OPEN AIMJ ORIGINAL ARTICLE

Comparative Study Between the Effect of Letrozole Versus Letrozole with Metformin in Treatment of Anovulation in Overweight Women

Obstetrics & Gynecology

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Received *for publication January 25, 2022;* ***Accepted*** *July 30, 2022;* ***Published online*** *July 30, 2022.*

doi: *10.21608/aimj.2022.118648.1815*

Citation: *Hamada S. , Abdallah K. , Samir K. Comparative Study Between the Effect of Letrozole Versus Letrozole with Metformin in Treatment of Anovulation in Overweight Women.AIMJ. 2022; Vol.3-Issue7 : 89-95.*

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ABSTRACT

Background: Ovulation disorders account for around 30% of infertility and are frequently accompanied by irregular menstrual (oligomenorrhoea) or an absence of periods (amenorrhea). Several therapies are easy and efficient, so couples might only require limited contact with doctors. This makes it simpler for a couple to retain a private love connection than in stressful situations.

Aim of the work: To assess the impact of letrozole with letrozole plus metformin as an ovulation inducing agent in anovulatory overweight women.

Patients and methods: Prospective study was performed on total 100 anovulatory overweight women attending infertility outpatient Clinic in Al-Hussein University Hospitals and Dar Ismail Hospital for Obstetrics and gynecology, Alexandria, Egypt, from 1st March to 31st December 2019.

Results: There was an insignificant rise in the cumulative pregnancy rate between the metformin-letrozole and the letrozole groups. In the metformin-letrozole group, 42% of the patents got pregnant, compared with 36% of the patients in the letrozole group. There were no significant differences between the letrozole and the metformin-letrozole groups regarding ovulation rate, number of patients has growing follicle, number of growing follicles (follicles ≥ 18) at day 12, number of ruptured follicles after 48 hours of injection of HCG, serum E2, Parity, clinical presentation, Period of infertility, FSH, LH. There has been a significant rise in group B (8.77) compared to group A (8.23) as regards endometrial thickness.

Conclusion: : Metformin added to letrozole does not improve the outcome of an overweight ovulated woman except that it improves endometrial thickness only.

Keywords: *Anovulation; Letrozole; Metformin; overweight.*

Disclosure: *The authors have no financial interest to declare in relation to the content of this article. The Article Processing Charge was paid for by the authors.*
Authorship: *All authors have a substantial contribution to the article.*

INTRODUCTION

Ovulation disorders are responsible for around 30% of all infertility cases, and they're often accompanied by irregular menstruation (oligomenorrhoea) or period absence (amenorrhea). Several of the therapies are easy and efficient, so couples might only need to see a doctor once or twice. This makes it simpler for a couple to retain a private love connection than it would be in the stressful, technological setting of an aided pregnancy. Nevertheless, ovulation stimulation does not work for all types of anovulation. Medical or surgical stimulation can be used to treat anovulation, but the cause of the anovulation affects whether or not ovulation induction is feasible. [1].

In women, ideal body weight is linked to the onset and preservation of reproductive functions; underweight (BMI > 18.5 kg/m2), overweight (BMI 25–29 kg/m2), and obesity (BMI ≤ 30 kg/m2) are all linked to a higher risk of anovulatory infertility 2.

Overweight and obesity are linked to irregular menstrual periods, lower spontaneous and aided fertility, and a higher rate of abortion [3]. Excess weight and a central body fat distribution are linked to a higher risk of normogonadotrophic anovulation 4. Although the mechanism by which weight hinders fertility is uncertain, such patients have reduced levels of sex hormone-binding globulin (SHBG), as well as higher androgen, insulin production, and insulin resistance [5].

Metformin is a biguanide anti hyperglycemic drug that has been proven to alleviate hyperandrogenism, hyperinsulinemia, and monthly cyclicity for both obese and non-obese PCOS women, most probably due to its beneficial impacts on insulin elimination and abdominal obesity [6].

New evidence indicates that insulin receptor phosphorylation and insulin receptor substrates could be one of metformin's methods of action [7].

Metformin also seems to have cardio-protective impacts on serum lipids and plasminogen activator inhibitor (PAI)-1, suggesting that it could reduce the chance of developing T2D [8].

Letrozole is a powerful aromatase inhibitor with good ovulation potential; it blocks estrogen synthesis by a direct effect on hypothalamic-pituitary-ovarian function, which may lead to a rise in rates of pregnancy. [9].

A more physiologic hormonal activation of the endometrium, decreased multi-pregnancy rates via single-follicle recruitment, a better adverse effect profile with fewer vasomotor and mood signs, and quick elimination are all possible advantages of aromatase inhibitors [10].

The study's goal is to compare the effects of letrozole versus letrozole combined with metformin as an ovulation-inducing agent in anovulatory overweight women.

PATIENTS AND METHODS

After ethical committee approval and written consents from the patients, this prospective study was performed on total 100 Anovulatory overweight women attending infertility outpatient Clinic in Al-Hussein University Hospitals and Dar Ismail Hospital for Obstetrics and gynecology, Alexandria, Egypt, from 1st March to 31st December 2019.

Study population: Anovulatory overweight women attending infertility outpatient Clinic in Al-Hussein University Hospitals and Dar Ismail Hospital for Obstetrics and gynecology, Alexandria, Egypt with the following inclusion criteria:

Inclusion criteria: Anovulatory infertile women for more than one year associated with overweight, BMI ranging from 25 to 29 kg /m², Aged from 21- 35 years old, Standard parameters of the husband's semen, Normal value of prolactin hormone.

Exclusion criteria: Hypersensitivity to letrozole or metformin, Obese women with BMI ≥29 kg/m² or women with BMI <25 kg/m², FSH above 11 mg, Any other cause of infertility other than anovulation due to overweight as uterine factor, tubal factor, male factor, ovarian pathology or endometriosis, Any medical disorder that may affect pregnancy or systemic disease (cardiovascular, renal, hepatic, CNS diseases and hypo or hyperthyroidism), Missed patient, Discontinuation of drug due to its side effects.

Study Procedures: All participants were submitted to the following:

A series of blind envelopes numbered 1 to 100 were used to divide the patients into two groups at random. Every patient has been allowed to take an envelope and has been classified into one of two groups:

• Group A: Letrozole group (envelopes number 1-50)

• Group B: Metformin- Letrozole group (envelopes number 51-100).

History: including

The age (female partner and male partner), parity, gravidity, pregnancy results and complications, period length, and the start and intensity of dysmenorrhea, sexual dysfunction, and frequency of coital, The length of infertility, as well as the outcomes of any prior assessments and therapies, Previous surgery, its rationale, and results, as well as a history of or exposure to sexually transmitted diseases, Past abnormal pap smears and treatment, present drugs and allergies, occupation, and tobacco, alcohol, and other drug usage, Birth defects in the family, mental retardation, early menopause or reproductive failure, thyroid disease symptoms, pain in the pelvic or abdomen, galactorrhea, hirsutism, or dyspareunia.

Examination: including Weight and BMI (BMI =Weight (Kg) / Height in metrer2), Thyroid enlargement, nodules, or pain, breast secretions and their characteristics, androgen excess symptoms, vulva, vaginal, cervix, uterus, adnexa, pelvic or abdominal pain, organ enlargement or masses, vaginal or cervical abnormalities, secretions, or discharges, tenderness, mass, or nodularity in the adnexa or cul-de-sac.

Investigation:

BMI is computed by dividing a person's weight in kilograms by the square of their height in meters.

Image:

Transvaginal ultrasound (1st or 2nd day of menses, at day 12, after taken HCG by 48 hours, when missed period).

Hysterosalpingograghy (before starting induction).

Laboratory:

Semen analysis for her husband (before starting induction).

Hormonal profile FSH, LH, prolactin and TSH at time of 1st or 2nd day of menses.

E2 at day 12 (mature follicles).

Study details and follow up:

The table was randomly divided into two therapy groups: group A, letrozole (50 women), and group B, metformin–Letrozole (50 women).

Patients in group A received 2.5 mg of letrozole oral tablets (Femara; Novartis Pharma Services, Switzerland) every day for 5 days starting on the third day of the menstrual cycle, while all patients in group B got metformin HCl (Cidophage; Chemical Industries Development, Cairo, Egypt), 500 mg thrice every day for 6–8 weeks, accompanied by 2.5 mg of letrozole oral tablets (Femara; Novartis Pharma Services, Switzerland) every day starting on the third day of the menstrual cycle for 5 days. Metformin has only been discontinued when a pregnancy has been confirmed.

Transvaginal ultrasound (TVS) was used to monitor all patients on the 1st or 2nd day of menses to exclude any ovarian cysts and on day 12 of the period to determine the mean follicular diameter and thickness of the endometrium. To exclude ovarian hyperstimulation syndrome, RIA measured serum E2 (in picograms/millilitre) at the moment of HCG administration, employing direct double antibody kits (Pantex, Santa Monica, CA).

When one follicle measuring at least 18 mm has been identified, the HCG (a total of 5,000 IU IM, Choriomon; IBSA, Lugano, Switzerland) has been given. Patients have been instructed to have intercourse 24–36 hrs following receiving HCG injections, and a transvaginal ultrasound has been done after 48 hours of triggering to make sure rupture of follicles and ovulation occur. In the absence of menstruation, serum HCG has been measured two weeks later to diagnose pregnancy. In the instance of a woman who had ovulated and had a delayed menstrual cycle, β-HCG has been measured, and pregnancy has been confirmed via transvaginal

sonography. Metformin has been stopped when a woman becomes pregnant, and the fetal heart rate has been observed.

Sample Size: According to sample size justification (Steven Thompson equation), the sample size was estimated utilizing the PASS program, and the study included 100 anovulatory overweight women.

$$n = \frac{N \times p(1-p)}{\left[\left[N-1\times\left(d^2 \div z^2\right)\right]+ p(1-p)\right]}$$

Outcome measures:

The primary outcome: the number of follicles that were developing and mature, serum E2 when the follicle became mature before giving triggers to exclude ovarian hyperstimulation syndrome, and triple line endometrial thickness, ovulation rate, and number of ruptured follicles, side effects of the drugs taken.

Secondary outcome: pregnancy (verification of pregnancy was accomplished via a urine test utilizing a pregnancy test kit and transvaginal ultrasound. These women were followed up on and managed as antenatal once the pregnancy was confirmed).

Ethical Considerations: The patient data was anonymous. Patient confidentiality was protected as data presentation was not by the patient's name but by diagnosis. All participants were asked to give their informed consent. It was in Arabic language and confirmed by date and time. Confidentiality was preserved by assigning a number to the patients' initials and only the investigator knew it.

Conflict of interest: the candidate declared that there's no conflict of interest and the cost of the study was paid by the candidate.

Statistical analysis: Analysis is to be performed using SPSS for Windows v20.0. Data should be given in the form of a range, mean, and standard deviation (for numeric parametric variables); a range, median, and inter-quartile range (for numeric non-parametric variables); or numbers and percentages (for categorical variables). The difference between two independent groups should be analyzed utilising an independent student's t-test, the mean difference, and its 95 % CI (for numeric parametric variables); or a chi-squared test, the risk ratio, and its 95% CI (for categorical variables). Binary logistic regression analysis is to be performed for estimating the association between good/poor response and the measured variables ROC curves are to be constructed for estimating the validity of measured variables as predictors of good or poor response validity is to be presented in terms of sensitivity, specificity, PPV, and NPV values and their corresponding 95% Cis significance level is set at 0.05.

RESULTS

This study includes 100 patients with anovulation divided into two groups with following study.

		Groups						T-Test	
		Group A			Group B			t	P-value
Age (Years)	Range	22.1	-	35	23	-	35	-0.560	0.576
	Mean ±SD	27.720	±	4.516	28.200	±	4.036		
BMI (kg/m^2)	Range	26.5	-	29	26.5	-	29	-0.788	0.433
	Mean ±SD	27.200	±	0.821	27.320	±	0.698		

t: Student t-test, p: p value for comparing between the studied groups and *: Statistically significant at $p \leq 0.05$

Table 1: Comparison of the two study groups based on age and BMI.

Table (1) shows that there were insignificant changes between two groups as regard age, BMI (p-value 0.576, 0.433) respectively.

		Groups				Chi-Square	
		Group A		Group B			
		N	%	N	%	X^2	P-value
Parity	Nulliparous	35	70.00	30	60.00	1.099	0.295
	Multiparous	15	30.00	20	40.00		
Clinical presentation	Oligo/anovulation	25	50.00	25	50.00	0.000	1.000
	Hyperandrogenism	10	20.00	10	20.00		
	Polycystic ovaries	15	30.00	15	30.00		

Table 2: Comparison of the two study groups based on different parameters.

Table (2) shows that there were insignificant changes between two groups as regard parity and clinical presentation p-value 0.295, 1.000 respectively.

Period of infertility (Years)	Groups						T-Test	
	Group A			Group B			t	P-value
Range	1.5	-	5	2	-	4.5	0.513	0.609
Mean ±SD	3.030	±	0.784	2.950	±	0.776		

Table 3: Comparison of the two study groups based on infertility duration

Table (3) shows insignificant difference between two groups according to period of infertility.

		Groups						T-Test	
		Group A			Group B			t	P-value
FSH (IU/mL)	Range	2.8	-	7.5	3.3	-	6.5	-0.538	0.592
	Mean ±SD	4.888	±	1.206	5.010	±	1.058		
LH (IU/mL)	Range	12	-	14.5	10	-	14	1.564	0.121
	Mean ±SD	12.660	±	0.866	12.310	±	1.324		

Table 4: Comparison of the two study groups based on FSH and LH (IU/mL)

Table (4) shows that there were insignificant changes between two groups as regard to FSH, LH p-value 0.592, 0.121 respectively.

No of Patient has growing follicles	Groups				Chi-Square	
	Group A		Group B			
	N	%	N	%	X^2	P-value
No	15	30.00	10	20.00	2.000	0.368
One	25	50.00	25	50.00		
Two	10	20.00	15	30.0 0		

Table 5: Comparison of the two study groups based on the number of patients with growing follicles

Table (5) shows insignificant changes between two groups according to number of patients has growing follicles.

No of growing follicles at day 12	Groups				Chi-Square	
	Group A		Group B			
	N	%	N	%	X^2	P-value
No	15	25.00	10	15.38	1.252	0.263
Yes	45	75.00	55	84.62		

Table 6: Comparison of the two study groups based on the number of growing follicles (follicles ≥ 18).

Table (6) shows there were insignificant changes between the two groups in terms of the number of growing follicles (follicles ≥ 18) at day 12 (P-value 0.263)

Serum E2 (pg/mL) At time of HCG	Groups						T-Test	
	Group A			Group B			t	P-value
Range	100	-	298	100	-	298	-1.196	0.235
Mean ±SD	211.100	±	63.309	226.220	±	63.106		

Table 7: Comparison of the two study groups based on serum E2 (pg/mL)

Table (7) shows there were insignificant changes between the two groups in terms of serum E2 (p- value 0.235).

Endometrial thickness (mm) At time of HCG	Groups						T-Test	
	Group A			Group B			t	P-value
Range	6.6	-	9.5	6.7	-	11	-2.558	0.012*
Mean ±SD	8.230	±	1.023	8.770	±	1.087		

Table 8: Comparison of the two study groups based on endometrial thickness at the time of HCG need

Table (8) shows that there was a significant rise in group B (8.77) compared to group A (8.23) (p-value 0.012).

No of ruptured follicles	Groups				Chi-Square	
	Group A		Group B			
	N	%	N	%	X^2	P-value
No	5	11.11	8	14.55	0.044	0.834
Yes	40	88.89	47	85.45		

Table 9: Comparison of the two study groups based on the number of ruptured growing follicles

Table (9) shows in comparison between two groups as regard number of ruptured follicles after 48 hours of injection of HCG there were insignificant changes between two groups (p-value 0.834).

Pregnancy rate	Groups				Chi-Square	
	Group A		Group B			
	N	%	N	%	X^2	P-value
No	32	64.00	29	58.00	0.378	0.539
Yes	18	36.00	21	42.00		

Table 10: Comparison between two groups according to pregnancy rate /cycle

Table (10) shows in comparison between two groups as regard pregnancy rate/cycle there were insignificant changes between two groups (p-value 0.539).

Side effects	Groups				Chi-Square	
	Group A		Group B			
	N	%	N	%	X^2	P-value
Nausea	20	40.00	45	90.00	25.319	<0.001*
Vomiting	20	40.00	45	90.00	25.319	<0.001*
Stomach upset	25	50.00	25	50.00	0.000	1.000
Diarrhea	20	40.00	35	70.00	7.919	0.005*
Weakness	25	50.00	25	50.00	0.000	1.000
Dizziness	25	50.00	25	50.00	0.000	1.000
Drowsiness	20	40.00	30	60.00	3.240	0.072
Difficult breathing	10	20.00	20	40.00	3.857	0.050*
Tiredness	20	40.00	20	40.00	0.000	1.000
Blurred vision	25	50.00	20	40.00	0.646	0.421
Breast pain	25	50.00	25	50.00	0.000	1.000
Bloating	25	50.00	20	40.00	0.646	0.421
Difficult sleeping	25	50.00	20	40.00	0.646	0.421
Headache	25	50.00	20	40.00	0.646	0.421
Night sweats	25	50.00	20	40.00	0.646	0.421

Table 11: Comparison between two groups according to side impacts of the drugs utilized in induction.

Table (11) shows in the comparison between the two groups as regards the side impacts of the drugs utilized on induction. There was a significant increase in group B side effects (nausea, vomiting, and difficult breathing) and an insignificant difference in others.

DISCUSSION

Ovulation disorders are responsible for around 30% of all infertility cases, and they're often accompanied by irregular menstruation (oligomenorrhoea) or period absence (amenorrhea). Several of the therapies are easy and efficient, so couples might only need to see a doctor once or twice. This makes it simpler for a couple to retain a private love connection than it would be in the stressful, technological setting of an aided pregnancy. Nevertheless, ovulation stimulation does not work for all types of anovulation. Medical or surgical stimulation can be used to treat anovulation, but the cause of the anovulation affects whether or not ovulation induction is feasible. [1].

Normal weight for adults is characterized by the WHO as a BMI of 18.5-24.99 kg/m2, overweight with a BMI of 25-29.9 kg/m2 or more, and obese with a BMI of 30 kg/m2 or more. Obesity is accepted as an association and not a diagnostic criterion by the consensus definition of PCOS, as only 40-50 percent of women with PCOS are overweight. Appropriate endocrine investigations must remove other causes of menstrual disorders and hyperandrogenism [11].

The oral anti-estrogen clomiphene citrate (CC) or the aromatase inhibitor (AI) letrozole are the first-line treatments for inducing ovulation, with parenteral gonadotropin treatment or laparoscopic ovarian diathermy (LOD) being the second-line treatments (drilling). Metformin, an insulin sensitizer, might have a role in some patients [12].

Eventually, combination treatments, like metformin plus CC (metformin+CC) and metformin plus letrozole (metformin+letrozole), were developed and are now frequently employed to stimulate ovulation in CCR-PCOS women. The comparative efficacy of such therapies, on the other hand, is unknown [13].

The current research aims to assess the efficiency of letrozole vs. letrozole with metformin as ovulation-inducing agents by observing 100 patients with anovulation divided into two groups.

In the present study we found that two groups matching as regard age, BMI, parity, Period of infertility (year), Clinical presentation, FSH, LH with no significant between all p-value (0.576, 0.433, 0.295, 0.609, 1.000, 0.592, 0.121).

Hurley et al. [14] found that a total of 268 OI/IUI cycles have been evaluated, with 159 receiving LE-M and 109 receiving LE, which agrees with our results. When the two groups were compared, there were no significant differences in age, AMH, or BMI [14].

Also, Sohrabvand et al., [15] found that there were no significant statistical differences between Group A (letrozole) and Group B (letrozole metformin) in terms of the average demographic factors such as age, BMI, infertility duration, and regular menstruation following metformin [15].

In the present study we found that there were insignificant changes between two groups as regard Total no of growing follicles at day 12 follicles >18 mm p-value 0.263. there were insignificant changes between two groups as regard serum E2 p-value 0.235.

In agreement with Ng et al. [16] who tested the impact of metformin on ovulation, they found that there were insignificant changes between the metformin group and control as regards ovarian volume, and this is comparable with our result [2].

Stadtmauer et al., [17] found that there were insignificant changes between group received metformin and group not as regard FSH, Follicles $ 18 mm, E2 level day of hCG (pg/mL), and Total no. of oocytes and this in consistent with our result [17].

On the other hand, Hashim et al., [18] showed that the average number of oocytes retrieved is unaffected in metformin-treated patients. The average number of matured oocytes and embryos cleaved, however, has grown. Fertility and clinical pregnancy rates are also increasing. Metformin causes insulin-like growth factors in the preovulatory follicular fluid to be modulated [18].

In the present study, we found that there were insignificant changes between the two groups as regards to endometrial thickness at hCG. There had been a significant rise in group B (8.77) compared to group A (8.23), p-value < 0.012.

In agreement with our results, Rabia Mohsin et al., [19] found significant change between higher endometrial thickness at day HCG of letrozole metformin group than letrozole alone.

On other hand, EL-Gharib et al., [20] found non-significant change between endometrial thickness in both letrozole and letrozole metformin groups.

In the present study we found that in comparison between two groups as regard ruptured follicle/cycle there were insignificant changes between two groups p-value 0.834.

In the present study we found that in comparison between two groups as regard pregnancy rate /cycle there was insignificant changes between two groups p-value 0.539.

In terms of letrozole adequacy, our findings are consistent with those of Elnashar et al., [21] Badawy et al., [22] and Nupur et al., [23] studies, which found that pregnancy/cycle rates with letrazole were 13.6%, 12.2%, and 14.2%, respectively. Al-Omari et al., [24], Atay et al., [25], and Begum et al., [26] in which pregnancy/cycle were 17.5%, 25%, 19%, and 15.1% separately. Sohrabvand et al., [15] detailed that the rate of pregnancy in the metformin-letrozole bunch was 34.5% [15].

Multiple randomized preliminaries inspecting clinical pregnancy rates in metformin-treated people vs. fake treatment are underpowered and neglect to distinguish any improvement with metformin [27, 28].

Our results disprove those of Rabia Mohsin et al., [19] who found a high pregnancy rate in patients getting letrozole in addition to metformin versus letrozole alone.

Liu et al., [29] revealed a pregnancy pace of 57.9% in letrozole in addition to metformin gathering and just 46.8% in patients who got letrozole alone.

Another examination directed by Elgafor et al., [30] who revealed that letrozole, in addition to metformin blend, can have a triumph pace of 90.57% and fruitful pregnancy in 34.50% females.

While Davar et al., [31] announced a pregnancy pace of just 8.3% in PCOS ladies, these creators found a very lower speed of pregnancy acceptance after letrozole and metformin mix.

On the other hand, Rabia Mohsin et al., [19] found significant difference according to pregnancy /cycle, ovulation /cycle which letrozole metformin group higher than letrozole alone.

Lastly, we conclude that the expansion of metformin to letrozole does not improve the overweight an ovulated ladies except improving endometrial thickness.

CONCLUSION

Adding metformin to letrozole in anovulatory overweight women do not affect ovulatory response but it increases endometrial thickness at time of HCG, as following :

There were insignificant changes between two groups as regard age, BMI, parity, period of infertility, clinical presentation, FSH, LH.

There were insignificant changes between two groups as regard No. of growing follicles >18 mm although increase number of growing follicle in letrozole metformin group than letrozole alone.

There were significant changes between two groups as regard to Endometrial thickness at hCG there were significant increase in group B than group A.

-There were insignificant changes between two groups as regard serum E2.

In comparison between two groups as regard ruptured follicles/cycle there was insignificant changes between two groups although number of ruptured follicles in group B increase than group A.

In comparison between two groups as regard pregnancy rate/cycle there were insignificant changes between two groups although pregnancy rate in group B increase than group A.

Conflict of interest : none

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