Journal of American Science

Websites:
http://www.jofamericanscience.org
http://www.sciencepub.net

Emails:
editor@sciencepub.net
sciencepub@gmail.com

MARSLAND PRESS
Multidisciplinary Academic Journal Publisher

Role of L- Carnitine as Adjuvant Therapy with Letrozole for Ovulation Induction in Women with Polycystic Ovarian Syndrome (PCOS)

Mohanad Ashraf Ezz Eldin , Mohamed Ali Mohamed, Mohamed Mahmoud Mohamed

Department of Obstetrics and Gynecology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
E-mail: Mohand_EG@Yahoo.Com

Abstract: Background: Polycystic Ovarian Syndrome (PCOS) is a common endocrine disorder that impacts females who are in their reproductive years. There was a correlation between this syndrome and the presence of bigger and dysfunctional ovaries, higher concentration of androgens, insulin resistance and several other significant variables associated with the condition. L-carnitine (LC)is a small molecule that is soluble in water and has a crucial role in the breakdown of fats and the production of energy through the oxidation of fatty acids in mitochondria. L-carnitine has the potential to enhance ovarian function and boost the risk of a successful pregnancy. **Aim of the work:** To assess the effect of adding L-carnitine with letrozole for inducing ovulation in females with polycystic ovary syndrome, we examined the changes in endometrial thickness as well as ovulation rate, clinical and chemical pregnancy. **Patients and Methods:** blinded randomized controlled investigation, whereas two hundred females with PCOS diagnosed according to **Rotterdam criteria (2003)**, were shared and equally distributed to double groups, each group involved one hundred females. The first group added L-carnitine to letrozole, while the second group took letrozole alone with an evaluation of ovulation induction. **Results:** The accumulated ovulation rate was statistically significantly raised in the first group than in the second group. Also, accumulated chemical and clinical pregnancy rates were higher in the first group than in the second group. The endometrial thickness was highly statistically significantly reduced in the participants of first group compared to the participants of second group. **Conclusions:** The evaluated variables of the research results demonstrated that adding L-carnitine to letrozole throughout ovulation induction in polycystic ovarian syndrome patients improved the endometrial thickness, ovulation rate, clinical and chemical pregnancy rates.
[Mohanad Ashraf Ezz Eldin, Mohamed Ali Mohamed, Mohamed Mahmoud Mohamed**. Role of L- Carnitine as Adjuvant Therapy with Letrozole for Ovulation Induction in Women with Polycystic Ovarian Syndrome (PCOS).** *J Am Sci* 2024;20(6):64-72]. ISSN 1545-1003 (print); ISSN 2375-7264 (online). http://www.jofamericanscience.org 03. doi:10.7537/marsjas200624.03.

Keywords: L-carnitine, Letrozole, Ovulation Rate, Chemical Pregnancy, Clinical pregnancy, Endometrial Thickness, PCOS, CC.

1. Introduction:

PCOS is a disorder that influences both the endocrine system and the reproductive system. It typically affect females in their childbearing years. It is frequently associated with the presence of enlarged and dysfunctional ovaries, high concentration of androgens, insulin resistance and other characteristics that are connected to this syndrome. Prior to menopause, approximately ten percent of women have polycystic ovary syndrome and experience its associated difficulties [(1)].

The elevated LH to FSH ratio and raised frequency of GnRH are recognized as the primary factors contributing to polycystic ovary syndrome. However, the precise etiology and pathophysiology of the condition have not been fully understood [(2)].

In general, hyperandrogenism decreases the level of SHBG, resulting in an elevated concentration of free testosterone. Polycystic Ovary Syndrome females were found to exhibit elevated levels of testosterone in their plasma, which can be converted to estrone in adipose tissue. The heightened conversion of estrone to estradiol impacts the development of follicles and raises the LH to FSH ratio, leading to impaired ovulation [(3)].

Letrozole is inhibiting the aromatase enzyme and is prescribed to induce ovulation. An important benefit of letrozole is its ability to act as a reversible enzyme inhibitor. It inhibits the conversion of androgen to estrogen leading to a rise in testosterone levels. It is indicated for use during times when clomiphene citrate (CC) is ineffective in cases with polycystic ovary syndrome, those who respond poorly to treatment, endometriosis, older women and breast cancer patients. One significant benefit of this medication compared to clomiphene citrate is that it lacks any negative impact on the endometrium and cervical mucus by reducing estrogen levels. It lowers the occurrence of multiple pregnancies and lessens the risk of OHSS [(4)].

Letrozole has lately become more commonly used for treating anovulatory infertility as compared to clomiphene citrate. The primary detrimental consequences include vasomotor symptoms for example: hot flashes, nausea and exhaustion. It is not recommended for females who are at risk of developing osteoporosis, endometrial hyperplasia or endometrial neoplasia [(4)].

L-carnitine is crucial in the processes of fat metabolism and the production of acyl-coenzyme A esters [(5)]. It has significant functional capacities to control the metabolic and oxidative states of the woman reproductive system. The susceptibility of this system to the demands of free radicals necessitates the implementation of advanced techniques to counteract their effects. To achieve this objective, the 'quasi vitamins' L-carnitine and acetyl L-carnitine can be employed either separately in conjunction with one another or with additional antioxidants [(6)].

L-carnitine Furthermore, it plays an essential role in aiding weight loss by controlling the body's ability to process glucose, improving insulin action and stimulating fatty acid metabolism. Some possible mechanisms are making it easier for insulin-sensitive tissues to get rid of extra acyl groups and for long-chain free fatty acids to get into the mitochondrial matrix. Several researchers have found that females with PCOS have significantly reduced concentrations of both free and total LC in their bloodstream. LC supplementation resulted in a notable enhancement of ovulation and cumulative pregnancy rates in cases diagnosed with polycystic ovary syndrome [(7)].

It is expected that L-carnitine will enhance ovarian function and increase the risk of pregnancy in this research. The main purpose of this experiment was to examine the positive impacts of adding L-carnitine to letrozole as treatment for inducing ovulation in cases with polycystic ovary syndrome.

2. Patients and Methods:

This research was performed between November 2023 and April 2024 on 200 women who underwent induction of ovulation attending Al-Hussien University Hospital in Cairo throughout the time of the research.

The research involved infertile females submitted to induction of ovulation using letrozole and L-carnitine. The selected candidates were established into two groups: the first took letrozole with the addition of L-carnitine as an ovulation induction, and the second took letrozole only.The cases involved in the research were aged from twenty to forty years, with no conception for at least one year. The married women diagnosed with PCOS based on **Rotterdam criteria (2003)** for the diagnosis of PCOS (2 of 3) are: (A) oligo-ovulation and/or anovulation, (B) polycystic ovaries diagnosed by ultrasound (if there were twelve or more follicles measuring two to nine millimeters in diameter or enhanced ovarian volume more than 10 ml), (C) clinical (the condition known as hirsutism is characterized by an abnormally high rate of terminal hair growth that is distributed in a men pattern and/or biochemical signs of hyperandrogenism which increased level of serum free testosterone). Also, we aim to achieve fertility through consistent sexual activity and steer clear of any additional factors contributing to infertility. Semen analysis is normal for husbands. We exclude individuals with endocrine abnormalities, medical diseases, hyperprolactinemia and ovarian pathology. Also, we exclude patients with tubal and severe cervical factors, uterine anomalies, pelvic inflammatory disease and endometritis. Also, Patients who are currently on any hormonal or chronic medications are at risk. Individuals with a history of ovarian hyperstimulation syndrome and severe chromosomal genetic abnormalities. Both women and husbands experience sexual dysfunction, and any form of contraception can also contribute to this.

With respect to the distribution of the candidates, letrozole alone or L-carnitine and letrozole, letrozole was nearly equally distributed among both groups. All the tested candidates were subjected to induction of ovulation by using letrozole dose (2.5 mg) tablets (Femara, Novartis, Egypt) (Figure 1). The medication was administered at a dosage of five milligrams per day for a duration of five days, starting on the 3rd day and stopping on the 7th day of the menstrual cycle. If pregnancy was not achieved, the induction continued for three consecutive cycles.

Figure 1: Letrozole (Femara, Novartis, Egypt)

L-carnitine was given to the first group only in dose of (2 gm) per day (1 gm) tablet (L-Carnitine Plus, Mepaco, Egypt) (Figure 2). Beginning on the 1st day of the menstrual cycle and continuing until the day when the pregnancy test is performed. If the test show a positive result, the administration of the medication was stopped. On the other hand, if the test showed a negative result, the medication was given for the following three cycles of ovulation stimulation.

Figure (2): L-carnitine (L-Carnitine Plus, Mepaco, Egypt)

All the women who took part were closely watched using a pelvic ultrasound, tests for hormones (LH, FSH, estradiol, and prolactin), liver function tests, random blood sugar, renal function tests and a baseline transvaginal ultrasound on day two or three of their period to rule out the presence of an ovarian cyst.

The main purpose of our research was to determine whether the addition of L-carnitine to letrozole improved the thickness of the endometrium on the day of human chorionic gonadotropin administration in cases with polycystic ovary syndrome to induce ovulation.

Secondary purpose included an increase in the cumulative rate of ovulation as well as chemical and clinical pregnancy among cases with polycystic ovary syndrome when L-carnitine was added with letrozole to induce ovulation.

Statistical analysis:

The statistical framework for social sciences version 23.0 (SPSS Inc., Chicago, Illinois, USA), was utilized to analyze the collected data. The quantitative data were reported in the form of ranges and means ± standard deviation. Furthermore, qualitative variables were delineated in percentage form. The normality of the information was examined utilizing the Kolmogorov-Smirnov and Shapiro-Wilk tests. The statistical calculator was utilized with a ninety-five percent confidence interval, a ninety-five percent power of the study and a five percent acceptable margin of error. The level of significance was determined by assigning values below 0.05 (significant), below 0.001 (highly significant) and above 0.05 (insignificant) as P values respectively.

Ethical Considerations:

The research project received ethical approval from Research Ethics Committee of the Department of Obstetrics and Gynecology of the Faculty of Medicine at Al-Azhar University, Egypt. Obtained written informed permission from all the participants. The study procedure adhered to the Helsinki Declaration, which is the ethical standard set by the World Medical Association for conducting human experimentation.

3. Results:

We established the following based on the variables measured for the trial participants:

The table (1) demonstrates no statistically significant variance among groups 1 and 2 according to their hormonal profiles (at basal day 3) before 3 months of starting of induction regarding FSH (mIU/ml), LH (mIU/ml) and prolactin (ng/ml) with a p-value ($p>0.05$), while there was a highly statistically significant distinction among groups regarding E2 (pg/ml) with a p-value ($p<0.001$).

Table (1): Comparison between group 1 and group 2 according to Hormonal profile (Basal Day 3) before 3 months.

Hormonal profile (Basal Day 3) Before 3 months	Group 1(n=100)	Group 2(n=100)	Test value	p-value	Sig.
FSH (mIU/ml)					
Mean±SD	1.22±0.47	1.32±0.57	-1.401	0.163	NS
Range	0.2-2.5	0.5-2.3			
LH (mIU/ml)					
Mean±SD	25.66±7.82	24.13±7.84	1.374	0.171	NS
Range	13.7-47.8	11-55			
E2 (pg./ml)					
Mean±SD	75.65±17.19	101.51±30.28	5.158	0.001	HS
Range	50.1-113	51.6-210.9			
Prolactin (ng/ml)					
Mean±SD	20.64±5.35	18.32±10.69	1.927	0.064	NS
Range	9-32.1	1-39.1			

Using: t-Independent Sample t-test for Mean±SD.
HS: Highly significant, S: Significant, NS: Non-significant.

The table (2) showed highly statistically significant higher mean value of FSH (mIU/ml) after 3 months of induction in group 1 (7.25±1.37) comparing to group 2 (3.69±1.61) with p-value

(p<0.001).Also, highly statistically significant decrease mean value of LH (IU/ml) after 3 months of induction in both groups but the group 1 better than the group 2 with p-value (p<0.001). As well as highly statistically significant decrease mean value of E2 (pg/ml) after 3 months of induction in both groups but the group 1 better than the group 2 with p-value (p<0.001). While there isn't statistically significant variance among group 1 and group 2 regarding prolactin (ng/ml) with a p-value (p>0.05).

Table (2): Comparison among group 1 and group 2 according to Hormonal profile (Basal Day 3) After 3 months.

Hormonal profile (Basal Day 3) After 3 months	Group 1 (n=100)	Group 2 (n=100)	Test value	p-value	Sig.
FSH (mIU/ml)					
Mean±SD	7.25±1.37	3.69±1.61	16.880	0.001	HS
Range	4.7-10.5	1.5-8.2			
LH (mIU/ml)					
Mean±SD	6.49±1.61	12.76±5.32	-11.288	0.001	HS
Range	3.6-10	7.3-32.9			
E2 (pg./ml)					
Mean±SD	49.05±14.3	57.41±19.15	4.135	0.001	HS
Range	20.5-79.8	20-101.2			
Prolactin (ng/ml)					
Mean±SD	15.09±7.15	14.70±6.63	0.397	0.692	NS
Range	3.5-30.9	2-26.5			

Using: t-Independent Sample t-test for Mean±SD.
HS: Highly significant, S: Significant, NS: Non-significant.

Table (3) shows no statistically significant reduction of ovarian volume between group 1 and group 2 before 3 months of induction with p-value (p>0.05), but there was highly statistically significant reduction of ovarian volume in group 1 (9.21±3.16) comparing to group 2 (12.19±3.00) after 3 months with p-value (p<0.001).

Table (3): Comparison among group 1 and group 2 according to Ovarian Volume (ml) before and after induction.

Ovarian Volume (ml)	Group 1 (n=100)	Group 2 (n=100)	Test value	p-value	Sig.
Ovarian Volume Before 3 months					
Mean±SD	19.49±6.12	19.91±4.93	-0.534	0.594	NS
Range	10-37	9-30			
Ovarian Volume After 3 months					
Mean±SD	9.21±3.16	12.19±3.00	-6.838	0.001	HS
Range	3-18	6-22			

Using: t-Independent Sample t-test for Mean±SD.
HS: Highly significant, S: Significant, NS: Non-significant.

Table (4) demonstrations highly statistically significant in mean value of Folliculometery (At day 12) in group 1 (22.52±3.40) comparing to group 2 (17.83±2.42) with p-value (p<0.001).

Table (4): Comparison among group 1 and group 2 according to Folliculometery (At day 12).

Folliculometery (At day 12)	Group 1 (n=100)	Group 2 (n=100)	Test value	p-value	Sig.
Mean±SD	22.52±3.40	17.83±2.42	11.235	0.001	HS
Range	14-29	11-22			

Using: t-Independent Sample t-test for Mean±SD.
S: Significant, NS: Non-significant, HS: Highly significant.

In the table (5): The rate of ovulation rate in group 1 was 84% (84/100) and in Group 2 66% (66/100). The Odds ratio for rate of ovulation rate was 2.7 with a ninety five percent confidence interval varying from 1.4 to 5.3, there was statistically significant with p-value (p=0.003). Also, the rate of chemical pregnancy in group 1 was 52% (52/100) and in Group 2 24% (24/100). The Odds ratio for chemical pregnancy rate was 3.47 with ninety five percent confidence interval varying from 1.9 to 6.3, there was highly statistically significant with p-value (p=0.001). As for the rate of clinical pregnancy in group 1 was 41% (41/100) and in Group 2 19% (19/100). The Odds ratio for a clinical pregnancy rate was 3.0 with ninety five percent confidence interval varying from 1.6 to 5.6, there was highly statistically significant with p-value (p=0.001).

Table (5): Comparison among group 1 and group 2 according to Outcome.

Outcome	Group 1 (n=100)	Group 2 (n=100)	OR (95% C.I.)	p-value	Sig.
Ovulation rate (%)	84 (84.0%)	66 (66.0%)	2.7 (1.4-5.3)	0.003	S
Chemical pregnancy	52 (52.0%)	24 (24.0%)	3.4 (1.9-6.3)	0.001	HS
Clinical pregnancy#	41 (41.0%)	19 (19.0%)	3.0 (1.6-5.6)	0.001	HS

#Clinical pregnancy (gest.sac with fetal cardiac pulsation), OR: Odds ratio, C.I.: Confidence interval
HS: Highly significant, S: Significant, NS: Non-significant.

The table (6) demonstrates: no statistically significant variance among group 1 and group 2 according to endometrial thickness at day of HCG administration before of induction. but there is highly statistically significant reduction means value of endometrial thickness in group 1 comparing to group 2 at 1st month, 2nd month and 3rd month with p-value (p<0.001).

Table (6): Comparison among group 1 and group 2 according to endometrial thickness (mm) at day of HCG administration.

Endometrial thickness at day of HCG administration (mm)	Group 1 (n=100)	Group 2 (n=100)	Test value	p-value	Sig.
Before of induction					
Mean±SD	21.55±2.75	22.22±2.68	-1.253	0.321	NS
Range	15-25	18-28			
First month					
Mean±SD	16.72±2.80	20.49±2.68	-9.354	0.001	HS
Range	10-22	16-26			
Second month					
Mean±SD	14.89±2.78	18.38±2.99	-7.694	0.001	HS
Range	10-20	12-25			
Third month					
Mean±SD	12.83±2.73	16.35±3.12	-6.940	0.001	HS
Range	9-18	11-23			

Using: t-Independent Sample t-test for Mean ± SD.
HS: Highly significant, S: Significant, NS: Non-significant.

4. Discussion

Infertility is characterized as the inability to conceive following one year or more of unprotected sexual intercourse. Approximately ten to fifteen percent of couples of reproductive age have this problem. Infertility can be caused by a variety of conditions, one of which is anovulation. Polycystic ovarian syndrome is the primary reason for anovulatory infertility, impacting approximately five to ten percent of females in their reproductive years [8].

Research conducted by Celik et al [9] found that females with polycystic ovary syndrome had significantly fewer levels of LC compared to the healthy control group Fenkci et al., (2008) [10] proposed that the presence of HA and/or IN in non-obese

females with PCOS might be related to a reduction in the overall levels of LC in the bloodstream.

In their study, the concentrations of serum total LC were evaluated by Fenkci et al. [10] in non-obese females with PCOS (n = 27, ranging from sixteen to thirty-seven years) and compared to those of healthy adult females (n=thirty). The participants were all among the ages of sixteen & thirty-seven. Compared to women who don't have PCOS, women who do have it have much higher levels of testosterone, dehydroepiandrosterone, LH, LDL and fasting insulin. Their levels of total L-carnitine are much lower (40.5±5.7 micromole per liter vs 91.1±15.2 micromole per liter in the control group). Therefore, it is assumed that the addition of LC may aid in the reversal of the metabolic abnormalities related to PCOS.

In research performed by Samimi et al.[7], it was discovered that supplementation of LC (250 milligrams per day orally for a duration of twelve weeks) resulted in a significant decrease in waist, BMI and hip circumference in females with polycystic ovarian syndrome (mean age 24.8±5.5 years). Additionally, the investigation found that LC supplementation enhanced glycemic management by lowering blood glucose levels and counteracting insulin resistance. It's possible that the rise in beta-oxidation of basal metabolic rates and fatty acids that is caused by LC is responsible for this improvement. In 2017, Jamilian et al. [11] demonstrated that LC supplementation is not only effective in improving parameters in cases of polycystic ovary syndrome, but it also has good impacts on other health parameters. In the study, patients with polycystic ovarian syndrome who took oral LC supplementation (250 milligrams for a duration of twelve weeks) experienced a reduction in lipid peroxidation, an improvement in improved mental and general health and total antioxidant capacity.

The encouraging findings from the literature and prior research prompt a proposal to investigate the inclusion of LC in conjunction with letrozole for inducing ovulation in Polycystic Ovary Syndrome cases. Hence, the purpose of this investigation was to evaluate the beneficial impacts of adding L-carnitine to letrozole for inducing ovulation in cases with polycystic ovary syndrome. The randomized controlled experiment took place at Al-Hussien University Hospital in Cairo. The research was performed on a group of 200 women aged among twenty and forty years of age who had polycystic ovary syndrome and a history of infertility, after excluding other potential reasons for infertility. The cases are categorized into two groups: the first group involves a one hundred patients receiving L-carnitine and letrozole, while the second group consists of one hundred cases receiving letrozole alone.

Regarding the baseline demographic characteristics of the research population, there wasn't statistically significant distinction between groups 1 and group 2 in terms of age and BMI with p-value greater than 0.05.

In a study conducted by Gharib [12], researchers evaluated the impact of incorporating LC into letrozole treatment for ovulation in forty cases of polycystic ovarian syndrome. The participants were assigned randomly to two groups: Group A (n = 20) in which patients were administered five milligrams of letrozole from the 3rd to the 7th day of the menstrual cycle together with a daily dose of two grammes of L-carnitine and Group B (n=20) which patients were given five milligrams of letrozole along with a placebo. Both groups were similar in terms of age and BMI.

Our research found no statistically significant distinction in the length of infertility "year" among group 1 and group 2 as shown by p-value greater than 0.05. In addition, Gharib [12] discovered that both groups had similar durations of infertility.

There wasn't significant distinction in the levels of FSH (mIU/ml), LH (mIU/ml) and prolactin (ng/ml) between groups 1 and 2 on basal day 3 before three months prior and the p-value ($p>0.05$) indicates that this lack of difference is statistically insignificant. However, there was a significant distinction in the levels of E2 (pg/ml) among the two groups with highly significant p-value ($p<0.001$).

After three months, the hormonal profile analysis on basal day 3 showed significantly higher mean value of FSH (mIU/ml) in group 1 (7.25±1.37) compared to group 2 (3.69±1.61) with p-value of less than 0.001. Also, the average levels of LH (IU/ml) and E2 (pg/ml) went down highly significant in both groups over the next three months but Group 2 better than Group 1 with p-values of less than 0.001 for both comparisons. However, there wasn't statistically significant distinction among groups 1 and group 2 in terms of prolactin (ng/ml) with p-value greater than 0.05.

Gharib [12] discovered that both groups exhibited similar hormonal profiles, specifically in terms of LH and follicle-stimulating hormone, following three months on baseline day 3.

In our research, we observed significantly higher average value of folliculometry (on day 12) in group 1 and was measured at 22.52±3.40 compared to group 2 which had measurement of 17.83±2.42 with p-value of fewer than 0.001.

The research performed by Ismail et al.[13] examined the impacts of adding L-carnitine to CC in cases with clomiphene-resistant polycystic ovary syndrome. They discovered highly significant variance ($P<0.0001$) among both groups, with the LC group having a higher mean number of follicles

compared to the placebo group. Similarly, the study by Latifian et al. [15] investigated the addition of L-carnitine to CC throughout the follicular and luteal phases in cases with clomiphene-resistant polycystic ovarian syndrome. They also reported significant variance (P<0.05) in favor of the females who received L-carnitine.

In research performed by Kortam et al.[4], the effectiveness of supplementing L-carnitine with clomiphene citrate was evaluated in 94 females with polycystic ovary syndrome to determine its impact on ovulation and pregnancy rates. The females were randomly divided into two identical groups. The group L (n = 47) gotten a combination of one hundred milligrams of Clomiphene citrate and three grammes of LC orally from the third to the seventh day of the menstrual cycle, with L-carnitine continuing until the day of the pregnancy test. The group C (n = 47) received one hundred milligrams of CC orally from the third to the seventh day of the menstrual cycle. The Letrozole group had a greater number of pre-ovulatory follicles with a diameter of seventeen millimeters or more. There was an extremely significant distinction (P<0.01) among the group L (1.6 ± 1.2 follicles) and the group C (0.8 ± 0.7 follicles).

The research found statistically significant distinction in ovulation rate among Group 1 (84%) and Group 2(66%). The odds ratio for the rate of ovulation was 2.7, with a confidence interval of ninety-five percent varying from 1.4 to 5.3. The p-value was 0.003, indicating statistically significant distinction. This agrees with previous research by Ismail et al. [13], which also reported highly significant difference (P<0.0001) in ovulation rate among two groups: one receiving Clomiphene citrate and L-carnitine (64.7%) and the other receiving Clomiphene citrate and placebo (17.6%). Similarly, the discoveries of the research performed by Latifian et al. [15] align with our results, as they observed statistically significant distinction (P<0.05) in favor of females who received L-carnitine. Additionally, Gharib [12] discovered that the rate of ovulation was significantly higher in the group that received L-carnitine eighty-five percent compared to the placebo group (60%) with p= 0.04.

Furthermore, there was significant distinction in the rate of chemical pregnancy between Group 1 (fifty-two percent) and Group 2 (forty-two percent) with an odds ratio of 3.47 and a 95% confidence interval varying from 1.9 to 6.3. The p-value was 0.001, indicating strong statistical significance. Additionally, Gharib[12] discovered that the chemical pregnancy rate was greater in the L-carnitine group (50%) compared to the placebo group (40%) with a significant p-value of 0.04.

In our study, we found significant variance in the rate of clinical pregnancy among Group 1 and Group 2. The rate of clinical pregnancy in Group 1 was forty-one percent (forty-one out of one hundred), whereas in Group 2 it was nineteen percent (ninety out of one hundred). The odds ratio for the clinical pregnancy rate was 3.0 with ninety-five percent confidence interval varying from 1.6 to 5.6. The p-value was 0.001, indicating highly significant variance among the two groups. This finding is consistent with previous research by Ismail et al., (2014), which also reported highly significant difference (p<0.0001) in pregnancy rates among two groups. According to the findings of that investigation, the group that was given Clomiphene citrate and L-carnitine had pregnancy rate of 51.5 percent, whereas the group that was given Clomiphene citrate and placebo had pregnancy rate of 5.8 percent. In the same way, an investigation conducted by Latifian et al., (2015) similarly found statistically significant distinction (p<0.05) in favor of females who were given L-carnitine.

Gharib[12] discovered that the clinical pregnancy rate was greater in the LC group compared to the placebo group with rates of 20% and 15% correspondingly. This distinction was statistically significant with a p-value of 0.02. However, Kortam et al., (2020) found no statistically significant distinction (P > 0.05) in pregnancy rates between the group L (8.5%) & the group C (6.4%).

Ismail et al. [13] found that adding L-carnitine to CC in cases of Clomiphene-resistant polycystic ovarian syndrome had consistent outcomes. They found that LC supplementation along with Clomiphene citrate therapy significantly improved the ovulation rate (64.4% versus 17.4%) with p-value of less than 0.0001. Additionally, LC supplementation led to higher pregnancy rate (51.5% vs. 5.8%) with p-value of less than 0.0001 in clomiphene-resistant females with polycystic ovarian syndrome. L-carnitine supplementation also had positive effects on the development of stimulated follicles, increasing the number and rate at which they reached a diameter of 17 mm or more. Furthermore, the serum levels of estradiol (E2) and progesterone were found to be enhanced by LC supplementation. When the patients took LC supplements, not only did their reproductive health improve, but their lipid profiles and BMI also improved because of the supplementing. Based on the endometrial thickness at the day of HCG administration (measured in millimeters), there wasn't statistically significant distinction between group 1 and group 2 before induction, as indicated by p-value greater than 0.05. However, there was significant reduction in the average endometrial thickness in group 1 compared to group 2 at the first, second and 3rd months with a p-value less than 0.001.

This study's findings on the reduction in endometrial thickness were inconsistent with those of

a previous study by Edris and Barakat [17]. In their study, infertile women who suffered at least one failed implantation in intracytoplasmic sperm injection and frozen embryo transfer cycles were co-treated with LC demonstrated significantly thicker endometrium compared to those who were not treated with L-Carnitine (9.8±1.2mm vs. 8.4±0.7mm). Additionally, the group treated with L-Carnitine had higher chemical pregnancy rate (74.2% vs. 35.4%) and higher clinical pregnancy rate (54.8% vs. 22.6%) compared to the non-LC group with statistically significant differences.

The results of this study did not match up with those from Gharib [12] who found that the LC group had significantly higher mean endometrial thickness than the placebo group. The endometrial thickness was shown to be larger in the L-carnitine group compared to other groups. Furthermore, it was observed that the mean thickness of endometrial tissue within the L-Carnitine group significantly increased each month with continued LC usage.

A clinical trial was conducted on fifty females who experienced infertility and ovulatory disorders despite undergoing up to two rounds of stimulation with CC and gonadotropin but did not develop any dominant follicles. The purpose of the trial was to investigate the impact of adding L-carnitine on the rate of follicular growth and fertility in the subsequent cycle. The results showed that 64% of the females developed a dominant follicle and in twenty percent of the cycles a positive pregnancy outcome was observed. The average endometrial thickness was significantly higher when L-carnitine was used compared to when it was not used according to a study by Latifian et al., in 2015 [15].

Ismail et al.[13] found statistically significant distinction ($P<0.0001$) among both groups. The LC and CC groups had thicker endometrium than the placebo group at the time of HCG injection. Additionally, Latifian et al.[15] reported statistically significant distinction ($P<0.05$) in favor of women who received LC.

Conclusion

In conclusion, our data show that adding L-carnitine to letrozole throughout the induction of ovulation in cases with polycystic ovarian syndrome improves not only the ovulation rate but also the chemical and clinical pregnancy rate and endometrial thickness.

Conflict of interest statement:

The authors declared that there were NO conflicts of Interest.

Disclosure:

The authors have no financial interest to declare in relation to the content of this article.

Authorship:

All authors have a substantial contribution to the article.

References:

[1]. Sadeghi HM, Adeli I, Calina D, Docea AO, Mousavi T et al.: Polycystic Ovary Syndrome: A Comprehensive Review of Pathogenesis, Management, and Drug Repurposing. Int J Mol Sci. 2022; 23(2):583. doi: 10.3390/ijms23020583.

[2]. Ganie MA, Vasudevan V, Wani IA, Baba MS, Arif T, Rashid A: Epidemiology, pathogenesis, genetics & management of polycystic ovary syndrome in India. Indian J. Med Res. 2019; 150:333–344. doi: 10.4103/ijmr.ijmr_1937_17.

[3]. Macut D, Bjekić-Macut J, Rahelić D, Doknić M: Insulin and the polycystic ovary syndrome. Diabetes Res Clin Pract. 2017; 130:163-170. doi: 10.1016/j.diabres.2017.06.011.

[4]. Sharma M, Balasundaram P: Ovulation Induction Techniques. [Updated 2023 Jun 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK574564/.

[5]. Kamangar F, Okhovat JP, Schmidt T, Beshay A, Pasch L et al.: Polycystic Ovary Syndrome: Special Diagnostic and Therapeutic Considerations for Children. Pediatr Dermatol. 2015; 32(5):571-8.

[6]. Agarwal A, Sengupta P, Durairajanayagam D: Role of L-carnitine in female infertility. Reprod Biol Endocrinol. 2018; 16(1):5.

[7]. Samimi M, Jamilian M, Ebrahimi FA, Rahimi M, Tajbakhsh B, Asemi Z: Oral carnitine supplementation reduces body weight and insulin resistance in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Clin Endocrinol (Oxf). 2016;84(6):851-7.

[8]. Conway G, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Franks S et al.: European survey of diagnosis and management of the polycystic ovary syndrome: results of the ESE PCOS Special Interest Group's Questionnaire. Eur J Endocrinol. 2014 ;171(4):489-98.

[9]. Celik F, Kose M, Yilmazer M, Köken GN, Arioz DT, Kanat Pektas M: Plasma L-carnitine levels of obese and non-obese polycystic ovary syndrome patients. J Obstet Gynaecol. 2017 ;37(4):476-479.

[10]. Fenkci SM, Fenkci V, Oztekin O, Rota S, Karagenc N: Serum total L-carnitine levels in

non-obese women with polycystic ovary syndrome. Hum Reprod. 2008 ;23(7):1602-6.

[11]. Jamilian H, Jamilian M, Samimi M, Afshar Ebrahimi F, Rahimi M et al.: Oral carnitine supplementation influences mental health parameters and biomarkers of oxidative stress in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. Gynecological Endocrinology, 2017; 33(6), 442–447.

[12]. Gharib WF: The Effect of Adding L-Carnitine to Induction of Ovulation with Letrozole among PCOS Patients. Austin J Obstet Gynecol., 2019; 6(3): 1141.

[13]. Ismail AM, Hamed AH, Saso S, Thabet HH: Adding L-carnitine to clomiphene resistant PCOS women improves the quality of ovulation and the pregnancy rate. A randomized clinical trial. Eur J Obstet Gynecol Reprod Biol., 2014 ;180:148-52. doi: 10.1016/j.ejogrb.2014.06.008.

[14]. Kortam M, Abdelrahman R, Fateen H: L-Carnitine and Clomiphene Citrate for induction of ovulation in women with Polycystic Ovary Syndrome : Randomized controlled trial. Evidence Based Women's Health Journal, 2020; 10(1): 1-7.

[15]. 1Latifian S,Hamdi K,Totakhneh R: Effect of Addition of L-Carnitine in Polycystic Ovary Syndrome (PCOS)Patients with Clomiphene Citrate and Gonodotropin Resistant. Int.J.Curr.Res.Aca.Rev., 2015; 3(8): 469-476.

[16]. Edris Y, Barakat E: Supplementation with L-Carnitine improves uterine receptivity in women with prior implantation failure during frozen embryos transfer: A double-blinded, randomized, placebo-controlled clinical trial. Evidence Based Women's Health Journal, 2018; 8(3): 236-244. doi: 10.21608/ebwhj.2018.15474.

6/11/2024