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Research Article

The Effect of Adding L-Carnitine to Induction of Ovulation with Letrozole among PCOS Patients

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Abstract

Background: Polycystic Ovarian Syndrome (PCOS) is a common endocrine system disorder that affects women in their reproductive age. L-Carnitine (LC) is a small water-soluble molecule that plays an important role in fat metabolisms. It also plays a basic role in the normal mitochondrial oxidation of fatty acids and generation of energy. In this context, LC is expected to play a positive role in enhancing the ovarian function and conception rate. This work was primarily designed to assess those positive effects of adding L-Carnitine to letrozole during induction of ovulation among PCOS patients.

Objective: To assess the effect of adding LC to letrozole during induction of ovulation among PCOS patients in terms of endometrial thickness changes, ovulation rate, and conception rate.

Setting: Department of Obstetrics and Gynecology, Suez Canal University Hospitals, Ismailia, Egypt.

Patients and Methods: This prospective randomized clinical trial included 40 PCOS patients diagnosed according to Rotterdam criteria, 2003. The patients were randomly allocated into two groups: Group A (n=20), where patients received 5mg letrozole from day three until day seven of the cycle plus L-carnitine 2g daily; and Group B (n=20) received 5mg letrozole with placebo.

Main Outcome Measures: The cumulative ovulation rate, endometrial thickness changes, chemical and clinical pregnancy rate.

Results: The cumulative ovulation rate was significantly higher among the LC group compared to placebo group (85% *vs* 60% with significant p value = 0.04). Both the cumulative chemical and clinical pregnancy rate were higher among the LC group compared to placebo group (50% & 40% *vs* 20% & 15% respectively, with significant p value = 0.04 & 0.02 respectively).The mean endometrial thickness was much higher among the LC group compared to the placebo group throughout the study with significant p value.

Conclusion: The adding of LC to letrozole during induction of ovulation among patient with PCOS improves not only endometrial thickness but also ovulation rate as well as chemical and clinical pregnancy rate.

Keywords: L-carnitine; PCOS; Letrozole

Introduction

Polycystic Ovarian Syndrome (PCOS) is a common endocrine system disorder that affects women in their reproductive age. It represents a condition in which the ovaries become studded with small follicles of a diameter ranging between 2 and 9 mm, which may develop in one or both ovaries, and/or ovarian volume in at least one ovary exceeding 10ml, together with variable degrees of anovulation, menstrual irregularities, and insulin resistance [1].

Systematic women screening according to the National Institutes of Health (NIH) diagnostic criteria estimated that 4-10% of women of reproductive age suffer from PCOS [2]. It was once considered as a disorder of adult women, but recent evidence suggests that PCOS is a lifelong syndrome, manifesting since prenatal age. According to the Rotterdam diagnostic criteria, the prevalence of PCOS in adolescents varies from 3% to 26% [3]. The exact prevalence of the disease during childhood is still considered unknown [4].

L-Carnitine is a small water-soluble molecule that plays an important role in fat metabolisms. It also plays a crucial role in the normal mitochondrial oxidation of fatty acids and generation of Acyl-CoA esters.

L-Carnitine also prevents damages caused by oxygen free radicals to the cellular membrane and DNA. It contributes to the mitochondrial oxidation of fatty acids with long chains, which increase the supply of energy to the cells. L-Carnitine is responsible for neutralization of free radicals, removal of superoxide anions, and inhibition of lipid peroxidation, thus preventing hydrogen peroxide damages [5]. In this context, L-Carnitine is expected to play a positive role in enhancing the ovarian function and conception rate. This work was primarily designed to assess those positive effects of adding L-Carnitine to letrozole during induction of ovulation among PCOS

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patients.

Patients and Methods

Patients

This is a prospective randomized clinical trial which was performed at the department of Obstetrics and Gynecology, Suez Canal University hospital. This study was approved by the faculty ethical committee; and all patients gave an informed consent before inclusion in the study. This study included 40 patients with PCOS between the age of 20 and 35 years. The diagnosis of PCOS was based on the 2003 Rotterdam criteria for diagnosis of PCOS. All of them had a normal husband's semen analysis, and absent any other cause of infertility. Patients with any endocrine abnormality, medical disorders, hyperprolactinemia, ovarian pathology, or running on any hormonal or chronic medications were excluded from the study.

They were randomly allocated into 2 groups, the first group (L-carnitine (LC) group) included 20 patient who underwent induction of ovulation with letrozole with the addition of L-carnitine. The second group (placebo) underwent ovulation induction with letrozole plus placebo.

Methods

After obtaining informed consent all the patients in the study were subjected to detailed history taking, general , and local examinations. Hormonal profile assessment included FSH, LH, estradiol, prolactin, RBS, liver function tests and renal function tests.

Induction of ovulation: Induction of ovulation was done using letrozole (2.5mg tablets). It was given in a dose of 5mg per day for 5 days starting from day three to day seven of the cycle. The induction was continued for three successive cycles if pregnancy was not achieved.

L-carnitine intake: L-carnitine was given in a dose of 2g per day (1g tab) starting from first day of menstrual cycle and continued till the day when the pregnancy test is done. If the test was positive the drug was discontinued if not the drug was continued for the 3 successive cycles of ovulation induction.

Follow up and assessment: All patients were assessed by transvaginal ultrasound prior to induction of ovulation to assess ovarian volume and antral follicular count to help diagnosis of PCOS. A count more than 12 follicles of the 2-9mm cohort per single ovary and/or ovarian volume more than 10ml were considered as ultrasound criteria for PCOS. Also, the transvaginal ultrasound helped to exclude women with ovarian pathology from the study and those with functional cysts, which may confound the results of ovulation induction. Again, folliculometry was done using serial transvaginal ultrasound starting from day eight of the cycle till the day of human chorionic gonadotropin (HCG) administration. Failure of induction was diagnosed when there is no dominant follicle (10mm) by day ten of the cycle. The number of stimulated follicles and endometrial thickness was recorded in each group. B-hcg was done in blood after 14 days from the day of HCG administration. If the test is positive L-carnitine was discontinued if not then another cycle of ovulation induction was considered. The induction of ovulation was repeated for 3 successive cycles if pregnancy was not achieved. Chemical pregnancy was diagnosed when B-hcg was more than 5miu/ml while clinical pregnancy was diagnosed when at least a single gestational sac with positive fetal cardiac activity was detected by transvaginal ultrasound.

Table 1: Basic characteristics of both groups.

Characteristic	LC Group	Placebo Group	P Value
FSH	5.93 ±1.022	5.82 ± 0.97	0.14 (NS)
LH	6.77 ± 1.56	6.85 ± 1.61	0.39 (NS)
BMI	28.25 ± 1.76	27.49 ± 2.26	0.23 (NS)
Age	24.65 ± 2.059	24.15 ± 2.49	0.11 (NS)
Duration Of Infertility	2.8 ± 0.83	3.1 ± 1.09	0.06 (NS)
Ovarian Volume	9.8 ±1.94	9.3 ± 1.45	0.2 (NS)

NS: non-significant.

Table 2: Cumulative ovulation rate, chemical and clinical pregnancy rate.

Characteristic	LC Group	Placebo Group	P Value
Ovulation rate	85%(n=17)	65% (n=13)	0.04
Chemical pregnancy	50% (n=10)	20% (n=4)	0.04
Clinical pregnancy	40% (n=8)	15% (n=3)	0.02

Table 3: Endometrial thickness among both groups throughout the study.

Characteristic	LC Group	Placebo Group	P Value
First month	10.34 ± 1.25	7.76 ± 0.73	0.002
Second month	10.6 ± 1.18	7.45 ± 0.64	0.002
Third month	10.7 ± 0.95	7.66 ± 0.83	0.001

Results

Table 1: Basic characteristics of the study population. Both groups were comparable as regard age, BMI, duration of infertility. They were also comparable in the basal day 3 FSH, basal day 3 LH, and ovarian volume.

Table 2: Cumulative ovulation rate, chemical and clinical pregnancy rate among both groups after 3 months of the study. The cumulative ovulation rate was significantly higher among LC group compared to placebo group (85% and 60% respectively value=0.04). Again, both the chemical and clinical pregnancy rate was higher among LC group compared to placebo group (50% & 40% *vs* 20% & 15% respectively, with significant p value = 0.04 & 0.02 respectively).

Table 3: Mean endometrial thickness at the day of HCG administration among both groups throughout the study. Throughout the study the mean endometrial thickness among the LC group was significantly much higher than the placebo group. Not only did the endometrial thickness recorded higher level among LC group, but also with the continuous use of LC it was noticed that the mean endometrial thickness within the LC group was progressively increasing from month to month.

Discussion

PCOS is a common endocrine disorder among females during reproductive age. Although it was always considered as a common cause of ovarian infertility but many authors, prefer to consider it as a systemic metabolic disorder, since the main pathophysiological mechanisms underlying this syndrome include obesity, insulin resistance and hyperinsulinemia. Women with PCOS also have an

imbalance between male and female hormones, as their ovaries tend to produce androgens in excessive amounts. Fenkci et al, suggested that hyperandrogenism and/or insulin resistance in the non-obese women with PCOS may be associated with decreased total serum LC levels [6].

Fenkci et al, measured the serum total LC levels in non-obese women with PCOS (n =27; aged between 16 to 37 years) compared to that of healthy adult women (n=30). PCOS patients have significantly lower total LC (40.5±5.7 μmol/L; in control: 91.1±15.2 μmol/L), but higher levels of Dehydroepiandrosterone (DHEA), testosterone, Luteinizing Hormone (LH), Low-Density Lipoproteins (LDL) and fasting insulin compared to healthy women [6]. Hence the assumption that adding LC may help to reverse the metabolic disorders associated with PCOS.

Samimi et al, found that LC supplementation (250mg per day orally for 12 weeks) lead to significant reduction in body BMI, weight, waist and hip circumference together with improved glycemic control in women with PCOS (mean age 24.8±5.5 years). This indicated that LC supplementation improves PCOS by decreasing blood glucose levels and opposing insulin resistance [7], which could perhaps be attributed to LC-induced increase in beta-oxidation of fatty acids and basal metabolic rates [8].

Not only LC supplementation is expected to improve parameters in PCOS patients, but it could also exert positive effects on other health parameters in PCOS patients. This was demonstrated in a recent study whereby oral LC supplementation (250mg for 12 weeks) among patients with PCOS decreased lipid peroxidation, improved total antioxidant capacity and improved general and mental health parameters [9].

These promising results from the literature and previous studies lead the idea to test the adding of LC to letrozole during induction of ovulation among PCOS patients.

This study included 40 patients with PCOS between the age of 20 and 35 years. The diagnosis of PCOS was based on the 2003, Rotterdam criteria for diagnosis of PCOS, all of them had a normal husband's semen analysis, and absent any other cause of infertility. Patients with any endocrine abnormality, medical disorders, hyperprolactinemia, ovarian pathology, or running on any hormonal or chronic medications were excluded from the study. They were randomly allocated into 2 groups, the first group (L-carnitine group) included 20 patient who underwent induction of ovulation with letrozole with the addition of L-carnitine. The second group (placebo) underwent ovulation induction with letrozole plus placebo.

L-carnitine was given in a dose of 2g per day (1g tab) starting from first day of menstrual cycle and continued till the day when the pregnancy test is done. If the test was positive the drug was discontinued if not the drug was continued for the 3 successive cycles of ovulation induction. Induction of ovulation was done using letrozole (2.5mg tablets). It was given in a dose of 5mg per day for 5 days starting from day three to day seven of the cycle. The treatment was continued for three successive cycles if pregnancy was not achieved.

It was found that the cumulative ovulation rate was much higher among the LC group compared to control (85% and 60% respectively, with p value=0.04). Again the cumulative chemical pregnancy rate was much higher among the LC group compared to placebo group (50% and 20 % respectively, with p value =0.04).

These results came consistent to Ismail et al, who tested the addition of LC to clomiphene citrate in clomiphene-resistant PCOS. They found that LC supplementation along with clomiphene citrate treatment improved both ovulation (64.4% *vs.* 17.4%; < 0.0001) and pregnancy (51.5% *vs.* 5.8%; p < 0.0001) rates in clomiphene-resistant women with PCOS. LC supplementation also improved the number and rate at which the stimulated follicles developed (to a diameter of ≥17mm), and increased serum levels of both estradiol (E2) and progesterone. LC supplementation not only improved reproductive health, but also enhanced the patients' lipid profile and Body Mass Index (BMI) [10].

Although the results of the aforementioned study came along with this study in context , but there is a difference in values between this study and Ismail et al work which is probably due to different sample size and the use of letrozole instead of clomiphene citrate in this work.

In context with the favorable LC outcomes, in this work the clinical pregnancy rate was also much higher among the LC group compared to placebo (40% *vs* 15% respectively ,with significant p value= 0.02), which may impose that LC not only helps in improving the results of ovulation induction and conception but also assists in early pregnancy success.

The previous observation of LC favorable role in early pregnancy success through increasing the clinical pregnancy rate might be attributed to increase in endometrial receptivity which was evident through the increase in the mean endometrial thickness at the day of HCG administration throughout the study among the LC group compared to placebo (10.34±1.25 & 10.6±1.18 & 10.7±0.95 *vs* 7.76±0.73 & 7.45±0.64 & 7.66±0.83 respectively, with significant p value = 0.002 & 0.002 & 0.001 respectively).

The result of this work regarding increase in endometrial thickness and receptivity came consistent with the work of Yehia E. & Ehab B. in which infertile women with at least one prior implantation failure in ICSI/FET cycles co-treated with L-Carnitine showed significantly thicker endometrium (mm)compared to non LC (9.8±1.2 mm *vs.* 8.4±0.7 mm, respectively with significant p value) and higher chemical pregnancy rate 46 (74.2%) in LC *vs.* 22 (35.4%) in non LC with significant p value. Also, higher clinical pregnancy rate (34 (54.8%)) in LC *vs* 14 (22.6%) in non LC with significant p value [11].

In a clinical trial, 50 women with complaints of infertility and ovulatory disorders that at least were under two times stimulation with Clomiphene Citrate and Gonadotropin, but no dominant follicles, were selected, and the effects of adding L-Carnitine on follicular growth rate and fertility have been examined in the next cycle. A dominant follicle was viewed in 64% and results of pregnancy in 10 cycles (20%) was positive. The mean endometrial thickness with L-Carnitine was significantly higher than without L-Carnitine [12].

The improvement of ovulation and conception with the addition

of LC is through its direct action on three important functions in oocytes as it increases energy production by transferring palmitate into mitochondria and maintaining acetyl CoA/CoA ratio, it also reduces oxidative stress and lipotoxicity by scavenging free radicals and removing excess palmitate, and finally it promotes oocyte growth and maturation by decreasing the rate of apoptosis.in conclusion LC maintains cellular energy [13], reduces oxidative stress [5] and minimizes cell death by apoptosis [14], which are necessary for proper oocyte growth and maturation of blastocyst.

Conclusion

The adding of LC to letrozole during induction of ovulation among patient with PCOS improves not only endometrial thickness but also ovulation rate as well as chemical and clinical pregnancy rate.

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