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Effect of Addition of L-Carnitine in Polycystic Ovary Syndrome (PCOS) Patients with Clomiphene Citrate and Gonodotropin Resistant

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A B S T R A C T

Infertility is defined as the inability to conceive after one year of unprotected sex, i.e. without using contraceptives. Ovulatory disorders are responsible for female infertility in 30-40% of occasions. In individuals with ovulatory dysfunctions, and particularly in those suffering from Polycystic Ovary Syndrome (PCO), ovulation induction is achieved through various regimens. However, conventional dosages do not yield adequate results in some patients with PCO; while some of them are, indeed, responsive to increased dosages. Adding L-Carnitine to therapeutic regimens could potentially result in desirable follicle counts, with the same conventional dosage. The aim of this study was to investigate the effects of adding L-Carnitine on successful of treatment in patient with PCO resistance to Clomiphene citrate and Gonadotropin. In a clinical trial (before-and-after) study that performed in Department of OG of Tabriz University of Medical Science on patients with infertility, the effects of adding L-Carnitine to the regimen of patients with PCO resistance to Clomiphene Citrate and Gonadotropin evaluated. In this study, 50 women with complaints of infertility and ovulatory disorders that at least were under two period's stimulation with Clomiphene Citrate and Gonadotropin, but no dominant follicles, were selected, and the effects of L-Carnitine on their dominant follicle growth rate and fertility have examined in the next cycle. Mean age of studied patients was 27.98±4.61 year. Mean BMI of studied patients was 26.97±4.04. In second period, The Ovulation induction with L-Carnitine, of 50 therapeutic cycles, in 32 cycles, at least, a dominant follicle was viewed (64%) and results of pregnancy in 10 cycles (20%) was positive. The mean number of used gonadotropin in stimulation period with L-Carnitine was not significantly different from the non L-Carnitine phase. Significant difference was not found in mean of right ovary follicles size in phase with and without L-Carnitine but mean of left ovary follicles size in with L-Carnitine phase was significantly greater than left ovary follicles size in without L-Carnitine phase. The mean endometrial thickness in the phase with L-Carnitine was significantly more than the phase without L-Carnitine.

Introduction

Ovulatory dysfunction accounts for 30 to 40% of infertility in women (1) and the prevalence of this condition prior to menopause is 5 to 10% (1-3). PCOS (Polycystic Ovary Syndrome) is one of the important clinical disorders associated with anovulation and infertility (2, 4). The first step toward the treatment of PCOS is weight reduction and the second step is medical treatment (1).

Currently, anti estrogen medicines such as Clomiphene Citrate, Letrozole or even Tamoxifen Citrate are used in the first round of treatment for PCOS patients (4). The major application of Clomiphene is in women who suffer from infertility caused by normogonadotropic, normoestrogenic, and normoprolactinemic ovulations, which also include PCOS (5). Clomiphene citrate and gonadotropin are also used in the IUI and ART treatment cycles (6-8).

If the patient fails in ovulation with a maximum dosing of 150 mg of Clomiphene or if the patient does not demonstrate a proper response after 6 months of treatment with Clomiphene (in the absence of other infertility factors), other ovarian stimulation methods and techniques such as IUI are employed (4). Results and evidence obtained from ART cycles indicate that a high level of oxygen free radicals has a destructive effect on the phases of follicle growth, fertilization and implantation. Particularly, the cause outbreak of apoptosis in the nucleus and cytoplasm of the ovule, sperm and blastomere in the presence of high levels of the aforementioned free radicals was explained in the past (9).

L-Carnitine is a small water-soluble molecule that plays an important role in fat metabolisms. It also plays a fundamental 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. This molecule 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. Therefore, L-Carnitine is capable of preventing hydrogen peroxide damages.

Hence, this research was conducted to examine the contribution of L-Carnitine to ovarian stimulation and fertilization in PCOS patients who are resistant to Clomiphene citrate and gonadotropins. The research hypothesis was that addition of L-Carnitines leads to an increase in the response to treatment and a decrease in the side effects of Clomiphene and gonadotropin on the endometrium and cervical mucus. So far, this supplement has been employed in the studies of IVF but no report has been presented on PCOS patients receiving ovarian stimulation treatments. The goal of this research was to examine the effect of adding L-Carnitine to PCOS patients who were resistant to Clomiphene citrate and gonadotropin.

Materials and Methods

In a before-after clinical trial that was carried out in Tabriz on patients with infertility, the effect of adding L-Carnitine was studied on PCOS patients who were resistant to clomiphene citrate and gonadotropin.

The study population included 50 patients who aged between 20 and 35 years. The FSH, LH and estradiol of patients varied in

the normal range in patients who had received at least two rounds of diet therapy with Clomiphene citrate and gonadotropin ampoule but had showed no response.

Inclusion Criteria

The study included patients with a history of infertility and resistance to Clomiphene citrate and gonadotropin who aged between 20 and 30 years and FSH, LH, AMH and estradiol levels in the normal range. The patients also were not using antioxidants.
Lack of other infertility factors such as the tubal or male factor, etc. was also among the inclusion criteria.

Exclusion Criteria

The exclusion criteria for this research included sensitivity to L-Carnitine and lack of interest in participating in the research.

Patients who aged between 20 and 35 years and had normal ovarian reserves, which were determined by measuring FSH, LH, estradiol and AMH were included in the research. The patients also had received at least two rounds of diet therapy with Clomiphene citrate (100-150) and gonadotropin but showed no responses and no dominant follicle was formed.

In the ovarian stimulation cycle, the treatment included Clomiphene citrate (100-150 mg) and gonadotropin ampoule (3 to 5 ampoules). From the third day of treatment with Clomiphene citrate, as the dominant follicle was observed, two vials of oral L-Carnitine were added every 12 hours (1 vial=1 gram) until the HCG injection. Afterwards, the number of dominant follicles and diameter of the endometrium would be recorded and HCG would be prescribed. The proper timing for sexual intercourse was also taught to the patients to increase the possibility of fertilization. The support to the luteal phase was provided using progestin products. Treatment consequences including the number of dominant follicles and success of chemical pregnancy ($^{+}$BHCG) were compared before and after the administration of L-Carnitine.

Moral Considerations

The written and informed consent of the participants was obtained prior to the study. All of the patients' information remained confidential and the resulting information was only used to attain the research goals. It is worth mentioning that the expenses imposed by adding L-Carnitine to the routine therapeutic diet of patients were paid by the researchers and executors of this project.
All of the possible complications of using this new treatment were explained to the participants before taking part in this research. Vomiting, nausea, headache, diarrhea, Rhinorrhea, restlessness and sleep problems are among the possible side effects of this medical treatment. However, these side effects have been reported rarely and in our study none of the patients experienced any significant side effect of the treatment.

Result and Discussion

In this study, 50 women who complained about infertility in the former cycles of ovarian stimulation and did not experience the growth of dominant follicles were selected to examine the effect of L-Carnitine on the response of the treatment cycle to ovarian stimulation and development of fertility. The examination results are presented in the following. The mean age of patients under study was 27.98 ± 4.61 years.
Two patients had regular the menstrual cycles whereas 48 patients were experiencing oligomenorrhea. Hirsutism was

observed in 13 patients while galactorrhea was observed in 8 patients. Moreover, 45, 5, and 6 patients were taking Metformin, Levothyroxine, and Cabergoline, respectively. Table (1) presents the experimental findings about the patients.

The result of pregnancy tests on 10 patients was positive.In the absence of L-Carnitine, the treatment protocol for 40 patients included 10 mg of Clomid and that of the other 10 patients included 15 mg of Clomid. In the presence of L-Carnitine, the treatment protocol for 38 patients included 10 mg of Clomid and that of 12 patients included 15 mg of prescribed Clomid. Results of examination of demographic and experimental parameters based on pregnancy test results are shown in Table (3).

Table.1 Demographic findings of patients

	Pregnancy		P	Total
	Positive	Negative		
Age	28.00 ± 4.87	27.95 ± 4.29	0.969	27.98 ± 4.61
Weight	70.52 ± 9.61	69.16 ± 11.87	0.660	70.00 ± 10.43
Height	1.62 ± 0.05	1.61 ± 0.04	0.433	1.61 ± .05
BMI	27.01 ± 3.46	26.92 ± 4.95	0.941	26.98 ± 4.04

Table.2 Follicle size and endometrial thickness in patients with and without L-Carnitine

	Pregnancy		P	Total
	Positive	Negative		
Without L-Carnitine				
Gonadotropin count	6.71 ± 1.85	7.00 ± 2.07	0.626	6.81 ± 1.91
Right Ovary Follicle Size	14.64 ± 2.60	14.18 ± 3.05	0.584	14.47 ± 2.74
Left Ovary Follicle Size	14.84 ± 2.81	15.28 ± 4.03	0.655	15.00 ± 3.27
Endometrial Thickness	8.35 ± 1.97	8.10 ± 2.21	0.686	8.26 ± 2.04
With L-Carnitine				
Gonadotropin count	5.33 ± 1.75	5.14 ± 1.88	0.749	5.27 ± 1.78
Right Ovary Follicle Size	14.14 ± 2.24	12.83 ± 3.05	0.096	13.65 ± 2.62
Left Ovary Follicle Size	14.39 ± 2.02	13.12 ± 2.39	0.063	13.91 ± 2.23
Endometrial Thickness	7.51 ± 1.34	7.70 ± 1.88	0.680	7.58 ± 1.55

Table.3 Laboratory findings of patients

	Pregnancy		P	Total
	Positive	Negative		
FSH	6.54 ± 2.68	6.04 ± 2.21	0.517	6.36 ± 2.51
Estradiol	48.82 ± 20.92	41.24 ± 1.47	0.353	46.45 ± 21.05
TSH	2.92 ± 1.59	2.37 ± 1.09	0.192	2.71 ± 1.43
PRL	201.12 ± 143.20	161.86 ± 180.99	0.412	185.25 ± 158.85

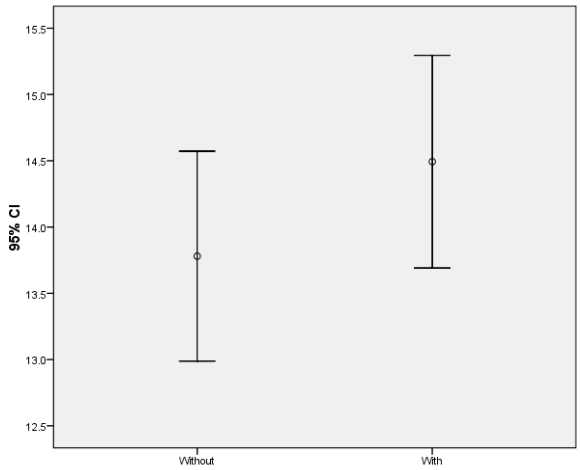

Figure.1 Distribution of Right Ovary Follicle Size in patients with and without L-Carnitine

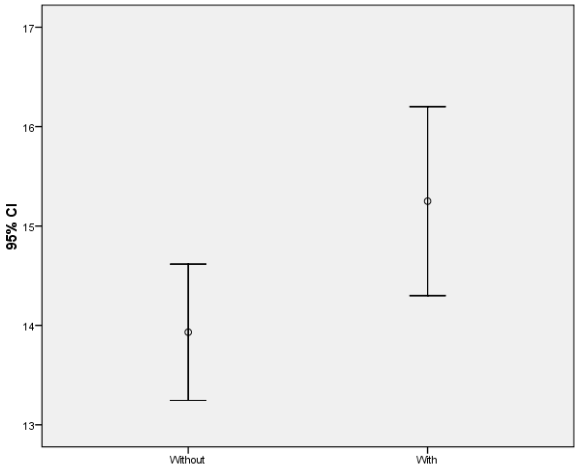

Figure.2 Distribution of Left Ovary Follicle Size in patients with and without L-Carnitine

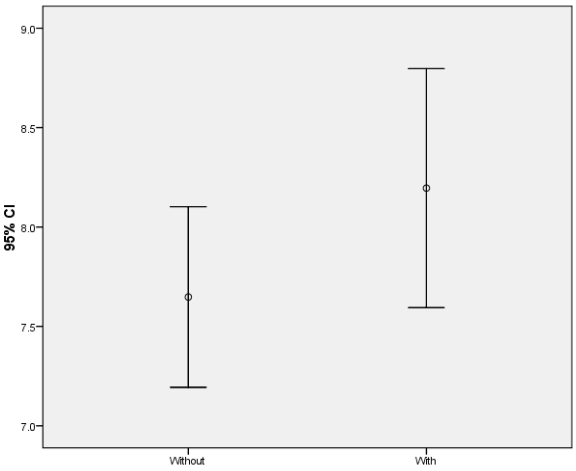

Figure.3 Distribution of endometrial thickness in patients with and without L-Carnitine

Infertility is defined as the lack of pregnancy observed following one year of unprotected sexual intercourse.

About 85 to 90% of healthy couples achieve pregnancy within one year and most of them experience pregnancy during 6 months. Hence, infertility influences about 10 to 15% of couples. Contrary to the common belief, the prevalence of fertility has remained almost unchanged in the past three decades while the assessments and treatments of infertility have changed drastically during this period. Several important advancements in this field have had the highest contribution. The most important advancement was IVF and other assisted reproductive technologies (ART). Direct observation of fetal growth and factors influencing the fetus in the IVF cycles provides for further understanding of the normal cycle events and intervention in the treatment cycles to achieve better results.

In the research by Abdelrazik et al. it was reported that the embryo-culture method along with L-Carnitine supplements is a cost-effective method for improving embryogenesis from embryo-culture. It was also stated that this method can be useful for the enhancement of IVF results (10). In our research, using a L-Carnitine supplement the improvement of the growth of dominant follicles was observed in 32 patients (64%) and the result of the pregnancy tests of 12 (24%) out of the 50 participants became positive. The aforementioned patients did not develop any dominant follicles in the cycles without L-Carnitine.

A 2004 study reported an ovulation rate of 62% using Tamoxifen and an ovulation rate of 47% with Clomiphene (11). In the research by Nardo the rates of ovulation in the Tamoxifen and Clomiphene groups were 67% and 42%, respectively (12).

In our study, the mean diameter of endometrium in the L-Carnitine phase was significantly higher than the mean diameter of endometrium in the absence of L-Carnitine (P=0.029). One of the problems of the cycles of ovarian stimulation by Clomiphene is the anti-estrogenic effect of Clomiphene on the endometrium. This effect sometimes leads to a small diameter of endometrium and infertility even in spite of successful ovulation.

An endometrium diameter higher than 8 mm in the ovarian stimulation cycles and in the IVF cycles is associated with an increase in fertility (4). In a study by Wu et al. in the infertility department of Peking University in China the effects of L-Carnitine were investigated. It was reported that the use of L-Carnitine increases fertility (10).

Fenkci et al. conducted a study in the Denizli University of Turkey to examine the level of L-Carnitine in infertile women with PCO. The researchers stated that the level of L-Carnitine declined in the participants and recommended further investigations into the therapeutic effect of L-Carnitine on patients (13).

In a study that was carried out by Abdelrazik et al. (2008) in University of Egypt with the aid of the Infertility Center of Cleveland Clinic in Ohio (America) the effects of L-Carnitine on the improvement of fertility with assisted reproductive methods were studied. It was stated that the use of L-Carnitine leads to the improvement of fertility along with ART methods (14).

In a study by Mansour et al. that was carried out in the infertility center of the Department of Obstetrics and Gynecology of Cleveland University in Ohio (America) the effect of L-Carnitine on the

improvement of fertility in infertile women was studied. It was reported that the use of L-Carnitine supplements along with ART methods led to the improvement of fertility conditions in the participants (15).

Conclusion

In this research, 50 women complaining about infertility were selected to study the effect of L-Carnitine on the ovulation and fertility conditions of the women. Research results revealed that administration of L-Carnitine to treatment-resisting PCO patients, whose ovaries contained no dominant follicle following the treatment, led to a considerable change in the response of ovaries. In the intervention phase, with the administration of L-Carnitine dominant follicles were observed in the ovaries of 64% of patients and 20% of the patient had positive pregnancy tests. In the cycles accompanied by L-Carnitine the diameter of the endometrium was significantly higher in addition to the growth of dominant follicles.

Suggestions

Based on the research results, the use of L-Carnitine supplements is recommended for infertile women receiving treatments. Moreover, further studies and comparison of L-Carnitine, results with the results of other methods and medicines are also suggested.

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