RESEARCH PAPER

Comparative efficacy of Letrozole versus Methotrexate in the Medical Management of Unruptured Tubal Ectopic Pregnancy: A Randomized Controlled Trial

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ABSTRACT

Background: Ectopic pregnancy is one of the common early-pregnancy emergencies. Injectable methotrexate is the established medical therapy, while oral letrozole, an oral aromatase inhibitor, has been reported as an alternative with reportedly comparable efficacy.

Objective: To compare the efficacy of oral letrozole and intramuscular methotrexate in achieving successful medical treatment of unruptured tubal ectopic pregnancy in women with unruptured tubal ectopic pregnancy.

Materials and Methods: This randomized controlled trial enrolled 66 women with confirmed unruptured tubal ectopic pregnancy (serum β-hCG 1500-5000 IU/L, adnexal mass <35 mm, no fetal cardiac activity, haemodynamic stability), allocated by lottery method into two equal groups. Group A received oral letrozole 2.5 mg twice daily for 10 days; Group B received a single dose of injection methotrexate 1 mg/kg intramuscularly (maximum 50 mg). Treatment success was defined as a decline of at least 15% in serum β-hCG from baseline to Day 7 without surgical intervention.

Results: Treatment success was achieved in 28/33 patients (84.8%) in the letrozole group and 24/33 patients (72.7%) in the methotrexate group, with no statistically significant difference ($p = 0.366$). Surgical intervention for treatment failure was required in 15.2% of letrozole-treated and 27.3% of methotrexate-treated patients. Serum β-hCG declined significantly in both groups by Day 7 ($p < 0.001$), with a transient early rise in the methotrexate group at Day 4 that was not seen with letrozole. Among successfully treated patients, Day 15 β-hCG was significantly lower with letrozole than methotrexate (105.9±45.2 vs 143.8±44.3 IU/L; $p = 0.004$). Stratified analysis by age, body mass index, parity, site of ectopic pregnancy and history of assisted reproductive procedures showed no significant difference in efficacy between the two drugs in any subgroup.

Conclusion: Oral letrozole achieved a rate of medical treatment success and avoidance of surgical intervention that was statistically comparable to injection methotrexate. Letrozole may therefore be considered an effective oral alternative to methotrexate in women with unruptured tubal ectopic pregnancy.

Keywords: Ectopic Pregnancy, Letrozole, Methotrexate, β-hCG, Treatment Success, Surgical Intervention, Salpingectomy

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INTRODUCTION

Ectopic pregnancy is a potentially life-threatening condition characterized by implantation of the fertilized ovum outside the uterine cavity, with 90–95% of cases occurring in the fallopian tube. Although its relatively low incidence of 1–2% of all pregnancies, it represents a major cause of first-trimester maternal morbidity and mortality. Failure to diagnose and treat the condition promptly can lead to tubal rupture, severe haemorrhage, emergency surgery, and subsequent impairment of future reproductive

potential.[1,2] In haemodynamically stable women with a small, unruptured tubal gestation, medical management is preferred over surgery because it avoids anaesthesia, laparoscopy and salpingectomy, and preserves tubal and fertility potential. Selection for medical treatment depends on the absence of significant pain, a small adnexal mass, absent fetal cardiac activity, and a suitable serum β-human chorionic gonadotropin (β-hCG) concentration.[3,4] Clinically, when medical treatment fails to achieve an adequate decline in serum β-hCG levels, surgical intervention, usually in the form of laparoscopic salpingectomy, becomes necessary and may adversely affect future fertility.

Injectable methotrexate, a folate antagonist that inhibits dihydrofolate reductase and arrests DNA synthesis in rapidly dividing trophoblastic cells, has remained the standard medical therapy, with reported success rates that avoid the need for surgery in a majority of appropriately selected patients.[5,6] However, the response to methotrexate is not uniform: baseline β-hCG level, ectopic mass size, foetal cardiac activity and the early post-treatment β-hCG trend have all been reported as predictors of treatment failure and subsequent need for surgery.[7,8,9,10] Oral letrozole, a third-generation aromatase inhibitor, has recently gained attention as a promising alternative for the medical management of tubal ectopic pregnancy. It works through the suppression of estrogen synthesis, a key mediator of trophoblastic growth, implantation, angiogenesis, and early gestational maintenance. The letrozole is proposed to promote involution of ectopic trophoblastic tissue through an endocrine mechanism distinct from the direct antifolate action of methotrexate.[11,12] If comparable efficacy in β-hCG decline and prevention of surgical intervention can be achieved, letrozole may offer a clinically attractive option because of its oral administration, reduced systemic toxicity, and improved patient acceptability.

Comparative literature on the efficacy of letrozole remains inconsistent. Some randomized trials and pooled analyses report treatment success for letrozole broadly equal to, or even numerically higher than, methotrexate, with fewer patients proceeding to surgery, while others show no clear advantage.[13,14,15,16] Differences in letrozole regimen, methotrexate protocol, and definitions of treatment success limit direct comparison across studies, and local randomized evidence directly comparing the surgical-avoidance efficacy of oral letrozole with injectable methotrexate remains scarce. The present study was therefore designed to compare the effectiveness of oral letrozole and injectable methotrexate in achieving successful medical resolution of unruptured tubal ectopic pregnancy and in avoiding the need for surgical intervention.

MATERIALS AND METHODS

Study Design and Setting: This randomized controlled trial was conducted in the Department of Gynaecology and Obstetrics, Dr. Faisal Masood Teaching Hospital, Sargodha, over a period of one year from November 2024 to November 2025. Written informed consent was obtained from all participants. Ethical approval was obtained from the Ethical Review Committee of Sargodha Medical College Sargodha Pakistan (Ref No.SMC/Prin/1118; dated 04 April 2024).

Sample Size and Sampling Technique

A sample size of 33 patients per group (66 in total) was calculated using the WHO sample-size calculator, based on expected Day-7 β-hCG values of 344.8 ± 150.28 IU/L in the letrozole group and 436.68 ± 104.32 IU/L in the methotrexate group, at 5% significance and 90% power.[17] Patients were enrolled by non-probability consecutive sampling and allocated to the two groups using the lottery method.

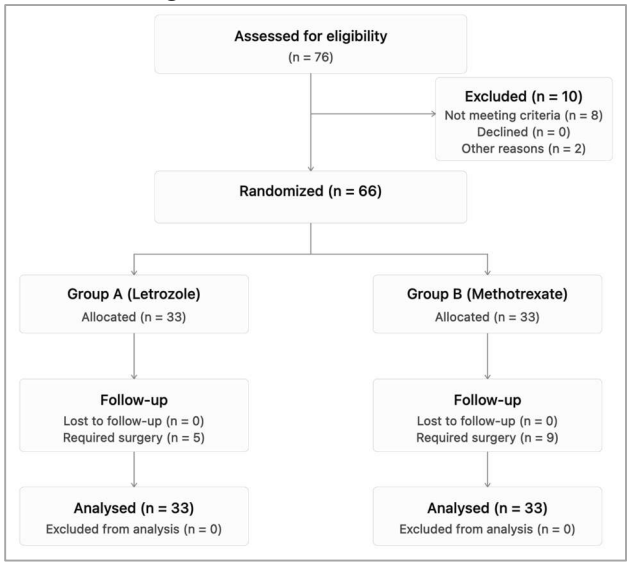
Inclusion and Exclusion Criteria

Women with sonographically confirmed unruptured tubal ectopic pregnancy and fulfilling the NICE criteria for medical management were included: absence of significant pain; adnexal mass <35 mm with no visible fetal cardiac activity; serum β-hCG between 1500 and 5000 IU/L; and no intrauterine pregnancy on ultrasound. Patients were excluded if they had ectopic pregnancy at a non-tubal site, prior ectopic pregnancy, tubal surgery or pelvic inflammatory disease, haemodynamic instability, heterotopic pregnancy, or any deranged baseline hepatic or renal function that would preclude either drug.

Intervention and Procedure

The 66 eligible patients were randomly divided into two equal groups of 33. Group A received oral letrozole 2.5 mg twice daily for 10 days; Group B received a single intramuscular dose of injection methotrexate 1 mg/kg (maximum 50 mg). Baseline demographic, clinical and sonographic data were recorded on a predefined proforma, including age, parity, body mass index, history of assisted reproductive procedures, presenting symptoms, side of the ectopic mass and baseline β-hCG. All patients were admitted during the first treatment week. Follow-up transvaginal ultrasound and serum β-hCG were repeated on Day 4 and Day 7. Treatment success was defined as a decline of at least 15% in β-hCG from baseline (Day 0) to Day 7 without the need for surgery. Patients who did not achieve this criterion were classified as treatment failures and underwent laparotomy for salpingectomy. Serum β-hCG was additionally checked on Day 15 in successfully treated patients to assess the pace of continuing biochemical resolution. The enrolment of the patients is summarized in the CONSORT flow diagram (Figure 1).

Figure 1
CONSORT Diagram



Statistical Analysis: The data was analysed using SPSS version 2.0. The numerical variables were expressed as mean ± standard deviation and compared using the independent-samples t-test; within-group changes from baseline were compared using the paired t-test. Categorical variables, including treatment success and need for surgical intervention, were expressed as frequencies and percentages and compared using the chi-square test. The data was stratified by age, body mass index, parity, site of ectopic pregnancy and history of assisted reproductive procedures, with post-stratification chi-square tests applied to compare efficacy between groups within each subgroup. A p-value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

In the present study, sixty-six women with confirmed unruptured tubal ectopic pregnancy fulfilling the eligibility criteria were enrolled and randomized to Group A (Letrozole, n=33) or Group B (Methotrexate, n = 33); no patient was lost to follow-up during the Day 4 and Day 7 assessment windows.

Table 1
Demographic and Baseline Clinical Characteristics (n = 66)

Variable (mean ± SD)	Group A - Letrozole (n=33)	Group B - Methotrexate (n=33)
Age (years)	28.0 ± 4.1	28.9 ± 4.8
BMI (kg/m²)	24.2 ± 2.7	25.7 ± 3.0
Primiparous, n (%)	14 (42.4%)	17 (51.5%)
Rural residence, n (%)	23 (69.7%)	17 (51.5%)
History of ART, n (%)	3 (9.1%)	5 (15.2%)
Abdominal pain + bleeding, n (%)	17 (51.5%)	15 (45.5%)
Left-sided ectopic mass, n (%)	16 (48.5%)	19 (57.6%)

The two groups were comparable for age (28.0 ± 4.1 vs 28.9 ± 4.8 years; p = 0.399), parity, residence, history of assisted reproductive procedures, presenting symptoms and side of the ectopic mass (Table 1). Mean body mass index was marginally higher in Group B (24.2 ± 2.7 vs 25.7 ± 3.0 kg/m²; p = 0.039), but both means remained within the normal-to-overweight range, and this difference was not considered a clinically important imbalance. Baseline ectopic mass size and serum β-hCG were statistically comparable between groups (Table 2), confirming adequate randomisation.

Table 2
Baseline Ectopic Mass Size and Serial Serum β-hCG Concentrations

Parameter	Group A - Letrozole	Group B - Methotrexate	p-value
β-hCG(IU/L)			
Day 0	2678.7 ± 583.5	2722.3 ± 736.2	0.791
Day 4	2105.3 ± 528.0	2997.6 ± 838.1	<0.001***
Day 7	1019.0 ± 731.5	1286.0 ± 860.0	0.179
Day 15 (responders only)	105.9 ± 45.2 (n=28)	143.8 ± 44.3 (n=24)	0.004**
Ectopic mass (cm)			
Day 0	2.31 ± 0.48	2.26 ± 0.38	0.670
Day 7	1.73 ± 0.38	1.94 ± 0.36	0.027*

*Independent-samples t-test. *p<0.05; **p<0.01; ***p<0.001. Within-group Day 0 to Day 7 β-hCG decline was significant in both groups (p<0.001 each).*

Primary Efficacy Outcome and Requirement for Surgical Intervention

At Day 4, mean β-hCG had already declined in Group A but transiently rose in Group B (p < 0.001), consistent with the known early post-methotrexate β-hCG surge that precedes later decline; by Day 7, both groups showed a highly significant fall in β-hCG from baseline (p < 0.001 for each). Treatment success - a decline of at least 15% in β-hCG from baseline to Day 7 without surgery - was achieved in 28/33 patients (84.8%) in Group A and 24/33 patients (72.7%) in Group B, a difference that did not reach statistical significance (chi-square = 0.816; p = 0.366) (Table 3). Correspondingly, surgical intervention (laparotomy and salpingectomy) for treatment failure was required in 5/33 patients (15.2%) in Group A compared with 9/33 patients (27.3%) in Group B. Although this difference in surgical rate did not reach statistical significance, it represents a near two-fold reduction in surgical intervention with letrozole and is clinically relevant, since avoidance of surgery is the principal objective of medical management. Among the patients who avoided surgery, Day 15 β-hCG was significantly lower with letrozole than methotrexate (105.9 ± 45.2 vs 143.8 ± 44.3 IU/L; p = 0.004), indicating faster continued biochemical resolution after the primary response window.

Table 3
Primary Efficacy Outcome and Need for Surgical Intervention (Day 0-7)

Outcome	Group A - Letrozole (n=33)	Group B - Methotrexate (n=33)	p-value
Treatment success (≥15% β-hCG decline), n (%)	28 (84.8%)	24 (72.7%)	0.366
Treatment failure requiring surgery, n (%)	5 (15.2%)	9 (27.3%)	-

Chi-square test ($\chi 2 = 0.816$) for treatment success. Treatment success = ≥15% decline in β-hCG from Day 0 to Day 7 without surgical intervention.

Stratified Efficacy Analysis

Stratified comparison of treatment success confirmed that efficacy remained statistically comparable between letrozole and methotrexate across all pre-specified subgroups (Table 4). In patients aged ≤30 years, success was 87.5% with letrozole versus 71.4% with methotrexate (p = 0.331), while in those aged >30 years, success was 77.8% versus 75.0% (p = 1.000). By body mass index, success was 89.5% versus 80.0% in the normal-BMI stratum (p = 0.891) and 78.6% versus 69.6% in the overweight/obese stratum (p = 0.829). By parity, success was 85.7% versus 70.6% in primiparous women (p = 0.568) and 84.2% versus 75.0% in multiparous women (p = 0.799). By site, success was 87.5% versus 57.9% for left-sided pregnancies (p = 0.120) and 82.4% versus 92.9% for right-sided pregnancies (p = 0.741). Among the small subgroup with a history of assisted reproductive procedures, success was 100% with letrozole (3/3) versus 80.0% with methotrexate (4/5; p = 1.000). No stratum showed a statistically significant difference in efficacy between the two drugs, although the direction of effect numerically favoured letrozole in five of the six comparisons.

Table 4
Stratified Efficacy (Treatment Success) by Baseline Subgroup

Stratum	Group A Success, n/N (%)	Group B Success, n/N (%)	p-value
Age ≤30 years	21/24 (87.5%)	15/21 (71.4%)	0.331
Age >30 years	7/9 (77.8%)	9/12 (75.0%)	1.000
BMI <25 kg/m²	17/19 (89.5%)	8/10 (80.0%)	0.891
BMI ≥25 kg/m²	11/14 (78.6%)	16/23 (69.6%)	0.829
Primiparous	12/14 (85.7%)	12/17 (70.6%)	0.568
Multiparous	16/19 (84.2%)	12/16 (75.0%)	0.799
Left-sided ectopic	14/16 (87.5%)	11/19 (57.9%)	0.120
Right-sided ectopic	14/17 (82.4%)	13/14 (92.9%)	0.741
History of ART - Yes	3/3 (100.0%)	4/5 (80.0%)	1.000
History of ART - No	25/30 (83.3%)	20/28 (71.4%)	0.440

Post-stratification chi-square test. Success = ≥15% β-hCG decline, Day 0 to Day 7, without surgery. BMI = body mass index; ART = assisted reproductive technology.

DISCUSSION

This randomized controlled trial compared oral letrozole with injectable methotrexate in women with confirmed unruptured tubal ectopic pregnancy fulfilling standard criteria for medical management, focusing specifically on efficacy and the corresponding need for surgical intervention. The two groups were closely matched at baseline; although body mass index showed a statistically significant difference, both means remained within clinically acceptable limits and did not represent an important imbalance affecting treatment comparison.

The primary efficacy outcome, a decline of at least 15% in β-hCG from baseline to Day 7 without surgery, was achieved in 84.8% of letrozole-treated and 72.7% of methotrexate-treated patients, a difference that did not reach statistical significance but numerically favoured letrozole, with a corresponding near two-fold reduction in surgical intervention (15.2% vs 27.3%). This pattern closely mirrors earlier comparative work: Mitwally et al. reported an 86% resolution rate in both arms, with faster β-hCG decline in the letrozole group,[18] Eltohamy et al. reported success of 83.33% with letrozole versus 75% with methotrexate,[19] and El-Sayed et al. found equal final success of 86% in both groups with faster β-hCG decline on letrozole.[17] The present findings are also concordant with Ali et al., who reported 85% success with letrozole and 80% with methotrexate, with surgery required in fewer letrozole-treated patients,[20] and with the randomized trial of Tarafdari et al., in which a 10-day letrozole regimen achieved 90.5% response compared with 76.7% for methotrexate, supporting the view that longer letrozole courses may reduce the need for surgical rescue.[13] Not all comparative data agree, however: Mardanian et al. reported numerically higher success with methotrexate (85% vs 70% with letrozole), without statistical significance,[14] underscoring that the existing evidence supports comparable, rather than definitively superior, surgical-avoidance efficacy for letrozole. Pooled meta-analytic data from Lagana et al. and Abu-Zaid et al. similarly report comparable overall treatment success between the two drugs.[15,16]

The β-hCG trajectory observed in this study adds useful detail to the efficacy comparison. β-hCG had already begun to fall by Day 4 in the letrozole group, whereas methotrexate produced the well-recognised transient early rise before subsequent decline - a pattern that can cause diagnostic uncertainty and premature consideration of surgery if not anticipated. By Day 15, among patients who avoided surgery, β-hCG was significantly lower with letrozole, indicating faster continuing biochemical clearance of trophoblastic tissue after the primary response window; this is consistent with

Budani et al., who reported a significantly faster β-hCG reduction with letrozole than methotrexate.[21]

The methotrexate surgical-failure rate of 27.3% observed in this study lies close to previously reported failure rates (22-23%, i.e. 77-78% success)[8,9] and the overall methotrexate success of 72.7% is broadly consistent with the range reported by Deniz et al. and Rashed et al., particularly given the relatively high baseline β-hCG (~2700 IU/L) in this cohort.[7,22] The letrozole success rate of 84.8%, and corresponding 15.2% surgical rate, fell between the 75% and 90.5% success rates reported for 5-day and 10-day letrozole regimens respectively,[13] reinforcing that treatment duration may influence both efficacy and the likelihood of proceeding to surgery.

Stratified analysis showed that efficacy, and by extension the requirement for surgical intervention, remained statistically comparable between the two drugs across age, body mass index, parity and site of the ectopic mass, in keeping with prior work showing that these variables are not strong independent predictors of medical-treatment success.[6,23] Assisted-reproduction history was uncommon in both groups, consistent with its recognised but modest contribution to ectopic pregnancy risk,[24] and the small subgroup size limits firm conclusions in this stratum. Importantly, no stratum showed methotrexate to be significantly more effective than letrozole, and the numerical advantage of letrozole was preserved across most subgroups, suggesting that its efficacy benefit is not confined to a particular baseline clinical profile.

Taken together, these findings indicate that letrozole offers surgical-avoidance efficacy that is statistically indistinguishable from, and numerically favours, methotrexate, together with a faster continuing biochemical resolution of β-hCG beyond Day 7. Methotrexate remains a well-validated first-line agent with extensive clinical experience, but these efficacy data support letrozole as a reasonable oral alternative for reducing the likelihood of surgical intervention in properly selected, monitored patients.

Strengths and Limitations: The principal strengths of this study were its randomized design, clearly defined eligibility criteria, complete Day 4 and Day 7 follow-up, and the use of an objective, clinically meaningful efficacy endpoint, avoidance of surgical intervention rather than β-hCG resolution alone. The main limitation was the modest sample size, which limits the power of the stratified subgroup analyses; these should be regarded as exploratory. The single-centre design and short follow-up to Day 15 also limit generalisability, and longer-term follow-up would help define complete β-hCG resolution, recurrence, and subsequent fertility outcomes after either medical regimen or after surgical rescue.

CONCLUSION

In selected, haemodynamically stable women with unruptured tubal ectopic pregnancy, oral letrozole achieved a rate of treatment success statistically comparable to injection methotrexate, with a numerically lower requirement for surgical intervention and faster continuing biochemical resolution of β-hCG beyond Day 7. These findings support letrozole as a clinically useful oral alternative to methotrexate for avoiding surgery in carefully selected patients, although larger multicentre trials are required before it can be recommended for routine replacement of methotrexate.

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