Outcome of Letrozole versus Laparoscopic Ovarian Drilling in Infertile Women with PCOS Resistant to Clomiphene Citrate

Abdel-Aziz F.A[1], Taha W.S[2] and Amin A.M[3]

[1]Professor of Obstetrics and Gynecology, Faculty of Medicine, Al-Azhar University, Egypt
[2]Lecturer of Obstetrics and Gynecology, Faculty of Medicine, Al-Azhar University, Egypt
[3]Resident physician of Obstetrics and Gynecology, Tamia Hospital, Fayoum, Egypt
draminmohammed@gmail.com

Abstract: Objective: to compare letrozole versus laparoscopic ovarian drilling, to detect which is an attractive option with its administration, cost, safety, profile and effectiveness in treating clomiphene citrate-resistant Polycystic ovary syndrome. **Design**: Prospective randomized trial. **Setting:** El-Hussein University Hospital**,** Cairo, Egypt. **Patient and methods:** 40 women with clomiphene citrate-resistant poly cystic ovary syndrome, women were randomly allocated into either the laparoscopic ovarian drilling group or letrozole group (groups A and B, respectively). No medical leading was made during the decision-making process. Group A (n = 20) underwent laparoscopic ovarian drilling, and group B (n = 20) received 2.5 mg letrozole twice daily from days 3 to 7 of menses for up to six cycles. A 6-month follow-up was performed. **Results:** There was no significant difference between the two groups in the baseline clinical data (Age, BMI, Infertility (type and duration) and Parity). There was a statistically significant difference in ovulation rate (65 % in group B vs 30 % in group A, $p<0.05$) and regular cycle rate (80 % in group B vs 45 % in group A, $p<0.05$), although it shows no statistically significant difference in Clinical Pregnancy rate (35 % in group B vs 20 % in group A, $p= 0.083$). **Conclusion:** the results of the present study indicated that letrozole might be an alternative to laparoscopic ovarian drilling in the treatment of clomiphene citrate-resistant polycystic ovary syndrome, further evaluation with a significant number of patients is recommended.

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1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorders in women of childbearing age. It's prevalence, using different diagnostic criteria, has been reported to be 6.8%-18%, and it is estimated that a large number of patients are not diagnosed **(Teede et al., 2010)**. It is characterized by 0hyperandrogenism, chronic oligo-an ovulation and insulin-resistance **(Tehrani et al., 2011).**

Clomiphene citrate remains the first‐line of treatment for ovarian stimulation in PCOS; however, 15-40% of women do not resume ovulation following clomiphene citrate treatment, which is defined as clomiphene citrate‐resistance (**NIHCE, 2004**). So, clomiphene resistance is defined as three cycles of failure to ovulate or six cycles of ovulation without pregnancy (**Al-Omari et al., 2004**).

Clomiphene citrate-resistant polycystic ovary syndrome is a challenging in treatment. Classically gonadotropins and laparoscopic ovarian drilling were the traditional treatment (**Palomba et al., 2009**). Although they are effective yet they are expensive and may carry risks.

Aromatase inhibitors have become an alternative to clomiphene citrate as first-line therapy for stimulation of ovulation in ovulating and non-ovulating infertile women (**Homburg, 2008**; **Mitwally and Casper, 2001**). Letrozole is a potent and selective third-generation aromatase inhibitor as opposed to laparoscopic ovarian drilling, there are no need for hospitalization, general anesthesia as it is an attractive option with its oral route of administration, cost, safety, profile and effectiveness in ovulation induction and ovarian stimulation (**Lee and Ledger, 2011**), as opposed to clomiphene, is rapidly excreted **(Mitwally and Casper, 2001)**, and causes ovulation in 60%–80% of patients (**Abu Hashim et al., 2009**); in clomiphene-resistant patients, it causes ovulation in 62% of cases, and pregnancy occurred in 14.7% of patients. Letrozole does not have any adverse effects on the fetus and is safe (**Rouzi and Ardawi, 2006; Abu Hashim et al., 2009; Jirege and Patill, 2010**). Letrozole decreases the secretion of estrogen both in the brain and in the periphery, and causes an increase in gonadotropins, which in turn causes maturation of the ovarian follicles (**Hajishafiha et al., 2014**).

The aim of the present study was to compare letrozole with laparoscopic ovarian drilling, to detect which is an attractive option with its administration, cost, safety, profile and effectiveness in treating

clomiphene citrate-resistant polycystic ovary syndrome.

2. Patients and Methods

Patient selection

This prospective study was attended in El-Hussein University Hospital in the period from December 2017 to July 2018, in where we included 40 women, which diagnosed with PCOS based on the revised 2003 Consensus Diagnostic Criteria for PCOS (Rotterdam criteria). Women were randomly allocated into either the laparoscopic ovarian drilling group or letrozole group (groups A (n=20) and B (n=20), respectively). No medical leading was made during the decision-making process. This study designed according to ethical committee rules of obstetric and gynecology, for all women in the study explanation of the study procedures was done and informed consent was taken.

Inclusion criteria

Were as follows: Age more than 20 and less than 40 years old, body mass index (BMI) < 26 kg/m2, Clomiphene resistance, patent tubes, Normal semen analysis parameters of the husband according to the modified criteria of the World Health Organization (**Sills et al., 2004**), All patients will be requested to follow a normal diet and rest regime, Avoid intense physical activities in any form and mental stress and fatigue.

Exclusion criteria

Were as follows: Age less than 20 year or more than 40 years, Body mass index (BMI) >26 kg/m2, Non-PCOS, Current or previous (within the last 6 months) use of oral contraceptives, glucocorticoids, antiandrogens, antidiabetic or antiobesity drugs, or other hormonal drugs, Neoplastic, metabolic, hepatic, or cardiovascular disorder or other concurrent medical illness (i.e. diabetes, renal disease, or malabsorptive disorders), Pelvic diseases, Previous pelvic surgery, Male factor infertility.

Intervention and follow-up

The women were randomly allocated into either the laparoscopic ovarian drilling group or letrozole group (groups A and B, respectively). No medical leading was made during the decision-making process. Once the patients had been allocated to one of the two groups, the treatment was revealed to the investigator.

In group A

Laparoscopy was performed under intravenous general anesthesia with the patient in a supine position. A 5-mm incision will be made in the navel, through which a long sheath punctured into the abdominal cavity, and the inflatable pneumoperitoneum will be placed. Another two 5-mm incisions will be made on the right and left lower abdomen and the surgical instruments will be inserted into the abdominal cavity. The patient will be adjusted into a position with the head high up, the pelvic organs will be exposed and a comprehensive exploration of the pelvic organs will be made, focusing on the structure and position of the adjacent organs of the bilateral ovaries. Once immobilized, each ovary will be cauterized at 4–6 points, using a monopolar electrosurgical needle, according to the size of each ovary. Following cauterization, a bilateral tubal hydrotubation with methylene blue was performed. During the procedure, the pelvis was irrigated using physiological saline. Ringer's solution plus dexamethasone was added into the abdominal cavity to avoid adhesion. The total duration of the procedure, as well as any intra-operative or post-operative complications, was noted.

Table 1: comparison between the groups in Basic Data

Variable	LOD group (A) n=20	Letrozole group (B) n=20	P value
	Means ± SD		
Age (years)	25.9 ± 5.05	26.5 ± 4.86	0.715 (N.S)
BMI (Weight/Heightin meter^2)	25.22 ± 5.06	24.94 ± 5.09	0.140 (N.S)
Infertility duration (years)	2.75 ± 0.910	3.15 ± 0.745	0.163 (N.s)
Variable	N (%)		P value
Infertility type: 1ry 2ry	 14 (70.0) 6 (30.0)	 13 (65.0) 7 (35.0)	0.748 (N.s)
Parity: 0 1	 14 (70.0) 6 (30.0)	 13 (65.0) 7 (35.0)	0.748 (N.s)

In group B

2.5 mg twice daily letrozole oral tablets was administered on the 3rd day of menses and then every day for 5 days (**Malloch, 2013**). Treatment was repeated for up to six cycles if the patient failed to ovulate.

Patients were followed-up for 6 months after the treatment in both groups, folliculometry was done to detect follicular growth and ovulation after giving hcg for triggering ovulation after follicular growth to 18mm.

Finally, Comparisons of regular menses, follicular growth, ovulation and pregnancy rates were made.

Methods of statistical analysis of data:

The collected data was organized, tabulated and statistically analyzed using SPSS software statistical computer package version 16 (SPSS Inc, USA). The measurement data are presented as the mean ± standard deviation (SD). Paired t-test was used in comparing between the differences of parameters.

3. Results

In the present study we didn't record any statistically significant difference between the two groups in terms of age, BMI, infertility duration, infertility type and parity (**Table** 1).

Results showed a statistically significant difference in ovulation rate (65 % in group B vs 30 % in group A, $p<0.05$) and regular cycle rate (80 % in group B vs 45 % in group A, $p<0.05$). Although it showed no statistically significant difference in Clinical Pregnancy rate (35 % in group B vs 20 % in group A, $p= 0.083$) (**Table 2**).

Table (2): comparison between both groups as regards reproductive outcomes following treatment:

Groups / Variables	LOD group (A) N %	Letrozole group (B) N %	P value
Ovulation, n/total n (%)	6 (30.0 %)	13 (65.0 %)	0.031
Regular Cycles, n/total n (%)	9 (45.0 %)	16 (80.0 %)	0.031
Clinical Pregnancy Rate	4/20 (20.0 %)	7/20 (35.0 %)	0.083 (N.s)

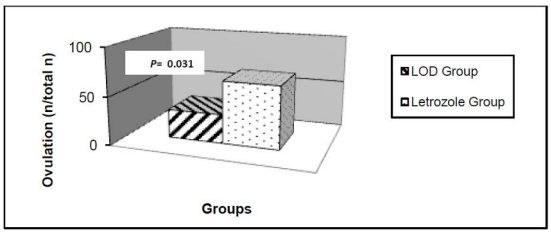

Figure (1) ovulation rate for the studied groups

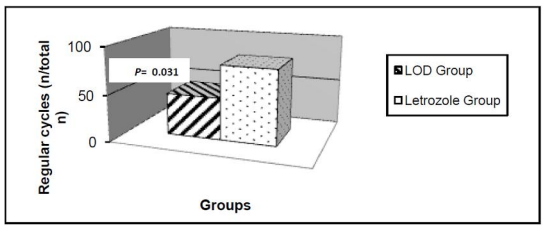

Figure (2) Regular cycles for the studied groups

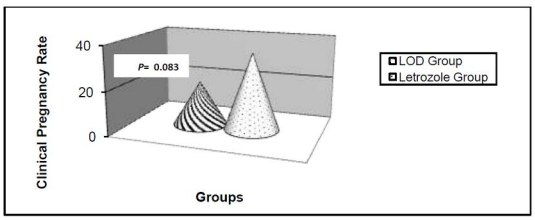

Figure (3) Clinical pregnancy rate for the studied groups

4. Discussion

Clomiphene citrate-resistant polycystic ovary syndrome is a challenging in treatment. Classically gonadotropins and laparoscopic ovarian drilling were the traditional treatment (**Palomba et al., 2009**). Although they are effective yet they are expensive and may carry risks. Recently letrozole was investigated to be an appropriate alternative. It is an attractive option with its oral route of administration, cost, safety, profile and effectiveness in ovulation induction and ovarian stimulation (**Lee and Ledger, 2011**).

El nashar et al. (2006) and **Al-Omari et al. (2004)** have suggested that the mechanisms by which letrozole stimulate ovulation may have two parts: The central and the peripheral mechanisms. In the central mechanism, letrozole acts on the hypothalamus and pituitary in the early follicular phase, and aromatase is then inhibited. The conversion of testosterone to estrogen is hindered and levels of estrogen in the body are reduced to terminate the negative feedback effect of the hypothalamuth or pituitary. FSH is secreted and promotes follicular maturation and ovulation.

In the peripheral mechanism, aromatase is a rate limiting enzyme for testosterone production. Letrozole mainly act as an AI and prevents the conversion of testosterone to estrogen; testosterone rapidly accumulates in the ovary and FSH receptor gene expression is amplified directly or indirectly; therefore, the follicle is more sensitive to FSH. In addition testosterone can stimulate insulin like growth factor, as well as other endocrine and paracrine factors, which promotes the follicular development and ovulation together with FSH (**Baruah et al., 2009**).

In laparoscopic ovarian drilling burning and puncturing the follicle is the main mechanism as it encourages follicular fluid flow and reduces or

eliminates the influence of abnormal hormone and factor levels in the follicle on ovarian function. Furthermore, surgery destroys some of the abnormal structure of the ovary and partially mitigates the abnormal function; therefore, the synthesis of hormones and growth factors in the ovary is subsequently normalized (**Salah, 2013**).

The present study compared the reproductive outcomes of women with clomiphene citrate-resistant polycystic ovary syndrome after administration of the aromatase inhibitor letrozole and after laparoscopic ovarian diathermy.

In the present study we didn't record any statistically significant difference between the two groups in terms of age, BMI, infertility duration, infertility type and parity (**Table 1**).

In the present study we recorded that ovulation rate in the letrozole group was 65.0% which was significantly higher (P = 0.031) than that in the laparoscopic ovarian diathermy group 30% **(Table 2) (Figure 1).** This ovulation rate is comparable to results from **Ibrahim et al. (2017)** and **Abdellah** (**2011**); who found ovulation rates of 70% and 59%, respectively, on using letrozole for the induction of ovulation. In contrast, **Abu Hashim et al. (2010)**; found that the ovulation rate was 65.4% in women who received letrozole and 69.3% in women who underwent laparoscopic ovarian diathermy, with no significant difference between the 2 groups.

Regarding regular cycles, our study recorded 16 women (80%) with regular cycles in letrozole group which was significantly higher (P = 0.031) than 9 women (45%) in LOD group **(Table 2) (Figure 2)**. This is in accordance with the result of **Ibrahim et al., (2017)** and **Liu et al., (2015)** who stated that regular cycles were 87.5% and 81.6% respectively, on using letrozole for the induction of ovulation.

In our study, the clinical pregnancy rate in the letrozole group was 35%, higher than that in laparoscopic ovarian diathermy group 20%, although these differences were not statistically significant **(Table 2) (Figure 3).** Our results find support in studies by **Liu et al. (2015)** and **Nejad et al. (2008)** who found pregnancy rate of 40.8% and 32.8% respectively, on using letrozole for the induction of ovulation.

In the present study, from the previous findings we founded that letrozole was more effective as a fertility treatment than laparoscopic ovarian diathermy in women with clomiphene citrate-resistant polycystic ovary syndrome. Ovulation, regular cycles, and clinical pregnancy were more likely after treatment with letrozole.

Finally there were no reported complications of laparoscopic ovarian drilling also, Letrozole was generally well tolerated.

Conclusion

In conclusion, the results of the present study indicate that letrozole might be an alternative to laparoscopic ovarian drilling in the treatment of clomiphene citrate-resistant polycystic ovary syndrome, further evaluation with a significant number of patients is recommended.

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