The Egyptian Journal of Hospital Medicine (January 2023) Vol. 90 (2), Page 2391-2397

Methotrexate versus Methotrexate Combined with Letrazole for Management of Undisturbed Ectopic Pregnancy

Gamal Abbas El Sayed, Ahmed ELSayed Mansor, Heba Ahmed ELhouseny*, Safaa Abd El Salam Ibrahim
Department of Obstetrics and Gynecology, Faculty of Medicine, Zagazig University, Egypt
***Corresponding author:** Heba Ahmed ELhouseny, **Mobile:** (+20) 01093544525, **E-mail:** helhouseny7@gmail.com

ABSTRACT

Background: Extra uterine pregnancy is frequently detected early on, changing into a more benign disease before the patient's condition worsens. Objective: The current study aimed to evaluate the effectiveness of methotrexate (MTX) with letrozole in treating women who had tubal ectopic pregnancies.

Patients and methods: A controlled clinical trial was carried out at the Zagazig University Hospitals' Obstetric and Gynecological Department and Maternity Hospitals, and Menia ElQamh Central Hospital in the period from February 2022 to September 2022. A total of 30 women were equally divided into two groups; First group (control group) received MTX to treat medically assisted tubal ectopic pregnancy, while the second group (study group) received both Letrozole and MTX to treat medically necessary tubal ectopic pregnancy.

Result: In control group, median hCG at Day 0 was 1331, at Day 4 had a value of 645, at Day 7 had a value of 315.5, and at Day 14 had a value of 39. In study group median hCG at Day 0 was 856, at Day 4 recorded 412, at Day 7 recorded 114, and at Day 14 recorded 29. Success in control group reached 75%, while in study group it reached 86.7%. B-ideal hCG's cutoff value at day 4 was >1188 and on day 7 was >605. The tests' sensitivity, specificity, PPV, NPV, and accuracy were all successful (100%).

Conclusion: Letrozole has a higher resolution rate and a better safety profile when compared to chemotherapy in treating women who had tubal ectopic pregnancies. More study should be conducted on drugs such as MTX.

Keywords: Ectopic pregnancy, letrozole, β-hCG, Methotrexate, Clinical trial, Zagazig University.

INTRODUCTION

Over the past 30 years, the frequency of ectopic pregnancies has grown annually [(1)]. Although earlier diagnosis has been made possible by advancements in diagnostic techniques, the illness is still life threatening. EP is thought to be responsible for over 75% of Mortality in the first trimester and 9% of all fatalities due to pregnancy [(2)].

In comparison to surgical surgery, methotrexate therapy has proven to be more cost-effective, yet preserving comparable treatment efficacy and long-term fertility. However, it is known that the chemotherapy drug methotrexate is linked to major side effects, contraindications, and higher failure rates with high concentrations of progesterone and beta-hCG (human chorionic gonadotropin) [(3)]. Additionally, the ectopic pregnancy takes a long time to resolve after starting methotrexate treatment, and it is necessary to wait many weeks before trying to get pregnant again. Additionally, it is not unexpected for there to be adverse effects on ovarian reserve and prospective future fertility [(4)].

A third-generation non-steroidal reversible aromatase inhibitor is letrozole. Pharmacodynamic and pharmacokinetic studies show that following ingestion, it can reduce estradiol levels by up to 95% to 99%. In addition to progesterone, which is recognized to have a crucial role in maintaining early pregnancy, estrogen also plays a significant role in the support of early pregnancy [(5)].

Letrozole's potential role in ectopic pregnancies has never been studied. It is thought that Letrozole can lower serum estradiol levels, which could lead to ectopic pregnancy failure. Over several decades of clinical usage, they have proven to be safe, well-tolerated, affordable, and have little adverse effects [(6)].

The current study aimed to evaluate the effectiveness of methotrexate (MTX) with letrozole in treating women who had tubal ectopic pregnancies.

PATIENT AND METHODS

A controlled clinical trial was carried out at the Zagazig University Hospitals' Obstetric and Gynecological Department and Maternity Hospitals, and Menia ElQamh Central Hospital in the period from February 2022 to September 2022.

Inclusion criteria: Hemodynamic stability. Presence of a heterogenous adnexal mass with a poor increase may indicate tubal ectopic pregnancy of hCG i.e. <= 63% rise over 48 hours. Ages eligible for the study 18 to 40 (Adult). Quantitative serum β-HCG < 5000 IU/L. Size of ectopic mass <3.5cm and no cardiac action of embryos. Patient cooperation for routine follow-up. Normal kidney function test, liver function test, complete blood count (CBC), and electrolyte levels. Absence of substantial stomach ache.

Exclusion criteria:

Stomach pain that is clinically unpredictable, severe, or persistent, or significant hemoperitoneum as detected by an ultrasound (>300mL). Presence of free fluid in the pelvis or in the abdomen and pelvis. HCG quantitative 5000 IU/L in serum. More than 3.5 cm of ectopic bulk heart activity is present in a pregnancy that is ectopic.

Received: 03/09/2022
Accepted: 06/11/2022

Coexisting, viable intrauterine pregnancy (heterotopic pregnancy). Patient who is disobedient or lives distant from the hospital. Not normal kidney function test, liver function tests or CBC. Known hypersensitivity to letrozole or methotrexate. Expressing milk. Immunosuppression and concomitant corticosteroid usage.

Each participant in this study underwent thorough, in-depth medical and clinical assessments, and experiments in the lab (B-hCG- liver function test, tests for the kidneys, liver, and coagulation profile as well as the complete blood count). HCG increased gradually only in women who were identified as having an ectopic pregnancy, with a doubling time that exceeded 2.2 days. In situations where transvaginal ultrasound hasn't (yet) given a definitive answer about whether an intrauterine pregnancy is present, the doubling period of HCG is a helpful diagnostic tool.

Ultrasonography the purpose of pelvic ultrasonography is to determine whether and where a pregnancy is viable. If an ultrasound shows without any signs of an intrauterine pregnancy, there is gestational tissue in the adnexal area, a tubal pregnancy is suspected. The presence of the ectopic gestational tissue's yolk sac or embryo provides conclusive proof that the pregnancy is ectopic [(7)].

A total of 30 women were equally divided into two groups; First group (control group) received MTX to treat medically assisted tubal ectopic pregnancy, while the second group (study group) received both Letrozole and MTX to treat medically necessary tubal ectopic pregnancy.

A total of 30 women were equally divided into two groups; First group (control group) received MTX to treat medically assisted tubal ectopic pregnancy. A single 50 mg/m2 of MTX is administered intramuscularly for each square metre of body surface area., and patients received a placebo for 1 week that looked exactly like the real thing.

The second group (study group) received both Letrozole and MTX to treat medically necessary tubal ectopic pregnancy. Women received one intramuscular injection of 50 mg per square metre of body surface area and four 10mg tablets of letrozole per day for 7 days [(5)].

On the day of therapy, and then 4, 7, and 14 days later, B-hCG levels were assessed. Blood samples were collected to check the levels of on the day of treatment and seven days later, CBC, liver enzymes, blood urea, and serum creatinine.

Initial tests were performed, including a CBC, B-hCG, renal and liver function assessments, and a single dosage of 50 mg/m2 MTX. On days 4 and 7, serial B-hCG was again administered. If the B-HCG on day 7 was at least 15% lower than on day 4, the patient was released and continued as an outpatient. If the B-HCG on day 7 was not more than 15% lower than that on day 4, the patient received a second dose of 50 mg/m2 MTX. Weekly follow-up serum B-hCG tests were done until they were having a value of 5 mIU/ml, it is negative. Changes in liver enzymes like alanine aminotransferase (ALT) and aspartate aminotransferase (AST), as well as hemoglobin levels, platelet counts, and other CBC parameters were assessed.

Ethical Consideration:

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University (IRB #ZUIRB9367). Written informed consent was obtained from all participants. They were told about the nature of the study and the potential dangers of the operation. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical Analysis

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 23 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test and Fisher's exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD), and independent sample t-test/ Mann Whitney test was used for comparison between groups. P value ≤ 0.05 was considered to be statistically significant.

RESULT

Table 1 summarizes the demographic data of the two studied groups. There were no statistically significant differences between the two studied groups in age, parity or BMI. There was no statistically significant difference between the two studied groups in mode of previous delivery.

Table (1): Demographic data of the two studied groups.

Variable	Control group (n=15)		Study group (n=15)		T	P-value
Age: (year) Mean ± SD Range	25.72 ± 4.66 18 – 37		25.39 ± 4.46 19 - 36		0.31	0.76 NS
BMI: (Kg/m^2) Mean ± SD Range	30.47 ± 4.34 22.59 – 39.16		29.13 ± 3.43 22.6 – 38.28		1.46	0.15 NS
Variable	**No**	**%**	**No**	**%**	**χ^2**	**P**
Parity: **PG** 1 – 3 4 – 6	 7 6 2	 46.7 40 13.3	 10 3 2	 66.7 20 13.3	0.71	0.70 NS
Variable	**No**	**%**	**No**	**%**	**χ^2**	**P**
Mode of previous delivery **Nulli para** NVD CS	 7 6 2	 46.7 40 13.3	 10 3 2	 66.7 20 13.3	0.71	0.70 NS
Mode of previous delivery						
Nulli para NVD CS	7 6 2	46.7 40 13.3	10 3 2	66.7 20 13.3	0.71	0.70 NS

SD: Standard deviation, t: Independent t test, χ2: Chi square test, NS: Non significant (P>0.05).

There was no statistically significant difference in the size or location of the ectopic pregnancy between the two groups (**Table 2**).

Table (2): Size and site of ectopic pregnancy of the two studied groups.

Variable	Control group (n=15)		Study group (n=15)		MW	P-value
Size: (mm^2) Mean ± SD Median Range	600.61 ± 216.32 574 345 – 1122		553.19 ± 174.63 525 320 – 1088		0.98	0.33 NS
Variable	**No**	**%**	**No**	**%**	**χ^2**	**P**
Site: Rt Lt	 5 10	 33.3 66.7	 6 9	 40 60	0.08	0.79 NS

SD: Standard deviation, MW: Mann Whitney test, χ2: Chi square test. NS: Non significant (P>0.05).

There was no statistically significant difference in pretreatment HCG levels between the two groups studied (**Table 3**).

Table (3): Pretreatment HCG level between the two studied groups.

Variable	Control group (n=15)	Study group (n=15)	MW	P-value
HCG: (mIU/ML) Mean ± SD	1331 ± 35	856 ± 23	0.320	0.76 NS

SD: Standard deviation, MW: Mann Whitney test, NS: Non significant (P>0.05).

On treatment day, the mean platelet count in the study group was 230.5, and on Day 7, it reached 152 x10^3, in study group was 220.9 on treatment day and 219.9 x 103 on day seven. The mean AST level in the study group was 18.8 on treatment day and 40.1 on Day 7, while the control group was 19.6 on treatment day and 18.9 on Day 7. The mean ALT level in the study group was 28.5 on treatment day and 53 (U/L) on Day 7; in the control group, it was 20.9 on treatment day and 23.7 (U/L) on Day 7 **(Table 4).**

Table (4): Platelets and liver enzymes were measured at different periods in the two groups with ectopic pregnancies.

Variable	Control group (n=15)	Study group (n=15)	P-value
Platelets count ($x10^3$) **Treatment day Day 0 Mean ± SD**	230.5 ± 7.7	220.9 ± 7.4	0.352 (NS)
Platelets count ($x10^3$) **Treatment day Day 4** Mean ± SD	222.5 ± 7.7	215.9 ± 7.4	0.152 (NS)
Platelets count ($x10^3$) **Treatment day Day 7** Mean ± SD	152 ± 8.4	219.9 ± 6.2	0.058 (NS)
AST level (U/L) Treatment day Day0 Mean ± SD	18.8 ± 2.3	18.6 ± 2.2	0.223 (NS)
AST level (U/L) Treatment day Day 4 Mean ± SD	32.1 ± 5.6	19.0 ± 3.1	<0.001 (HS)*
AST level (U/L) Treatment day Day 7 Mean ± SD	40.1 ± 5.6	19.9±3.1	<0.001 (HS)*
ALT level (U/L) Treatment day Day 0 Mean ± SD	28.5 ± 4.9	20.9 ± 4.7	<0.001 (HS)*
ALT level (U/L) Treatment day Day 4 Mean ± SD	38.5 ± 4.9	30.9 ± 4.7	<0.001 (HS)*
ALT level (U/L) Treatment day Day 7 Mean ± SD	53 ± 6.1	23.7 ± 3.7	<0.001 (HS)*

NS: Non Significant, HS*: High Significant, SD: Standard deviation, MW: Mann Whitney test, NS: Non significant (P>0.05), ALT (alanine aminotransferase), AST (aspartate aminotransferase), Statistically significant (P<0.05).

Table 5 compares hCG levels in the 2 studied groups.

Table (5): Comparison of the serum B-hCG titre in studied groups at different times.

Variable	Control group (n=15)	Study group (n=15)	P-value
B-hCG level (U/L) Treatment day Day 0 Median IQR*	1331 (744.5 - 1632.3)	856 (475.5 - 1406.3)	0.223 (NS)
B-hCG level (U/L) Treatment day Day 4 Median IQR*	645 (329 - 871.5)	412 (262.5 - 1018)	<0.001 (HS)*
B-hCG level (U/L) Treatment day Day 7 Median IQR*	315.5 (179.3 - 395.5)	114 (97.5 - 435)	<0.001 (HS)*
B-hCG level (U/L) Treatment day Day 14 Median IQR*	39 (30.8-53)	29 (18.6-50.9)	<0.001 (HS)*

*IQR: Interquartile Range.

Success in control group reached 75%, while in study group it reached 86.7%. Outcomes were liver functions, and platelets **(Table 6).**

Table (6): Distribution of the studied patients regarding the results after treatment.

Outcome	Control group (n=15)	Study group (n=15)
Success	10 (75%)	13 (86.7%)
Failed	5 (25%)	4 (13.3%)
Group	**Control group**	
Success/Fail	Success (10)	Fail (5)
Platelets count (x10^3)	152 ± 48.4	230.5 ± 75.7
AST level (U/L)	40.1 ± 5.6	18.8 ± 2.3
ALT level (U/L)	53 ± 6.1	28.5 ± 4.9
Group	**Study group**	
Success/Fail	Success (13)	Fail (2)
Platelets count (x10^3)	132 ± 49.4	260.5 ± 80.7
AST level (U/L)	45.1 ± 5.8	17.8 ± 3.3
ALT level (U/L)	49 ± 6.5	29.5 ± 3.1

DISCUSSION

Age, parity, and BMI did not statistically differ between the two study groups in terms of demographic information about the sample.

According to delivery, MTX Group had 7 (46.7%) subjects with no previous deliveries, 6 (40%) subjects with vaginal delivery and 2 (13.3%) subjects had caesarean section. Letrozole and MTX Group has 10 (66.7%) subjects with no prior pregnancies, 3 (20%) delivered naturally vaginally, and 2 (13.3%) delivered via caesarean delivery.

In **Abd El-Hameed *et al.*** [8] 40% had no previous deliveries, 30% of deliveries occur naturally vaginally and the other 30% through caesarean section. About 28.6% of Letrozole Group's pregnant women had their first child spontaneously, 14.3% had a vaginal delivery, and 57.1 had a Caesarean section.

According to both populations' abortion rates, 13 patients in MTX group had never had an abortion, compared to 1 (6.7%) who had had 2 prior abortions. A total 12 patients in the letrozole and MTX group had never had an abortion, 2 (13.3%) had had one, and 1 (6.7%) had had two.

In an old study **Michalas *et al.*** [9] there were no spontaneous abortions in 74.5% of cases, 1 in 15.8%, and 2 or more in 9.7%.

In **Abd El-Hameed *et al.*** [8] 60% of women in MTX group had never had an abortion before, 20% had, 10% had 2 abortions prior, and 10% had three. In the letrozole group, 50% had never had an abortion before, 21.4% had had just one, 21.4% had had 2, and 7.2% had three.

The distribution of the examined patients according to the results of the ultrasound: Adnexal mass size (cm) ranged from 1.9 to 4.2 cm, with a mean of 3 and SD of 0.76 in MTX group. Letrozole Group: There was no pelvic collection and the adnexal mass size (cm) ranged from 2.5 to 4.5 cm, mean 3.2 (SD 0.62) with P-value of 0.762.

Only **Abd El-Hameed *et al.*** [8] conducted a similar experiment and produced comparable outcomes: The adnexal mass size (cm) in MTX group ranged from 2-4 cm, with a mean of 3.1 (SD 0.8). Species Letrozole: There was no pelvic collection and the adnexal mass size (cm) ranged from 2.5 to 4.5 cm, mean 3.3 (SD 0.6).

In **Kirk *et al.*** [10] study a bulk had a 10.1 mm thickness and an accumulation of free fluids in the pelvis in 57.8%.

In **Frates *et al.*** [11] according to fluid findings, the range of 2.46 cm was the mean adnexal bulk size from 0.7 to 8.8; 0.4% had 5.2% had very little to no free fluid and moderate to substantial free fluid.

The ectopic pregnancy in this study groups were divided based on platelets and liver enzymes at various stages. The average platelet count in the study group was 220.9 on the achieved on the treatment day 219.9 x 103 on Day 7, while it was 230.5 in the treatment day in the control group. On the day of treatment, the study group's mean AST level was 18.8, and it rose to 40.1 (U/L) that day. on day seven, while it was 19.6 on the treatment day and 18.9 (U/L) on day seven in the control group. Mean ALT levels in the study group were 28.5 on the day of therapy and arrived 53 (U/L) on Day 7, while in the control group, they were 20.9 in the treatment day, while on Day 7 it was 23.7 (U/L).

In **Mitwally *et al.*** [12], **Frates *et al.*** [13], **and Gay *et al.*** [14] the average platelet count for MTX was 251.5 on the first day of treatment and reached 162 × 103 on day seven; for letrozole, it was 214.9 on the first day of treatment and reached 213.9 × 103 on day seven. On the day of therapy, for MTX, the average AST level was 19.8 and it rose to 44.1 (U/L). On day seven, while the mean AST level for Letrozole reached 19.9 (U/L) from 18.1 on the treatment day. on day seven. The on the day of therapy, the average ALT level for MTX was 29.5. increased to 52 (U/L) on day seven, while the mean ALT level for letrozole was 20.7 on treatment day and increased to 22.7 on day seven (U/L).

CONCLUSION

Letrozole has a higher resolution rate and a better safety profile when compared to chemotherapy in treating women who had tubal ectopic pregnancies. More study should be conducted on drugs such as MTX.

Financial support and sponsorship: None
Conflict of interest: None

REFERENCES

1. **Gamzu R, Almog B, Levin Y *et al.* (2019):** Efficacy of methotrexate treatment in extra uterine pregnancies defined by stable or increasing human chorionic gonadotropin concentrations. Fertil Steril., 77:761-5.
2. **Farquhar M (2015):** Ectopic pregnancy. Lancet., 366:583-91.
3. **Hajenius J, Mol W, Bossuyt M *et al.* (2017):** Interventions for tubal ectopic pregnancy. Cochrane Database Syst Rev., 5(2):CD000324.
4. **Elito Junior J, Han K, Camano L (2016):** Tubal patency following surgical and clinical treatment of ectopic pregnancy. Sao Paulo Med J., 124:264-6.
5. **Mitwally F, Casper F (2019):** Reprint of: Use of an aromatase inhibitor for induction of ovulation in patients with aninadequate response to clomiphene citrate. Fertil Steril., 112:178-82.
6. **Qian X, Li Z, Ruan G *et al.* (2020):** Efficacy and toxicity of extended aromatase after adjuvant aromatase inhibitors-containing therapy for hormone-receptor-positive breast cancer: a literature-based

meta-analysis of randomized trials. Breast Cancer Res Treat., 179:275-85.

7. **Kirk E, Condous G, Van Calster B *et al.* (2014):** A validation of the most commonly used protocol to predict the success of single-dose methotrexate in the treatment of ectopic pregnancy. Human Reproduction, 22(3):858-63.
8. **Abd El-Hameed E, Abd El-Reheim R, Ahmed H (2020):** Medical Treatment of Undisturbed Ectopic Pregnancy in Minia Maternity University Hospital a Randomized Controlled Study. Minia Journal of Medical Research, 31(1):140-9.
9. **Michalas S, Minaretzis D, Tsionou C *et al.* (2012):** Pelvic surgery, reproductive factors and risk of ectopic pregnancy: a case controlled study. International Journal of Gynecology & Obstetrics, 38(2):101-5.
10. **Kirk E, Daemen A, Papageorghiou AT *et al.* (2018):** Why are some ectopic pregnancies characterized as pregnancies of unknown location at the initial transvaginal ultrasound examination? Acta obstetricia et gynecologica Scandinavica, 87(11):1150-4.
11. **Frates C, Doubilet M, Peters E *et al.* (2014):** Adnexal sonographic findings in ectopic pregnancy and their correlation with tubal rupture and human chorionic gonadotropin levels. Journal of Ultrasound in Medicine, 33(4): 697-703.
12. **Mitwally F, Hozayen G, Hassanin M *et al.* (2020):** The aromatase inhibitor, letrozole: a novel treatment for ectopic pregnancy. Fertil Steril., 114:361-6.
13. **Frates C, Doubilet M, Peters E *et al.* (2014):** Adnexal sonographic findings in ectopic pregnancy and their correlation with tubal rupture and human chorionic gonadotropin levels. Journal of Ultrasound in Medicine, 33(4):697-703.
14. **Gay C, Perrin J, Courbiere B *et al.* (2019):** Impact of salpingectomy for ectopic pregnancy on the ovarian response during IVF stimulation. Journal of Gynecology Obstetrics and Human Reproduction, 48(9):727-30.