The effect of L-carnitine on adolescent polycystic ovary syndrome patients with irregular cycles

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Abstract

Background: Polycystic Ovarian Syndrome (PCOS) is a complex endocrine disorder that affects women in their reproductive age. L-Carnitine (LC) is a small water-soluble molecule that plays a basic role in the normal mitochondrial oxidation of fatty acids and generation of energy. Consequently LC is expected to play a positive role in enhancing ovarian functions. This work was primarily designed to assess those positive effects of treatment with LC among adolescent PCOS patients.

Objective: To assess the effect of treating adolescent PCOS patients with LC, in terms of improvement in menstrual irregularities, hormonal imbalance and body weight.

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

Patients and Methods: This prospective randomized clinical trial included 25 adolescent PCOS patients with menstrual irregularity between the age of 14 and 19 years. They were given LC in a dose of 1 g daily for three months. Hormonal profile, menstrual pattern and body mass index (BMI) were assessed before and three months after treatment.

Main outcome measures: Changes in menstrual cycle, hormonal profile and body weight.

Results: The mean BMI decreased significantly after treatment from 29.34 ± 1.73 to 27.88 ± 1.45 (p value = 0.03). Prior to treatment, all the participants complained of menstrual irregularity, the most common form of menstrual irregularity was oligomenorrhea representing 56% (n=14) followed by irregular cycles (32% , n = 8) ,and finally secondary amenorrhea (12% , n =3).After treatment with LC for 3 months 36% (n=9) of the study population regained regular cycles.

Conclusion: Treatment of adolescent PCOS patient with LC help in regaining regular cycles and proved to be efficient in decreasing BMI and further large scale studies may be needed with larger sample sizes and more longer treatment period to elude all potential beneficial effects of LC in this age group.

Keywords: L-carnitine, PCOS, adolescent

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Introduction

Polycystic Ovarian Syndrome (PCOS) is a common endocrine system disorder that affects women in child bearing period as well as during adolescence. (1).

PCOS is characterized by a heterogeneous symptoms and signs, including a variable intermingling features of ovarian dysfunction (oligo-ovulation or anovulation or menstrual irregularity and/or character-

istic polycystic ovarian morphology) and androgen excess (hirsutism and/or hyperandrogenemia) , with the exclusion of other endocrine disorders such as hyperprolactinemia and non-classic congenital adrenal hyperplasia.(2)

The prevalence of PCOS ranges from 6% to 20% according to the criteria used for diagnosis, which may broaden or narrow the inclusion of patients.(3,4) In the past PCOS was considered as a disorder of adult women, but recent evidence suggests that PCOS is a lifelong syndrome, with variable manifestations and late complications. The exact prevalence of the disease during childhood is still considered unknown (5).

The external features of PCOS are primarily due to androgen excess. Any adolescent with persistent menstrual irregularities or features of hyperandrogenism should be suspected of having PCOS. Hyperandrogenism is due to ovarian thecal cells overproduction of testosterone. Hyperandrogenism manifests as hirsutism, acne, temporal balding, deepening of voice, increased muscle mass, decreased breast size. It has been noted that one third of women presenting with acne are diagnosed as having PCOS. Premature adrenarce and the occurrence of hirsutism before puberty have been associated with PCOS in adolescents. (6)

L-Carnitine is a water-soluble molecule with important role in fat metabolisms. It also plays a crucial role in mitochondrial oxidation processes of fatty acids and energy production through generation of Acyl-CoA esters. Some studies showed that supplementation with LC improves PCOS through several mechanism including decreasing blood glucose levels ,regulating production of gonadotropins and antagonizing insulin resistance, which could perhaps be attributed to LC-induced increase in beta-oxidation of fatty acids and basal metabolic rates .(7)

Women with PCOS also have hormonal imbalance with possibility of ovarian production of excess androgens. One study suggested that hyperandrogenism and/or insulin resistance in women with PCOS may be associated with decreased total serum LC levels, denoting that a normal serum level of LC may play a crucial role for preventing insulin resistance and hyperandrogenism.(8)

From the previous view we can deduct that LC is expected to play a positive role in enhancing the ovarian function and improving features associated with PCOS. Review of literature showed very few data about using LC in adolescents with PCOS. This work was primarily designed to assess those positive effects of LC in adolescent PCOS patients with irregular cycles.

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 board, and informed consent was given by the patient as well as parents before inclusion in the study. This study included 25 patients with PCOS between the age of 14 and 19 years with documented menstrual irregularities. Although the diagnosis of PCOS was based on the 2003 Rotterdam criteria for diagnosis of PCOS, but the following recommendations were considered:

• A detailed history was taken from each participant as well as from her mother regarding the sustainability and pattern of menstrual irregularity, because the overlap between normal pubertal development and characteristic features of PCOS may confound an accurate diagnosis of PCOS among adolescent girls.

• Other disorders associated with irregular menses or hyperandrogenism need to be excluded from diagnostic consideration, so patients with any endocrine abnormality, medical disorders, hyperprolactinemia, ovarian pathology, or running on any hormonal or chronic medications were excluded from the study.

• Oligomenorrhea or any other form of menstrual irregularity has to persist for more than 2 years when diagnosing PCOS in adolescent girls with clinical features of androgen excess such as hirsutism and biochemical hyperandrogenism , to avoid misdiagnosing physiological pubertal changes as PCOS features.(8)

• Insulin resistance, hyperisulinemia and obesity were excluded as criteria for diagnosis in adolescent.

• Less weight is given to ultrasound criteria, especially follicular count, since all cases were done through trans-abdominal route which is less sensitive than tran-vaginal in detailed follicular counting.

Methods

After obtaining informed consent all the participants in the study were subjected to detailed history taking with emphasis on menstrual history. General and local examinations. Hormonal profile assessment included basal day 3 FSH, basal day 3LH, TSH, prolactin, and total testosterone. Pelvic ultrasound

was done for assessment of the uterus and both ovaries. As was mentioned before the diagnosis of PCOS was based on the 2003 Rotterdam consensus for diagnosis of PCOS, putting in consideration the recommendations discussed above due to the more complexity of diagnosis among adolescent, at least 2 of the following three criteria were needed for diagnosis; menstrual irregularities or anovulation and/or clinical or biochemical hyperandrogenism and/or characteristic ultrasound morphology.

In this study we emphasized on the criteria of menstrual irregularity to be included in all cases and persisted for at least more than 2 years after menarche to avoid false diagnosis of normal pubertal incidental changes as PCOS. A cycle length between 22 days to 35 days was recognized as regular cycles. Secondary amenorrhea was defined as a cycle length more than 180 days or 6 months. Irregular cycles were defined as overlapped repeated occurrence of cycles less than 21 days or more than 41 days, and finally Oligomenorrhea was defined as a cycle length of 42 -180 days .

Clinical features of hyperandrogenism included persistent acne and hirsutism (assessed through Ferriman and Gallawy score),total serum testosterone more than 70 ng/dl was used as a biochemical marker for hyperandrogenism .

A count more than 12 follicles of the 2-9mm cohort per single ovary and/or ovarian volume more than 10 ml were considered as ultrasound criteria for PCOS. Much weight was given to ovarian volume then follicular count since all cases were done through trans-abdominal route which is less sensitive than tranvaginal in detailed follicular counting.

LC was given in a dose of 1 g per day (1 g tab) for 3 successive months. After the 3 months of the treatment a detailed menstrual history was taken again. BMI recording, hormonal profile and pelvic ultrasound were repeated.

Diet control was offered for all the participants in order to avoid the confounding effect of excess high caloric food intake, this was done through prescribing high protein, low carbohydrate diet, at least three meals per day which are low in sugar and fat and high in fruit, fresh vegetables and salad. Light sustained exercise such as walking, cycling or swimming for at least an hour at a time several times per week.

Results

The mean age among the study population was 16.52 ± 1.58 years. The mean FSH was 4.92 ± 0.94 iu/l , while the mean LH was 6.04 ± 1.56 iu/l .Mean ovarian volume was 9.32 ± 2.48 ml, while the mean BMI was 29.34 ± 1.73 kg/m2. Finally, the mean total testosterone was 60 ± 27.1 ng/dl. (Table 1)

The most common form of menstrual irregularity was oligomenorrhea representing 56% (n=14) followed by irregular cycles (32%, n = 8), and finally secondary amenorrhea (12%, n =3). (Table 2)

After the treatment with LC for 3 months there was a significant decrease in BMI from 29.34 ± 1.73 to 27.88 ± 1.45 (p value = 0.03). (Table 3)

Following the treatment with LC for 3 months 36% (n=9) of the study population regained regular cycles. (Table 4)

Discussion

Polycystic Ovarian Syndrome (PCOS) is a common endocrine system disorder that affects women in child bearing period as well as during adolescence. PCOS is characterized by heterogeneous symptoms and signs, including variable intermingling features of ovarian dysfunction and/or androgen excess. (2)

The prevalence of PCOS ranges from 6% to 20% according to the criteria used for diagnosis, which may broaden or narrow the inclusion of patients.(3,4) In the past PCOS was considered as a disorder of adult women, but recent evidence suggests that PCOS is a lifelong syndrome, with variable manifestations and late complications . The exact prevalence of the disease during childhood is still considered unknown (5).

The external features of PCOS are primarily due to androgen excess. Any adolescent with menstrual irregularities or features of hyperandrogenism should be suspected of having PCOS.(6)

Although many studies have been conducted to demonstrate the beneficial role of LC in fertility and improvement of variable health parameters among PCOS, but there is very few data about such beneficial role among adolescent PCOS patients. The aim of this work was to test such positive effects of LC supplementation among adolescent PCOS patient with menstrual disorders.

This study included 25 patients with PCOS between the age of 14 and 19 years with documented men-

strual irregularities. All the patients in the study were subjected to detailed history taking with emphasis on menstrual history. General and local examinations. Hormonal profile assessment included basal day 3 FSH, basal day 3LH, TSH, prolactin, and total testosterone. Pelvic ultrasound was done for assessment of the uterus and both ovaries. LC was given in a dose of 1 g per day (1 g tab) for 3 successive months. After the 3 months of the treatment a detailed menstrual history was taken again and followed for the next 3 months. BMI recording, hormonal profile and pelvic ultrasound were repeated.

The mean age among the study population was 16.52 ± 1.58 years. Prior to treatment, the mean FSH was 4.92 ± 0.94 iu/l , while the mean LH was 6.04 ± 1.56 iu/l. The mean ovarian volume was 9.32±2.48 ml, while the mean BMI was 29.34 ± 1.73 kg/m2. Finally, the mean total testosterone was 61 ± 27.1 ng/dl.

The most common form of menstrual irregularity among the study population was oligomenorrhea representing 56% (n=14) followed by irregular cycles (32%, n = 8), and finally secondary amenorrhea (12% , n =3).

The distribution of menstrual irregularities among adolescents in this study differed from that of Bhavana V. 2017, In his work 80 adolescent PCOS patients with menstrual irregularities between 10 and 20 years were allocated into 2 groups, one group was treated with metformin for 6 months while the other group with placebo. The main form of menstrual irregularity in his work was irregular periods representing 83.75% (n=67), followed by secondary amenorrhea (5% , n = 4), then menorrhagia (8.75% .n=7). The differences in the pattern of menstrual irregularity between both studies may be due to different ethnic background, sample size and the different age ranges as Bhavana V. extended the age range down to 10 years which may be confounded with dysfunction uterine bleeding that may commonly intercepted in the first 2 to 3 years following menarche.(10)

In this work, After the treatment with LC for 3 months there was a significant decrease in BMI from 29.34 ± 1.73 to 27.88 ± 1.45 (p value = 0.03). Several studies documented such weight reducing effect of LC among PCOS. In a prospective, randomized, placebo-controlled, double-blind trial to determine the effects of oral LC supplementation on weight loss and lipid profiles in women with PCOS, it was found that the supplementation of LC in a dose of 250 mg per day orally for 12 weeks lead to significant reduction in body weight, BMI, waist and hip circumference in women with PCOS. Increase in the basal metabolic rates and excess beta-oxidation of fatty acids were the proposed mechanisms for the LC-moderated effects. (11)

As for the hormonal profile before and after the treatment, none of the hormones measured showed any significant change following LC treatment for the 3 months of the study, but still the only hormonal change that was close to significance was the decrease of total testosterone from 61 ± 27.1 to 58 ± 23.9 (p value =0.08) . Such decrease in biochemical hyperandrogenism was suggested by Some authors who concluded that hyperandrogenism and/or insulin resistance in the non-obese women with PCOS may be associated with decreased total serum LC levels and that normal serum levels of LC may be mandatory for normal ovarian function. They measured the serum total LC levels in non-obese women with PCOS and compared it to normal control. They found that PCOS patients have significantly lower total LC (40.5 ± 5.7 μmol/L vs. 91.1 ± 15.2 μmol/L), higher levels of dehydroepiandrosterone (DHEA), testosterone, luteinizing hormone (LH), low-density lipoproteins (LDL) and fasting insulin compared to control. (9)

From that point it is proposed that the close to significance decrease in total testosterone in this work might have been significant if the sample size was larger or if the treatment was continued for longer time.

The main outcome of the study was the significant change in menstrual pattern before and after the treatment. As was mentioned before it was assured during selection of patient that a persistent menstrual irregularity was documented for at least 2 years, so generally speaking 100% of the study population showed menstrual irregularity (oligomenorrhea representing 56% (n=14) followed by irregular cycles (32% , n = 8) ,and finally secondary amenorrhea (12% , n =3)) .

Following the treatment with LC for 3 months, 36% (n=9) of the study population regained regular cycles. The percentage of oligomenorrhea decreased from 56% (n= 14) to 32 % (n= 8) ,while irregular cycles decreased from 32% (n = 8) to 24% (n=6), and finally secondary amenorrhea decreased from 12% (n =3) to 8% (n=2).

Such positive improvement in cycle pattern among PCOS adolescents treated with LC for three months in this work confirms the consistency of the variable favorable actions of LC on female fertility (specially PCOS).

This improvement following LC treatment is caused through both direct and indirect actions. The direct action on ovarian cells and oocyte specially include an increased energy production by transferring palmitate into mitochondria and maintaining acetyl CoA/CoA ratio, it promotes cellular growth and maturation by decreasing the rate of apoptosis, and finally reducing oxidative stress by scavenging free radicals and removing excess palmitate. (12)

LC acts indirectly through affecting the HPG axis to regulate reproductive hormone secretion. The highest LC concentration in neuronal cells is in the hypothalamus where it decreases neuronal cell death. It is reported that LC cause K+-induced depolarization in hypothalamic neuronal cells thus increasing its secretory activity. it is proposed that treatment with LC increases serum levels of other reproductive hormones, like estradiol, progesterone, LH and decreases prolactin. Through this indirect effect, it prevents PCOS, amenorrhea and other problems related to the female reproductive cycle. (13,14)

Conclusion

Treatment of adolescent PCOS patient with LC may help to regain regular cycles and proved to be efficient in decreasing BMI and further large scale studies may be needed with larger sample sizes and longer treatment period to elude all potential beneficial effects of LC in this age group.

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Appendix

TABLE (1) : Basic characteristics of the study population

Characteristic	Mean ± SD	RANGE
Age (years)	16.52±1.58	14-19
FSH (iu/l)	4.92 ± 0.94	3.7-7
LH (iu/l)	6.04± 1.56	4-9
PROLACTIN(ng/ml)	7.08±1.7	3-12
TSH(mu/l)	2.51 ± 0.57	1.6-3.8
BMI (kg/m^2)	29.34 ± 1.73	26.4-32
OVARIAN VOLUME(ml)	9.32±2.48	6-15
TOTAL TESTOSTERONE(ng/dl)	61±27.1	20--120
Hyperandrogenic features	**n**	**percentage**
Acne	7	28%
Hirsutism	4	16%

TABLE (2) : Different patterns of menstrual irregularities among the study population prior to treatment

Menstrual pattern	n	percentage
oligomenorrhea	14	56%
irregular cycles	8	32%
secondary amenorrhea	3	12%

Table (3) : Basic characteristic of the study population before and three months after the treatment

Characteristic	Before	After	P value
FSH (iu / l)	4.92 ± 0.94 3.7-7	4.76 ± 0.87 3.9-6.8	0.13
LH (iu / l)	6.04± 1.56 4-9	5.72 ± 1.94 4-10	0.38
OVARIAN VOLUME (ml)	9.32±2.48 6-15	9.12 ± 1.86 7-14	0.19
BMI (kg/m^2)	29.34 ± 1.73 26.4-32	27.88±1.45 26-31	0.03*
Total testosterone(ng/dl)	61±27.1 20-120	58 ±23.9 20-110	0.08

*significant p value

TABLE (4) Different pattern of menstrual irregularity 3 months after treatment

Menstrual pattern	n	percentage
Normal cycles	9	36% (n=9)
oligomenorrhea	8	32% (n=8)
irregular cycles	4	24 % (n=4)
secondary amenorrhea	2	8% (n=2)