Letrozole a Novel Treatment for Undisturbed Ectopic Pregnancy

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Abstract

Background: The fallopian tube is where ectopic pregnancies most frequently occur. Methotrexate or minimally invasive surgery can successfully treat the majority of early-detected tubal ectopic pregnancy cases.

Objectives: This study's objective is to evaluate letrozole as a potential new treatment for ectopic pregnancy.

Patients and methods: The Obstetrics and Gynecology Department of Qena University Hospital carried out this cohort study. The study included 40 cases with non-disturbed ectopic tubal pregnancy. They were divided into two groups; group took Letrozole (20 cases), and group took methotrexate (20 cases). The duration of the study ranged from 6- 12months.

Results: as regard success of treatment was achieved in 85% of letrozole cases versus 80% in methotrexate cases with insignificant differences. Maternal morbidity was insignificant between two groups as in letrozole group 2 cases transferred to surgery and 1 case shifted to methotrexate, in methotrexate 4 cases transferred to surgery.

Conclusion: Success rates for both treatment arms of letrozole and methotrexate were 86%. Even though the difference was statistically significant, women treated with letrozole rather than methotrexate tended to experience a faster decline in B-Human Chorionic Gonadotropin levels.

Keywords: Letrozole; Undisturbed ectopic pregnancy; beta HCG; Medical treatment; Methotrexate.

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Introduction

A key factor in maternal morbidity and occasionally fatality is ectopic pregnancy. Extra-uterine pregnancies make for 1.3–2% of all reported pregnancies **(Farquhar 2005).** Ectopic pregnancy must be treated quickly and successfully. Ectopic pregnancy may be treated with surgery, medication, or pregnancy. For early, unruptured ectopic pregnancy, methotrexate is the preferred medication; however, for advanced or ruptured ectopic pregnancy, salpingectomy or other surgical treatments are frequently needed. Methotrexate has an effectiveness rate of up to 93% and can be given in a single dose or multiple doses **(Auger et al., 2020).** Third-generation aromatase inhibitor letrozole reduces the production of oestrogen. Androstenedione is changed into estrone by the enzyme aromatase, which also changes testosterone into estradiol **(Auger et al., 2020).**

According to a recent study assessing the drug's effects on a group of 42 women who had unbroken ectopic pregnancies in a nonrandomized prospective cohort study, letrozole has been shown to be beneficial in treating ectopic pregnancy medically. Letrozole's superior safety profile compared to a chemotherapeutic medication like methotrexate and its encouragingly high resolution rate should motivate further study **(Mitwally et al., 2020).** In our nation, letrozole is marketed as femara and is made by the NOVARTIS Company. This study's objective was to evaluate letrozole as a potential new treatment for ectopic pregnancy.

Patients and methods

This was a cohort study curried out Qena University Hospital, department of Obstetrics and Gynaecology.

Ethical consideration: the ethics committee of south valley university, Qena, Egypt, has given its approval to this research.

Ethical code number: SVU-MED-OBGO24-1-21-3-168.

Inclusion criteria: All patients with early pregnancy who attend to outpatient clinic and emergency section of obstetrics and gynecology department whom full fill the following

Inclusion criteria: Adult female > 18 yrs (age of legal consent), non-disturbed ectopic tubal pregnancy, β- hcg level < 5000 IU/ L, adenexal mass < 35 mm , absent heart beat in gestational sac, hemodynamically stable patients, confirmed diagnosis with ultrasonography and consent the patient to practise in the study and post treatment monitoring

Exclusion criteria: Other ectopic pregnancies, disturbed ectopic pregnancy (of any degree), any abnormality in blood tests (CBC, PT, PC, and INR), Heterotopic pregnancy**,** previous ectopic pregnancy and single fallopian tube

Samples: This work conducted on group of women with early pregnancy full fill the inclusion criteria from mars 2021 to mars 2022

Study tools: Detailed history and clinical examination, investigations (CBC, PT, PC, β-HCG), pelvi- abdominal Ultrasonography and sample group would receive 5 mg of letrozole (2.5 mg twice daily) for 5 days

Research outcome measures: Primary (main): success of treatment, normalization the level of β-HCG <10 IU/L without any additional medical treatment or surgical intervention. **Secondary:** Evaluate maternal morbidity, evaluation of the decrease in β-HCG level (Beta human chorionic gonadotropin level would be measured at the day of treatment , day 4, day 7) the decrease of the level of β- HCG should be > 15% at the day 7 if the decrease in β-HCG level < 15 % at the day 7 the treatment is failed and we go for treatment with methotrexate or surgical treatment, resolution of adnexal mass by ultrasonography, side effects such as nausea, vomiting, headache , dizziness, lower abdominal pain and admission, hospitalization and follow up.

Statistical analysis

IBM SPSS software, version 20.0, was used to enter and analyse data. IBM Corporation and Armonk, New York. The qualitative data were described using numbers and percentages. The distribution's normality was assessed using the Kolmogorov-Smirnov test. The range (minimum and maximum), mean, standard deviation, median, and interquartile range were used to characterise quantitative data (IQR). At the 5% level of significance, the results' significance was evaluated.

The used tests were: Chi-square test: comparing several categories using categorical variables. When more than 20% of the cells have an anticipated count lower than five, Fisher's Exact or Monte Carlo techniques are employed to compensate for chi-square. t-test for students: For quantitative variables with normally distributed distributions, to compare two study groups. Mann Whitney test: To assess whether any quantitative

variables have abnormal distributions between the two research groups. Use the Friedman test to compare between more than two periods or stages and quantitative data with an irregular distribution. Pairwise comparisons are subject to Dunn's Post-hoc Test.

Results:

Table 1. Comparison between the two studied groups according to age and BMI

Variables	Letrozole (n = 20)	Methotrexate (n = 20)	t	p
Age (years)				
Min. – Max.	18.0 – 37.0	18.0 – 35.0		
Mean ± SD.	27.45 ± 5.63	27.05 ± 5.08	0.236	0.815
Median (IQR)	27.50(24.0 – 32.0)	27.50(24.0 – 32.0)		
BMI (Kg/m^2)				
Min. – Max.	25.0 – 29.0	25.0 – 29.0		
Mean ± SD.	26.25 ± 1.07	26.25 ± 1.07	0.0	1.000
Median (IQR)	26.0(25.5 – 27.0)	26.0(25.5 – 27.0)		

IQR: Inter quartile range SD: Standard deviation t: Student t-testp: p value for comparing between the studied groups

(Table .1) shows that there were insignificant differences between two groups as regard demographic data. There was significant decrease in level of BHCG in letrezole and methotrexate group in 1st , 4th and 7th day, (**Table .2)**

Table 2. Comparison between the three studied periods according to β-HCG level in each group

β-HCG level	1stday	4thday	7thday	Fr	p
Letrozole					
Min. – Max.	1340.0 – 4830.0	320.0 – 4680.0	210.0 – 4880.0		
Mean ± SD.	2743.0 ± 1227.4	1414.7 ± 1005.5	880.4 ± 1098.6	25.900	<0.001*
Median (IQR)	2405.0 (1687.5 – 3766.5)	1069.0 (927.5 – 1850.0)	435.0 (320.0 – 885.0)		
Sig. bet. periods.	p_1=0.003*,p_2<0.001*,p_3=0.040*				
Methotrexate					
Min. – Max.	1320.0 – 4830.0	320.0 – 4880.0	237.0 – 4885.0		
Mean ± SD.	2831.9 ± 1291.0	1652.7 ± 1274.4	1189.6 ± 1413.1	15.700*	<0.001*
Median (IQR)	2400.0 (1719.0 – 4159.5)	1160.0 (937.5 – 1940.0)	640.0 (450.0 – 920.0)		
Sig. bet. periods.	p_1=0.027*,p_2<0.001*,p_3=0.082				

IQR: **Inter quartile range** SD: **Standard deviation; Fr**: **Friedman test**, Sig. bet. periods was done using **Post Hoc Test** (**Dunn's);** p: p value for comparing between the studied periods**;** p_1: p value for comparing between **1st day** and**4th day;** p_2: p value for comparing between **1st day** and**7th day;** p_3: p value for comparing between **4th day** and**7th day;** *: Statistically significant at $p \leq 0.05$

As regard adnexal mass mean level was 3.38 in letrozole group and 3.5 in methotrexate group with insignificant differences (**Table .3).**

Table 3. Comparison between the two studied groups according to adnexal mass size

Adnexal mass size (cm)	Letrozole (n = 20)	Methotrexate (n = 20)	t	p
Min. – Max.	2.50 – 4.40	2.80 – 4.40		
Mean ± SD.	3.38 ± 0.56	3.50 ± 0.51	0.706	0.848
Median (IQR)	3.50(2.9 – 3.9)	3.50(3.0 – 3.9)		

IQR: **Inter quartile range** SD: **Standard deviation t: Student t-test**; p: p value for comparing between the studied groups

Table 4. Comparison between the two studied groups according to platelets count

Platelets count ($\times 10^3/\mu l$)	Letrozole (n = 20)	Methotrexate (n = 20)	U	p
Treatment day				
Min. – Max.	123.0 – 235.0	12.0 – 235.0		
Mean ± SD.	214.7 ± 23.22	212.1 ± 24.51	184.50	0.678
Median (IQR)	217.0(212.0 – 225.0)	217.0(210.0 – 222.5)		
Day 7				
Min. – Max.	123.0 – 232.0	123.0 – 232.0		
Mean ± SD.	212.1 ± 22.42	201.3 ± 23.48	103.00*	0.008*
Median (IQR)	215.0(211.0 – 220.0)	210.0(193.0 – 211.5)		
p_1	**0.002***	**<0.001***		

IQR: **Inter quartile range** SD: **Standard deviation U: Mann Whitney test**; p: p value for comparing between the studied groups; p_1: p value for **Wilcoxon signed ranks test** comparing between **Treatment day** and **Day 7**; *: Statistically significant at $p \leq 0.05$

As regard platelets count mean level in treatment group was 214.7 , 212.1 in both groups respectively with insignificant differences but after 7 days of treatment level decreased to 212.1 , 201.3 respectively with significant decrease in methotrexate group than letrezole group, (**Table .4).** As regard success of treatment was achieved in 85% of letrezole cases versus 80% in methotrexate cases with insignificant differences, (**Table.5).** Maternal morbidity was insignificant between two groups as in letrezole group 2 cases transferred to surgery and 1 case shifted to methotrexate, in methotrexate 4 cases transferred to surgery, (**Table .6).**

Table 5. Comparison between the two studied groups according to success of treatment

Success of treatment	Letrozole (n = 20)		Methotrexate (n = 20)		χ^2	^{FE}p
	No.	%	No.	%		
No	3	15.0	4	20.0	0.173	1.000
Yes	17	85.0	16	80.0		

χ^2: **Chi square test** FE**: Fisher Exact** p: p value for comparing between the studied groups

Table 6. Comparison between the two studied groups according to maternal morbidity

Maternal morbidity	Letrozole (n = 20)		Methotrexate (n = 20)		χ^2	^{MC}p
	No.	%	No.	%		
No	17	85.0	16	80.0		
Perform surgery	1	5.0	3	15.0		
Shift to methotrexate	1	5.0	0	0.0	2.143	0.796
Hemodinamic unstable perform surgery	1	5.0	1	5.0		

χ^2: **Chi square test** MC: **Monte Carlo**; p: p value for comparing between the studied groups

Side effect was insignificantly between two groups as 2 cases in letrezole group suffered from headache , 1 case had dizziness , 1 case had nausea \vomiting and 1 case had lower adominal pain and headache , in methotrexate group 1 case had headache , 1 case had dizziness , 1 case had nausea\vomiting and 2 cases had Lower abdominal pain, Headache, **(Fig.1).**

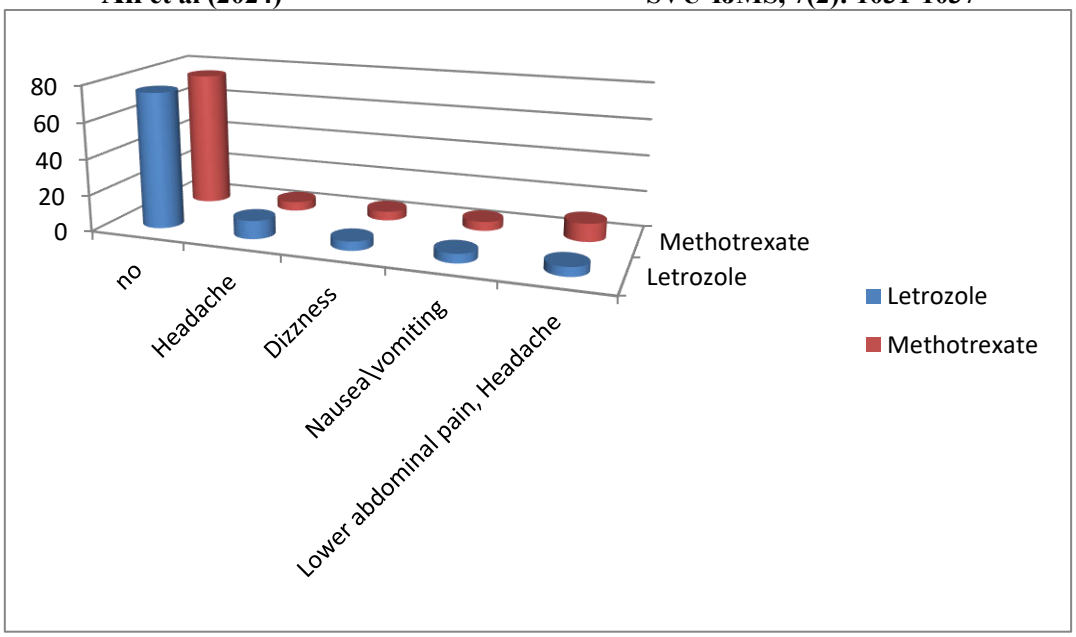

Fig.1. Comparison between the two studied groups according to side effects

Hospitalization in 2 cases in letrezole group and 4 cases in methotrexate group with insignificant differences (**Table.7)**

Table 7. Comparison between the two studied groups according to hospitalization

Hospitalization	Letrozole (n = 20)		Methotrexate (n = 20)		χ^2	FE p
	No.	%	No.	%		
No	18	90.0	16	80.0	0.784	0.661
Yes	2	10.0	4	20.0		

χ^2: **Chi square test** FE**: Fisher Exact;** p: p value for comparing between the studied groups

Discussion

Ectopic pregnancy is the primary factor in maternal morbidity and mortality. According to estimates, 2% to 5% of pregnancies brought on by assisted reproduction and 1% to 2% of all pregnancies are ectopic. Even if the overall mortality rate has decreased, up to 6% of all maternal deaths are still brought on by ectopic pregnancy rupture **(Panelli et al., 2015).** The light of the demography of the population being studied. The demographics of the two groups rarely varied from one another. Our findings corroborated those of **Mitwally et al. (2020),** who found no differences in age, BMI, or parity between the three groups (the control (laparoscopic), and the two experimental groups) that were statistically significant (letrozole and methotrexate). Similar to this, **El-Hameed et al. (2020)** reported that their study involved thirty-four (34) patients of undisturbed ectopic pregnancy who were randomly assigned to three groups. Of these patients, ten (10) underwent laparoscopic salpingostomy, Methotrexate was given as a single dose (1 mg/kg IM) to ten (10) patients, and Letrozole 2.5 mg and Norethisterone 5 mg were given to the other fourteen (14) instances. The two groups' differences in age, BMI, and prior obstetric history were not very significant. Ectopic pregnancy can be surgically treated conservatively, and laparoscopic surgery appears to be an option even for patients who are poor surgical candidates, such as those who are very obese. In non-ruptured patients, laparoscopic salpingostomy is the preferred surgical technique. However, nonsurgical treatment for ectopic pregnancy may avoid the unfavourable postoperative adhesions that frequently arise from surgical manipulation of the fallopian tubes **(Dagar et al., 2018)**.

Letrozole is a third-generation aromatase inhibitor drug which has been advocated for medical treatment of undisturbed ectopic **(Auger et al., 2020)**.

According to the results of the current investigation, there were no appreciable variations between the two groups' HCG levels on the first, fourth, and seventh days. In the letrozole and methotrexate groups, the level of BHCG significantly decreased on days 1, 4, and 7. Study by **Mitwally et al., (2019)**, which showed that the fall in hCG levels was quicker in the letrozole group when compared to the methotrexate group, confirmed our findings.

Although **Mitwally et al. (2020)** showed that there was no measurably significant difference in the levels of b-hCG after the introduction of medication. The letrozole group experienced a faster decline in b-hCG levels than the methotrexate group, although the difference was not statistically significant. It's crucial to take notice of their expressed desire to be able to provide details about the direction of b-hCG levels in order to provide illustrations of how they reacted to the examined medications. In any case, on the grounds that the b-hCG examines were acted in a few labs, perceived interlaboratory fluctuation would restrict the speculations. The review's blemish would likewise be aggravated by the modest number of patients remembered for the review. The ongoing review showed that as respect adnexal mass mean level was 3.38 in letrozole bunch and 3.5 in methotrexate bunch with unimportant contrasts. Pelvic assortment not established in that frame of mind in the two gatherings. As per our outcomes, investigation of **El-Hameed et al., (2020)** as they detailed that the mean adnexal mass size in Laparoscopy bunch was (3.8), in Methotrexate bunch was (3.1) and in Letrozole bunch (3.3) with P worth of (0.096).

In the concentrate in our grasp, respect research center measures; as respect platelets include mean level in treatment bunch was 214.7, 212.1 in the two gatherings separately with unimportant contrasts however following 7 days of treatment level diminished to 212.1, 201.3 separately with critical decline in methotrexate bunch than letrozole bunch.

In accordance with our outcomes, investigation of **Mitwally et al., (2019)** on the grounds that they guaranteed that methotrexate use was connected to more prominent degrees of liver chemicals and diminished degrees of platelets (the distinctions in the two boundaries were genuinely huge). AHM levels were lower in the methotrexate bunch than in the letrozole and careful gatherings three months following treatment. Be that as it may, there was no genuinely huge abatement in AMH levels. Moreover, there was no genuinely tremendous contrast in hemoglobin levels toward the beginning of treatment between the three patient gatherings, as per **Mitwally et al. (2020).** The hemoglobin levels in the methotrexate treatment bunch genuinely fundamentally dropped following 7 days, rather than the medical procedure and letrozole therapy gatherings. Additionally, greater liver protein levels and lower blood platelet counts were linked to methotrexate use. The differences in these borders were actually fairly significant.

90 days following prescription, the methotrexate group had lower AMH levels than the letrozole and cautious groups, although the difference was not very significant. **Rezaei et al.,(2021)** study 's found that patients' CBC and serum organic chemistry characteristics on the seventh day of the evaluation were not substantially different across groups. The present review showed that as respect progress of treatment was accomplished in 85% of letrozole cases versus 80% in methotrexate cases with unimportant contrasts. Maternal bleakness was irrelevant between two gatherings as in letrozole bunch 2 cases moved to a medical procedure and 1 case moved to methotrexate, in methotrexate 4 cases moved to a medical procedure. Our outcomes were upheld by investigation of **El-Hameed et al., (2020)** as they announced that the achievement rate following laparoscopic medical procedure was 90% (1/10 patients), neither essentially unique in relation to that in the Methotrexate bunch 80% (8/10 patients) nor fundamentally not quite the same as that in the Letrozole bunch 78.6% (11/14 patients). Out of 14 cases, 11 were dealt with effectively with letrozole (78.6%). 2 cases required a medical procedure and 1 case required single portion of methotrexate. In the investigation of **Mitwally et al., (2020),** In every one of the two medication treatment gatherings, similar number of patients — 12 out of 14 (86%) — had their ectopic pregnancy totally settled.

The two patients who got fruitless methotrexate treatment in the long run expected a medical procedure because of hemostatic shakiness. One patient in the letrozole bunch experienced hemodynamic shakiness, and in the subsequent patient, medical procedure was settled on after the b-HCG levels neglected to diminish 4 days following letrozole drug.

According to **Mirbolouk et al. (2015),** out of 370 patients, 285 (or 77.1%) received effective treatment with MTX, compared to 80% in our review. After an average of 5.4 (territory 2-15) days, 85 patients (or 22.9%) required a medical operation. Beta-human chorionic gonadotropin (-HCG) on day 1 and the decrease in -HCG between days 1 and 4 were the greatest indicators of single piece MTX treatment effectiveness. With the successful treatment outcomes, the starting HCG value was calculated to be 1375 IU/mL.The momentum study showed that secondary effect was irrelevantly between two gatherings as 2 cases in letrozole bunch experienced migraine, 1 case had unsteadiness, 1 case had sickness \vomiting and 1 case had lower stomach agony and migraine, in methotrexate bunch 1 case had migraine, 1 case had discombobulation, 1 case had nausea\vomiting and 2 cases had Lower stomach torment, Cerebral pain. Hospitalization in 2 cases in letrozole gathering and 4 cases in methotrexate bunch with immaterial contrasts.

A synchronized chemical creation between the mother, the placenta, and the hatchling is important to begin and support pregnancy. It is easy to refute whether estrogen contributes altogether to the inception and upkeep of early pregnancy. As per exploratory information, progesterone alone can save a pregnancy following corpus luteum extraction without the utilization of simultaneous estrogen treatment. It has reported fruitful pregnancies in circumstances where estrogen levels are very low, such aromatase deficiency. Moreover, the shortfall of reliable proof of estrogen receptors in trophoblast and the early placenta of pregnancy shows that estrogen doesn't play a critical capability in the beginning phases of pregnancy **(Tal and Taylor 2021).**

Clinical treatment with methotrexate for undisturbed ectopic pregnancy plays its distinct part as an option in contrast to laparoscopy. Letrozole enjoys the benefit of simple organization and high security profile when contrasted with methotrexate.

Conclusion

Medical treatment with methotrexate for undisturbed ectopic pregnancy has its definite role as an alternative to laparoscopy. Letrozole has the advantage of easy administration and high safety profile when compared to methotrexate.

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