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The Aromatase Inhibitor "Letrozole" Versus Methotrexate for Management of Undisturbed Ectopic Pregnancy

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ABSRTACT

Background: Ectopic pregnancy affects approximately 1% of pregnancies and is a leading cause of maternal mortality in the first trimester. Timely and appropriate treatment of ectopic pregnancy is critical. Ectopic pregnancy may be managed surgically, medically, or expectantly.

Aim of the Study: To evaluate the efficacy and safety of medical treatment of undisturbed ectopic pregnancy either by Methotrexate or by aromatase inhibitors "Letrozole" treatment in order to Improve outcomes of undisturbed ectopic pregnancy at Zagazig University Hospitals.

Patients and Methods: Randomized interventional clinical trial which was conducted in Obstetric and gynecological department of Zagazig University Hospitals. The study included 48 patients who have undisturbed ectopic pregnancy,Patients were randomly distributed into two equal groups (24 Methotrexate) (24 Letrozole); all patients were subjected toexamination (general, abdominal, pelvic): as regard pulse, blood pressure, respiratory rate, evaluation of vital signs, measurement weight height (BMI), and Pelvic examination, and also Investigations (Laboratory – Ultrasonography).

Results:According to the distribution of the studied patients regarding the results after treatment. Success in Methotrexate Group reached 75%, while in Letrozole Group it reached 83.33%

Conclusion: This is a comparative, prospective, interventional, randomized clinical study that was conducted in the Obstetrics and gynecological department of Zagazig University Hospitals. Our study showed a promisingly high-resolution rate and better safety profile that Letrozole has compared with a chemotherapeutic agent such as Methotrexate should encourage further studies.

Keywords: Aromatase Inhibitor; Letrozole; Methotrexate; Ectopic Pregnancy

1. Introduction

Ectopic pregnancy affects approximately 1% of pregnancies and is a leading cause of maternal mortality in the first trimester[1]. Timely and appropriate treatment of ectopic pregnancy is critical. Ectopic pregnancy may be managed surgically, medically, or expectantly. Surgical treatment with salpingectomy or salpingostomy is required typically for advanced or ruptured ectopic pregnancy, whereas Methotrexate is the first-line medical treatment for early unruptured ectopic pregnancy. Methotrexate can be administered as single or multidose regimens, with success rates reaching 93% [2].

Methotrexate is a folic acid antagonist that inhibits the enzyme dihydrofolate reductase, which converts folic acid to tetrahydrofolate, a cofactor needed in DNA and RNA synthesis. By inhibiting dihydrofolate reductase, Methotrexate interrupts trophoblast proliferation and induces abortion. Methotrexate is as effective as salpingostomy for ectopic pregnancy and does not appear to affect future fertility [3].

Methotrexate is a chemotherapeutic agent that can have adverse consequences, including nausea, vomiting, conjunctivitis, stomatitis, gastritis, impaired liver function, bone marrow suppression, and photosensitivity. Methotrexate is not indicated for patients with ruptured ectopic pregnancy, hemodynamic instability, or b-human chorionic gonadotropin (HCG) levels >5,000 mIU/mL, all signs of more advanced ectopic pregnancy. Other contraindications include immunodeficiency, anemia, thrombocytopenia, pulmonary disease, peptic ulcer, hepatic or renal dysfunction, and breastfeeding. Thus, alternate medical treatments are needed [4,5].

Methotrexate is associated with: Long intervals until resolution of the ectopic pregnancy, the need to wait for several weeks before another attempt at pregnancy, and future fertility potential are not unexpected [6].

In this issue of Fertility and Sterility,[7] assessed the use of Letrozole for the 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.

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Mitwally et al[7]**.**Designed a nonrandomized trial of 42 women with ectopic tubal pregnancy. Women selected their treatment and were divided into three arms of 14 patients administered Letrozole, Methotrexate, or salpingectomy. The letrozole arm received 5 mg daily for 10 days, whereas the methotrexate arm received a single intramuscular injection at a dose of 50 mg/m2. b-human chorionic gonadotropin levels were measured on treatment days and 4, 7, and 14 days later. Undetectable b-hCG levels indicated resolution of ectopic pregnancy. The authors monitored hemoglobin levels, blood platelet counts, liver enzymes, renal function, and antimuellerian hormone.[7].
According to their results, 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 non-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. Letrozole had no impact on antimuellerian hormone levels three months after treatment. The results are promising, although Letrozole was compared with single-dose Methotrexate, which is somewhat less effective than the multidose regimen[8].

2. Patients and Methods

2.1. Technical design:

2.1.1. Site of Study:

This study was conducted in the Obstetrics and gynecological department of Zagazig University Hospitals.

2.1.2. Sample size:

By Assuming that number of patients admitted with inclusion criteria of undisturbed ectopic pregnancy is 8 (eight)/months. So, in the duration of 6 months, the sample size equals 48 patients (24 Methotrexate) (24 Letrozole) taken as a comprehensive sample. Two study groups: Methotrexate (group 1) and Letrozole (group 2) Consecutive women with undisturbed tubal ectopic pregnancy, medical treatment with Methotrexate (group 1) and medical treatment with Letrozole (group 2)

2.1.3. Inclusion Criteria:

Pregnancies in women between 18 and 40 years old. Ectopic pregnancy diagnosis was confirmed by the admitting physician associated with b-HCG titers beyond the discrimination zone of at least 1,500 mIU/mL.
Patients who have undisturbed ectopic pregnancy. Who are:have no significant pain, have an un ruptured tubal ectopic pregnancy with an adnexal mass smaller than 35mm with no visible heartbeat have a serum human chorionic gonadotropins level less than 3000 IU/liter and do not have an intrauterine pregnancy (as will be confirmed on an ultrasound scan).

The diagnosis of ectopic pregnancy:
The absence of an intrauterine gestational sac on vaginal ultrasound examination and/or gestational age of at least six weeks was confirmed by a positive pregnancy test at least 2 weeks before the diagnosis of ectopic pregnancy

2.1.4. Exclusion Criteria:

An undisturbed ectopic pregnancy and significant pain, An undisturbed ectopic pregnancy with an adnexal mass of 35 mm or larger, An undisturbed ectopic pregnancy with a fetal heartbeat visible on an ultrasound scan, An undisturbed ectopic pregnancy and a serum human chorionic gonadotropins level of 5,000 IU/liter or more, intrauterine pregnancy, hemoglobin level <10 g/dL, platelets count <150,000/mL , and elevated liver enzymes, blood urea, or serum creatinine.

2.2. Operational Design:

2.2.1. Study design:

Randomized interventional clinical trial.
All patients were subjected to the following: First, informed consent was obtained. Then, Full history taking: Name, age, sex, marital status, telephone no., address, occupation and residence, Menstrual history includingthe age of menarche, menstrual disturbance, dysmenorrheal, related symptoms., Obstetric history, including parity and mode of delivery, and Personal history of chronic disease and medications.

1. Examination (general, abdominal, pelvic):General examination: as regard pulse, blood pressure, respiratory rate, evaluation of vital signs, measurement weight height (BMI), and Pelvic examination.
2. Investigations: (Laboratory – Ultrasonography).

Laboratory Investigations: (complete blood count - coagulation profile - kidney function test - liver function test).

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Ultrasonography: Pelvic ultrasonography (focus on evaluating the viability and location of the pregnancy.
*Transvaginal sonography (TVS) is more sensitive than abdominal sonography to diagnose ectopic pregnancy.

2.2.2. Ectopic picture:
1-Uterus:
-No intrauterine pregnancy
-Pseudo gestational sac: may be detected. It is the result of an intracavitary fluid collection caused by sloughing of decidua situated in the midline of the uterine cavity
2-Fallopian Tube:
-Hematosalpinx or peritubal hematoma
-A ring-like mass that may have a yolk sac or embryonic pole with or without cardiac activity (sure sign)

-Free fluid in peritoneum: (internal hemorrhage)
-Color Doppler: a ring of color (ring of fire) may be seen around the extrauterine gestational sac and helps to locate it
3. Management of cases (medical treatment received, outcome maternal).
4. Follow up by ultrasound and b-HCG

2.2.3. treatment:
Methotrexate treatment group: Women have received one intramuscular injection of 50 mg per square meter of body surface area
Letrozole treatment group: Letrozole was administered as two 2.5-mg tablets every day for ten days
The b-HCG levels were measured on the day of treatment and then 4, 7, 14 days after treatment.
Complete blood count, liver enzymes, blood urea, and serum creatinine levels were obtained on the day of treatment and seven days after treatment.

2.2.4. Outcomes:
The primary outcome:
A complete resolution of the ectopic tubal pregnancy as determined by serum b-HCG levels below laboratory immunoassay detection is as follow:
b-HCG was measured on day 0, day 4, day 7, day 14 till reaching below laboratory immunoassay measures
The secondary outcome:
Including changes in hemoglobin levels, blood platelets count, and liver enzymes—aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

2.3. Administrative design:
Approval was obtained from Zagazig University Institutional Review Board (IRB).

2.4. Statistical Analysis:
Data were checked, entered, and analyzed using SPSS version 23 for data processing. The following statistical methods were used for the analysis of the results of the present study.
Data were expressed as number and percentage for qualitative variables and mean $\pm$ standard deviation (SD) for quantitative ones.

3. Results
Obtained data were presented as mean ± SD, ranges, numbers, and percentages as appropriate. Nominal variables were analyzed using Chi-squared ($\chi 2$) test. Continuous variables were analyzed using unpaired Student's t-test or Univariate two-group repeated measures "mixed-design" analysis of variance (ANOVA) with post hoc Dunnett's test as appropriate. Nominal and non-normally distributed variables were analyzed using the Mann-Whitney U test. Statistical calculations were performed using Microsoft® Office Excel 2016 and SPSS (Version 20, 2011). P-value < 0.05 was considered statistically significant.
Table (1) shows the demographic data of the studied group. Age ranged from 50-78 years with a mean value of 64±14 years.

Table (1): Distribution of studied sample according to patient's demographic data.

Characteristics	**No. of patients (%)**
Age: mean ± SD [range] (years)	27 ± 11.5
BMI	21.5 ± 2.1
Occupation	Engineering, Medical,teaching, nursery, butchery, and

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	plowing fields
Address	Egypt, Sharkia

Data are represented as mean ± SD. A total number of patients (n) = 48. Data were expressed by number and percent of the patients

Obstetric history:

Table(2), Show the Parity of the two groups. Methotrexate group show 10 (41.67%) no parity, 10 (41.67%) low parity and 4 (16.67%) with high parity, while Letrozole Group show 7 subjects (29.167%) with no parity 15 (62.5%) Low parity and 2 (8.33%) High (P3 or more).

Table(2): The Parity of the two groups.

Variable	Methotrexate Group	Letrozole Group
NP	**10 (41.67%)**	**7 (29.167%)**
Low (P1 or P2)	**10 (41.67%)**	**15 (62.5%)**
High (P3 or more)	**4 (16.67%)**	**2 (8.33%)**

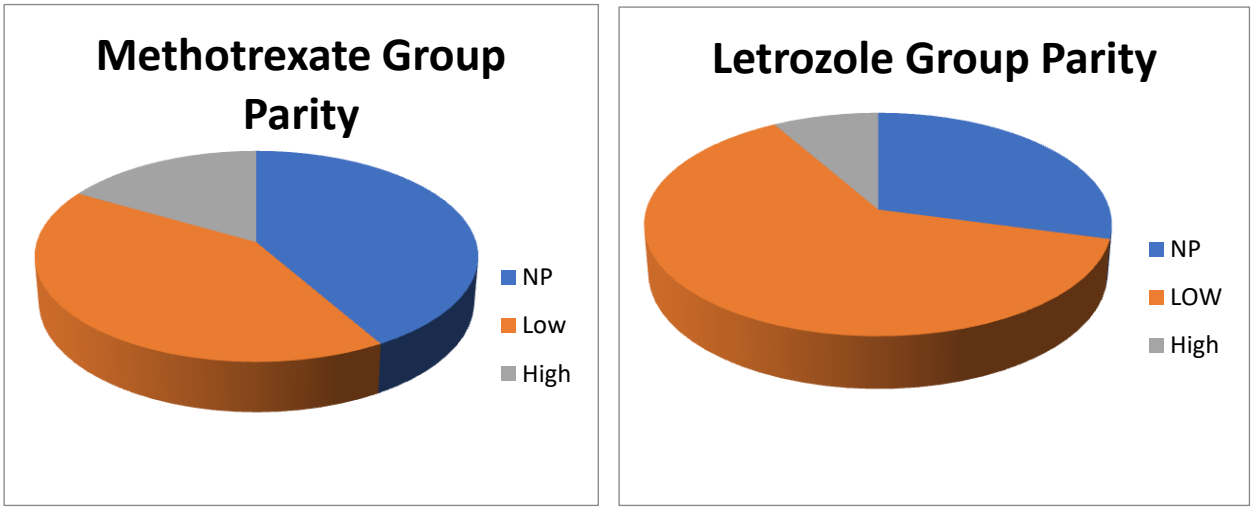

Figure (1): Show Parity of the two groups

Table (3), Shows Previous deliveries of both groups. Methotrexate Group with ten subjects (41.67%) had no Previous deliveries, 3 (12.5%) with Spontaneous Vaginal Delivery, and 11 (45.833%) with Caesarean Section. Letrozole Group has seven subjects (29.167%) with no Previous deliveries, 4 (16.67%) with Spontaneous Vaginal Delivery, and 13 (54.167%) with Caesarean Section.

Table (3): Previous deliveries of both groups

Variable	Methotrexate Group	Letrozole Group
NP	**10 (41.67%)**	**7 (29.167%)**
SVD (Spontaneous Vaginal Delivery)	**3 (12.5%)**	**4 (16.67%)**
C/S (Caesarean Section)	**11 (45.833%)**	**13 (54.167%)**

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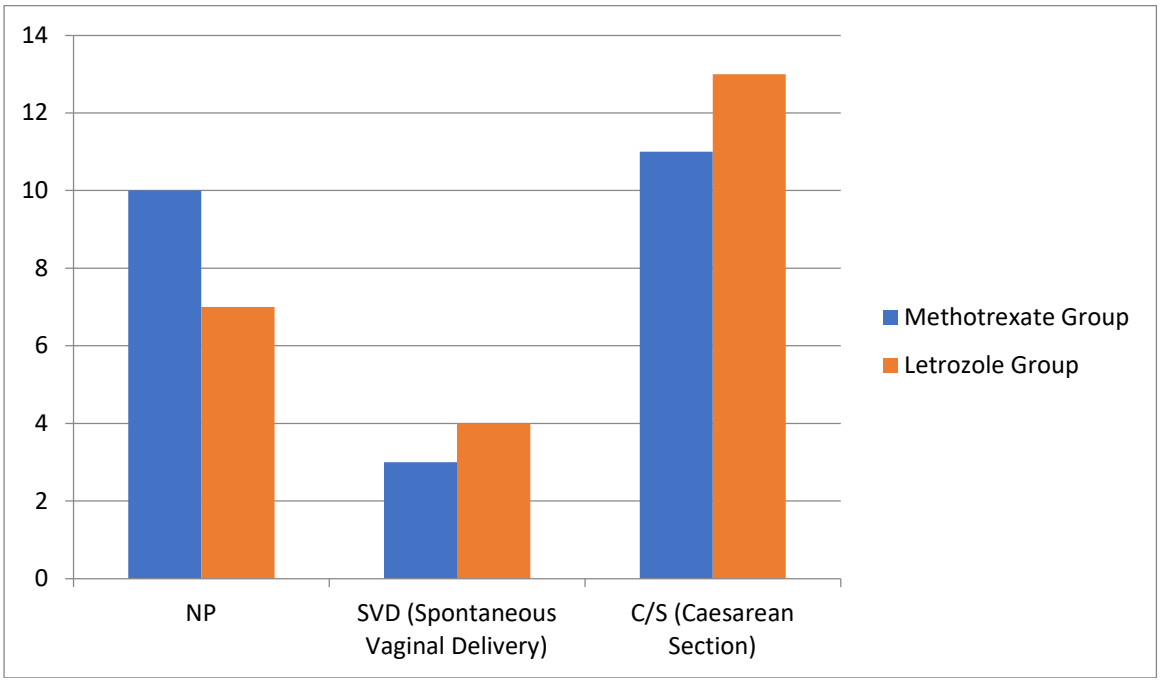

Figure (2): Shows Previous deliveries of both groups.

Table (4): show Previous Abortion of both groups, in the Methotrexate Group, 14 subjects with no previous abortion, 5 (20.833%) with one previous abortion, 3 (12.5%) with two previous abortions, and 2 (8.33%) with three previous abortions. In Methotrexate Group 12 subjects with no previous abortion, 5 (20.833%) with one previous abortion, 5 (20.833%) withtwo previous abortions, and 2 (8.33%) with three previous abortions.

Table (4): Previous Abortion of both groups

Number	Methotrexate Group	Letrozole Group
0	**14 (58.33%)**	**12 (50%)**
1	**5 (20.833%)**	**5 (20.833%)**
2	**3 (12.5%)**	**5 (20.833%)**
3	**2 (8.33%)**	**2 (8.33%)**

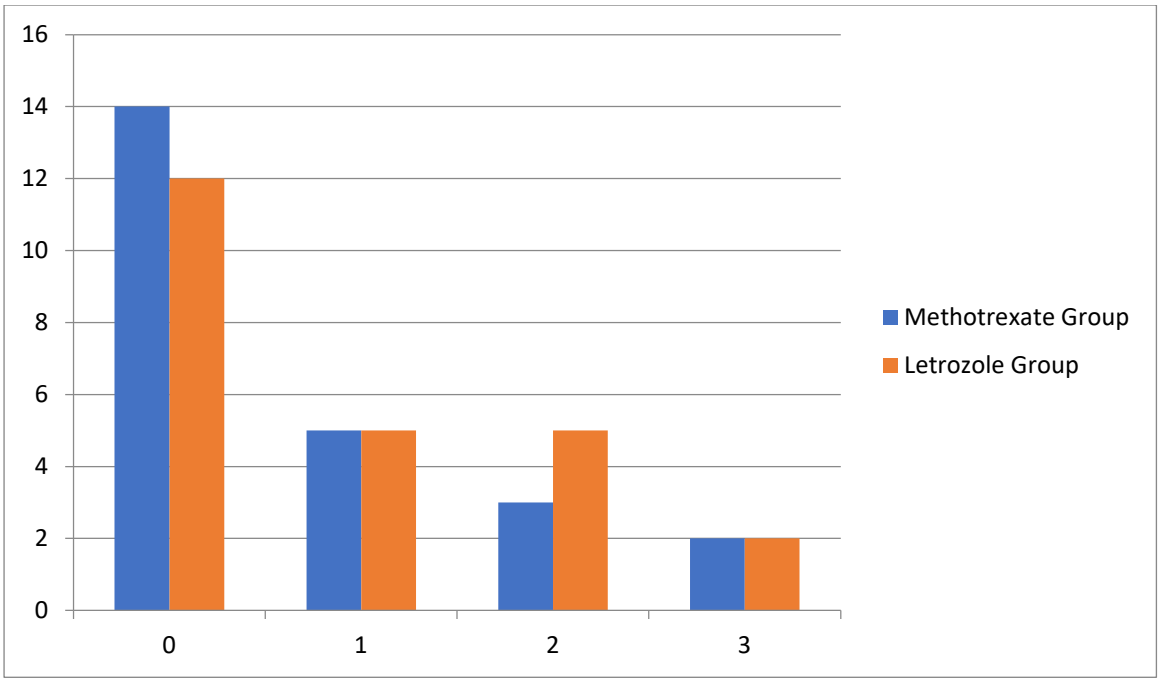

Figure (3): Show Previous Abortion of both groups

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Table (5) Shows the distribution of the studied patients regarding their ultrasound findings: Methotrexate Group, Adnexal mass size (cm) ranged between 1.9 - 4.2 cm with a mean of 3 and SD of 0.76. Letrozole Group, Adnexal mass size (cm) ranged between 2.5 - 4.5 cm with a mean of 3.2 and SD of 0.62. P-value of 0.762 with no Significant difference of both groups and no pelvic collection.

Table (5): Distribution of the studied patients regarding their ultrasound findings.

Adnexal mass size (cm)	**Methotrexate Group**	**Letrozole Group**	**P value**
Range	**1.9-4.2 cm**	**2.5-4.5 cm**	**0.762**
Mean ± SD	**3.0 ± 0.76**	**3.2 ± 0.62**	
Pelvic Collection	**No pelvic Collection**	**No pelvic Collection**	**Non-Significant**

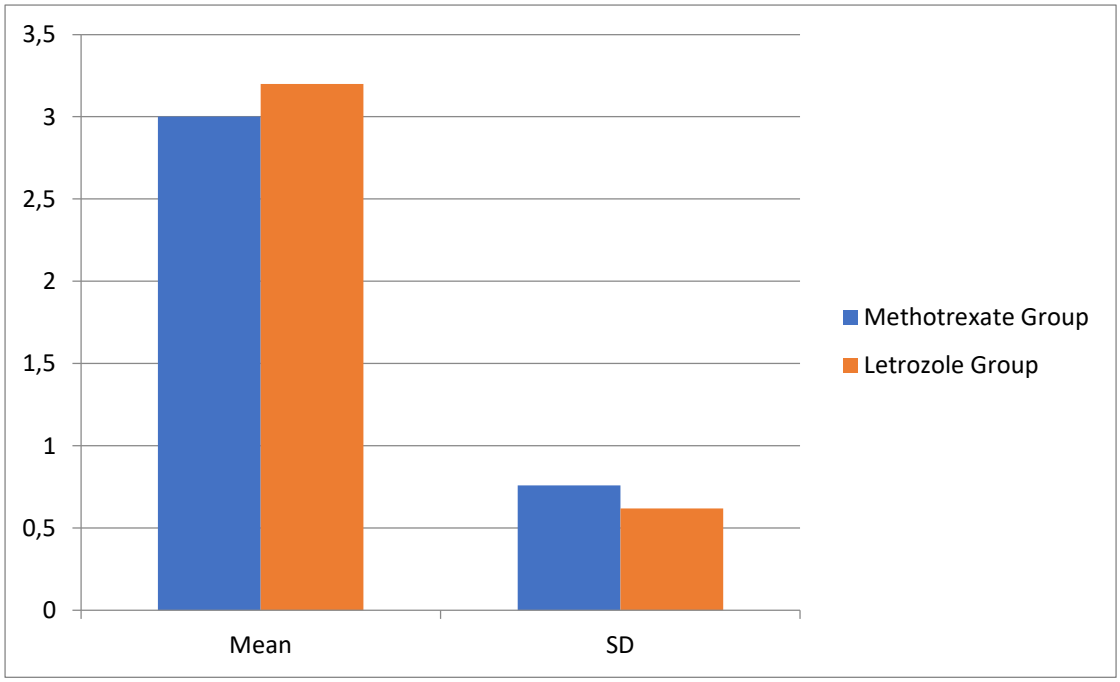

Figure (4): Adnexal mass size (cm) mean & SD.

Table (6) Shows Platelets and liver enzymes at different times between the three ectopic pregnancy groups. The mean of Platelets count in Methotrexate was 230.5 in treatment day and on Day 7 reached 152 * 103, in Letrozole was 220.9 in treatment day and on Day 7 reached 219.9 * 103. The mean AST level in Methotrexate was 18.8 on the treatment day and on Day 7 reached 40.1 (U/L), in Letrozole was 19.6 on treatment day and on Day 7 reached 18.9 (U/L). The mean of ALT level in Methotrexate was 28.5 in treatment day and on Day 7 reached 53 (U/L), in Letrozole was 20.9 in treatment day and on Day 7 reached 23.7 (U/L).

Table (6): Platelets and liver enzymes at different times between the three ectopic pregnancy groups.

Lab. test	**Methotrexate**	**Letrozole**	**P value**
Platelets count (*10^3)			
Treatment day	230.5±75.7 (162–380)	220.9±71.4 (157–383)	0.352
Day 7	152±48.4 (111–272)	219.9±63.2 (162–365)	0.058
P value	<0.001	0.747	
AST level (U/L)			

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Treatment day	18.8±2.3(17–24)	18.6±2.2 (15–24	0.223
Day 7	40.1±5.6 (31–52)	19.9±3.1 (15–27)	< 0.001
P value	< 0.001	0.056	
ALT level (U/L)			
Treatment day	28.5±4.9 (20–35)	20.9±4.7 (12–28)	< 0.001
Day 7	53±6.1 (38–63)	23.7±3.7 (17–27)	< 0.001
P value	< 0.001	< 0.05	

Values are meanstandard deviation (range) unless stated otherwise. ALT¼alanine aminotransferase; AST¼aspartate aminotransferase a statistically significant (P<.05)

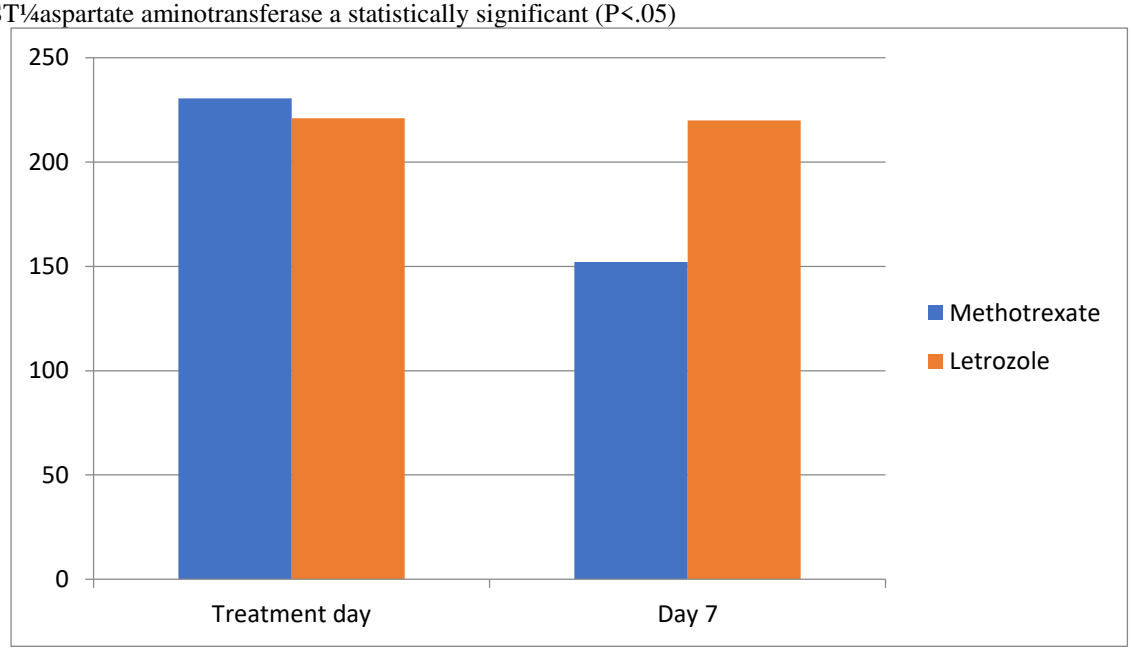

Figure (5) Shows the Means of Platelets count (*103) in both groups**.**

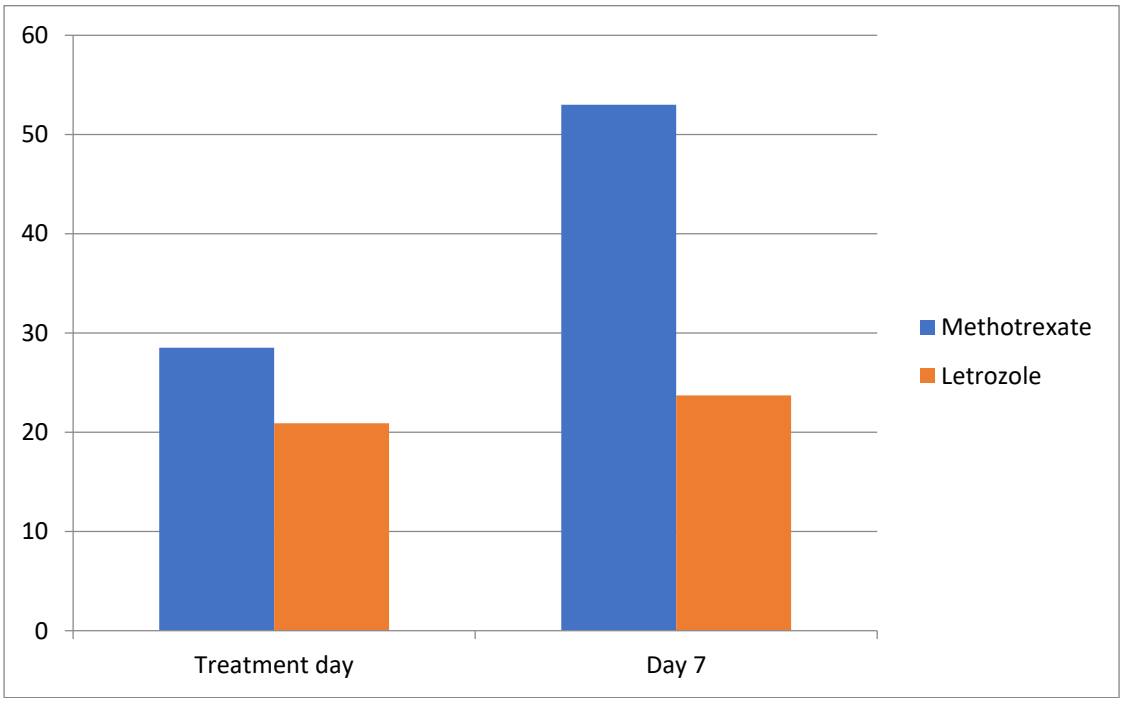

Figure (6) Shows the Means of AST level (U/L) in both groups.

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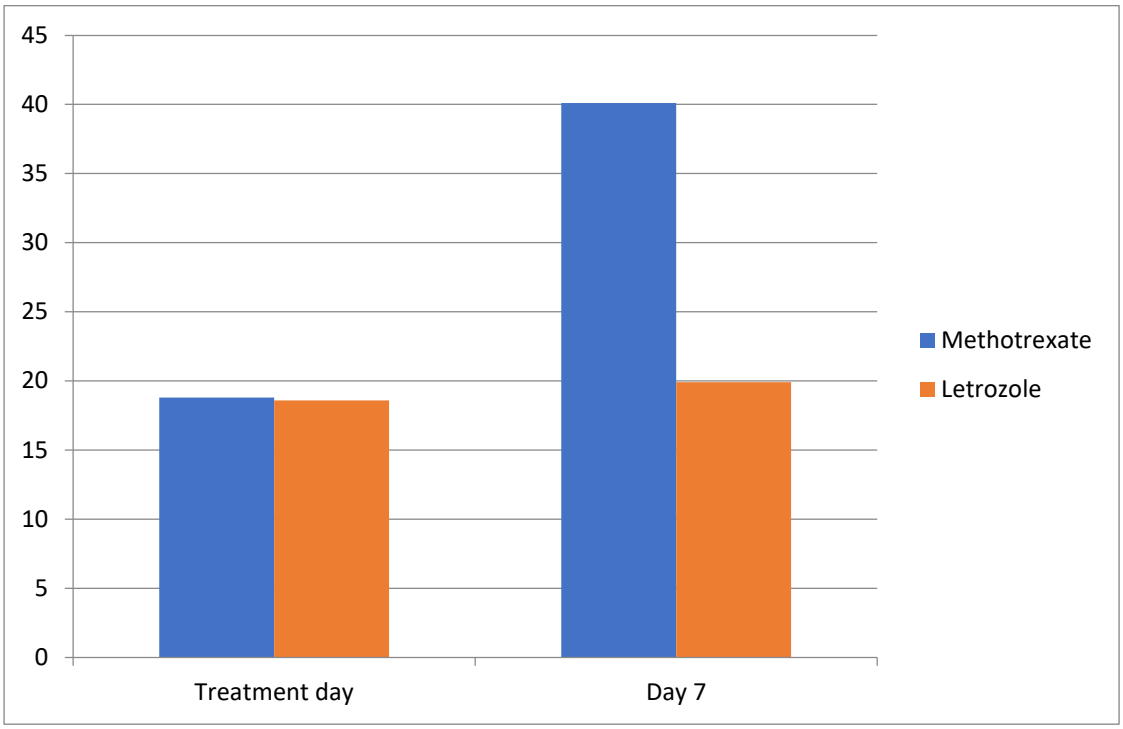

Figure (7) Shows the Means of ALT level (U/L) in both groups.

Table (7) Shows the Pre therapeutic (Basal) B-HCG titrein the different groups. The mean of Methotrexate Group was 1331 with SD of 235 and Mean of Letrozole Group was 856 with SD 123.

Table (7): The Pre therapeutic (Basal) B-HCG titrein the different groups.

Pre therapeutic B-HCG titre (mIU/ML)	**Methotrexate Group**	**Letrozole Group**	**P value**
value	1331 ± 235	856 ± 123	0.320
Significance			Non-Significant

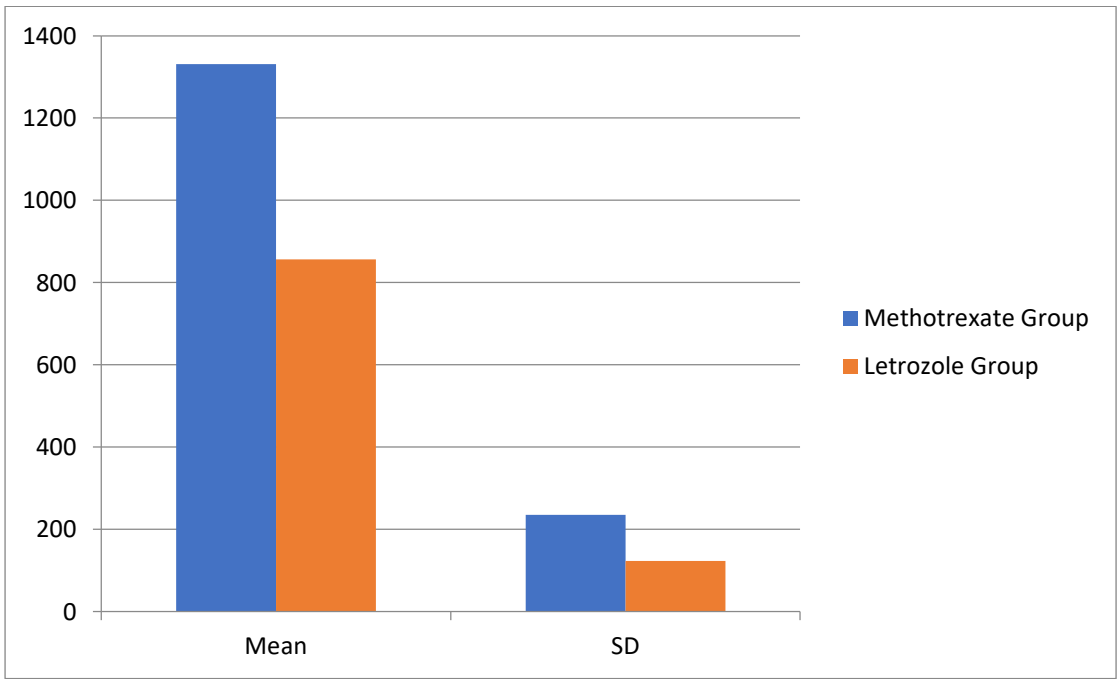

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Figure (8): Shows the Pre therapeutic (Basal) B-HCG titrein the different groups.

Table (8) Shows a Comparison of the serum B-HCG titre in the Methotrexate group at different times. Median at Day 1was 1331, Day 4 was 645, at day 7 was 315.5 and day 14 was 39.

Table (8): Comparison of the serum B-HCG titre in Methotrexate group at different times.

Methotrexate group	**Day 1**	**Day 4**	**Day 7**	**Day 14**
Median **IQR**	1331 (744.5 - 1632.3)	645 (329 - 871.5)	315.5 (179.3 - 395.5)	39 (30.8-53)
P Value				
Day 1		0.093	0.152	0.011
Day 4			0.101	0.011
Day 7				0.011

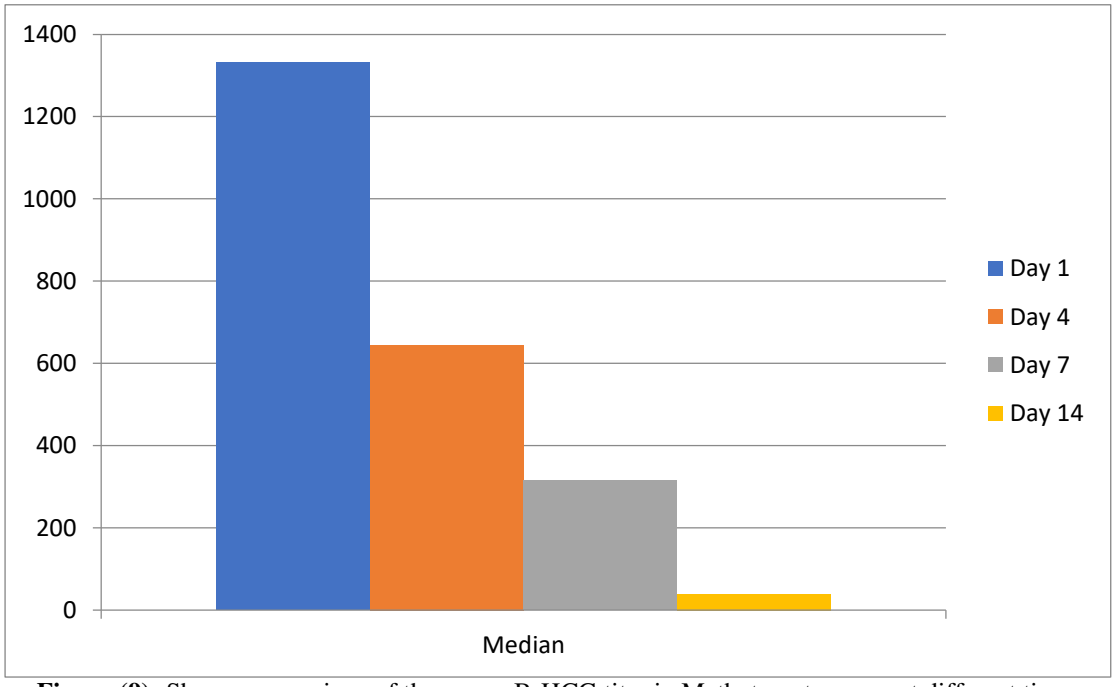

Figure (9): Shows comparison of the serum B-HCG titre in Methotrexate group at different times

Table (9): Shows Comparison of the serum B-HCG titre in the Letrozole group at different times. Median at Day 1was 856, Day 4 was 412, at day 7 was 114 and at day 14 was 29.

Letrozole group	**Day 1**	**Day 4**	**Day 7**	**Day 14**
Median **IQR**	856 (475.5-1406.3)	412 (262.5-1018)	114 (97.5-435)	29 (18.6-50.9)
P Value				
Day 1		0.089	0.156	0.003
Day 4			0.103	0.003
Day 7				0.003

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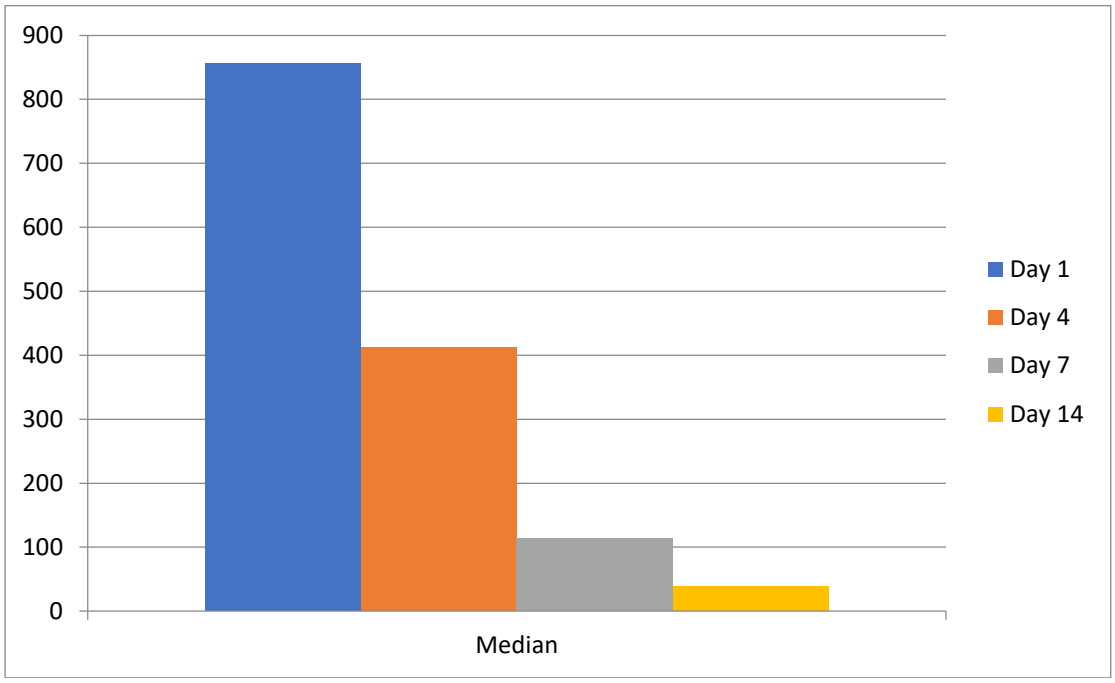

Figure (10): Shows Comparison of the serum B-HCG titre in Letrozole group at different times

Table (10) shows the distribution of the studied patients regarding the results after treatment. Success in Methotrexate Group reached 75%, while in Letrozole Group it reached 83.33%

Table (10): Distribution of the studied patients regarding the results after treatment.

Outcome	**Methotrexate Group**	**Letrozole Group**
Success	18 (75%)	20 (83.33%)
Failed	6 (25%)	4 (16.67%)

Table (11) Shows B-HCG titre on days 4 & 7 as a prediction of failure treatment after using Letrozole. The optimal cutoff of B-HCG at day 4 was > 1188, and on day 7 was > 605. Sensitivity, Specificity, PPV, NPV, Accuracy of the tests all reached 100%.

Table (11): B-HCG titre on days 4 & 7 as a prediction of failure treatment after using Letrozole

	On Day 4	**On Day 7**
Optimal cutoff of B-HCG	> 1188	> 605
95% CI	0.749-1	0.749-1
P value	< 0.001	< 0.001
Sensitivity **Specificity** **PPV** **NPV** **Accuracy**	100%	100%

4. Discussion

Ectopic pregnancy is a major cause of maternal morbidity and mortality. The estimated rate of ectopic pregnancy ranges between 1% to 2% of all pregnancies and 2% to 5% of pregnancies achieved after assisted reproduction. Although the overall mortality has decreased over time, mortality from ruptured ectopic pregnancy still accounts for up to 6% of all maternal deaths [9].

The reported incidence of ectopic pregnancy in the United States has been increasing over the years. Whether thehigher reported incidence reflects a true increase in the incidence of ectopicpregnancy or is secondary to an improvement in diagnostic techniques is unknown. Both factors probably play a role [10].

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The available interventions for treating ectopic pregnancy include surgery and medical management with Methotrexate. Methotrexate treatment has been found to be more cost-effective than surgical management while maintaining similar treatment success and future fertility [11].

However, the chemotherapeutic agent methotrexate is known to be associated with significant adverse effects and contraindications as well as increased failure rates, with high beta-human chorionic gonadotropin (b-hCG) and progesterone levels. In addition, methotrexate treatment is associated with a long interval until the resolution of the ectopic pregnancy and the need to wait for several weeks before another attempt at pregnancy [7].

Also, possible negative effects on ovarian reserve and future fertility potential are not unexpected[12].

Third-generation aromatase inhibitors such as Letrozole are well established in clinical use for suppressing estrogen production in women with breast cancer. Their safety, high tolerability, low cost, and associated minimal adverse effects have all been established over several decades of clinical use. This group of aromatase inhibitors, including Letrozole, has been shown to successfully block estrogen production in women of reproductive age[13].

We studied the use of the aromatase letrozole for the treatment of ectopic pregnancy in comparison with Methotrexate.

The aim of this study is to Improving outcomes of undisturbed ectopic pregnancy at Zagazig University Hospitals. We hypothesizeda promisingly high-resolution rate and better safety profile that Letrozole has compared with a chemotherapeutic agent such as Methotrexate should encourage further studies, that by inhibiting the estrogen synthetase (the aromatase enzyme), progesterone would not exert its physiological role in maintaining early pregnancy, which would include ectopic tubal pregnancy.

Our objective is to evaluate the efficacy and safety of medical treatment of undisturbed ectopic pregnancy either by Methotrexate or by aromatase inhibitors “Letrozole” treatment.

This comparative, prospective, interventional, randomized clinical study. This study was conducted in the Obstetrics and gynecological department of Zagazig University Hospitals.

Patients were randomly assigned into two equal-sized groups by closed envelop technique; The study will be two groups: Methotrexate (group 1) and Letrozole (group 2). Consecutive women with undisturbed tubal ectopic pregnancy medical treatment with Methotrexate (group 1) and medical treatment with Letrozole (group 2).

As demographic data of the studied group, age Mean was 27 with an SD of 11.5 years, and BMI mean 21.5 with an SD of 2.1.

In our study Methotrexate group show 10 (41.67%) no parity, 10 (41.67%) low parity, and 4 (16.67%) with high parity, while the Letrozole Group show 7 subjects (29.167%) with no parity 15 (62.5%) Low parity and 2 (8.33%) High (P3 or more).

In **(Abd El-Hameed et al., 2020)** [13] Methotrexate group show 40% with no parity, 40% low parity, and 20% with high parity, while the Letrozole Group shows 28.5% with no parity, 64.3% Low parity, and 7.2 High (P3 or more).

In an old paper **(Kendrick et al., 1996)** [14], In Ectopic pregnancy cases, 51.4% showed one parity, 32.6% showed two parity, and 15.9% showed three parities or more.

A recent study **(Anyanwu &Titilope, 2021)** [15]as parity level 0 was 14%, 1 was 32.6%, 2 was 18.6%, 3 was 4.7%, 4 was 14% and 5 or more was 16.3%.

About delivery, Methotrexate Group with ten subjects (41.67%) had no Previous deliveries, 3 (12.5%) with Spontaneous Vaginal Delivery, and 11 (45.833%) with Caesarean Section. Letrozole Group has seven subjects (29.167%) with no Previous deliveries, 4 (16.67%) with Spontaneous Vaginal Delivery, and 13 (54.167%) with Caesarean Section.

In **(Abd El-Hameed et al., 2020)** [13]. 40% no Previous deliveries, 10% with Spontaneous Vaginal Delivery, and 50% with Caesarean Section. Letrozole Group has 28.6% with no Previous deliveries, 14.3% with Spontaneous Vaginal Delivery, and 57.1 with Caesarean Section.

In an old study **(Michalas et al., 1992)** [16],non-cesarean section operation was 41.2% and with Cesarean operation reached 56.8%

According to abortion of both groups. In the Methotrexate Group, 14 subjects with no previous abortion, 5 (20.833%) with one previous abortion, 3 (12.5%) with two previous abortions, and 2 (8.33%) with three previous abortions. In Methotrexate Group 12 subjects with no previous abortion, 5 (20.833%) with one previous abortion, 5 (20.833%)with two previous abortions, and 2 (8.33%) with three previous abortions.

In an old study **(Michalas et al., 1992)** [16].spontaneous abortion was 0 in 74.5% cases, 1 in 15.8% cases 2 or more in 9.7% cases.

In **(Abd El-Hameed et al., 2020),** [13]. In the Methotrexate Group, 60% with no previous abortion, 20% with one previous abortion, 10% with two previous abortions, and 10% with three previous abortions. In the Methotrexate Group, 50% with no previous abortion, 21.4% with one previous abortion, 21.4%with 2 previous abortions, and 7.2%with three previous abortions.

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Distribution of the studied patients regarding their ultrasound findings: Methotrexate Group, Adnexal mass size (cm) ranged between 1.9 - 4.2 cm with a mean of 3 and SD of 0.76. Letrozole Group, Adnexal mass size (cm) ranged between 2.5 - 4.5 cm with a mean of 3.2 and SD of 0.62. P-value of 0.762 with no Significant difference of both groups and no pelvic collection.

Only **(Abd El-Hameed et al., 2020)** [13]. **D**id the same investigation and showed similar findings:Methotrexate Group, Adnexal mass size (cm) ranged between 2-4 cm with a mean of 3.1 and SD of 0.8. Letrozole Group, Adnexal mass size (cm) ranged between 2.5 - 4.5 cm with a mean of 3.3 and SD of 0.6. P-value of 0.740 with no Significant difference of both groups and no pelvic collection.

In **(Kirk et al., 2008)** [17] .Mass thickness was 10.1 mm with an SD of 5.7, and pelvic collection of free fluids was 57.8%.

In **(Frates et al., 2014)** [18]. Mean adnexal mass size in cm was 2.46 and ranged between 0.7 and 8.8., according to fluids findings, 0.4% was with moderate/large free fluid, and 5.2% was with small to no free fluid.

In our study according to Platelets and liver enzymes at different times between the ectopic pregnancy groups. The mean of Platelets count in Methotrexate was 230.5 in treatment day and on Day 7 reached 152 * 10^3, in Letrozole was 220.9 in treatment day and on Day 7 reached 219.9 * 10^3. The mean AST level in Methotrexate was 18.8 on treatment day and on Day 7 reached 40.1 (U/L), in Letrozole was 19.6 on treatment day and on Day 7 reached 18.9 (U/L). The mean of ALT level in Methotrexate was 28.5 in treatment day and on Day 7 reached 53 (U/L), in Letrozole was 20.9 in treatment day and on Day 7 reached 23.7 (U/L).

In **(Mitwally et al., 2020)** [7]Mean of Platelets count in Methotrexate was 251.5 in treatment day, and on Day 7 reached 162 * 10^3, in Letrozole was 214.9 in treatment day and on Day 7 reached 213.9 * 10^3. The mean AST level in Methotrexate was 19.8 on treatment day and on Day 7 reached 44.1 (U/L), in Letrozole was 18.1 on treatment day and on Day 7 reached 19.9 (U/L). The mean of ALT level in Methotrexate was 29.5 in treatment day and on Day 7 reached 52 (U/L), in Letrozole was 20.7 in treatment day and on Day 7 reached 22.7 (U/L).

In **(Park et al., 2010)** [19].As assessment for Methotrexate after treatment mean of platelet count was 275 (10^9/L), AST (IU/L) was 22 and SD was 6.37, and ALT (IU/L) was at a mean of 18 and SD of 9.02.

In **(Ozdemir et al., 2016)**[20]. ALT Before treatment was at a mean of 24.25 (IU/L), and AST was at a mean of 26.50 (IU/L). After seven days of treatment, ALT was at a mean of 51.50 (IU/L), and AST was at a mean of 40.37 (IU/L).

In our study Pre therapeutic (Basal) B-HCG titre in the different groups. Mean of Methotrexate Group was 1331 with SD of 235 and Mean of Letrozole Group was 856 with SD 123.

In **(Mitwally et al., 2020)** [7].The mean of Methotrexate Group was 1415 with and Mean of Letrozole Group was 1065.

In **(Abd El-Hameed et al., 2020)** [13].The mean of Methotrexate Group was 1328 with IQR of (734.5- 1647.3) and Mean of Letrozole Group was 865 with IQR (485.5- 1416.3).

According to serum B-HCG titre in Methotrexate group at different times. Median at Day 1was 1331, Day 4 was 645, day 7 was 315.5, and at day 14 was 39.

In **(Maleki et al., 2020)**[21]. Show high difference Serum hCG values were measured and compared on days 4 and 7 after Methotrexate; that were 47200 and 49000, respectively. However, huge difference may be due to estimation during pregnancy.

In **(Mitwally et al., 2020)**[7].serum B-HCG titre in Methotrexate group at different times. The median at Day 4 was 710.5, at day seven was 344 and at day 14 was 35.5.

In **(Abd El-Hameed et al., 2020)** [13].serum B-HCG titre in Methotrexate group at different times. Median at Day 1was 1328, Day 4 was 640, at day 7 was 314.5 and at day 14 was 39.5.

Serum B-HCG titre in Letrozole group at different times. Median at Day 1was 856, Day 4 was 412, at day 7 was 114 and at day 14 was 29.

In **(Mitwally et al., 2020)** [7].Serum B-HCG titre in the Letrozole group at different times. The median at Day 4 was 512.5, at day seven was 191.5 and on day 14 was 22.5.

In **(Abd El-Hameed et al., 2020)** [13].serum B-HCG titre in Letrozole group at different times. Median at Day 1was 865, Day 4 was 405, Day 7 was 180, and Day 14 was 29.

According to the distribution of the studied patients regarding the results after treatment. Success in Methotrexate Group reached 75%, while in Letrozole Group it reached 83.33%

Only **(Abd El-Hameed et al., 2020)** [13].Did a similar investigation and results were: Success in Methotrexate Group reached 80%, while in Letrozole Group it reached 78.6%.

5. Conclusion

This is a comparative, prospective, interventional, randomized clinical study that was conducted in the Obstetrics and gynecological department of Zagazig University Hospitals. Our study showed a promisingly high-resolution rate and better safety profile that Letrozole has compared with a chemotherapeutic agent such as Methotrexate should encourage further studies.

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