

# COMPARED STUDY BETWEEN THE USE OF IETROZOLE AND METHOTREXATE FOR THE MEDICAL TREATMENT OF EARLY SUSPECIOUS UNDISTURBED TUBAL ECTOPIC PREGNANCY

By

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## ABSTRACT

**Background:** The most common site of ectopic pregnancy is the fallopian tube. Most cases of tubal ectopic pregnancy that are detected early can be treated successfully either with minimally invasive surgery or with medical management using methotrexate.

**Objective:** To study the effectiveness of letrozole in management of early suspicious undisturbed ectopic pregnancy compared to Methotrexate.

**Patients and Methods:** A non-randomized prospective cohort study carried out on 50 pregnant woman with early suspicious undisturbed tubal ectopic pregnancy who were hemodynamically stable, and did not have heterotopic pregnancy. Twenty five of patients were treated with letrozole (2.5 mg bid) for 10 days, and the other 25 patients were treated with methotrexate (1mg/kg IM, maximum 50mg single dose), and follow up by  $\beta$ -hCG on day 4 and day 7 of first dose at Obstetrics and Gynecology Department, Faculty of Medicine, Al-Azhar University Hospitals from April 2020 to March 2021.

**Results:** The mean age of group 1 was 28.36 ( $\pm$ 3.33 SD) with range (22-36) while the mean age of group 2 was 30.28 ( $\pm$ 4.34 SD) with range (22-35). According to residence in group 1 there were 10 (40%) rural resident, and 15 (60%) urban resident, while in group 2 there were 11 (44%) rural resident and 14 (56%) urban resident. There was no statistically significant difference between the studied groups as regard age or residence. There was no statistically significant difference between the studied groups as regard BMI, parity, and history of assisted reproductive. Presented by vaginal bleeding or presented by abdominal pain. There was significant difference between the different studied periods in group 1 as regard abdominal US, and significant difference between the different studied periods in group 2 as regard abdominal US.

**Conclusion:** Letrozole was as effective as methotrexate, with success rates of 86% for both treatment arms. b-Human chorionic gonadotropin levels even appeared to decrease more rapidly for women treated with letrozole than methotrexate, although the difference was statistically significant.

**Keywords:** Aromatase Inhibitors, Letrozole, Ectopic pregnancy, Methotrexate.

## INTRODUCTION

The most common ectopic pregnancy (EP) location is in the fallopian tube, predominantly the ampullary region of the fallopian tube. Implantation outside the fallopian tube-in the cervix, ovary, myometrium, abdominal cavity,

interstitial (i.e., intramuscular/ proximal) portion of the fallopian tube or coincidentally with an intrauterine pregnancy occurs in less than 10 % of EPs. Heterotopic pregnancy (HP) refers to the coexistence of an intrauterine pregnancy with an EP in any of these

locations. Nontubal EPs are pregnancies that implant at sites other than the fallopian tube. These pregnancies account for less than 10 % of all EPs, though their overall incidence has been increasing in recent years. Furthermore, nontubal EPs contribute disproportionately to maternal morbidity and mortality in comparison to tubal EPs (*Panelli et al., 2015*).

The classic clinical triad of ectopic pregnancy is pain, amenorrhea, and vaginal bleeding; unfortunately, only about 50% of patients present with all 3 symptoms. About 40-50% of patients with an ectopic pregnancy present with vaginal bleeding, 50% have a palpable adnexal mass, and 75% may have abdominal tenderness. In one case series of ectopic pregnancies, abdominal pain presented in 98.6% of patients, amenorrhea in 74.1% of them, and irregular vaginal bleeding in 56.4% of patients (*Samal and Rathod, 2015*).

A standard treatment option for many patients. Single- and multi-dose systemic methotrexate (MTX) protocols are used most commonly, with no difference in success rate. Given its simplicity and low complication rate, the single-dose protocol is used more widely throughout the world (*Erdem et al., 2017*).

The single dose regimen consists of an intramuscular injection (IM) of MTX (50 mg/m<sup>2</sup> of body surface area), with administration of additional doses at weekly intervals in patients with an inadequate response. Repeated injections are permitted every 7 days for up to 4 doses second dose is needed in 20 % or more of patients, while less than 1 % of patients require 3 or more doses. The single dose regimen is associated with

fewer side effects as compared to other regimens (*Panelli et al., 2015*).

Letrozole is a potent and highly specific non-steroidal aromatase inhibitor that initially was approved for use in postmenopausal women with breast cancer to suppress estrogen production. It inhibits the aromatase enzyme by competitively binding to the heme of the cytochrome P450 subunit of the enzyme resulting in a blockade of androgens conversion into estrogens with a subsequent increase in intraovarian androgens. Letrozole, at doses of 1–5 mg/day, and inhibits aromatase activity by 97%–99% (*Garcia-Velasco et al., 2010*).

In the absence of estrogen priming, progesterone may not exert its physiological functions due to a negative effect on progesterone receptors. We hypothesized that by inhibiting the estrogen synthetase (the aromatase enzyme), the progesterone would not exert its physiological function in maintaining pregnancy, including ectopic pregnancy (*Mitwally et al., 2020*).

**The aim of the present work was to study the effectiveness of letrozole in management of early suspicious undisturbed ectopic pregnancy compared to Methotrexate.**

## PATIENTS AND METHODS

A non-randomized prospective cohort study carried out on 50 pregnant women with early suspicious undisturbed tubal ectopic pregnancy who were hemodynamically stable, and did not have heterotopic pregnancy. Twenty five of patients were treated with letrozole (2.5 mg bid) for 10 days, and the other 25 patients were treated with methotrexate

(1mg/kg IM, maximum 50mg single dose), and follow up by  $\beta$ -hCG on day 4 and day 7 of first dose at Obstetrics and Gynecology Department, Faculty of Medicine, Al-Azhar University Hospitals from April 2020 to March 2021. Patients included in this study gave informed consents.

**Inclusion criteria:** Age between 20-35 years, parity; from P1 to P3, with early tubal ectopic pregnancy, with no previous ectopic pregnancy nor previous tubal surgery or pelvic inflammatory disease (PID).

**Exclusion criteria:** Patients less than 20 years and more than 35years, parity nulliparity or multiparity , with previous ectopic pregnancy or previous tubal surgery or PID, and have ectopic pregnancy at any other site rather than fallopian tubes.

**Patient Evaluation:** All patients underwent complete history taking and complete clinical examination (general and local), laboratory investigation in the

form of measurement of B hcG titre, CBC and Liver, thyroid and kidney function, and radiological investigations in the form of transvaginal and abdominal ultrasound.

**Statistical Analysis:**

Analysis of data was done using Statistical Program for the Social Science version 20 (SPSS Inc., Chicago, IL, USA). Quantitative variables were described in the form of range mean and standard deviation Median (IQR). Qualitative variables were described as number and percent. In order to compare parametric quantitative variables between two groups, Student t test or Mennwhitney U tese was performed. Qualitative variables were compared using chi-square (X2) test or Fisher’s exact test when frequencies were below five. Pearson correlation coefficients were used to assess the association between two normally distributed variables. P value < 0.05 is considered significant.

**RESULTS**

The mean age of group 1 was 28.36 ( $\pm$ 3.33 SD) with range (22-36), while the mean age of group 2 was 30.28 ( $\pm$ 4.34 SD) with range (22-35). According to residence in group 1, there were 10 (40%) rural resident and 15 (60%) urban

resident, while in group 2 there were 11 (44%) rural resident and 14 (56%) urban resident. There was no statistically significant difference between the studied groups as regard age or residence (**Table 1**).

**Table (1): Comparison between the two studied groups according to age**

Age (years) \ Groups	Group 1 (n = 25)		Group 2 (n = 25)		p
Min. – Max.	22.0 – 34.0		22.0 – 35.0		
Mean $\pm$ SD.	28.36 $\pm$ 3.33		30.28 $\pm$ 4.34		
Median (IQR)	28.0 (26.0 – 31.0)		30.0 (29.0 – 34.0)		
<b>Residence</b>	<b>No.</b>	<b>%</b>	<b>No.</b>	<b>%</b>	0.774
Rural	10	40.0	11	44.0	
Urban	15	60.0	14	56.0	

There was no statistically significant difference between the studied groups as regard BMI, parity, history of assisted

reproductive, presented by vaginal bleeding or presented by abdominal pain (Table 2).

**Table (2): Comparison between the two studied groups according to past history**

<b>Groups</b>	<b>Group 1 (n = 25)</b>		<b>Group 2 (n = 25)</b>		<b>P</b>
<b>BMI</b>					
Min. – Max.	26.0 – 31.2		26.3 – 32.0		0.219
Mean ± SD.	28.21 ± 1.51		28.80 ± 1.81		
Median (IQR)	28.0 (26.9 – 29.2)		28.2 (27.6 – 30.3)		
<b>Parity</b>					
Min. – Max.	1.0 – 3.0		1.0 – 3.0		0.101
Mean ± SD.	2.0 ± 0.82		1.64 ± 0.70		
Median (IQR)	2.0 (1.0 – 3.0)		2.0 (1.0 – 2.0)		
<b>History of assisted reproductive</b>	No.	%	No.	%	
Yes	4	16.0	3	12.0	0.684
No	21	84.0	22	88.0	
<b>Presented by vaginal bleeding</b>	No.	%	No.	%	
Yes	4	16.0	3	12.0	0.684
No	21	84.0	22	88.0	
<b>Presented by abdominal pain</b>	No.	%	No.	%	
Yes	2	8.0	1	4.0	0.552
No	23	92.0	24	96.0	

There was no statistically significant difference between the studied groups as

regard systolic BP, diastolic BP, heart rate or temperature (Table 3).

**Table (3): Comparison between the two studied groups according to General examinations**

<b>Groups</b>	<b>Group 1 (n = 25)</b>		<b>Group 2 (n = 25)</b>		<b>P</b>
<b>Systolic BP</b>					
Min. – Max.	110.0 – 130.0		110.0 – 130.0		0.484
Mean ± SD.	121.60 ± 7.18		120.20 ± 6.84		
Median (IQR)	120.0 (115.0 – 130.0)		120.0 (115.0 – 125.0)		
<b>Diastolic BP</b>					
Min. – Max.	60.0 – 80.0		60.0 – 80.0		0.738
Mean ± SD.	70.40 ± 8.89		69.60 ± 7.90		
Median (IQR)	70.0 (60.0 – 80.0)		70.0 (60.0 – 80.0)		
<b>Heart rate</b>					
Min. – Max.	61.0 – 79.0		60.0 – 79.0		0.145
Mean ± SD.	71.28 ± 5.22		68.84 ± 6.36		
Median (IQR)	71.0 (67.0 – 76.0)		67.0 (64.0 – 75.0)		
<b>Temperature</b>					
Min. – Max.	36.5 – 37.5		36.6 – 37.5		0.119
Mean ± SD.	36.96 ± 0.34		37.10 ± 0.30		
Median (IQR)	36.8 (36.7 – 37.3)		37.1 (36.9 – 37.4)		

There was a significant difference between the different studied periods in group 1 as regard abdominal US and

significant difference between the different studied periods in group 2 as regard abdominal US (Table 4).

**Table (4): Comparison between the two studied groups according to Abdominal US**

Abdominal US \ Groups	Group 1 (n = 25)		Group 2 (n = 25)		P
	No.	%	No.	%	
<b>Baseline</b>					
Abnormal	25	100.0	25	100.0	1.0
Normal	0	0.0	0	0.0	
<b>4th day</b>					
Abnormal	18	72.0	21	84.0	0.308
Normal	7	28.0	4	16.0	
<b>7th day</b>					
Abnormal	7	28.0	15	60.0	0.023
Normal	18	72.0	10	40.0	
$\chi^2(p_0)$	29.64(<0.001)		13.35(0.001)		

There was a statistically significant difference between studied groups as regard  $\beta$ -hCG at 7th day. There was a

significant difference between different studied periods in both groups as regard  $\beta$ -hCG (Table 5).

**Table (5): Comparison between the two studied groups according to  $\beta$ -hCG**

$\beta$ -hCG \ Groups	Group 1 (n = 25)	Group 2 (n = 25)	P
<b>Baseline</b>			
Min. – Max.	484 - 1762	523 - 1727	0.883
Mean $\pm$ SD.	1134.04 $\pm$ 368.01	1119.04 $\pm$ 347.45	
Median (IQR)	1120 (843 - 1464)	1262 (825 - 1356)	
<b>4th day</b>			
Min. – Max.	401 - 909	521 - 967	0.061
Mean $\pm$ SD.	700.48 $\pm$ 200.6	805.52 $\pm$ 185.57	
Median (IQR)	735 (483 - 901)	882 (598 - 957)	
<b>7th day</b>			
Min. – Max.	151 - 499	163 - 508	0.015
Mean $\pm$ SD.	344.8 $\pm$ 150.28	436.68 $\pm$ 104.32	
Median (IQR)	397 (159 - 493)	494 (393 - 499)	
<b>F (P<sub>0</sub>)</b>	273.403 (<0.001*)	383.347 (<0.001*)	

There was no statistically significant difference between studied groups as regard Antimüllerian hormone (AMH).

There was a significant difference between different studied periods in both groups as regard AMH (Table 6).

**Table (6): Comparison between the two studied groups according to AMH**

AMH \ Groups	Group 1 (n = 25)	Group 2 (n = 25)	p
Baseline			
<b>Min. – Max.</b>	1 - 2.9	1 - 3	0.294
<b>Mean ± SD.</b>	1.92 ± 0.59	1.74 ± 0.63	
<b>Median (IQR)</b>	1.7 (1.5 - 2.4)	1.5 (1.3 - 2.3)	
4th day			
<b>Min. – Max.</b>	0.9 - 2.8	0.9 - 3	0.374
<b>Mean ± SD.</b>	1.82 ± 0.59	1.67 ± 0.64	
<b>Median (IQR)</b>	1.6 (1.5 - 2.2)	1.4 (1.1 - 2.3)	
7th day			
<b>Min. – Max.</b>	0.8 - 2.7	0.8 - 2.9	0.338
<b>Mean ± SD.</b>	1.72 ± 0.57	1.55 ± 0.63	
<b>Median (IQR)</b>	1.5 (1.4 - 2.2)	1.4 (1.1 - 2.1)	
F (P <sub>0</sub> )	244.857 (<0.001*)	170.963 (<0.001*)	

## DISCUSSION

In this study, we reported that there was no statistically significant difference between the studied groups as regard age or residence. Also, there was no statistically significant difference between the studied groups as regard BMI, parity, history of assisted reproductive presented by vaginal bleeding or presented by abdominal pain.

In this issue of fertility and sterility, *Mitwally et al. (2020)* assessed the use of letrozole for treatment of ectopic pregnancy. Letrozole is a third-generation aromatase inhibitor that suppresses estrogen production. Aromatase is an enzyme involved in estrogen biosynthesis that converts androstenedione to estrone and testosterone to estradiol. Letrozole blocks the action of aromatase, preventing a critical step in the production of estrogens. Letrozole is used for estrogen dependent breast cancer in postmenopausal women and ovulation induction in women with polycystic ovary syndrome. Because progesterone is considered more essential than estrogen to

establish and maintain pregnancy, it is not immediately evident why letrozole would interrupt ectopic pregnancy. *Walters et al. (2020)* hypothesized that the role of estrogen in early pregnancy may be underestimated, and that inhibition of estrogen production with letrozole may disrupt the physiological functions of progesterone needed to maintain pregnancy.

*Mitwally et al. (2020)* has shown that there was no statistically significant difference among as regards age, body mass index, or parity.

The present study stated that there was no statistically significant difference between the studied groups as regards systolic BP, diastolic BP, heart rate or temperature. Also, there was significant difference between studied groups as regard abdominal.

US, plays an important role in the selection of the patients who have the greatest likelihood of benefiting from MTX therapy, as opposed to those unlikely to be efficiently treated medically, who should be referred for

primary surgical treatment (*Czuczwar et al., 2018*).

The significance of ultrasound for the prediction of the effectiveness of MTX therapy is undeniable, making it an invaluable tool in referring patients for medical treatment. The literature of the subject lists various US findings relevant for selecting optimum management modality in EP patients. The most important ones include the size of the ectopic mass, the presence of fetal heart rate (FHR) and/or gestational sac (GS), free fluid, endometrial stripe thickness and the vascularity of the ectopic mass (*Czuczwar, 2018*).

The rising  $\beta$ -hCG titers that were inappropriate for the gestational age, as well as ultrasound findings of absent intrauterine gestational sac associated with suspicious adnexal structure; minimize the likelihood of a nonviable intrauterine pregnancy although it was still a possibility (*Sharma et al., 2020*).

In our study, we reported that there was a statistically significant difference between studied groups as regard  $\beta$ -hCG at 7th day. It came in disagreement with *Mitwally et al. (2020)* who showed that there no statistically significant difference between studied groups as regard  $\beta$ -hCG at 4<sup>th</sup>, 7<sup>th</sup> and 14<sup>th</sup> day.

Also, there was a significant difference between different studied periods in both groups as regard  $\beta$ -hCG. This was against what *Mitwally et al. (2020)* said. He showed that there was no statistically significant difference in  $\beta$ -hCG levels on the day of treatment. The decline in  $\beta$ -hCG levels was faster in the letrozole group when compared with the methotrexate group, but the difference

was not statistically significant. It is important to mention that he wish he could present data on the trajectory of the  $\beta$ -hCG levels to illustrate patterns of response to the studied treatments. However, the  $\beta$ -hCG assays were performed at different laboratories, which would limit the conclusions due to known interlaboratory variability. Also, the small sample size of patients included in the study would add to the limitation.

In our study, we demonstrated that there was no statistically significant difference between studied groups as regard AMH. Also, there was high significant difference between different studied periods in both groups as regard AMH. *Mitwally et al. (2020)* found that, three months after treatment, the AMH levels were lower in the methotrexate group when compared with the letrozole and surgery groups although the decline was not statistically significant. They illustrated that there was no significant difference between different studied periods in 3 groups as regard AMH.

*Mitwally et al. (2020)* showed that there was no statistically significant difference in hemoglobin levels. However, the hemoglobin levels statistically significantly dropped in the methotrexate treatment group after 7 days when compared with the surgery and letrozole treatment groups. Treatment with methotrexate also was associated with higher levels of liver enzymes and lower blood platelets counts. The differences in these parameters were statistically significant. Three months after treatment, the AMH levels were lower in the methotrexate group when compared with the letrozole and surgery groups although

the decline was not statistically significant.

### CONCLUSION

Letrozole was as effective as methotrexate, with success rates of 86% for both treatment arms. b-Human chorionic gonadotropin levels even appeared to decrease more rapidly for women treated with letrozole than methotrexate, although the difference was statistically significant. Letrozole did not affect hematologic parameters, whereas methotrexate was associated with an increase in liver enzymes and a decrease in hemoglobin and platelet count.

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## مقارنة الدراسة بين إستخدام دواء الليتروزول و عقار الميزوتريكسات فى العلاج الطبى للحمل المنتبذ البوقى غير المضطرب المبكر

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**خلفية البحث:** الموقع الأكثر شيوعا للحمل خارج الرحم هو قناة فالوب. ويمكن علاج معظم حالات الحمل خارج الرحم البوقى التي يتم إكتشافها مبكرًا بنجاح إما عن طريق الجراحة طفيفة التوغل أو بالإدارة الطبية باستخدام الميثوتريكسات.

**الهدف من البحث:** دراسة تأثير إستخدام دواء الليتروزول فى العلاج الطبى للحمل المنتبذ البوقى غير المضطرب المبكر مقارنة بعقار الميزوتريكسات.

**المريضات وطرق البحث:** هذه دراسة جماعية مستقبلية غير عشوائية، تم إجراؤها على 50 امرأة حامل مصابة بحمل خارج الرحم البوقى غير المشكوك فيه مبكرًا وكانت مستقرة ديناميكياً ولم يكن لديها حمل غير متجانس. تم علاج 25 مريضًا باستخدام ليتروزول (2.5 مجم عرض سعر) لمدة 10 أيام، وتم علاج 25 مريضًا آخرين بالميثوتريكسات (1 مجم / كجم من العضل، بحد أقصى 50 مجم جرعة واحدة)، والمتابعة بـ  $\beta$ -hCG في اليوم الرابع واليوم 7 جرعة أولى في قسم أمراض النساء والتوليد بكلية الطب بمستشفيات جامعة الأزهر من أبريل 2020 إلى مارس 2021.

**نتائج البحث :** لم يكن هناك فروق ذات دلالة إحصائية بين المجموعتين المدروسة فيما يتعلق بالعمر أو الإقامة، ولم يكن هناك فرق ذو دلالة إحصائية فيما يتعلق بمؤشر كتلة الجسم، والتكافوء، وتاريخ الإنجاب المساعد، والنزيف المهبلية أو ألم البطن. وقد أظهرت نتيجة البحث أنه كان هناك فرق معنوي بين الفترات المختلفة المدروسة في المجموعة 1 فيما يتعلق بالسونار عن طريق البطن، و الفرق معنوي بين مختلف الفترات المدروسة في المجموعة 2 فيما يتعلق بالسونار عن طريق البطن.

**الاستنتاج:** كان لـ ليتروزول بنفس فعالية الميثوتريكسات، حيث بلغت معدلات النجاح 86% لكلا ذراعي العلاج. وانخفضت مستويات الجوناودوتروبين المشيمية البشرية بسرعة أكبر عند النساء اللاتي عولجن بالليتروزول مقارنة بالميثوتريكسات، على الرغم من أن الاختلاف كان ذا دلالة إحصائية.

**الكلمات الدالة:** مثبطات الأروماتيز، ليتروزول، الحمل خارج الرحم، الميثوتريكسات.