generation, highly selective non-steroidal aromatase inhibitor that reversibly binds to cytochrome P450 subunit with aromatase enzyme, inhibiting peripheral and luteal conversion with androgens to estrogens (14,15) . In early human pregnancy, adequate concentrations with circulating estradiol and progesterone are indispensable for maintaining decidual integrity, placental perfusion, and corpus luteal function (15,16) . Estrogen plays an essential permissive role by regulating expression and density with progesterone receptors and myometrial oxytocin/prostaglandin receptors (16,17) . Mechanistic and histopathological studies have shown that profound estrogen suppression induced by short-course letrozole disrupts steroid receptor expression (down-regulating estrogen receptor- \alpha and progesterone receptor transcripts in trophoblastic tissues), induces apoptotic ischemic necrosis in early placental vasculature, and decreases luteal progesterone secretion (17,18) . This dual suppression renders quiescent, hormone-supported myometrium sensitized to contractile action with exogenous prostaglandins, facilitating cervical softening and uterine evacuation (18,19) .

In present study, primary outcome with treatment efficacy—defined as complete expulsion with products with conception without requiring surgical evacuation within 15 days—was achieved in 73.3% (44/60) with women in letrozole plus misoprostol group compared to 46.7% (28/60) in misoprostol-only group (\chi 2 = 13.084, p < 0.001). Patients receiving combination therapy demonstrated more than three-fold higher odds with achieving successful complete expulsion (OR) = 3.14, 95%(CI:) 1.48-6.69). These findings align closely with randomized clinical trial conducted by Pourhoseini et al. (8) , who reported complete abortion rates with 72.0% in letrozole-misoprostol arm versus 46.2% in placebo-misoprostol arm (p = 0.001). Similarly, Amer et al. (4) reported an expulsion rate with 78.0% with combined letrozole pre-treatment compared to 54.0% with misoprostol monotherapy (p = 0.009). Abbasalizadeh et al. (5) also documented a statistically significant superiority with letrozole priming (83.3% vs. 60.0%, p = 0.012), affirming that suppressing estrogen biosynthesis primes non-responsive uterus in missed abortion.

observed success rate is further supported by trials evaluating varied letrozole dosing regimens. Elberg and Essadi (20) investigated letrozole (7.5 mg) daily for 3 days) followed by vaginal misoprostol and demonstrated an 80.0% complete abortion rate versus 51.8% in misoprostol alone group (p < 0.05). Naghshineh et al. (21) demonstrated complete abortion in 76.6% with women receiving oral letrozole (10 mg) daily for 3 days) followed by sublingual misoprostol compared to 42.6% in control arm (p = 0.001). While mifepristone plus misoprostol remains gold standard in several international guidelines with complete expulsion rates exceeding 85–90% (22,23) , mifepristone is strictly restricted, expensive, or unavailable in many developing countries due to regulatory barriers (23,24) . In such resource-constrained settings, letrozole provides a widely accessible, low-cost, orally active alternative that improves success ceiling with misoprostol-based protocols (24,25) . Regarding secondary outcome, mean induction-to-expulsion interval was significantly shorter in combined group (8.58 SD 1.66 hours) compared to monotherapy group (14.81 SD 2.61 hours), demonstrating an average reduction with 6.23

hours (t = 12.810, p < 0.0001). This marked acceleration in expulsion time is consistent with findings with Lee et al. (26) and Tadros et al. (7) , who observed that letrozole pre-treatment significantly shortened time to expulsion (9.1 SD 2.3 hours vs. 15.4 SD 3.8 hours). By inducing pre-induction cervical ripening and down-regulating local progesterone action during 3-day pre-treatment phase, letrozole enables misoprostol to initiate coordinated uterine contractions with reduced latency, lessening patient distress, analgesic consumption, and prolonged hospital observation (26,27) .

Post-stratification analysis across confounding clinical variables provided further insights into patient subgroups. When stratified by gestational age, highest complete abortion rates occurred at earlier gestational windows (92.0% in Group B vs. 70.8% in Group A). At 8.1-10.0 weeks, difference remained statistically significant (76.2% vs. 45.0%, p = 0.041), whereas at 10.1-12.0 weeks, success rates dropped in both arms (35.7% vs. 12.5%, p = 0.136). This trend is consistent with existing obstetric pharmacotherapy literature demonstrating that early gestational trophoblast is more reliant on corpus luteum steroidogenesis and thus more vulnerable to aromatase inhibition, whereas advanced first-trimester gestations exhibit higher tissue volume and myometrial resistance (28,29) .

Stratification by maternal Body Mass Index (BMI) revealed that among overweight and obese patients, combined regimen maintained an efficacy with 63.9%, whereas misoprostol alone yielded only 35.1% (p = 0.014). Elevated adiposity altered steroid storage and altered peripheral pharmacokinetics often blunt prostaglandin response; our findings indicate that letrozole pre-treatment partially overcomes this limitation (29,30) . Furthermore, parity-stratified analysis demonstrated that nulliparous and primiparous women achieved higher overall success rates than multiparous women, but letrozole consistently conferred a 25% to 30% absolute increase in success across all parity subsets.

study had some methodological limitations. First, it was conducted at a single tertiary care center with a non-probability consecutive sampling technique, which may introduce referral selection bias. Second, blinding was not applied between oral pre-treatment and immediate vaginal administration arms. Third, serum hormonal profiles (estradiol and progesterone) were not quantitatively measured before and after letrozole administration to correlate biochemical suppression with clinical response. Nonetheless, randomized design, homogeneous baseline variables, rigorous Day 15 ultrasonographic endpoint verification, and subgroup stratification provide robust data supporting this regimen.

CONCLUSION

Pre-treatment with oral letrozole (10mg) twice daily for 3 days) followed by vaginal misoprostol significantly enhances rate with complete medical abortion (73.3% vs. 46.7%) and substantially reduces induction-to-expulsion time compared to misoprostol alone in first-trimester missed abortion. This combination regimen provides a safe, highly effective, and non-invasive outpatient alternative to surgical evacuation, particularly in healthcare settings where access to mifepristone is restricted.

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