

This is a provisional PDF only. Copyedited and fully formatted version will be made available soon.



P O L I S H G Y N E C O L O G Y

# GINEKOLOGIA POLSKA

ORGAN POLSKIEGO TOWARZYSTWA GINEKOLOGICZNEGO  
THE OFFICIAL JOURNAL OF THE POLISH GYNECOLOGICAL SOCIETY

ISSN: 0017-0011

e-ISSN: 2543-6767

## Off-label letrozole for tubal pregnancy monotherapy is not an alternative to methotrexate: a prospective cohort study

**Authors:** Iwona M. Gawron, Dorota Babczyk, Robert Jach

**DOI:** 10.5603/gpl.100131

**Article type:** Research paper

**Submitted:** 2024-04-05

**Accepted:** 2024-06-17

**Published online:** 2024-09-02

This article has been peer reviewed and published immediately upon acceptance.  
It is an open access article, which means that it can be downloaded, printed, and distributed freely,  
provided the work is properly cited.  
Articles in "Ginekologia Polska" are listed in PubMed.

## **Off-label letrozole for tubal pregnancy monotherapy is not an alternative to methotrexate: a prospective cohort study**

**Iwona M. Gawron, Dorota Babczyk, Robert Jach**

*Department of Gynecology and Obstetrics, Jagiellonian University Medical College,  
Cracow, Poland*

### **ABSTRACT**

**Objectives:** Inhibition of estradiol production by letrozole may interfere with physiological effects of progesterone necessary to maintain the pregnancy. Treatment of tubal pregnancy (TP) with letrozole would allow to avoid the disadvantages of methotrexate (MTX). The aim was to compare the effectiveness of letrozole with MTX in the management of TP.

**Material and methods:** A prospective open-label cohort study was conducted among women with TP and increasing B-human chorionic gonadotropin (B-hCG) concentrations. MTX was administered in a single dose of 100 mg intravenously, while letrozole in a dose of 5 mg orally for 10 days. Blood parameters (B-hCG, hemoglobin, creatinine, urea, transaminases, bilirubin) were tested on days 0, 4 and 7.

**Results:** Out of 22 eligible women, 14 received MTX and received 8 letrozole. Mean age, lesion diameter, gestation age in the MTX vs letrozole arm were: 31 vs 32 years ( $p = 0.3$ ), 13.2 vs 16.3 mm ( $p = 0.1$ ), 7 + 1 vs 7 + 0 weeks ( $p = 0.6$ ), respectively. In case of 4 women treated with letrozole and in 2 treated with MTX (4/8, 50% vs 2/14, 14.3%,  $p = 0.07$ ) the treatment was unsuccessful. There were no significant differences in blood parameters on days 0, 4 and 7 between both arms, except for the increasing urea concentration in the letrozole arm ( $p = 0.01$ ).

**Conclusions:** Even though the results did not reach statistical significance, it is likely that a larger study sample would confirm the trend of letrozole being less effective. The results did not support the use of letrozole in the studied regimen as an alternative to MTX.

**Keywords:** tubal pregnancy; letrozole; methotrexate; pharmacological treatment

**Corresponding author:**

Iwona M. Gawron

Department of Gynecology and Obstetrics, Jagiellonian University Medical College, Cracow, Poland

e-mail: [iwonagawron@gmail.com](mailto:iwonagawron@gmail.com)

## INTRODUCTION

Advances in the diagnostics of tubal pregnancy (TP), made with the introduction of modern ultrasonography and serial measurements of serum B-human chorionic gonadotropin (B-hCG) concentration, have changed TP from a life-threatening disease requiring surgery to a benign oligosymptomatic condition that can be managed conservatively, with one of the goals of treatment being minimal impact on reproduction [1]. Pharmacological treatment of early unruptured TP with methotrexate (MTX) is an alternative to elective laparoscopy for women refusing surgery and is then considered the first-choice medical treatment [2]. MTX, acting as a folic acid (FA) antagonist, binds to dihydrofolate reductase and inhibits the conversion of FA to tetrahydrofolate, a cofactor needed for DNA and RNA synthesis, thereby interrupting trophoblast proliferation and leading to miscarriage [3].

MTX can be administered in single-dose (intramuscular) or multi-dose (intravenous) regimens, with up to about 93% efficacy [4]. In our center, MTX is administered in a single dose of 100 mg intravenously, with the possibility of a repeat dose after 7 days. MTX is avoided in women with intraperitoneal bleeding due to ruptured TP and in more advanced TP with high concentration of B-hCG or present fetal heartbeat. Other medical conditions where it is not used include immunodeficiency, anemia, thrombocytopenia, respiratory disease, peptic ulcer disease, hepatic and renal dysfunction, and breastfeeding [2]. As a chemotherapeutic agent, MTX may cause side effects, most commonly fatigue, nausea, diarrhea, vomiting, headache, alopecia, mucositis, but liver dysfunction and bone marrow suppression may also occur [5].

Research data has shown that MTX is as potent as laparoscopic salpingostomy in the treatment of TP and does not appear to affect future fertility [6]. Its impact on ovarian reserve has not been confirmed either [7]. More recent studies have also indicated that MTX was not inferior to salpingostomy or expectant management in terms of future obstetric outcomes [8]. However, due to its possible prolonged accumulation [9] and presumed teratogenic effect, it is recommended to refrain from conceiving for 3 or even up to 6 months [10, 11] after its

administration, which can be a significant inconvenience for couples desiring pregnancy. For these reasons, alternative methods of pharmacological treatment of TP have been sought. It was hypothesized that the role of estradiol in early pregnancy may be underestimated [12], and inhibition of its production by administration of letrozole, a non-steroidal reversible competitive aromatase inhibitor, could interfere with the physiological functions of progesterone required to maintain pregnancy.

Letrozole is used in the treatment of hormone-dependent breast cancer in postmenopausal women [13], as well as in the induction of monoovulation [14] in selected cases of anovulatory infertility [15], with good tolerability and no significant side effects [13, 16]. Preliminary results showed that letrozole was as effective as intramuscular MTX in the single-dose regimen (86% effectiveness) [12]. However, the comparability of the two treatment arms was limited since women with more advanced TP and higher B-hCG concentrations were more likely to choose the treatment with better documented effectiveness. This may have had a significant impact on the reported results, as early ectopic pregnancies with low B-hCG concentration in the letrozole group could resolve spontaneously without treatment. Furthermore, it is debatable whether intramuscular MTX is as effective as intravenous. While older studies suggested lower efficacy with intramuscular administration, more recent studies have indicated similar effectiveness between the two modalities [2, 17]. Since the possibility of treating TP with letrozole would be particularly attractive due to the disadvantages of MTX, a prospective study of the effectiveness of letrozole versus MTX was performed.

### **Objectives**

The study aimed to evaluate and compare the effectiveness of letrozole and methotrexate in managing tubal pregnancy. The specific objectives included: I) evaluating and comparing the rate of treatment failures in both study arms, II) assessing and comparing the dynamics of B-hCG concentrations throughout the treatment in both study arms, III) analyzing and comparing the alterations in selected liver and kidney function biomarkers in both study arms.

### **MATERIAL AND METHODS**

A prospective cohort open-label tertiary single-center study (Clinical Department of Gynecological Endocrinology and Gynecology, University Hospital in Krakow, Poland) was conducted among women aged 18–45 diagnosed with TP between December 2020 and

December 2022. A positive opinion of the Jagiellonian University Bioethics Committee was obtained before the study began (no. 1072.6120.321.2020). The study was registered in the Protocol Registration and Results System (ClinicalTrials.gov) under number NCT05839561.

The database developed during the study was made available in the Harvard Dataverse [18]. The inclusion criteria were: I) tubal pregnancy confirmed on pelvic ultrasound, II) increasing serum B-hCG concentrations in at least two subsequent measures 48 hours apart, III) serum B-hCG concentration  $\leq 3000$  mIU/ml, and the exclusion criteria were as follows: I) hemodynamic instability or free fluid in lesser pelvis on pelvic ultrasound or acute pelvic pain, II) positive fetal heartbeat on pelvic ultrasound, III) heterotopic pregnancy, IV) contraindications to MTX.

Women who opted for elective surgical treatment and those who did not meet the criteria for conservative treatment were excluded. Eligible women were assigned to one of the two comparative therapeutic arms of the study based on their preference: I) monotherapy with MTX in a single dose of 100 mg intravenously on day 0 (MTX arm), and II) monotherapy with letrozole at a daily dose of 5 mg orally for 10 days from day 0 (letrozole arm). Qualification for the treatment of tubal pregnancy was preceded by a thorough gynecological examination, two-dimensional pelvic ultrasound with a transvaginal and transabdominal transducer (Samsung WS80A, Samsung Medison, South Korea), blood laboratory tests, i.e. B-hCG, hemoglobin, creatinine, urea, alanine (ALT) and aspartate transaminase (AST), gamma-glutamyl transferase (GGTP) and total bilirubin and discussion of possible treatment options with a specialist obstetrician-gynecologist.

The diagnosis of tubal pregnancy was confirmed by the ultrasound visualization of gestational sac or trophoblastic mass outside the uterine cavity in the projection of the fallopian tube (interstitial, isthmic or ampullary segment) [19], separate from the corpus luteum and immobile in relation to the adjacent anatomical structures. Color Doppler was used to help distinguish tubal pregnancy from other structures and to confirm typical vascularity. All women included in the study gave informed written consent to the treatment applied and to participate in the research. Blood parameters were tested on days 0, 4 and 7. The primary outcome measures included an uncomplicated decrease in B-hCG concentration and the need of conversion to laparoscopy due to tubal rupture, acute pain or undesirable increase in B-hCG concentration. Secondary outcome measures were episodes of adverse drug reactions manifested either clinically or laboratory. In the case of an adequate decrease in B-hCG concentration, women were discharged home after 7 days of observation for further monitoring for uneventful decline in B-hCG concentration in the outpatient setting.

### Statistical analysis

Categorical variables were represented numerically as counts (n, N) and percentages (%). Continuous variables were reported as mean  $\pm$  standard deviation (SD). Normality was evaluated using the Shapiro-Wilk test. The Chi-square test was used to compare qualitative variables across the study arms, while the student's t-test was employed for quantitative variables. The equality of variances was assessed using Levene's test. Differences across the arms were analyzed using ANOVA with repeated measurements. The assumption of sphericity was validated using Mauchly's test. Treatment failure rates in the two study arms were compared using Pearson's chi-squared test. Statistical significance was defined as two-sided p-values  $< 0.05$ . Statistical analyses were conducted using Statistica, Version 13 (TIBCO Software Inc. Stat Soft Poland).

### RESULTS

Of the 90 women hospitalized for non-heterotopic tubal pregnancy, 68 were excluded for the reasons listed in Table 1, and 22 eligible women were included in the study. Of these women, 14 received MTX (MTX arm) and 8 were treated with letrozole (letrozole arm). Comparative characteristics of both study arms in terms of selected qualitative and quantitative variables are presented in Table 2. Women from both study arms did not differ in terms of age, tubal lesion diameter and its lateralization, gestational age, or the occurrence of vaginal bleeding. Out of the 8 women in the letrozole arm, treatment proved ineffective in 4 of them, accounting for a 50% failure rate (4/8, 50%). In the MTX arm, 2 out of 14 women experienced unsuccessful treatment (2/14, 14.3%). Thus, the treatment efficacy was 50% for letrozole and 85.7% for MTX ( $p = 0.07$ ). Women in whom pharmacological treatment was successful compared to women who failed treatment did not differ in terms of vaginal bleeding ( $p = 0.34$ ), age ( $p = 0.5$ ), or size of the lesion on ultrasound ( $p = 0.2$ ). In contrast, the mean gestational age in women who were successfully treated was more advanced than in women who failed treatment (7 + 5 weeks vs 6 + 0 weeks, respectively,  $p = 0.025$ ). The mean concentrations of laboratory parameters monitored throughout the hospital stay are presented in Table 3, and the statistical significance of their variations is presented in Table 4. There was a noticeable trend, yet not reaching statistical significance ( $p = 0.08$ ), of increasing B-hCG concentrations in serial measurements on day 0, 4 and 7 in the letrozole arm, compared to the MTX arm (Fig.1). However, there was no difference in the dynamics of the rise in B-hCG in the letrozole arm in women who were successfully treated compared to those who

failed treatment ( $p = 0.43$ ). Although the increasing urea values in the letrozole arm compared to MTX on consecutive days were statistically significant ( $p = 0.01$ ), none of the women exceeded the upper reference limit. In terms of laboratory abnormalities, there was also 1 case of slight transient increase above the upper limit of the reference range in ALAT concentration on day 4 in the letrozole arm, while in the MTX arm 1 case of temporary increase in GGTP concentration on day 4 and 1 case of temporary rise in total bilirubin concentration on day 7 were encountered. These mild disturbances did not require medical treatment. Of the other side effects, only mild nausea was reported. All women who failed pharmacological treatment underwent laparoscopy.

## DISCUSSION

Pharmacological treatment of tubal pregnancy is an important therapeutic option for women wishing to avoid surgery, especially if it does not require a waiting period to conceive again. While the effectiveness of MTX in the treatment of TP was consistent with findings from prior studies [12, 20], the efficacy of letrozole as a treatment option did not demonstrate the same level of promise as previously stated [12, 20]. In the studied female population, letrozole was less likely than MTX to suppress the increase in B-hCG concentration, which resulted in treatment failure. Even though the results were not statistically significant, a larger study sample would likely confirm the trend that letrozole was less effective. The difference in the success rate compared to the pioneering study [12] could be attributed to the small size of both study groups, but still the indices were not in favor of treatment effectiveness. Although the study did not manage to demonstrate letrozole's non-inferiority to MTX, this does not mean that it would not be effective at a higher dose, as dose-dependent efficacy has been reported. This premise has justified the expectation that letrozole could prove to be an alternative in the case of contraindications to MTX and lack of consent for surgery. However, in the study [20] from which dose-effectiveness data were derived, the mean baseline concentration of B-hCG was relatively low. Even though the authors assumed the baseline B-hCG concentration  $< 3000$  mIU/ml as the inclusion criterion, the actual mean concentration was just over 1000 mIU/ml, which usually corresponds to a very early TP or to an aborted TP. Unfortunately, the authors did not provide the gestation age of the treated women, nor the information about the dynamics of B-hCG concentrations (declining or increasing). As is known from the literature, pharmacological treatment has no significant advantage over expectant management in the event of a decrease or low concentration of B-hCG [21, 22]. Our study found that in the letrozole arm the dynamics of B-hCG concentrations were similar

between women who achieved successful outcomes and those who experienced treatment failure, indicating that factors other than B-hCG concentrations influenced the effectiveness of the treatment. It was impossible to ascertain whether the differences in the outcomes resulted from TP's biological potential or the medication employed. In the cited study [20], also other aspects drew attention, such as the very low mean concentration of B-hCG (considerably below 100 mIU/ml) after 10 days of treatment with letrozole in cured women. Although B-hCG concentrations were not routinely monitored on day 11 in our study, when tested at this time, values were not as low when baseline B-hCG concentrations exceeded 2000 mIU/ml. On the other hand, the available literature indicates that the clearance of B-hCG following MTX administration varies significantly between individuals [23], which may also apply to letrozole. Moreover, it was reported that women decided on the method of treatment themselves, but it was not stated how the initially assumed equality in terms of the number of participants in each arm was achieved. Further research is needed to address these concerns. The laboratory abnormalities identified in our study were clinically asymptomatic and resolved spontaneously. While these abnormalities are typically attributed to MTX, some studies have shown that transient abnormalities occurred with letrozole at higher doses of 10 mg/day [20]. In contrast, in other studies of short-term therapy with letrozole, even higher doses were used without serious side effects [24, 25]. Given the brief duration of the therapy, the advantage of letrozole over MTX in terms of disturbing laboratory parameters is not clear. The primary consideration that would justify the need for an alternative to MTX is the need to delay pregnancy following its use. However, due to the absence of conclusive scientific evidence, the optimal length of waiting period before attempting to conceive again remains a matter of contention [26, 27]. As a result, a wide range of possible durations for this period has been proposed, varying from its omission to as long as 6 months [6, 9, 10]. Therefore, it is controversial when choosing a drug to be guided by the period required to wait until pregnancy, as its necessity is yet to be proven. Since the tested dosage of letrozole demonstrated considerably lower efficacy compared to MTX, the decision was made not to extend the study beyond the period covered by the primary approval of the bioethics committee to increase the sample size. To conclude, before deciding on the off-label use of letrozole, a drug with yet to be documented efficacy in the treatment of TP, the risk of failure should be weighed against the potential benefit. Since the biological mechanism by which letrozole is supposed to suppress the vital potential of trophoblast is not conclusively understood, it should not be considered as a therapeutic alternative. The limitations of the study are the small sample size, resulting in the lack of statistical significance and the lack of

randomization, which was not feasible due to the medico-legal regulations pertaining to informed consent. The goals of further research remain to understand the mechanism by which letrozole affects the development of pregnancy, to identify the target population that would benefit from treatment with letrozole, and to determine the appropriate dosing regimen.

## **CONCLUSIONS**

In view of the evidence pointing to lower effectiveness of letrozole, and given that the biological mechanism by which it is supposed to inhibit the development of pregnancy is not fully understood, letrozole in the studied regimen should not be considered as an alternative in the treatment of TP. The goals of further research remain to understand the mechanism by which letrozole affects the development of pregnancy, to identify the target population that would benefit from treatment with letrozole, and to determine the appropriate dosing regimen.

## **Article information and declarations**

### ***Ethics statement***

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Bioethics Committee of the Jagiellonian University (no. 1072.6120.321.2020). Informed written consent was obtained from all individual participants included in the study.

### ***Author contributions***

IG — contribution 45%: study design, data acquisition, analysis & interpretation, article writing and editing, critical revision, corresponding author; DB — contribution 20%: statistical analysis & interpretation of data, article writing; RJ — contribution 35%: study concept and design, assumptions, data acquisition, article writing, critical revision.

### ***Acknowledgments***

The authors express deep gratitude toward the women who, despite facing challenging health circumstances, consented to undergo experimental therapy for ectopic pregnancy.

### ***Funding***

Supported by the Jagiellonian University Medical College as part of the Department of Gynecological Endocrinology's own research. The study was not supported by any grant or external funding.

### ***Conflict of interests***

The authors declare no conflict of interest.

### **REFERENCES**

1. Baggio S, Garzon S, Russo A, et al. Fertility and reproductive outcome after tubal ectopic pregnancy: comparison among methotrexate, surgery and expectant management. *Arch Gynecol Obstet*. 2021; 303(1): 259–268, doi: [10.1007/s00404-020-05749-2](https://doi.org/10.1007/s00404-020-05749-2), indexed in Pubmed: [32852572](https://pubmed.ncbi.nlm.nih.gov/32852572/).
2. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 193: Tubal Ectopic Pregnancy. *Obstet Gynecol*. 2018; 131(3): e91–e9e103, doi: [10.1097/AOG.0000000000002560](https://doi.org/10.1097/AOG.0000000000002560), indexed in Pubmed: [29470343](https://pubmed.ncbi.nlm.nih.gov/29470343/).
3. Stika CS. Methotrexate: the pharmacology behind medical treatment for ectopic pregnancy. *Clin Obstet Gynecol*. 2012; 55(2): 433–439, doi: [10.1097/GRF.0b013e3182510a35](https://doi.org/10.1097/GRF.0b013e3182510a35), indexed in Pubmed: [22510625](https://pubmed.ncbi.nlm.nih.gov/22510625/).
4. Barnhart KT, Gosman G, Ashby R, et al. The medical management of ectopic pregnancy: a meta-analysis comparing "single dose" and "multidose" regimens. *Obstet Gynecol*. 2003; 101(4): 778–784, doi: [10.1016/s0029-7844\(02\)03158-7](https://doi.org/10.1016/s0029-7844(02)03158-7), indexed in Pubmed: [12681886](https://pubmed.ncbi.nlm.nih.gov/12681886/).
5. Sherbini AA, Gwinnutt JM, Hyrich KL, et al. RAMS Co-Investigators. Rates and predictors of methotrexate-related adverse events in patients with early rheumatoid arthritis: results from a nationwide UK study. *Rheumatology (Oxford)*. 2022; 61(10): 3930–3938, doi: [10.1093/rheumatology/keab917](https://doi.org/10.1093/rheumatology/keab917), indexed in Pubmed: [35078225](https://pubmed.ncbi.nlm.nih.gov/35078225/).
6. Capmas P, Bouyer J, Fernandez H. Treatment of ectopic pregnancies in 2014: new answers to some old questions. *Fertil Steril*. 2014; 101(3): 615–620, doi: [10.1016/j.fertnstert.2014.01.029](https://doi.org/10.1016/j.fertnstert.2014.01.029), indexed in Pubmed: [24559615](https://pubmed.ncbi.nlm.nih.gov/24559615/).
7. Boots CE, Hill MJ, Feinberg EC, et al. Methotrexate does not affect ovarian reserve or subsequent assisted reproductive technology outcomes. *J Assist Reprod Genet*. 2016; 33(5): 647–656, doi: [10.1007/s10815-016-0683-7](https://doi.org/10.1007/s10815-016-0683-7), indexed in Pubmed: [26943917](https://pubmed.ncbi.nlm.nih.gov/26943917/).
8. Hao HJ, Feng Li, Dong LF, et al. Reproductive outcomes of ectopic pregnancy with conservative and surgical treatment: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2023; 102(17): e33621, doi: [10.1097/MD.00000000000033621](https://doi.org/10.1097/MD.00000000000033621), indexed in Pubmed: [37115078](https://pubmed.ncbi.nlm.nih.gov/37115078/).

9. Ezhilarasan D. Hepatotoxic potentials of methotrexate: Understanding the possible toxicological molecular mechanisms. *Toxicology*. 2021; 458: 152840, doi: [10.1016/j.tox.2021.152840](https://doi.org/10.1016/j.tox.2021.152840), indexed in Pubmed: [34175381](https://pubmed.ncbi.nlm.nih.gov/34175381/).
10. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. *Arthritis Rheumatol*. 2020; 72(4): 529–556, doi: [10.1002/art.41191](https://doi.org/10.1002/art.41191), indexed in Pubmed: [32090480](https://pubmed.ncbi.nlm.nih.gov/32090480/).
11. Resman-Targoff BH. Medical therapy: where are we now? *Am J Health Syst Pharm*. 2006; 63(18 Suppl 4): S11–S18, doi: [10.2146/ajhp060363](https://doi.org/10.2146/ajhp060363), indexed in Pubmed: [16960243](https://pubmed.ncbi.nlm.nih.gov/16960243/).
12. Mitwally MF, Hozayen WG, Hassanin KMA, et al. Aromatase inhibitor letrozole: a novel treatment for ectopic pregnancy. *Fertil Steril*. 2020; 114(2): 361–366, doi: [10.1016/j.fertnstert.2020.04.001](https://doi.org/10.1016/j.fertnstert.2020.04.001), indexed in Pubmed: [32622660](https://pubmed.ncbi.nlm.nih.gov/32622660/).
13. Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. *N Engl J Med*. 2003; 348(24): 2431–2442, doi: [10.1056/NEJMra023246](https://doi.org/10.1056/NEJMra023246), indexed in Pubmed: [12802030](https://pubmed.ncbi.nlm.nih.gov/12802030/).
14. Mitwally MFM, Casper RF, Mitwally MF, et al. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. *Fertil Steril*. 2001; 75(2): 305–309, doi: [10.1016/s0015-0282\(00\)01705-2](https://doi.org/10.1016/s0015-0282(00)01705-2), indexed in Pubmed: [11172831](https://pubmed.ncbi.nlm.nih.gov/11172831/).
15. Franik S, Kremer J, Nelen W, et al. Aromatase inhibitors for subfertile women with polycystic ovary syndrome. *Cochrane Database of Systematic Reviews*. 2012, doi: [10.1002/14651858.cd010287](https://doi.org/10.1002/14651858.cd010287).
16. Begum MR, Ferdous J, Begum A, et al. Comparison of efficacy of aromatase inhibitor and clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. *Fertil Steril*. 2009; 92(3): 853–857, doi: [10.1016/j.fertnstert.2007.08.044](https://doi.org/10.1016/j.fertnstert.2007.08.044), indexed in Pubmed: [18177867](https://pubmed.ncbi.nlm.nih.gov/18177867/).
17. Alur-Gupta S, Cooney LG, Senapati S, et al. Two-dose versus single-dose methotrexate for treatment of ectopic pregnancy: a meta-analysis. *Am J Obstet Gynecol*. 2019; 221(2): 95–108.e2, doi: [10.1016/j.ajog.2019.01.002](https://doi.org/10.1016/j.ajog.2019.01.002), indexed in Pubmed: [30629908](https://pubmed.ncbi.nlm.nih.gov/30629908/).
18. Gawron I. Management of Tubal Pregnancy With Off-label Use of Letrozole in Monotherapy. *Harvard Dataverse*, V1. , doi: [10.7910/DVN/Z1G2M0](https://doi.org/10.7910/DVN/Z1G2M0).
19. Kirk E, Ankum P, Jakab A, et al. ESHRE working group on Ectopic Pregnancy. Terminology for describing normally sited and ectopic pregnancies on ultrasound: ESHRE recommendations for good practice. *Hum Reprod Open*. 2020; 2020(4): hoaa055, doi: [10.1093/hropen/hoaa055](https://doi.org/10.1093/hropen/hoaa055), indexed in Pubmed: [33354626](https://pubmed.ncbi.nlm.nih.gov/33354626/).
20. Alabiad MA, Said WMM, Gad AH, et al. Evaluation of Different Doses of the Aromatase Inhibitor Letrozole for the Treatment of Ectopic Pregnancy and Its Effect on Villous Trophoblastic Tissue. *Reprod Sci*. 2022; 29(10): 2983–2994, doi: [10.1007/s43032-022-00993-0](https://doi.org/10.1007/s43032-022-00993-0), indexed in Pubmed: [35701686](https://pubmed.ncbi.nlm.nih.gov/35701686/).
21. Naveed AK, Anjum MU, Hassan A, et al. Methotrexate versus expectant management in ectopic pregnancy: a meta-analysis. *Arch Gynecol Obstet*. 2022; 305(3): 547–553, doi: [10.1007/s00404-021-06236-y](https://doi.org/10.1007/s00404-021-06236-y), indexed in Pubmed: [34524502](https://pubmed.ncbi.nlm.nih.gov/34524502/).

22. Colombo GE, Leonardi M, Armour M, et al. Efficacy and safety of expectant management in the treatment of tubal ectopic pregnancy: a systematic review and meta-analysis. *Hum Reprod Open*. 2020; 2020(4): hoaa044, doi: [10.1093/hropen/hoaa044](https://doi.org/10.1093/hropen/hoaa044), indexed in Pubmed: [33134560](https://pubmed.ncbi.nlm.nih.gov/33134560/).
23. Helmy S, Koch M, Kölbl H, et al. Correlation of the volume of ectopic pregnancy and MTX therapy outcome: a retrospective cohort study. *Eur J Obstet Gynecol Reprod Biol*. 2015; 184: 108–111, doi: [10.1016/j.ejogrb.2014.09.038](https://doi.org/10.1016/j.ejogrb.2014.09.038), indexed in Pubmed: [25490001](https://pubmed.ncbi.nlm.nih.gov/25490001/).
24. Pritts EA, Yuen AK, Sharma S, et al. The use of high dose letrozole in ovulation induction and controlled ovarian hyperstimulation. *ISRN Obstet Gynecol*. 2011; 2011: 242864, doi: [10.5402/2011/242864](https://doi.org/10.5402/2011/242864), indexed in Pubmed: [22191042](https://pubmed.ncbi.nlm.nih.gov/22191042/).
25. Khojah M, Khayat S, Dahan MH. Comparison of in vitro fertilization cycles stimulated with 20 mg letrozole daily versus high-dose gonadotropins in Rotterdam Consensus ultra-poor responders: A proof of concept. *Int J Gynaecol Obstet*. 2022; 156(1): 102–106, doi: [10.1002/ijgo.13626](https://doi.org/10.1002/ijgo.13626), indexed in Pubmed: [33507538](https://pubmed.ncbi.nlm.nih.gov/33507538/).
26. Svirsky R, Ben-Ami I, Berkovitch M, et al. Outcomes of conception subsequent to methotrexate treatment for an unruptured ectopic pregnancy. *Int J Gynaecol Obstet*. 2017; 139(2): 170–173, doi: [10.1002/ijgo.12264](https://doi.org/10.1002/ijgo.12264), indexed in Pubmed: [28710772](https://pubmed.ncbi.nlm.nih.gov/28710772/).
27. Svirsky R, Rozovski U, Vaknin Z, et al. The safety of conception occurring shortly after methotrexate treatment of an ectopic pregnancy. *Reprod Toxicol*. 2009; 27(1): 85–87, doi: [10.1016/j.reprotox.2008.11.055](https://doi.org/10.1016/j.reprotox.2008.11.055), indexed in Pubmed: [19103279](https://pubmed.ncbi.nlm.nih.gov/19103279/).

**Table 1.** Indications for laparoscopy due to tubal pregnancy in the studied cohort of women

Variable	n/N	[%]
NV	19/90	21.1
HCG	13/90	14.4
APP/FF	13/90	14.4
EL	8/90	8.9
NV + APP/FF	5/90	5.6
FH + HCG	4/90	4.4
HCG + APP/FF	3/90	3.3
FH + APP/FF	2/90	2.2
FH + HCG + APP/FF	1/90	1.1

APP/FF — acute pelvic pain/ free fluid on pelvic ultrasound, EL — elective laparoscopy based on woman's preference, FH — positive fetal heartbeat, NV — non-viable pregnancy based on declining concentrations of B-human chorionic gonadotropin (B-hCG), HCG — concentration of B-hCG > 3000 mIU/ml

**Table 2.** Characteristics of the study population in terms of selected quantitative and qualitative variables

<b>Variable</b>	<b>Total (n = 22)</b>	<b>Letrozole arm (n = 8)</b>	<b>MTX arm (n = 14)</b>	<b>p</b>
Age [years]: Mean, SD, Min.- Max.	31, 4.1, 23–40	32, 4.5, 23–38	31, 3.9, 25–40	0.3
Lesion diameter [mm]: Mean, SD, Min.-Max.	14.3, 4.4, 7–24	16.3, 5.3, 8–24	13.2, 3.5, 7–18	0.1
Gestational age [weeks + days]: Mean, SD, Min.- Max.	7+0, 1+3, 4+4 – 10+2	7+0, 1+2, 5+1 – 8+4	7+1, 1+4, 4+4 – 10+2	0.6
Tubal pregnancy localization:				0.38
right	11 (50%)	3 (37.5%)	8 (57.1%)	
left	11 (50%)	5 (62.5%)	6 (42.9%)	
Vaginal bleeding	11 (50%)	4 (50%)	7 (50%)	1.0

**Table 3.** Values of means and standard deviations of selected blood laboratory parameters in both study arms on days 0, 4 and 7

<b>Variable</b>	<b>Letrozole arm D-0</b>	<b>Letrozole arm D-4</b>	<b>Letrozole arm D-7</b>	<b>MTX arm D-0</b>	<b>MTX arm D-4</b>	<b>MTX arm D-7</b>
B-hCG [mIU/ml]: Mean, SD	1464, 1219	2085, 2099	2554, 3050	1189, 828	1335, 1365	1011, 1341
Hb [g/dl]: Mean, SD	13.1, 0.4	12.9, 0.9	12.7, 1.0	13.2, 0.9	13.0, 1.1	12.9, 0.9
Creatinine [mg/dl]: Mean, SD	61.0, 10.1	61.9, 10.8	62.2, 10.6	61.0, 7.3	63.3, 6	65.4, 10.4
Urea [mmol/l]: Mean, SD	3.3, 0.7	3.4, 0.7	3.9, 0.5	3.8, 0.6	3.72, 0.76	3.4, 0.5
ALT [IU/l]:	20.6, 10.5	20.5, 11.4	19.5, 8.8	18.6, 5.2	18.4, 7.3	16.7, 6.4

Mean, SD						
AST [IU/l]:	21.0, 7.9	20.9, 6.2	20.0, 4.1	22.0, 3.8	20.1, 3.6	19.1, 3.9
Mean, SD						
GGTP [IU/l]:	13.9, 5.0	13.1, 3.8	11.1, 3.4	15.6, 9.7	15.6, 11.2	17.9, 13.4
Mean, SD						
Total bilirubin [mg/dl]:	9.7, 4.0	8.7, 4.2	8.3, 4.0	11.0, 9.27	10.2, 5.65	11.6, 6.0
Mean, SD						

**Table 4.** Statistical significance values of comparisons of the mean concentration values of selected laboratory parameters on days 0, 4 and 7 using a repeated measures ANOVA in both study arms

Variable	Letrozole arm D: 0-7	Letrozole arm D: 4-7	Letrozole arm D: 0-4-7	MTX arm D: 0-7	MTX arm D: 4-7	MTX arm D: 0-4-7	Letrozole vs MTX arm D: 0-4-7
B-hCG	0.2	0.29	0.17	0.65	0.13	0.7	0.08
Hb	0.3	0.29	0.45	0.03	0.41	0.09	0.97
Creatinine	0.09	0.6	0.21	0.29	0.93	0.37	0.7
Urea	0.06	0.04	0.07	0.05	0.17	0.15	0.01
ALT	0.423	0.52	0.64	0.76	1.0	0.96	0.82
AST	0.63	0.39	0.8	0.55	0.7	0.6	0.79
GGTP	0.24	0.37	0.3	0.84	0.36	0.45	0.36
Total bilirubin	0.28	0.6	0.41	0.23	0.37	0.34	0.74

**Figure 1.** Dynamics of serum B-hCG concentrations in both arms of the study on treatment days 0, 4 and 7

Dynamics of B-hCG concentration in both study arms during treatment (day 0, 4, 7).

Current effect (2, 38) = 2.6715,  $p = 0.082$ .

Vertical bars represent 95% confidence intervals.

