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COMPARISON BETWEEN USING LETROZOLE WITH METFORMIN AND CLOMIPHENE CITRATE WITH METFORMIN FOR OVULATION INDUCTION IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME

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ABSTRACT

Background: Polycystic Ovary Syndrome (PCOS) is one of the most common causes of anovulatory infertility. Currently, clomiphene citrate (CC) is considered the first-line therapy for ovulation induction for women with PCOS and infertility. Aromatase inhibitors (AIs) have been introduced as a new treatment option that could challenge CC for ovulation induction. **Aim of the Work**: The present study was designed to compare the efficacy of combined aromatase inhibitor (Letrozole) with metformin versus CC with metformin in PCOS patients. Patients and Methods: This study was done on 100 documented PCOS cases. They were divided into two groups, The 1st group received CC 50 mg twice daily from the 3rd day of cycle for 5 days and with metformin 500 mg 3 times daily as an adjunct with CC. The 2nd group received aromatase inhibitor (Letrozole) 2.5 mg twice daily from 3rd day of cycle for 5 days with metformin 500 mg 3 times daily as an adjunct with letrozole . These cases were followed up by transvaginal ultrasound folliculometry to document ovulation (size and number of follicles). **Results**: The results of the present study revealed both lines of treatment were effective in treatment of PCOS patients, with slight favorability in letrozole group but without statistically significant difference founded between CC group and letrozole group as regard ovulation rate, number of follicles at the end of first, second or third cycles, or as regard the diameter of follicles, i.e., both regimens showed efficacy to the same extent. **Conclusion**: both CC and letrozole are equally effective in treatment of infertility in PCOS patients, when combined with metformin treatment.

KEYWORDS: PCOS, clomiphene citrate, letrozole, metformin.

INTRODUCTION

Infertility has been attributed to various factors, amongst which anovulation is the cause in about 40% of all female infertility. Polycystic Ovary Syndrome (PCOS) is one of the most common causes of anovulatory infertility, affects 4-7% of women.[1]

Criteria used for diagnosing Polycystic Ovary Syndrome (PCOS) are the Rotterdam Criteria of which a woman must have two out of the followings: 1: Oligo- or anovulation. 2: Clinical and / or biochemical signs of hyperandrogenism 3: Polycystic ovaries (with the exclusion of related disorders).

With exclusion of other conditions with similar signs such as androgen-secreting tumors or Cushing's syndrome and thyroid dysfunction and hyperprolactinemia.

Anti estrogenic drug, such as Clomiphene citrate (CC) is considered the first line treatment for induction of ovulation in women with Polycystic Ovary Syndrome (PCOS). CC is given orally at a dose of 50-100 mg/day from 3rd day of cycle for 5 days. If patients fail to respond to 150 mg/day, they are considered as CC resistant.

Aromatase inhibitors (AIs) have been introduced as a new treatment option that could challenge CC for ovulation induction.[2]

Aromatase is a cytochrome P-450 hem protein containing enzyme complex (the product of the CYP19 gene) that catalyzes the rate-limiting step in the production of estrogens which is the conversion of androstenedione and testosterone via three hydroxylation steps to estrone and estradiol.

Aromatase activity is present in many tissues such as the ovaries, adipose tissue, muscle, liver, breast tissue, and in malignant breast tumors. The main sources of circulating estrogens are the ovaries in premenopausal women and adipose tissue in postmenopausal women.[3]

AIs can be applied for ovarian stimulation as its administration early in the follicular phase can induce ovulation by releasing the hypothalamus or pituitary from estrogen negative feedback on GnRH and gonadotropin secretion, leading to an increase in gonadotropin production which would stimulate ovarian follicular development.[4] AIs prevent the Androgen-Estrogen conversion and therefore interfere with the negative feedback at the level of the hypothalamus-pituitary. The increased pituitary gonadotropin output will in turn stimulate the ovaries.[5] In addition, they act locally in the ovary to increase follicular sensitivity to FSH. This may result from accumulation of intraovarian androgens, since conversion of androgen substrate to estrogen is blocked. Recent data support a stimulatory role for androgens in early follicular growth.[6]

In some studies, letrozole in contrast to CC is better as it increases endometrial thickness by upregulation of estrogen receptors. So, it increases pregnancy rate and also it decreases incidence of multiple pregnancy.[5,3] AIs reported to be effective in inducing ovulation, increased pregnancy rate, improve uterine environment, endometrial development with favorable cervical mucus.[5]

Insulin-sensitizing agents for example (Metformin)

Metformin is an oral anti-diabetic drug from biguanides class used for treatment of type II diabetes mellitus. It is a safe and effective drug that is used for the treatment of PCOS patients.[8] Metformin improves peripheral insulin sensitivity by reducing hepatic glucose production and increasing target tissue sensitivity to insulin. It also decreases androgens in both lean and obese women, leading to increased rates of spontaneous ovulation.[9]

Metformin may be used alone or in concert with other medications such as clomiphene citrate, it has been shown to increase the ovulatory response to clomiphene citrate in patients who were previously clomiphene-resistant.

PATIENTS AND METHODS

1- Patients

This prospective study was done on 100 infertile women from the Infertility Outpatient Clinic of Tishreen University Hospital, Lattakia, Syria.

Inclusion Criteria: A. 18-35 years old women that had been already diagnosed as primary infertility due to PCOS according to Rotterdam consensus criteria. B. Women with BM I> 25. C. Uterus is normal and tubes are patent by hystero-salpingography. D. Normal serum prolactin level (5-20 ng/ml). E. Normal semen analysis of the husband.

Exclusion Criteria: Uterine and adnexal pathology e.g. leiomyomata. Ovarian cysts > 6cm. Hyper- or Hypothyroidism. Previous surgery related to genital tract as per history. Impaired hepatic /renal function. Diabetes mellitus. Hyperprolatinaemia.

2- Methods

For all women, the following was done

a) Verbal consent after explanation of nature of study.

b) Complete history: At the first visit, detailed history was taken. It included; Personal history: age, marital status, special habits, occupation and duration of marriage. Menstrual history: menarche, menstrual cycle (length and duration), dysmenorrhea, mid cycle pain or discharge, intermenstrual bleeding and date of last menstrual period. History of chronic diseases: including diabetes mellitus and hypertension symptoms and signs suggestive of endocrine disorders. Surgical history: that includes laparoscopy e.g. (ovarian drilling) and laparotomy. Sexual history: frequency of intercourse and coitus problems. Women were also asked about previous investigations that had been done for infertility and any previous treatment that has been given for induction of ovulation.

c) Clinical examination: General examination, for signs of endocrine disorders. Breast examination for galactorrhea. Abdominal examination. Pelvic examination for uterine size and mobility, tenderness, uterine or adnexal masses.

d) Investigation: 1) Semen analysis. 2) Serum FSH and LH. 3) Serum prolactin. 4) Thyroid function tests. 5) Pelvic ultrasound was performed After enrollment, participants were randomly divided into two groups by using identical sealed envelopes technique into:

1- First group: included 50 women that took clomiphene citrate 50mg twice daily from 3rd day of cycle for 5 days with metformin500 mg three times daily as an adjunct with CC for all women.

2- Second group: included 50 women that took letrozole 2.5mg twice daily from 3rd day of cycle for 5 days with metformin 500 mg three times daily as an adjunct with letrozole for all women.

Follow up

These cases were followed up for one month by transvaginal ultrasound folliculometry to document ovulation, Folliculometry was done on day 11, 13 and day 15 of the cycle to detect number of growing follicles and size of follicles. Follicles measure more than 18mm were considered mature follicles.

Also measurement of endometrial thickness in (mm) at the greatest diameter perpendicular to the midsagittal plane in the fundal region including both layers of the endometrial cavity. Serum β-HCG was measured if the menses was delayed for one week for diagnosis of pregnancy chemically then followed up by TVS to detect gestational sac at (4 weeks of gestation) and fetal pulsation at (7 weeks of gestation).

RESULTS

In the present study we had 100 patients equally divided into two groups. Each group included 50 patients, the 1st group is CC with metformin group and the 2nd group is letrozole with metformin group as previously mentioned.

In the study, there was no statistically significant difference between CC group and letrozole group as regards age,in CC group mean age was 26.2 ± 3.8 years and in letrozole group mean age was 24.9 ± 4.1 years . As regards BMI mean BMI was 30.5 ± 1.2 in CC group and mean BMI was 31.6 ± 1.8 in letrozole group

Table (1): Comparison between CC and letrozole groups as regards age and BMI.

Patient's Groups Characteristics	CC with Metformin	Letrozole with metformin	P-value
Age(years)	26.2±3.8	24.9±4.1	0.3
BMI	30.5±1.2	31.6±1.8	0.8

In the present study, there was no statistically significant difference between CC group and letrozole group as regard pregnancy rate

There is only 2 cases get pregnant in CC group which represent (4%) of the group and only 3 cases in Letrozole group which represent (6%). All cases that got pregnant showed both chemical and clinical pregnancy.

Table (2): Comparison between CC and letrozole groups as regards pregnancy rate.

Pregnancy Rate	CC with Metformin	Letrozole with Metformin	P- value
	2(4%)	3(6%)	0.5

As regards to effect of treatment on ovulation, CC reported 29 cases (58%) ovulation after treatment, On the other hand, letrozole reported 33 cases (66%) ovulation after treatment. In conclusion both drugs affected ovulation nearly to the same extent (P >0.05).

Table (3): Effect of treatment on ovulation in studied groups.

Ovulation Rate	CC with Metformin	Letrozole with Metformin	P- value
	29(58%)	33(66%)	0.09

As regard mean follicular diameter in CC group, it was 19.36 ± 3.3 mm, while in letrozole group, it was 19.2 ± 3.4 mm and there was no statistically significant difference between both groups.

Table (5): Effect of treatment on the mean follicular diameter (MFD) in studied groups.

mean follicular diameter(MFD)	CC with Metformin	Letrozole with Metformim	P- value
	19.36±3.3	19.2±3.4	0.8

As regards number of follicles >18mm, there was no statistically significant difference between studied groups.

Table (6): Effect of treatment on the number of follicles >18mm.

number of follicles >18mm	CC with Metformin	Letrozole with Metformin	P- value
	1.10±0.4	1.18±0.6	0.3

No statistically significant difference was found between CC group and letrozole group as regard endometrial thickness, the results proved that, both drugs had nearly similar effects.

Table (7): Effect of treatment on endometrial thickness between the study groups.

Endometrial thickness	CC with Metformin	Letrozole with Metformin	P- value
	9.2±1.3	10.1±1.1	0.4

No statistically significant difference was found between CC group and letrozole group

DISCUSSION

PCOS is a common endocrine disorder that primarily affects women of reproductive age, with prevalence rates ranging from 5% to 10.

In 2013, a consensus panel established controversial definition (the Rotterdam criteria) for pco, to include at least 2 of the following criteria: Oligo- or anovulation (menses less than once every 35 days), Hyperandrogenism (laboratory-confirmed or clinical symptoms), or Polycystic ovaries ultrasound.

With exclusion of other conditions with similar signs such as androgen-secreting tumors or Cushing's syndrome and thyroid dysfunction and hyperprolactinemia.

Given these endocrine abnormalities, infertility is a common complication of PCOS. Studies have reported PCOS as the major cause of infertility in up to 20% of couples .

Clomiphene citrate has been considered first-line therapy for ovulation induction for women with PCOS and infertility.

Third-generation aromatase inhibitors (anastrozole, letrozole) have ovulation-inducing effects by inhibiting androgen-to-estrogen conversion. Centrally, this effect releases the hypothalamic/pituitary axis from estrogenic negative feedback, increases gonadotropin secretion, and results in stimulation of ovarian follicle maturity. Moreover, peripherally, aromatase inhibitors may increase follicular sensitivity to follicle-stimulating hormone (FSH).

These aromatase inhibitors have relatively short half-lives (~2 days), so estrogen target tissues (e.g., endometrium) are spared adverse effects.

Because of these mechanisms, it is postulated that aromatase inhibitors may have superior ovulation induction properties in terms of follicular growth and endometrium development which is important for embryo implantation.

The results of the present study revealed that all cases were homogenous in age, duration of infertility and BMI and showed that the pregnancy rate which is the secondary outcome of the study was more favorable in letrozole group than Cc group as it represent only (4%) in CC group and (6%) in letrozole group but without statistically significant difference between both group as regards ovulation rate which is the primary outcome of the study CC group showed ovulation rate (54%, 70% and 90%) of cases and letrozole group showed ovulation rate (60%,80% and 86%) of cases, with no statistically significant difference between both groups (P >0.05).

As regards mean follicular diameter, both regimens showed efficacy to the same extent with no statistically significant difference between both groups.

The present study showed cumulative endometrial thickness more favorable in letrozole group than CC group which was (9.2 ± 1.37) in CC group and (10 ± 1.31) in letrozole group. But without statistically significant difference between both groups.

The following are some studies which agreed with the results of our study. The study of Abo hashim et al.[15] which was done on 250 anovulatory women (582 cycles) with CC resistant PCOS. The patients received 2.5 mg of letrozole daily (123 patients, 285 cycles) or combined metformin-CC (127 patients, 297 cycles) for 3 treatment cycles. No significant difference regarding the pregnancy rate was observed between both groups.

The study of Badawy and colleagues.[16] who studied 438 infertile women (1063 cycles) with PCOS. Patients were randomized to treatment with 5 mg of letrozole daily (218 patients, 540 cycles) or 100 mg of CC daily (220 patients, 523 cycles). In this study, advantage to the use of letrozole over CC as a first-line treatment for induction of ovulation in women with PCOS was not observed as significant differences in ovulatory cycles, pregnancy rates or miscarriage rates were not found. In contrast to previous studies, endometrial thickness at the time of hcg administration was significantly greater in the cc group (9.2 versus 8.1 mm).

CONCLUSION

The present study showed that both CC and letrozole are equally effective in treatment of infertility in PCOS patients, when combined with metformin treatment. No statistically significant difference was found between CC group and letrozole group as regards pregnancy rate, ovulation rate, number of follicles in the end of first, second or third cycles, or as regards the diameter of follicles, both regimens showed efficacy to the same extent.

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