Letrozole Versus Tomoxifen in Infertile Woman with Clomiphene Citrate Resistant Polycystic Ovarian Syndrome

Original Article

Abd El-Haseib Salah Saad[1], Said Abd El-Atti Saleh[1], Asmaa Hazem Mahmoud El-Melih[2] and Mohamed Zakaria Sayer Dayer[1]

[1]*Department of Obstetrics & Gynecology, Faculty of Medicine, Menoufia University, Egypt*

[2]*Department of Obstetrics & Gynecology, Al Shohadaa General Hospital, Menoufia, Egypt*

ABSTRACT

Objectives: To compare the effects of Letrozole and Tamoxifen for induction of ovulation in clomiphene citrate resistant women with Polycystic Ovarian syndrome.

Patients and Methods: A prospective randomized study was conducted in the Department of Obstetrics & Gynecology of Menoufia University Hospital. The study was carried out on 80 clomiphene citrate resistant women with polycystic ovary syndrome divided into Group (1): received letrozole 2,5 mg tab orally twice per day from day 3 to day 7 of the menstrual cycle for three successive cycles (40 women, odd numbers). Group (2): received Tamoxifen 20 mg tab once per day from day 3 to day 7 of the menstrual cycle for three successive cycles (40 women, even numbers). In both groups, 10000 IU hCG was administrated when at least one mature follicle more than 18mm was observed during folliculometry.

Results: The mean number of follicles (≥18 mm) was higher in letrozole than tamoxifen group. Ovulation rate was significantly higher in letrozole than tamoxifen group (52.5% vs 20%) .There were no statistically significant differences between both groups regarding pregnancy rate.

Conclusion: Letrozole was eminent than tamoxifen in achieving a higher ovulation rate and should be considered for clomiphene citrate resistant women with polycystic ovarian syndrome.

Key Words: Clomiphene citrate resistant, letrozole, polycystic ovarian syndrome, tamoxifen.

Received: 09 September 2020, **Accepted:** 16 June 2023

Corresponding Author: Asmaa Hazem Mahmoud El-Melih, Department of Obstetrics & Gynecology, Al Shohadaa General Hospital, Menoufia, Egypt, **Tel.:** +2 010 1549 3580, **E-mail:** elkholy4eng@gmail.com

ISSN: 2090-7265, November 2023, Vol.13, No. 4

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is the most prevalent endocrine disorder among infertile women affecting approximately 4 to 12 % of women of reproductive age and considered the most common cause of anovulatory infertility (~75 %)[1]. It typically presents with anovulation (amenorrhoea. oligomenorrhoea or irregular cycles) associated with clinical and/or biochemical evidence of androgen excess (hirsutism, acne or alopecia) and polycystic ovaries by ultrasound[2].

Clomiphene citrate (CC) is the first common oral drug has been used to induce ovulation in PCOS women, but some women fail to conceive with this therapy. Clomiphene citrate (CC) is a selective estrogen receptor modulator that acts primarily by binding with estrogen receptors at the hypothalamus resulting in a drop of circulating estrogen to the hypothalamus and eventually increased gonadotrophin secretion and subsequent ovulation induction. Although CC results in ovulation in most patients, the pregnancy rates are disappointing[3]

Clomiphene citrate resistance, defined as failure to ovulate after receiving 150 mg of CC daily for 5 days per cycle for at least three cycles and occurs in ~ 15-40% in women with PCOS.Insulin resistance. Hyperandrogenemia, and morbid obesity represent the major risk factors involved in CC resistance, genetic predisposition is also suggested[4].

Tamoxifen (TMX) is another anti-estrogenic agent which is like to CC in structure has been considered for ovulation induction. Ovulation and pregnancy rates have been reported as 50-90%, 30-50% respectively[5] Tamoxifen has acceptable results in CC failure cases. The improved ovulation and pregnancy rates are mostly because of a higher score of cervical mucus[6].

Aromatase inhibitors (AI), aromatase is a cytochrome P-450 enzyme is responsible for the conversion of androgens to estrogens. (AI) block estrogen production, so the use of aromatase inhibitors may be useful in PCOS women who are resistant to anti-estrogen.[7] Letrozole, a potent aromatase inhibitor, it could be used for ovulation

 DOI:10.21608/EBWHJ.2023.44462.1112

with obvious lack of anti-estrogen adverse outcome as thin endometrium and poor cervical mucus due to its half-Life is shorter than clomiphene, so pregnancy rate is improved[8].

AIM OF STUDY

The aim of the present study was to compare the effects of Letrozole and Tamoxifen for ovulation induction in clomiphene citrate resistant women with Polycystic Ovarian syndrome.

PATIENTS AND METHODS

We conducted a prospective randomized study during the period from October 2019 till June 2020 at the Obstetrics & Gynecology outpatient clinic of Menoufia University Hospital. The study was carried out on 80 clomiphene citrate resistant women with polycystic ovary syndrome.

Clomiphene resistance was defined as failure to ovulate after administrating 150mg clomiphene citrate /day for 5 days for at least three successive cycles[9]

The selected cases were randomly divided, by sealed envelopes, into two groups

Group (1): received letrozole (Femara; Novartis) 2,5 mg tab orally twice daily from cycle day 3 to cycle day 7 for three successive cycles (40 women ,odd numbers).

Group (2): received Tamoxifen 20 mg tab once daily from cycle day 3 to cycle day 7 for three successive cycles (40 women , even numbers).

Inclusion criteria

Age from 20 to 35 year; primary or secondary infertility; diagnosed as polycystic ovary syndrome according to Rotterdam Criteria which must have two of three of these criteria; oligomenorrhea and/or anovulation, clinical and/or biochemical signs of hyperandrogenism and/or polycystic ovary on ultrasound; patent both tubes on hysterosalpingography and normal semen analysis.

Exclusion criteria

Infertility due to other causes of uterine & tubal pathologies; Male factor infertility; History of the pelvic inflammatory process.

Ethical consideration

The study was approved by the ethical committee of Faculty of Medicine, Menoufia University. Explaining the importance of the study to patients to become more interested and cooperative; The confidentiality of the patient's data was guaranteed; The patients had the right to refuse participation in this study and to end the meeting at any time they want without giving any reasons; Written informed consent from all participants was obtained after explanation of the procedures.

Patients evaluation

All women were subjected to: detailed history taking, physical examination and complete workup of infertile couples including semen analysis (to exclude male factor infertility), Hysterosalpingography (to exclude tubal or uterine factor infertility.) and hormonal profile (FSH,LH,TSH and prolactin levels)

Transvaginal ultrasound

Serial transvaginal ultrasound were done for each case for detection of ovulation, beginning from cycle day 10 & every other day with measurement of number & size of follicles & thickness of endometrium and 10000 IU hCG was administrated Intramuscular to trigger ovulation when at least one mature follicle more than 18mm in diameter was observed during folliculometry. These follow up was done for every case and for three successive cycles unless pregnancy occur after the 1st or the 2nd cycle.

Ultrasound to be done after one week from the triggering to confirm that the ovulation was occurred.

The occurrence of ovulation was determined by one of the following criteria: The development of a mature follicle of size ≥17 mm followed by its disappearance; change in the shape of the follicle , appearance of internal echoes within the follicle; presence of free fluid in the Douglas pouch[10].

Luteal phase support was done by micronized progesterone 100mg twice daily for 15 days and then pregnancy test was done for missed period cases.

Statistical Analysis

Results were tabulated and statistically analyzed by using a personal computer using MICROSOFT EXCEL 2016 and SPSS v. 21 (SPSS Inc., Chicago, IL, USA. Statistical analysis was done using: Descriptive: e.g. percentage (%), mean and standard deviation. Analytical: that includes: Chi-Squared ($\chi 2$), t test. A value of *P* less than 0.05 was considered statistically significant.

RESULTS

(Table 1) shows that, there were no statistically significant differences between the studied groups regarding age and BMI. The mean age of the studied patients in letrozole group was 28.5±6.82 years vs. 27.67±4.01 years in tamoxifen group. The mean BMI in letrozole group was 29.93± (kg/m2) vs 31.04± (kg/m2) in tamoxifen group

(Table 2) shows that, there were no statistically significant differences between the studied groups regarding basal FSH, basal LH, TSH, Prolactin, AMH, type of infertility and the duration of infertility

In letrozole group, the total number of patients with mature follicles >18 mm in diameter on hCG administration day was 24 patients ,while in tamoxifen group, the collective number of patients with mature follicles >18 mm on the day of hCG administration was only 11 patients (Table 3).

The diameter of the dominant follicle in day 14 of the 1st cycle was significantly higher in cases who received letrozole than in patients received tamoxifen (18.0±0.50 vs. 14.10±2.08) (p-value 0.034) (Table 4).

Ovulation rate was significantly higher in patients received letrozole than those received tamoxifen (52.5% vs. 20%). There were no statistically significant difference between both groups regarding pregnancy rate (Table 5).

Table 1: Main demographic characteristics of the studied groups (n= 80)

Parameters	Letrozole (n=40)	Tamoxifen (n=40)	T test	*P- value*
Age/year				
Mean ± SD	28.5±6.82	27.67±4.01	0.398	0.680
Range	20 - 31	23 - 30		
Weight/kg				
Mean ± SD	78.55±12.28	87.6±10.13	1.30	0.091
Range	62 - 95	72 - 101		
Height/cm				
Mean ± SD	162.05±15.22	168.1±1.93	0.075	0.800
Range	151-166	154-170		
BMI /(kg/m^2)				
Mean ± SD	33.55±2.93	32.18±1.45	0.022	0.950
Range	27.19-34.5	30.36-34.95		

BMI: body mass index**, NS:** non-significant at 95%, **S.D:** Standard deviation, **T test:** T-independent test

Table 2: Main clinical and laboratory characteristics of the studied groups (n= 80)

Parameters	Letrozole (n=40)		Tamoxifen (n=40)		t test	*P- value*
Basal FSH (mlU/ml)						
Mean ± SD	5.23±2.67		6.15±3.47		2.00	0.067^{NS}
Range	4 - 9.6		5.2 - 9			
Basal LH (mlU/ml)						
Mean ± SD	9.85±2.27		12.16±4.02		1.88	0.054 ^{NS}
Range	6.58 -14.6		10.5 - 16.7			
TSH						
Mean ± SD	2.81±0.069		2.7±1.12		0.52	0.700 ^{NS}
Range	0.93-3.7		0.92-3.1			
Prolactin						
Mean ± SD	16.5±3.28		١٥.٣٥±٣,٦٤		1.01	0.35 ^{NS}
Range	11.6-20		10.1-23.1			
AMH						
Mean ± SD	4.86±1.73		7.25±0.78		2.16	0.056 ^{NS}
Range	1.8-8		5.9-8.2			
Duration of infertility /year						
Mean ± SD	5.67±1.14		5.45±1.93		0.04	0.770 ^{NS}
Range	1.5 - 8		1.5 - 8			
Type of infertility	No.	%	No.	%	X^2	*P- value*
Primary	30	75.00	32	80.00	0.032	0.604 ^{NS}
Secondary	10	25.00	8	20.00		

FSH: follicle-stimulating hormone**, LH:** *luteinizing* hormone, **TSH:** thyroid stimulating hormone, **AMH:** anti-mullerian hormone, **t test:** T- independent test. **X^2:** Chai Square, **NS:** Non-significant.

Table 3: Folliculometry in three cycles of the studied groups (n= 80)

	TVS			No. of patients with follicle >18mm	No. of pregnancies
	day 10	day 12	day 14*		
Letrozole group					
First cycle					
• Diameter of follicle (mm)	5-7	7-9	9-19	7	0
• Mean diameter of follicle (mm)	6	8	18		
• Mean number of mature follicles	--	--	1.02		
Second cycle					
• Diameter of follicle (mm)	5-7	8-9	9-20	8	1
• Mean diameter of follicle (mm)	6	8.5	14.5		
• Mean number of mature follicles	--	--	1.12		
Third cycle					
• Diameter of follicle (mm)	6-9	9-10	11-20	9	1
• Mean diameter of follicle (mm)	7.5	9.5	15.5		
• Mean number of mature follicles	--	--	1.2		
Tamoxifen group					
First cycle					
• Diameter of follicle (mm)	5-8	8-9	9-19	3	0
• Mean diameter of follicle (mm)	6.5	8.5	14		
• Mean number of mature follicles	--	--	8.7		
Second cycle					
• Diameter of follicle (mm)	7-9	9-9	9-19	4	0
• Mean diameter of follicle (mm)	8	9	14		
• Mean number of mature follicles	--	--	8.92		
Third cycle					
• Diameter of follicle (mm)	6-9	9-10	11-19	4	1
• Mean diameter of follicle (mm)	8	9.5	15		
• Mean number of mature follicles	--	--	9.2		

TVS: Transvaginal ultrasonography * Day of hCG injection

Table 4: Diameter of follicle at day 10,12,14 of 3 cycles in the studied groups (n= 80)

Diameter of Follicle (mm)		Letrozole group (N=40)	Tamoxifen group (N=40)	Unpaired t test	*P- value*
1st cycle	Day 10	6.0±1.21	6.50±3.11	1.03	0.095
	Day 12	8.14±4.01	8.50±2.45	1.12	0.098
	Day 14	18.0±0.50	14.10±2.08	3.17	0.034*
2nd cycle	Day 10	8.16±5.90	6.30±0.85	2.10	0.045*
	Day 12	8.50±3.44	9.30±0.47	0.32	0.401
	Day 14	14.50±1.66	14.20±0.81	0.19	0.520
3rd cycle	Day 10	7.51±2.05	8.01±1.34	1.05	0.809
	Day 12	9.50±1.88	9.50±3.05	0.00	1.00
	Day 14	15.50±1.27	15.00±0.71	0.81	0.670

***:** Statistically Significant.

Table 5: Ovulation and pregnancy rates in the studied groups (n= 80)

		Letrozole group (N=40)		Tamoxifen group (N=40)		X^2	*P-value*
		No.	%	No.	%		
Ovulation Rate	+ve	21	52.50	8	20.00	5.92	0.015*
	-ve	19	47.50	32	80.00		
Pregnancy rate	+ve	2	5.00	1	2.50	1.23	0.075
	-ve	38	95.00	39	97.50		

X^2: Chai Square Test, *: Statistically Significant.

DISCUSSION

The current study compared the reproductive outcomes of women with CC-resistant PCOS after administration of the letrozole and tamoxifen. Our data showed that ovulation rate with letrozole (52.5%) was higher than with tamoxifen (20%).

Our findings showed that, there was no statistically significant difference between both groups regarding main demographic data (age and BMI). Consistent with our results, EL-Gharib and his colleagues who found that, there was no significant difference between both groups regarding age and BMI[11]. Sowedan and his colleagues also showed that, there was no significant difference between the studied groups concerning demographic data (age, BMI)[12].

In our study, there was no significant difference between both groups regarding hormonal profile (basal FSH, basal LH, TSH, prolactin and AMH), type of infertility and duration of infertility. Agreeing with our results, Ibrahim and his colleagues who conducted a study among 80 women with CC-resistant PCOS, 40 of them received 2.5 mg letrozole. They found that, there were insignificant differences regarding baseline hormonal levels, including LH, FSH, AMH[13]. These results were in agreement with (Abdellah *et al*.,[14] & Elnashar *et al*.,[15] & Badawy *et al*.,[16]).

The present study showed that, the total number of patients with follicles more than 18 mm in diameter on hCG administration day in letrozole group was 24 patients while in tamoxifen group, it was only 11 patients. Similar to our results, EL-Gharib and his colleagues who reported that the collective number of women with follicles more than 18 mm in diameter on hCG administration day in tamoxifen and letrozole groups was 8 and 21 respectively[11].

The diameter of the dominant follicle in day 14 of the 1st cycle was significantly larger in letrozole group than in tamoxifen group (18.0±0.50 versus. 14.10±2.08) (*p-value* 0.034). Ovulation rate was significantly superior in letrozole group than tamoxifen group (52.5% versus. 20%). There were no significant differences between the studied groups regarding pregnancy rate

On contrary, Alobaidy *et al*.,[5] reported that, the diameter of the dominant follicle was significantly higher in day 10,12, and 14 of the cycle in letrozole group than in tamoxifen group. Also, Athar and his colleagues conducted a study on 90 infertile women and found that, more follicles developed and higher clinical pregnancy rates were reported in the longer letrozole protocol[8]. These different results may be due to a different study design and regime.

Our study showed that, Letrozole was eminent than tamoxifen in achieving a higher pregnancy (5% vs. 2.5%) but the difference not reached the statistical significance. Ovulation rate was significantly higher in letrozole population (n=21, 52.75%) than tamoxifen group (n=8, 20%). Our results were consistent with EL-Gharib and his colleagues who reported that, the ovulation rate in letrozole group (23.33%) was higher than in tamoxifen group (8.89%). Regarding pregnancy rate, it was about 5.56% with letrozole, compared to 2.2% with tamoxifen. No significant difference was found between both groups[11].

Holzer and his colleagues also observed that letrozole had ovulation rate of 70-84% and pregnancy rate of 20-27% / cycle in clomiphene citrate resistant women with polycystic ovarian syndrome[18]. Higher follicular development and higher pregnancy rate were documented in the longer letrozole protocol (2.5 mg/day for 10 days) than in the standard protocol (5 mg/day for 5 days)[16]. A meta-analysis including 4 RCTs comparing tamoxifen and CC showed similar ovulation rate[19]. On contrary, the study of Kishk,[17] showed that both letrozole and tamoxifen have comparable ovulation and pregnancy rates with no statistically significant difference.

In accordance with our study, Seyedoshohadaei and his colleagues compared the effectiveness of letrozole, tamoxifen along with Clomiphene regarding pregnancy and ovulation rates among non-PCOS population and no significant difference was observed. Ovulation rates reported in their study were in line with our findings while pregnancy rates were higher (50% and 40% for letrozole and tamoxifen, respectively)[20]. This difference in pregnancy rate may be due to longer duration of follow up in their study (6 months) versus 3 months in our study. Elnashar and his colleagues recorded ovulation rate of 54.6% and pregnancy rate of 25% with letrozole regimen for ovulation induction in CC resistant PCOS women[15] . Ganesh and his colleagues also reported ovulation rate of 79.3% and pregnancy rate of 23.39% with letrozole protocol[21]. The relatively low pregnancy rate in our study may be attributed to using a relatively small dose of drugs.

CONCLUSION

Letrozole was eminent than tamoxifen in achieving a higher ovulation rate and should be considered for clomiphene citrate resistant women with polycystic ovarian syndrome.

CONFLICT OF INTERESTS

There are no conflicts of interest.

REFERENCES

1. Lauritsen MP, Pinborg A, Loft A, Petersen JH, Mikkelsen AL, Bjerge MR, *et al*. Revised Criteria for PCOS In WHO G Roup II Anovulatory Infertility–A Revival of Hypothalamic Amenorrhoea? Clinical Endocrinology. 2015; 82(4):584-91.
2. Roque M, Tostes AC, Valle M, Sampaio M, Geber S. Letrozole versus Clomiphene Citrate in Polycystic Ovary Syndrome: Systematic Review and Meta-Analysis. Gynecological Endocrinology. 2015; 31(12):917-21.
3. Onalan G, Zeyneloglu HB. Ovarian Stimulation Protocols. Manual of Ovulation Induction & Ovarian Stimulation Protocols. 2016:103.

4. Tessaro I, Modina SC, Franciosi F, Sivelli G, Terzaghi L, Lodde V, Luciano AM. Effect of Oral Administration of Low-Dose Follicle Stimulating Hormone on Hyperandrogenized Mice as a Model of Polycystic Ovary Syndrome. Journal of Ovarian Research. 2015; 8(1):64.
5. Alobaidy EJ, Mohammed IF, Saadi RK. Comparison the Effect of Letrozole And Tomoxifin In Infertile Women with Clomid Citrate Resistant in Polycystic Ovarian Syndrome. International Journal of Research in Pharmaceutical Sciences. 2017; 8(4):783-6.
6. Jie L, Li D, Yang C, Haiying Z. Tamoxifen versus clomiphene citrate for ovulation induction in infertile women. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2018; 228:57-64.
7. Ghomian N, Khosravi A, Mousavifar N. A Randomized Clinical Trial on Comparing the Cycle Characteristics of Two Different Initiation Days of Letrozole Treatment in Clomiphene Citrate Resistant PCOS Patients in IUI Cycles. International Journal of Fertility & Sterility. 2015; 9(1):17.
8. Athar R, Mehrnoosh M, Farzaneh A, Masoumeh H, Sobhanian S. Assessing an Optimal Regimen in Treatment of Infertility (Clomiphene Citrate, Tamoxifen and Vit. E versus Estrogen, Letrozole and Tamoxifen): A Double-Blind Control Trial. Pharmacology. 2015; 11(4):377-81.
9. Bae SA, Joo JK, Choi JR, Kim SS, Lee KS. Clinical outcomes of three-or five-day treatment with clomiphene citrate combined with gonadotropins and a timed intercourse cycle in polycystic ovary syndrome patients. Clinical and experimental reproductive medicine. 2015; 42(3):106.
10. Deepika K, Sindhuma D, Kiran B, Ravishankar N, Gautham P, Kamini R. Empty Follicle Syndrome Following Gnrha Trigger in PCOS Patients Undergoing IVF Cycles. Journal of Reproduction & Infertility. 2018; 19(1):16.
11. EL-Gharib MN, Mahfouz AE, Farahat MA. Comparison of Letrozole versus Tamoxifen Effects in Clomiphen Citrate Resistant Women with Polycystic Ovarian Syndrome. Journal of Reproduction & Infertility. 2015; 16(1):30.
12. Sowedan I, Salama K, El Shaer O. Tamoxifen versus Letrozole in Combination with Clomiphene Citrate to Stimulate Ovulation in Clomiphene-Resistant PCOS Women. Evidence Based Women's Health Journal. 2015; 5(4):207-12.
13. Ibrahim MH, Tawfic M, Hassan MM, Sedky OH. Letrozole Versus Laparoscopic Ovarian Drilling in Infertile Women with PCOS Resistant to Clomiphene Citrate. Middle East Fertility Society Journal. 2017;22(4):251-4.
14. Abdellah MS. Reproductive Outcome After Letrozole Versus Laparoscopic Ovarian Drilling for Clomiphene-Resistant Polycystic Ovary Syndrome. International Journal of Gynecology & Obstetrics. 2011;113(3):218-21.
15. Elnashar A, Fouad H, Eldosoky M, Saeid N. Letrozole Induction of Ovulation in Women with Clomiphene Citrate–Resistant Polycystic Ovary Syndrome May Not Depend on The Period of Infertility, The Body Mass Index, Or the Luteinizing Hormone/Follicle-Stimulating Hormone Ratio. Fertility and Sterility. 2006;85(2):511-3.
16. Badawy A, Mosbah A, Shady M. Anastrozole Or Letrozole For Ovulation Induction in Clomiphene-Resistant Women with Polycystic Ovarian Syndrome: A Prospective Randomized Trial. Fertility and Sterility. 2008;89(5):1209-12.
17. Kishk EA. Letrozole versus Tamoxifen for Ovulation Induction in Non-Polycystic Ovarian Syndrome Anovulatory Infertile Females. Evidence Based Women's Health Journal. 2019; 9(2):468-73.
18. Holzer H, Casper R, Tulandi T. A New Era in Ovulation Induction. Fertility and Sterility. 2006;85(2):277-84.
19. Boostanfar R, Jain JK, Mishell Jr DR, Paulson RJ. A Prospective Randomized Trial Comparing Clomiphene Citrate with Tamoxifen Citrate for Ovulation Induction. Fertility and Sterility. 2001;75(5):1024-6.
20. Seyedoshohadaei F, Tangestani L, Zandvakili F, Rashadmanesh N. Comparison of The Effect of Clomiphene-Estradiol Valerate Vs Letrozole On Endometrial Thickness, Abortion and Pregnancy Rate in Infertile Women with Polycystic Ovarian Syndrome. Journal of Clinical and Diagnostic Research: JCDR. 2016; 10(8): QC10.
21. Ganesh A, Goswami SK, Chattopadhyay R, Chaudhury K, Chakravarty B. Comparison of Letrozole With Continuous Gonadotropins and Clomiphene-Gonadotropin Combination for Ovulation Induction In 1387 PCOS Women After Clomiphene Citrate Failure: A Randomized Prospective Clinical Trial. Journal of Assisted Reproduction and Genetics. 2009;26(1):19-24.