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Metabolic Improvements From CoQ10 and ALA in PCOS Patients

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Abstract. Background: As more women search for natural solutions or prescription medications to manage their symptoms, supplements like Alpha Lipoic Acid and CoQ10 are growing in popularity. Combining these with a personalized plan can lead to better health outcomes and a higher quality of life. Aim of the study: the aim of the current research project is to evaluate the effect of combined administration of metformin, ALA and CoQ10 on PCOS metabolic and fertility parameters. Patients and methods: This clinical trial, which was randomized, single-blind, and actively controlled, took place in Diwaniyah, Iraq, from October 2024 to June 2025. Participants were randomly assigned to three different groups. The random assignment was carried out using computer-generated random numbers. Patients in Group Met. received Glucophage (500 mg; Merck, West Drayton, UK) three times per day; Group Met.+ALA patients were given metformin as in the first group along with ALA (600 mg, Batch no. 6N5483; Holzkrichen, Bavaria, Germany) three times daily; Group Met.+ALA+CoQ10 patients received metformin and ALA as in the second group, along with 200 mg of CoQ10 each day. All treatments were provided over a duration of 12 weeks. Result: Post-treatment, all three forms of management showed significant decline in average free Testosterone, LH and LH:FSH ratio, GnRH anti-body and ovarian volume ($p < 0.001$); the effect of Met. plus ALA plus CoQ10 was significantly more profound when contrasted to other 2 modes of therapy ($p < 0.05$). However, none of these treatment approaches was able to affect serum levels of FSH, prolactin and TSH significantly ($p > 0.05$).Conclusion: The combined use of metformin therapy, CoQ10 supplements and ALA supplements is associated with the most optimum hormonal and ultrasound characteristic in PCOS women by reducing the pathogenic effect of anti GnRHR antibody level.

Highlights:

1. Combined Metformin, ALA, and CoQ10 improved hormonal and ultrasound parameters in PCOS.
2. Significant reductions were observed in LH, free testosterone, LH:FSH ratio, and ovarian volume.
3. No significant changes were found in FSH, prolactin, or TSH levels.

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Introduction

One of the most prevalent hormonal conditions affecting women today is PCOS, or polycystic ovary syndrome [1]. Worldwide, a sizable portion of women suffer from PCOS [2]. It affects metabolism and reproductive health, making day-to-day living more difficult [3]. Hormonal abnormalities that disrupt ovulation and cause irregular periods are known as PCOS. Weight gain, particularly around the abdomen, thinning hair on the scalp, acne, oily skin, irregular or missed periods, and excessive facial or body hair are all linked to the disease. PCOS can lead to long-term problems if it is not properly managed [4].

Insulin resistance is common in women. Higher blood sugar levels and more fat storage, particularly around the waist, result from this. Hormonal imbalances can prevent ovulation, which affects fertility as well. One of the main causes of PCOS symptoms is insulin resistance [5]. The ovaries produce more androgens when the body doesn't react well to insulin. This spike interferes with ovulation and exacerbates symptoms like acne and hair growth [6]. According to data, insulin resistance affects up to 70% of women with PCOS [7]. By addressing this problem, symptoms are lessened and hormonal balance is improved, increasing the efficacy of treatments [8].

The drug metformin is mainly prescribed for type 2 diabetes, but it also effectively treats PCOS. It lowers blood sugar and stabilizes hormone levels by increasing the body's sensitivity to insulin. More regular cycles result from the ovaries being able to resume regular ovulation with better insulin function. Metformin has been linked in studies to improved blood sugar control, weight loss or easier weight management, decreased androgen levels, which can clear up acne and excess hair, increased chances of ovulation, and better menstrual regularity [9] [10] [11]. Metformin may have adverse effects, though, just like any other drug. The most frequent ones, particularly in the early stages, are nausea, upset stomach, or diarrhea. Starting with a lower dose and increasing it gradually is essential [12]. Supplementing with CoQ10 and Alpha Lipoic Acid can reduce the frequency and intensity of metformin side effects, thereby reducing the

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need for higher dosages of the drug [13] [14] [15]. As more women search for natural solutions or prescription medications to manage their symptoms, supplements like Alpha Lipoic Acid and CoQ10 are growing in popularity [13]. Combining these with a personalized plan can lead to better health outcomes and a higher quality of life [13] [14] [15]. Alpha lipoic acid (ALA), a naturally occurring antioxidant, can be found in trace amounts in foods like spinach and potatoes. It helps fight off free radicals, which are unstable substances that can damage cells. ALA aids in the mitochondria's energy production as well. Studies show that ALA enhances insulin sensitivity, reduces inflammation-related oxidative stress, balances hormones, enhances lipid profiles, lowers blood sugar, and promotes metabolic health [16] [17]

The antioxidant coenzyme Q10 (CoQ10), which provides energy to cells, especially the mitochondria, is naturally produced by the body. It also fights oxidative stress, which is a major cause of the tissue damage and inflammation that are common in PCOS. Research suggests that CoQ10 may improve ovarian function, improve egg quality, lower inflammation markers, and support metabolic health. Women with PCOS often report better hormonal balance and a better response to fertility treatments when taking CoQ10 [18] [19]. We suggest that the combination of these treatments targets different aspects of PCOS. Alpha lipoic acid fights oxidative stress, metformin improves insulin sensitivity, and CoQ10 boosts mitochondrial energy and fertility.

Therefore, the aim of the current research project is to evaluate the effect of combined administration of metformin, ALA and CoQ10 on PCOS metabolic and fertility parameters.

Patients and Methods

A. Study Design and Settings

This clinical trial, which was randomized, single-blind, and actively controlled, took place in Diwaniyah, Iraq, from October 2024 to June 2025. The study adhered to the principles outlined in the Declaration of Helsinki and received approval from the ethical committee at the College of Medicine/Al-Qadisiyah University prior to its initiation. Informed consent was obtained from all participants.

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B. Sample Size Estimation

The sample size was determined using a formula geared towards achieving a significance level below 0.05 and a statistical power exceeding 80%. Referencing a previous trial [20], we selected 4.4 μIU/ml as the standard deviation and 3.5 μIU/ml as the mean change (D) in insulin, which was the primary outcome. According to the calculation, 12 participants were required for each group; however, taking into account an anticipated 3 dropouts per group, the final total was set at 15 subjects for each group. Randomization was conducted using a computer-generated sequence, which was concealed in sequentially numbered, sealed, opaque envelopes maintained by the researcher.

C. Participants

The diagnosis of PCOS was based on the Rotterdam criteria [21]. The criteria for inclusion and exclusion were established as follows: Women aged 20 to 40 years with PCOS and a body mass index (BMI) under 30 were eligible for the study. Women who were menopausal, pregnant, or breastfeeding; those with diabetes; individuals with hepatic, renal, thyroid, or cardiovascular conditions; and those with heightened prolactin levels were excluded. Participants who had taken antioxidant supplements in the last three months, as well as those using ovulation induction medications or drugs that impact hormonal profiles like oral contraceptives, were not admitted. We also did not enroll participants who had followed a specific dietary or exercise regimen and those who consume tobacco or alcohol.

D. Grouping of Participants

Participants were randomly assigned to three different groups. The random assignment was carried out using computer-generated random numbers. Patients in Group Met. received Glucophage (500 mg; Merck, West Drayton, UK) three times per day; Group Met.+ALA patients were given metformin as in the first group along with ALA (600 mg, Batch no. 6N5483; Holzkrichen, Bavaria, Germany) three times daily; Group Met.+ALA+CoQ10 patients received metformin and ALA as in the second group, along with 200 mg of CoQ10 each day. All treatments were provided over a duration of 12 weeks.

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E. Laboratory Analysis

Serum samples were kept at -80°C until they were analyzed. The serum concentrations of insulin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, prolactin, and thyroid-stimulating hormone were measured using ELISA (Bioassay Technology Laboratory, Shanghai Korean Biotech, Shanghai City, China) following the instructions provided by the manufacturer. The samples were tested for GnRHR-AAbs using a synthetic 28-mer peptide (LifeTein, Somerset, NJ) from the ECL2 region of the human GnRHR as the coating antigen. Optical density (OD) readings were taken at 405 nm after 60 minutestosterone.

F. Assessment of Ovarian Volume

A transvaginal ultrasound exam (TVU) was performed using a Voluson 730 pro at 50/60 HZ with a transvaginal probe operating at a frequency of 6 MHz. The ovarian volume was assessed, typically found near the iliac vessels close to their bifurcation. The largest dimensions of both ovaries were recorded. Length and height were measured in centimeters, after which the probe was rotated by 90 degrees to record the width in centimeters. The ovarian volume was then calculated using the prolate ellipsoid formula (Length × Width × Height × 0.523) [22]. The Mean Ovarian Volume (MOV) was determined when ultrasonography allowed for measurement of both ovaries. If only one ovary was measurable, that measurement was used as the ovarian volume.

G. Statistical Analysis

All statistical analyses were done using the Statistical Package for Social Science, version 26 (IBM, Armonk, NY). $P < 0.05$ was considered statistically significant. For comparison of quantitative variables among groups, one way ANOVA test was used followed by post-hoc LSD multiple comparison test. For evaluation of therapeutic effect, post-treatment mean values were compared to baseline mean values using related groups t-test.

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Result and Discussion

A. Result

The current study enrolled 90 women with PCOS. The average of age of recruited women was 30.47; 30.33; and 30.90 year in cohorts of Met., Met. plus ALA and Met. plus ALA plus CoQ10, in that order. In terms of statistics, the difference in the average of age across cohorts of study exhibited no significance (p = 0.840), as explained in tab. 1.

Table 1. Minimum, maximum and mean age of PCOS patients according to group

Characteristic	**Met. group (30 member)**	**Met.+ ALA group (30 member)**	**Met.+ ALA plus CoQ10 group (30 member)**	**One way ANOVA *p*-value**
Age (years)				
Average ± StDev.	30.47 ± 4.36	30.33 ± 4.06	30.90 ± 3.12	0.840 N
Min.-Max.	22 -38	23 -37	23 -36	

N: not significant; ALA: alpha lipoic acid; CoQ10: Coenzyme Q10; StDev.: Standard deviation

1. Hormonal Evaluation

Prior to treatment course, the averages of free Testosterone, FSH, LH, prolactin and TSH were comparable among Met., Met. plus ALA and Met. plus ALA plus CoQ10 groups. Post-treatment, all three forms of management showed significant decline in average free Testosterone, LH and LH:FSH ratio ($p < 0.001$); the effect of Met. plus ALA plus CoQ10 was significantly more profound when contrasted to other 2 modes of therapy ($p < 0.05$). However, none of these treatment approaches was able to affect serum levels of FSH, prolactin and TSH significantly ($p > 0.05$), see Tab. 2.

Table 2. Effect of different treatment approaches on serum hormonal levels

Hormone	**Group A**	**Group B**	**Group C**
Free testosterone (ng/dl)			
Prior to therapy	20.82 ± 9.21	21.14 ± 9.85	21.01 ± 6.55
Post-therapy	19.81 ± 9.58 *, a	19.70 ± 9.66 *, a	18.75 ± 6.68 *, b

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FSH (mIU/ml)			
Prior to therapy	5.55 ± 0.70	5.49 ± 0.44	5.43 ± 0.45
Post-therapy	5.59 ± 0.75	5.53 ± 0.48	5.68 ± 0.48
LH (mIU/ml)			
Prior to therapy	16.70 ± 4.57	16.90 ± 3.05	16.63 ± 2.28
Post-therapy	12.89 ± 4.57 *, a	11.44 ± 2.51 *, b	10.80 ± 1.88 *, c
LH: FSH ratio			
Prior to therapy	3.01 ± 0.65	3.08 ± 0.69	3.06 ± 0.51
Post-therapy	2.31 ± 0.61 *, a	2.07 ± 0.52 *, b	1.90 ± 0.39 *, c
Prolactin (ng/ml)			
Prior to therapy	19.01 ± 7.32	20.38 ± 3.44	19.77 ± 3.04
Post-therapy	18.92 ± 7.30	20.24 ± 3.52	19.69 ± 2.96
TSH (mIU/ml			
Prior to therapy	1.96 ± 0.71	2.05 ± 0.75	1.96 ± 0.77
Post-therapy	1.91 ± 0.65	2.01 ± 0.68	1.94 ± 0.76

- FSH: follicle stimulating hormone
- LH: Luteinizing hormone
- TSH: Thyroid stimulating hormone
- *: significant paired t-test (before treatment vs. after treatment)
- a, b, c: to indicate significant difference after performing one way ANOVA and LSD multiple comparison test (a for highest mean followed by b then by c)

2. Level of GnRH-receptor auto-antibody

Prior to treatment course, the average of GnRHR anti-body levels of Met. group, Met. plus ALA group and Met. plus ALAplusCoQ10 group were 10.04, 10.29 and 10.15 mg/dl, in that order. Statistically speaking, no significant variance existed across cohorts of the investigation (p = 0.487). Post-treatment, all three forms of management showed significant decline in average GnRH anti-body concentration of PCOS women (p is less than 0.001); however, the amount of decline using Met. plus ALAplusCoQ10 is the most fruitful, with significant differences when groups were contrasted to each other groups (p is less than 0.001), see Tab. 3.

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Table 3. GnRH receptor auto-antibody level of enrolled PCOS patients according to group pre- and post-treatment

GnRH-Antibody	Met. group (30 member)	Met.+ ALA group (30 member)	Met.+ ALAplusCoQ 10 group (30 member)	One way ANOVA *p*-value
Prior to therapy				
Average ±StDev.	10.04 ± 3.18	10.29 ± 3.66	10.15 ± 3.66	0.487 N
Min.-Max.	5.3 -14.8	6.5 -16.6	7.1 -17.5	
Post-therapy				
Average ±StDev.	8.90 ± 3.44 a	9.06 ± 3.62 a	7.44 ± 3.51 b	<0.001 ***
Min.-Max.	5.1 -13.6	6.3-16.5	4.5 -14.9	
Related groups test	Lower than 0.001	Lower than 0.001	Lower than 0.001	

N: none significance; ***: significant at p ≤ 0.001; letters a, b and c indicated results of LSD multiple comparison test

3. Ultrasound characteristics

Prior to treatment course, the average ovary volume of Met. group, Met. plus ALA group and Met. plus ALAplusCoQ10 group was 14.13, 14.39 and 13.99 cm, in that order. Statistically speaking, there was no significant variance in average ovary volume across cohorts of the investigation (p = 0.361). Post-treatment, all three forms of management showed significant decline in average ovary volume of PCOS women (p = 0.001); however, the amount of decline using Met. plus ALAplusCoQ10 is the most fruitful, with significant differences when groups were contrasted to each other groups (p less than 0,001), see Tab. 4.

Table 4. Ovary volume of enrolled PCOS patients according to group pre- and post-treatment

Ovary volume (cm)	Met. group (30 member)	Met.+ ALA group (30 member)	Met.+ ALAplusCoQ 10 group	One way ANOVA *p*-value

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			(30 member)	
Prior to therapy				
Average ± StDev.	14.13 ± 2.09	14.39 ± 1.77	13.99 ± 3.09	0.361 N
Min.-Max.	10.7 -19.1	11.9 -18.7	5.8 -17.1	
Post-therapy				
Average ± StDev.	12.03 ± 4.10 a	12.16 ± 1.77 a	11.12 ± 2.52 b	0.001***
Min.-Max.	1.4 -19	11.9 -18.5	5.2 -14.4	
Related groups test	Lower than 0.001	Lower than 0.001	Lower than 0.001	

N: none significance; ***: significant at $p \leq 0.001$; letters a, b and c indicated results of LSD multiple comparison test

B. Discussion

In this study, we were aiming at exploring the efficacy and safety of ALA and CoQ10 supplementation in PCOS women treated using metformin. In our study, all three forms of management showed significant decline in average free testosterone, LH and LH/FSH ratio of PCOS women; however, the amount of decline using Met. plus ALAplusCoQ10 is the most fruitful. Thus, addition of CoQ10 improved the effect of metformin in optimizing serum free testosterone. We in addition observed no significant changes in serum prolactin or TSH levels. In support for present study findings, Kazerooni et al. came to the conclusion that Met. therapy in PCOS patients lowers Testosterone levels and significance improves the clinical presentation of hyperandrogenism [23]. In line with current study observation (Azimeh Izadi et al.) reported significance reduction in Testosterone level following supplementation with CoQ10 [24]. Moreover, in the systemic review and meta-analysis performed by (Zhang et al.), CoQ10 supplementation can at significance reduce serum Testosterone in women with PCOS [18] and this is consistent with current study observation. In the study of (Karamali and Gholizadeh), Q10 (Co-Q10) supplements lead to decline at significance of hormone Testosterone in women with PCOS [25].

In women with PCOS, Jannatifar et al. compared the effects of Met. and ALA with Met. alone. They found that both groups' mean total Testosterone decreased, but regrettably, the difference was not statistically significant [26]. Consequently,

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our findings contradict those of Jannatifar et al. [26]; nonetheless, concerning the current academic re-search we assessed free Testosterone but not total Testosterone concentration. Indeed one of important pathogenic hormonal abnormalities seen in PCOS is the increased in serum LH with high LH to FSH ratio [27], so reduction of LH level is going to normalize this ratio and Concerning the current academic re-search we have shown that concomitant use of CoQ10, ALA and Met. is more reliable than giving Met. alone to achieve this treatment mission. Jindal et al. looked at 60 PCOS-afflicted women between the ages of 16 and 40 who were receiving Met. for six months. They found that the mean blood LH level and the LH/FSH ratio had significantly decreased [28]. Nestler et al. also showed a comparable result. Met. treatment reduces hyperinsulinemia [29]. Because of the decreased pituitary sensitivity to gonadotrophin-releasing hormone, it is believed to be the reason for elevated LH secretion. LH response to GnRH is decreased by Met. treatment.

In one previous study, 34 individuals received 400-mg-ALA for twelve months, authors observed a substantial decrease in levels of hormones LH [30]. Similarly, another study recruited 26 teenagers with PCOS who had irregular periods and managed patients using ALA as 1000-mg and inositol as 400-mg for half a year [31]. Estradiol at significance became better and Testosterone and LH declined at significance. Via reducing LH and increasing estradiol concentration, this research showed that ALA may improve ovary activity and quality of egg; to the contrary, ALA can also lower high androgen level by reducing Testosterone. Another new study by Abu-Zaid et al. [32] came up to a conclusion that ALA therapy may result in decline in LH concentration at significance, thus adds support to our conclusions.

The concept that insulin secretion and metabolic patterns influence the signaling system related to hyperandrogenism and the regulation of ovulation elucidates the role of ALA [16]. ALA is recognized for its antioxidant properties and its ability to reduce oxidative stress, which has been associated with levels of insulin, Testosterone, and LH, and is a contributing factor to the onset of various disorders, including PCOS. As a beneficial supplement that effectively combats reactive oxidative species (ROS) and restores antioxidant molecules, ALA is a potent antioxidant that has been shown to decrease oxidative stress and insulin resistance.

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Although there have been relatively few studies examining inflammation and reproductive hormones in PCOS [33], ALA has the potential to enhance insulin production, reduce Testosterone levels, and regulate menstrual cycles. In addition, in accordance with present study finding, Azimeh Izadi et al. [24], found that CoQ10 administration resulted in significance reduction in serum LH level in women with PCOS. A number of possible mechanistic ways via which Co-Q10 can enhance functions of ovary were suggested, such as the antiapoptotic and antioxidant capabilities of Co-Q10, in addition to its acts on production of ATP inside mitochondrial organelles and stabilization of cell membrane [34].

Concerning the current academic re-search and Post-treatment, all three forms of management showed significant decline in average GnRH anti-body concentration of PCOS women; however, the amount of decline using Met. plus ALAplusCoQ10 is the most fruitful. As a matter of fact, a recently described autoantibody with agonist effect is becoming under focus aiming at discovery of therapeutic stratigies against this autoantibody in PCOS pathology; this antibody is directed against"gonadotropin-releasing hormone receptor (GnRHR)" [35]. Abnormalities in the axis "hypothalamic-pituitary-gonadal" set into existence via inflammatory-immune-directed alerations in this hormone or its receptor cab be a proposed pathogenesis for dysfunction in reproductive physiology, because excessive inflammatory-immune reaction has long been observed as a principal pathogenic mechanism in a variety of disorders [35]. A study has been carried out by Kem et al., with retrospective design demonstrated that women with the disease P-COS possess autoantibodies with agonistic effect directed to extracellular loop-2 for receptor of GnRH (ECL2), that might be of significance from pathophysiological perspective because of its ability to activate the receptor for long term [36].

With respect to Met., it has been shown that it can significantly reduce the level of GnRHR antibody in women with PCOS [37], thus supporting our current study findings. The exact mechanism by which Met. caused such reduction is not completely clear, however, we can suggest that the anti-inflammatory potential of Met. can lead to changes in cytokine levels that ultimately reduced the production of such autoantibodies. In fact, research has indicated that Met. has anti-inflammatory and disease-preventive effects. Met. has been demonstrated to block

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pro-inflammatory cytokines, induce apoptosis, and suppress cell proliferation in malignancies and arthritis [38].

On the other hand, no previous report discussed the therapeutic effect of ALA or CoQ10 on GrHR-AAb in women with PCOS. Thus, this is a point of originality Referring to our results. The mechanism of action of ALA and CoQ10 in reducing such autoantibodies level in women with PCOS is probably due to their anti-oxidant effect thus reducing inflammatory response in PCOS patients and hence reducing production of pro-inflammatory cytokines that may cause increase in this antibody level.

Concerning the current study and Post-treatment, all three forms of management showed significant decline in average ovary volume of PCOS women (p 0.001); however, the amount of decline using Met. plus ALAplusCoQ10 is the most fruitful. Indeed, the effect of Met. in reducing ovary volume and or DFS in women with PCOS is well established according to many previous reports [39] [40] [41] [42] [43] [44] [45]. The mechanism of Met. in reducing ovary volume is suggested to be due multiple factors. The first factor is that Met. treatment is associated with reduction in antral follicle count [45] by improving insulin sensitivity, reducing androgen level and improving ovulation leading to less number of follicles and hence less size. Another factor may be due to reduction in BMI in women with PCOS as a direct relation has been found between BMI and ovary volume [43]; however, the exact mechanism linking obesity to high ovarian volume is still incompletely understood. Our third suggestion that the overall improvement in hormonal profile (LH, LH/FSH ratio and free Testosterone), improvement in body weight and improvement in ovary function will all interact to cause reduction in mean ovary volume in PCOS women receiving Met..

With respect to CoQ10, Abdulameer and Kadhim in 2024 conducted a study to assess efficacy of Met. and Co-Q10 on PCOS women and they concluded that both treatment approaches using Met. alone or CoQ10 alone produces significance improvement in ovary volume in women with PCOS; however, combination of both agents resulted in more significance improvement [46]. With respect to ALA, there is no previous reports linking ovary volume changes or DFS in women with PCOS to ALA, but, there are reports about improvement in ovary function and oocyte

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characteristic in infertile women with PCOS who were subjected to ALA treatment and they attributed this improvement in ovarian function to the anti-oxidant capacity of ALA [16] [47]. Therefore, we can suggest that improvement of ovarian volume and reduction in DFS following administration of ALA in current study is due to improvement of ovulation in women with PCOS leading to reduction in antral follicle count and hence there will be reduction in overall ovary size. The improvement in ovary function concerning the current academic re-search is most likely due to anti-oxidant capacity of ALA.

Conclusions

The combined use of metformin therapy, CoQ10 supplements and ALA supplements is associated with the most optimum hormonal and ultrasound characteristic in PCOS women by reducing the pathogenic effect of anti GnRHR antibody level.

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