The Egyptian Journal of Hospital Medicine (July 2018) Vol. 72 (8), Page 4995-5000

A Comparison Of Efficacy Of Aromatase Inhibitors (Letrozole), Clomiphene Citrate And Recombinant F.S.H In Induction Of Ovulation In Polycystic Overian Syndrome

Emad Maarouf Abd - Allatif [1], Mofeed Fawzy Mohammed [1], Hossam Mohammed Abdel-Satar Doweir[2]

[1]Department of Obstetrics and Gynecology. Faculty of medicine, Al-Azhar University, Egypt.
[2]Department of Obstetrics and Gynecology.El-Rahmania Central Hospital,El-Behira Govenrate.

ABSTRACT

Background: Polycystic ovarian syndrome is also called hyper-androgenic anovulation syndrome.It is a set of symptoms due to elevated male hormone in women. The major features of PCOS include menstrual dysfunction, anovulation and signs of hyperandrogens Other signs and symptoms of PCOS include hirsutism, infertility, obesity, metabolic syndrome, diabetes and obstructive sleep apnea. On examination, finding in women with PCOS may include virilizing signs, acanthosis nigricans, hypertension and enlarged ovaries (may or may not present).Ovulation induction in women with PCOS suffering from anovulatory infertility includes the use of antioestrogen, insulin sensitisers, aromatase inhibitors (Letrozole), gonadotropin (FSH) and surgical treatment.

Objective: The present study aimed at comparing between the efficacy of aromatase inhibitors(letrizole), clomiphene citrate and recombinant (FSH) on induction of ovulation in polycystic ovarian syndrome.

Patients and Methods: the present study was conducted on 150 patients with polycystic ovarian syndrome according to the Rotterdam criteria for polycystic ovarian syndrome with history of menstrual disturbance and whose age ranged between 18-37 years. In the current study, patients were allocated into 3 equal groups: group A (Clomiphene citrate), group B (Letrizole) and group C (Recombinant FSH).

Results: Clomiphene citrate, letrizole and recombinant (FSH)were the common to be used for induction of ovulation in polycystic ovarian syndrome.In our study we proved that recombinant (FSH) is the most effective of these drugs,followed by letrizole and the least is clomiphene citrate.

Conclusion: PCOS is a major cause of infertility in women.Medical treatment (induction of ovulation) is one of the major methods of management of PCOS. Recombinant (FSH) has the higest efficacy in our study.

Keywords: PCOS, Clomiphene citrate, Letrizole, Recombinant, (FSH), Induction and Letrizole.

INTRODUCTION

Polycystic ovarian syndrome is also called hyper-androgenic anovulation syndrome which is a set of symptoms due to elevated male hormone in women. The major features of PCOS include menstrual dysfunction, anovulation and signs of hyperandrogens [(1)]. Life style modification of PCOS are considered the first line of treatment for women with PCOS which include diet control, exercise and weight loss. The second line is medical treatment which is reserved for anovulation, hirsutism and menstrual irregularities. At first oral contraceptives are given to induce regular menses. If symptoms such as hirsutism are not sufficiently alleviated an androgen blocking agent may be added [(2)].

The main medical treatment for induction of ovulation in cases of PCOS iccludes: firstly clomiphene citrate which has an anti - estrogenic effect.Clomiphene citrate is started early in the menestrual cycle and is taking for 5 days either from cycle days 3 through 7 or from day 5 through 9.Its starting dose is 50mg daily to be taken any time of day,if the patient doesnot ovulate in the starting dose 100mg dose of clomiphene is tried,if she did not ovulate 150mg dose is sometime tried.The average day that ovulation occurs is about 8 to 10 days after completing the 5 day course of clomiphene citrate [(3)].

Secondly, letrizole or aromatase inhibitors which induce ovulation through inhibiting enzyme aromatase so estrogen levels are suppressed in women with PCOS. This results in the brain and pituitary gland increasing the output of FSH which results in development of mature follicles in the ovary. The most common dose of letrizole is 2.5 mg per day on days 5 through 9 of the menstrual cycle. Sometimes it is given in a higher doses of 5 mg or 7.5 mg per day. The main advantage of letrizole in induction of ovulation is monovulation compared with clomiphene citrate which associated with a high rate of multiple pregnancies [(4)].

The third line of medical treatment of anovulation in PCOS is injectable recombinant FSH. When oral medication such as (letrizole or clomiphene citrate) fails to result in available pregnancy, injectable FSH is the next step was shots for infertility. Recombinant FSH has a high rate of multiple births mainly triplets because it will lead to several follicles at or near the mature

Received:21/6/2018
Accepted:30/6/2018

size by the end of induction. Recombinant FSH is usually given by sub-cutaneous injections on a daily basis. Daily injections continue for approximately 7-14 days. When one or more mature size follicles are seen on the ovaries with vaginal ultrasound, one injection of HCG is given intramuscularly to induce ovulation [(5)].

The aim of this study was to compare the efficacy of aromatase inhibitors (letrizole), clomiphene citrate and recombinant (FSH) in induction of ovulation in polycystic ovarian syndrome.

PATIENTS AND METHODS

This is a cross-sectional comparative prospective study included one hundred and fifty patients with polycystic ovarian syndrome according to the Rotterdam criteria for polycystic ovarian syndrome with history of menstrual disturbance. They were selected from those attending the Clinic of Obstetrics and Gynecology Outpatient Clinic at Al-Hussein Hospital, Al-AZHAR University from July, 2017 to june, 2018 with age from 18 up to 37 years old. **The study was approved by the Ethics Board of Al-Azhar University.**

Patients were allocated into three equal groups: group A:(Clomiphene citrate -Treated) included 50 womens, group B (Letrizole -Treated) included 50 women and group C (Recombinant FSH -Treated) included 50 women.

Group" A" received Clomiphene Citrate for 6 cycles in the form of one tablet 50 mg twice daily for a period of 5 days from the second day of cycle and follow up of cases by folliculometry.

Group" B " received letrozole for 6 cycles in the form of one tablet 2,5 mg twice daily for the period of 5 days from the second day of cycle and follow up of the cases by folliculometry.

Group" C " received recombinant FSH for 6 cycles in the form of Sc or Im ampoules by step-up protocol started by a dose of 75 IU daily for 3 days from the second day of each cycles and followed-up by floculometery till the size of the follicle is 10 mm³ then we fix the dose for sex cycles. If the size of the follicle <10 mm³ then, the dose is increased to 150 IU daily for 3 days followed by foliculometry till the follicular size becomes 10 mm³ then we fix the dose for the rest of the period, otherwise the dose is increased to 225 IU daily for the rest of the treatment period.

Stricit follow up of the patients in 3 groups was done monthly.Vaginal ultrasound was done to detect the follicular diameter of the dominant follicle and detection the efficacy of each drug.Laboratory tests also were done to detect ovulation such as serum estradiol (E2) in 13th day of cycle.

Statistical analysis

Data were statistically described in terms of range, mean±standard deviation (± SD), frequencies (number of cases), and relative frequencies (percentages) when appropriate. For comparing categorical data, Chi square (x^2) test was performed. A probability value (p value) less than 0.05 was considered statistically significant.

RESULTS

Comparison between the baseline characteristics was presented followed by comparison between the results of management among the three groups. Concerning the baseline characteristics, several items were compared. This included sociodemogrphic criteria including: (Age,period of infertility and type of infertility).

Concerning some of laboratory tests including (serum FSH, serum LH, LH\FSH ratio, serum testesterone and serum estradiol(E2)). In addition, the success rate of induction by each drug.

Table (1) represented the age of patients in each group, the statistical analysis revealed that in group I there was increase in age of women where pregnancy induced than those who failed (p = 0.001). While in group II and III there was no significant difference in age (p = 0.43 and 0.231 respectively).

Table (1): Age distribution in cases of the study in all groups.

Group III		Group II		Group I		Age
Failed	**Success**	**Failed**	**Success**	**Failed**	**Success**	
27-34	24-33	20-34	20-34	20-39	20-34	Range
30.88±1.99	27.02±2.48	26.81±4.14	25.86±4.2	29.35±4.89	24.65±3.99	Mean±SD
0.231 (NS)		0.43 (NS)		0.001 (S)		P
		0.231 (NS)				P1
0.301 (NS)						P2
0.228 (NS)				0.228 (NS)		P3

P "Comparison between succeeded and failed induction in the same group"

P1 "Comparison between succeeded induction in group I and II"

P2 "Comparison between succeeded induction in group II and III"

P3"Comparison between succeeded induction in group I and III"

Table (2): represented the period of infertility of patients of each group:Statistical analysis revealed that there was increase in period of infertility where pregnancy induction failed in group I and group III

while there was no significant difference between pregnancy induction and failure in group II (p = 0.016; 0.0003 and 0.386 respectively).

Table (2): The period of infertility in cases of the study in all groups.

Group III		Group II		Group I		Period of infertility
Failed	Success	Failed	Success	Failed	Success	
2-6	2-5	1-5	1-6	1.5-5	1-4	Range
3.95±0.99	2.97±0.67	2.55±1.10	2.42±1.10	2.97±0.97	2.29±0.92	Mean±SD
0.0003 (S)		0.386 (NS)		0.016 (S)		P
		0.401 (NS)				P1
0.257 (NS)						P2
0.307 (NS)				0.307 (NS)		P3

P "Comparison between succeeded and failed induction in the same group"

P1 "Comparison between succeeded induction in group I and II"

P2"Comparison between succeeded induction in group II and III"

P3 "Comparison between succeeded induction in group I and III"

Table (3): represented the type of infertility of patients of each group. The statistical analysis

revealed that the primary infertility was common in all groups (I, II and III) (p = 0.04, 0.038 and 0.021 respectively). Also, it was common in women who got pregnancy than those where pregnancy failed in groups II and III while the reverse in group I (p = 0.021, 0.01 and 0.02 Respectively).

Table(3): Type of infertility in cases of the study in all groups.

Group III		Group II		Group I		Type of infertility
Failed	Success	Failed	Success	Failed	Success	
14 (63.7%)	25 (89.3%)	17 (65.4%)	16 (66.7%)	15 (50%)	14 (70%)	Primary
8 (36.3%)	3 (10.7%)	9 (34.6%)	8 (33.3%)	15 (50%)	6 (30%)	Secondary
0.021 (S)	0.011 (S)	0.035 (S)	0.021 (S)	0.235 (NS)	0.02 (S)	P
		0.211 (NS)				P1
0.031 (S)						P2
0.0232 (S)				0.232 (S)		P3

P "Comparison between succeeded and failed induction in the same group"

P1 "Comparison between succeeded induction in group I and II"

P2 "Comparison between succeeded induction in group II and III"

P3 "Comparison between succeeded induction in group I and III"

Table (4):represented measuring of serum FSH (miul) in the 3rd day of cycle. Statistical analysis revealed that serum FSH had no significant difference between women who got or failed to have pregnancy in group I and II (p = 0.393 and 0.862); While increased in women who got pregnancy in group III (p = 0.0001). Also, statistical analysis regarding the serum level of FSH in women who had succeeded pregnancy induction in all groups revealed that there was a significant statistical increase in the serum level of FSH in group III than other groups (I and II) (P1 = 0.205, P2 = 0.031 and P3 = 0.022 respectively).

Table (4): Serum level of FSH in cases of the study in all groups.

Group III		Group II		Group I		FSH level
Failed	Success	Failed	Success	Failed	Success	
2.62-7.83	3.82-7.14	3.25-9.07	3.6-7.89	3.57-8.99	3.62-8.99	Range
3.94±1.43	5.41±0.86	5.61±1.8	5.69±1.25	6.11±1.59	6.53±1.8	Mean±SD
0.0001 (S)		0.862 (NS)		0393 (NS)		P
		0.205 (NS)				P1
0.031 (S)						P2
0.022 (S)				0.022 (S)		P3

P "Comparison between succeeded and failed induction in the same group"

P1 "Comparison between succeeded induction in group I and II"

P2 "Comparison between succeeded induction in group II and III"

P3 "Comparison between succeeded induction in group I and III"

Table (5): represented measuring of serum LH (miul) in 3rd day of cycle:Statistical analysis revealed that serum FSH had no significant difference between women who got or failed to have pregnancy in group I, II and III (p = 0.686; 0.064 and 0834 respectively). Also, there was no significant difference between all groups regarding LH (P1 = 0.205, P2 = 0.361, P3 = 0.251 respectively).

Table (5): Serum level of LH in cases of the study in all groups.

Group III		Group II		Group I		LH level
Failed	Success	Failed	Success	Failed	Success	
7.32-16.36	9.27-16.72	9.06-20.1	7.08-16.3	7.24-18.7	9.32-17.8	Range
12.3±2.04	12.19±1.69	13.42±2.79	12.08±2.19	13.16±2.53	13.46±2.47	Mean±SD
0.834 (NS)		0.064 (NS)		0.686 (NS)		P
		0.205 (NS)				P1
0.361 (NS)						P2
0.251 (NS)				0.251 (NS)		P3

P "Comparison between succeeded and failed induction in the same group"

P1 "Comparison between succeeded induction in group I and II"

P2 "Comparison between succeeded induction in group II and III"

P3 "Comparison between succeeded induction in group I and III"

Table (6):represented measuring LH\FSH ratio in each group. Statistical analysis revealed that there was significant decrease in the level of LH/FSH ratio in women who got pregnancy than in those who failed in group II and III (p = 0.018 and 0.021 respectively). While there was no significant change in group I (p = 0.470). in addition, statistical analysis regarding the LH/FSH ratio revealed that there was no statistical significant change in this ratio in all groups of the study (P1 = 0.31, P2 = 0.281, P3 = 0.222 respectively).

Table (6): Serum level of LH/FSH in cases of the study in all groups.

Group III		Group II		Group I		LH/FSH Ratio
Failed	Success	Failed	Success	Failed	Success	
2.06-4.26	1.91-2.8	1.8-4.1	1.68-3.49	1.72-3.03	1.72-2.84	Range
3.30±0.66	2.27±0.24	2.52±0.58	2.17±0.42	2.20±0.33	2.13±0.33	Mean±SD
0.021 (S)		0.018 (S)		0.470 (NS)		P
		0.31 (NS)				P1
0.281 (NS)						P2
0.222 (NS)				0.222 (NS)		P3

P "Comparison between succeeded and failed induction in the same group"

P1 "Comparison between succeeded induction in group I and II"

P2 "Comparison between succeeded induction in group II and III"

P3 "Comparison between succeeded induction in group I and III"

Table (7):represented measuring serum testesterone level (Pgm\ml): Statistical analysis revealed that there was decrease in serum testosterone in women who got pregnant than those who failed to get pregnancy in group I and group III (p = 0.001 and 0.004 respectively). While no significant change of its level in group II (p = 0.191). Also, statistical analysis regarding the serum level of testosterone in women who had succeeded pregnancy induction in all groups revealed that there was no significant statistical difference in the serum level of testosterone in all groups (P1 = 0.186, P2 = 0.275, P3 = 0.333 respectively).

Table (7): Serum testosterone in cases of the study in all groups.

Group III		Group II		Group I		Testosterone Level
Failed	Success	Failed	Success	Failed	Success	
3.9-6.42 5.24±0.77	3.8-5.7 4.64±0.52	2.57-6.07 3.54±0.79	0.8-8 3.13±1.29	2.9-4.8 3.84±0.44	2.59-4.32 3.42±0.43	Range Mean±SD
0.004 (S)		0.191 (NS)		0.001 (S)		P
		0.186 (NS)				P1
0.275 (NS)						P2
0.333 (NS)				0.333 (NS)		P3

P "Comparison between succeeded and failed induction in the same group"
P1 "Comparison between succeeded induction in group I and II"
P2 "Comparison between succeeded induction in group II and III"
P3 "Comparison between succeeded induction in group I and III"

Table (8):represented measuring serum level of estradiol (Pgm\ml) after the induction in the 14th day of cycle of each group. Statistical analysis revealed that there was a significant increase in the level of estradiol after therapy in women who got pregnancy than those who failed to get pregnancy in groups I, II and III (p = 0.001, 0.001 and 0.021 respectively). While, there was no significant difference in estradiol level after therapy in all groups in women who got pregnancy (P1 = 0.155, P2 = 0.266, P3 = 0.422 respectively).

Table (8): Serum estradiol before and at induction in cases of the study in all groups.

Group III		Group II		Group I		Estradiol level
After	Before	After	Before	After	Before	
297.8-390 341.8±25.9	227-390 288.4±38.1	308.8-390.7 346.8±30.3	267-390 312.8±31.5	297.8-390 341.8±25.9	227-390 288.4±38.2	Range Mean±SD
0.021 (S)		0.001 (S)		0.001 (S)		P
		0.155 (NS)				P1
0.266 (NS)						P2
0.422 (NS)				0.422 (NS)		P3

P "Comparison between succeeded and failed induction in the same group"
P1 "Comparison between succeeded induction in group I and II"
P2 "Comparison between succeeded induction in group II and III"
P3 "Comparison between succeeded induction in group I and III"

Table (9):represented the success rate of induction in each group:The success rate in group I was 40% (20/50) and in group II it was 48% (24/50) while in group III, it was 56% (28/50). The statistical analysis revealed that FSH regimen was the most successful one followed by Letrizole regimen and the least was clomophene (P1 = 0.024, P2 = 0.025 and P3 = 0.032). The success rate was common in primary infertility (55/72, 76.4%) while success in secondary infertility was 17/72 (23.6%).

Table (9): Success rate in the different groups according to the type of infertility.

Failure of induction		Success induction		Type of infertility
Secondary	Primary	Secondary	Primary	
15(50%)	15(50%)	6(30%)	14 (70%)	Group I
9(34.6%)	17(65.4%)	8(33.3%)	16(66.7%)	Group II
8(36.3%)	14(63.7%)	3(10.7%)	25(89.3%)	Group III
0.026(S) 0.221(NS) 0.031(S)	0.021(S) 0.231(NS) 0.023(S)	0.221(NS) 0.024(S) 0.025(S)	0.221(NS) 0.023(S) 0.031(S)	P1 P2 P3

P1 "Comparison between succeeded induction in group I and II"
P2 "Comparison between succeeded induction in group II and III"
P3"Comparison between succeeded induction in group I and III"

DISCUSSION

Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder affecting 6-10% of women of reproductive age and it accounts for 70-80% of anovulatory infertility [(6)]. Ovulation induction in women with PCOS suffering from anovulatory infertility includes the use of antioestrogen, insulin sensitisers, aromatase inhibitors, gonadotropin and surgical treatment [(7)].Despite the fact that pharmacological methods of ovulation induction are often effective, a large number of patients still have difficulty conceiving and they have a high risk of miscarriage that might be related to reduced endometrial receptivity[(8)].

The age of women in the study groups ranged between 20 and 37 years old and the mean ages were 24.65 years in group I, 25.86 years in group II and 27.02 years in group III. ***Seyedoshohadaei and his colleagues*** [(9)] found in their study that there was no significant difference between studied groups regarding age which was in agreement with our study.

Seyedoshohadaei and his colleagues [(9)]found in their study that there was no significant difference between studied groups concerning the period of infertility, which was in agreement with our study.

Seyedoshohadaei and his colleagues [(9)] found in their study that there was no significant difference between studied groups regarding type of infertility but our study showed that secondary infertility was common in clomiphene group (I) while primary was common in group III (FSH).

Chen and Wei [(10)] and **Yuan and his coworkers** [(11)] found that human chorionic

gonadotropin could significantly reduce serum FSH and LH levels and these results were consistent to the reported results, but in our study In our study we found increase in FSH in all groups especially in group III than other groups (I and II) with no difference in the serum level of LH in all groups and LH/FSH ratio in all groups of the study.

Akpinar and his colleagues [(12)] found in their study that the difference in the response to CC induction in the women with PCOS could be due to the differences in the LH level, LH/FSH ratio which disagree with our results.

Roth and his colleagues [(13)] found in their study that there was a significant reduction in the serum level of testosterone before and after treatment which disagree with our results. Our results revealed no difference in the serum level of testosterone in all groups.

Weiss and his colleagues [(14)] reported in their study that gonadotropins were a long-standing treatment for clomiphene-resistant women. A variety of injectable drugs was available (human menopausal gonadotropins (hMG), urinary FSH, and recombinant FSH). This was in agreement with our results.

Köninger and his colleagues [(15)] found in their study a high pregnancy rate (48%) with the use of FSH in PCOS which was in agreement with our results.

Franik and his colleagues [(16)] documented in their studies that aromatase inhibitors in PCOS found letrozole improved live births over clomiphene but not superior on it in getting pregnancy which contradicting with our results.

CONCLUSION

PCOS is a major cause of infertility in women.Medical treatment "ovulation induction" is one of the major methods of management of PCOS. Clomiphene citrate, letrozole, and FSH were the common to be used for treatment of ovulation induction. FSH was proved in our study to be the most effective of these drugs, followed by Letrozole and the least is clomiphene citrate.

REFERENCES

1. **Godman NF, Cobin RH, Futterweit W *et al.* (2015):** American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and PCOS Society disease state clinical review: guide to the best practices in the evaluation and treatment of polycystic ovary syndrome: part 1. Endocrinol Pract, 11: 1291-300.
2. **Omstein RM, Copperman NM, Jacobson MS (2011):** Effect of weight loss on menstrual function in adolescents with polycystic ovary syndrome. J Pediat Adolesc Gynecol., 3: 16-15.
3. **Legro RS, Brzyski RG, Diamond MP (2014):** Letrizole versus clomiphene for infertility in the polycystic ovary syndrome. N Engl J Med.,371(2): 119-29.
4. **Emery G (2014):** Letrizole produces more babies in women with polycystic ovary syndrome. https:// www. ncbi. nlm. nih. gov/ pmc/ articles /PMC4485297/
5. **Razi MH, Mohseni F, Dehghani Firouzabadi R *et al.* (2014):** Results from adding recombinant LH for assisted reproductive technology treatment: A randomized control trial. Iran J Reprod Med., 12(2): 111-6.
6. **Li J, Ng EHY, Victorin ES *et al.* (2016):** Comparison of acupuncture pretreatment followed by letrozole versus letrozole alone on live birth in anovulatory infertile women with polycystic ovary syndrome: a study protocol for a randomised controlled trial. BMJ Open, 6: e010955-e010968.
7. **Lin SQ, He FF, Chen ZJ *et al.* (2013):** Clinical progress of gynecological endocrinology, 1st eds., Beijing: Tsinghua Tongfang CD-ROM electronic publishing house.
8. **Wang CY, Ding CF (2012):** Research progress on insulin resistance and endometrial receptivity of polycystic ovary syndrome. Zhejiang Zhong Xi Yi Jie He Za Zhi., 22: 155-8
9. **Seyedoshohadaei F, Tangestani L, Zandvakili F *et al.* (2016):** Comparison of the Effect of Clomiphene- Estradiol Valerate vs Letrozole on Endometrial Thickness, Abortion and Pregnancy Rate in Infertile Women with Polycystic Ovarian Syndrome. J Clin Diag Res., 10(8): QC10-QC13.
10. **Chen LX, Wei JP (2015):** Clinical effect comparison of Cangfu Daotan decoction combined with clomiphene citrate tablets in the treatment of polycystic ovary syndrome. Pharmacol. Clinics Chin. Mater Medica, 31(02): 221-222.
11. **Yuan KC, Zhang GJ, Jin XS (2015):** Clinical observation on the effects of Tiaojingguchong decoction and clomiphene in treating infertility caused by polycystic ovarian syndrome. Pharmacol Clin Chin Mater Medica,31(06): 175-177.

12. **Akpinar F, Dilbaz B, Cirik DA *et al.* (2016):** The significance of anthropometric and endocrine parameters in ovulation induction with clomiphene citrate in women with polycystic ovary syndrome. Saudi Med J., 37(11): 1272-1275.
13. **Roth LW, Huang H, Legro RS *et al.* (2012):** Altering Hirsutism Through Ovulation Induction in Women With Polycystic Ovary Syndrome. Obstet Gynecol.,119(6): 1151-1156.
14. **Weiss NS, Nahuis M, Bayram N *et al.* (2015):** Gonadotrophins for ovulation induction in women with polycystic ovarian syndrome. Cochr Database of Syst Rev.,9: CD010290.
15. **Köninger TE, van der Houwen LE, Overbeek A *et al.* (2014):** Recombinant LH supplementation to a standard GnRH antagonist protocol in women of 35 years or older undergoing IVF/ICSI: a randomized controlled multicentre study. Hum Reprod., 28(10): 2804-12.
16. **Franik S, Kremer JAM, Nelen WL *et al.* (2014):** Aromatase inhibitors for subfertile women with polycystic ovary syndrome. https:// www. ncbi. nlm. nih. gov/ pubmed/ 24563180