Randomised Controlled Trial

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The effect of coenzyme Q10 intake on metabolic profiles in women candidates for in-vitro fertilization: a randomised trial

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Objective: Infertility and the pathogenesis of polycystic ovarian syndrome (PCOS) are both influenced by insulin resistance and dyslipidemia. Presumably, adding coenzyme Q10 (CoQ10) to these patients' diets will be beneficial. Therefore, this study aimed to examine the effects of CoQ10 supplementation on metabolic profiles in women candidates for in-vitro fertilization (IVF).

Trial design and methods: For this randomized, double-blinded, parallel, placebo-controlled clinical experiment, 40 PCOS-positive infertile women who were IVF candidates were included. They ranged in age from 18 to 40. The 20 participants in the two intervention groups received either CoQ10 or a placebo for 8 weeks. The expression of glucose transporter 1 (GLUT-1), peroxisome proliferator-activated receptor gamma (PPAR-γ), low-density lipoprotein receptor (LDLR), as well as metabolic profiles such as insulin metabolism and lipid profiles were evaluated. Quantitative RT-PCR determined the expression of GLUT-1, PPAR-γ, and LDLR on peripheral blood mononuclear cells. Lipid profiles and fasting glucose were assessed using enzymatic kits, and insulin was determined using Elisa kit.

Results: In comparison to the placebo, CoQ10 supplementation significantly reduced blood insulin levels (-0.3 ± 1.0 vs. 0.5 ± 0.7, $P = 0.01$) and insulin resistance (-0.1 ± 0.2 vs. 0.1 ± 0.2, $P = 0.01$), and increased PPAR-γ expression ($P = 0.01$). In infertile PCOS patients' candidates for IVF, CoQ10 supplementation showed no appreciable impact on other metabolic profiles. Also, CoQ10 supplementation revealed no significant impact on GLUT-1 ($P = 0.30$), or LDLR ($P = 0.27$) expression. Within-group changes in insulin levels ($P = 0.01$) and insulin resistance ($P = 0.01$) showed a significant elevation in the placebo group. When we adjusted the analysis for baseline BMI, baseline values of variables, and age, our findings were not affected.

Conclusions: Eight weeks of CoQ10 supplementation demonstrated positive benefits on PPAR-γ expression, insulin resistance, and serum insulin in infertile PCOS women candidates for IVF.

Keywords: CoQ10 supplementation, dyslipidemia, in vitro, insulin resistance

Introduction

Background

Polycystic ovary syndrome (PCOS) is a common disorder among women of reproductive age with an incidence of 6 – 20%[1]. Hyperandrogenism, menstrual irregularity, and polycystic ovarian morphology are a feature of this disease[2]. Infertility is a common problem in PCOS women[3,] and the risk of pregnancy complications is high in these patients[4]. The precise mechanism of PCOS is still uncertain, but the key role of genetic factors and insulin resistance should be considered[5]. Insulin resistance and hyperlipidemia are important causes of infertility and metabolic abnormalities, and they are prevalent in PCOS patients[6,7]. Metabolic abnormalities including impaired glucose tolerance and dyslipidemia are frequent in this syndrome, and it was estimated that the action of insulin is lessened in about 75% of PCOS patients[8,9]. Although the issue of the association between PCOS and insulin resistance has attracted a lot of attention, the primary origin mechanism is not yet fully understood[10].

Coenzyme Q10 (CoQ10) exists in the mitochondrial respiratory chain and interferes with the creation of adenosine

HIGHLIGHTS

- This randomized double-blind, placebo-controlled trial was conducted on 40 infertile polycystic ovary syndrome (PCOS) women candidates for IVF.
- Eight-week coenzyme Q10 (CoQ10) supplementation increased peroxisome proliferator-activated receptor gamma (PPAR-γ) expression in infertile PCOS women candidates for in-vitro fertilization (IVF).
- CoQ10 supplementation reduced insulin resistance, and serum insulin.

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triphosphate in cells[11]. Different studies have demonstrated that insulin resistance and metabolic and endocrine indexes can be improved by dietary CoQ10 supplementation in women with PCOS[12,13]. A recent meta-analysis reported that taking CoQ10 supplements by PCOS patients reduced complications by reducing fasting plasma glucose (FPG), homoeostasis model assessment-insulin resistance (HOMA-IR), fasting insulin, triglycerides, total cholesterol and low-density lipoprotein (LDL)-cholesterol, and also by increasing high-density lipoprotein (HDL)-cholesterol levels[14]. However, another meta-analysis announced that there were no notable alterations in levels of triglycerides, total cholesterol, and cholesterol subfractions by CoQ10 supplementation[15]. Also, it was observed that taking CoQ10 by women with PCOS-induced peroxisome proliferator-activated receptor gamma (PPAR-γ) expression reduced oxidized low-density lipoprotein receptor 1 (LDLR) expression[12]. In a study, it was reported that CoQ10 supplementation for 8 weeks significantly decreased triglyceride concentrations but did not affect HDL- and LDL-cholesterol levels[16]. In addition, there were no significant changes in HOMA-IR and insulin levels by receiving Q10 supplements for 12 weeks in people with type 2 diabetes[17]. Different factors, such as baseline values of metabolic profiles of the study participants, dosage of used CoQ10, ethnicity, and study duration, may affect the associations between CoQ10 intake, and blood levels of these variables[16,17].

Several studies among various patient populations showed that glycemic profiles were improved by taking CoQ10 supplements[18,19]. Moreover, many studies reported the favourable impacts of CoQ10 on lipid profiles[20,21]. Given the anti-diabetic and lipid-lowering effects of CoQ10[18,20], we hypothesized that CoQ10 supplementation might be beneficial in subjects with PCOS of IVF candidates. According to our knowledge, data on the effects of CoQ10 supplementation on glycemic control and markers of cardio-metabolic risk in infertile PCOS women candidates for IVF are limited. In addition, there are contradictions between the results of different studies.

Objectives

The goal of this experiment was to examine the influences of CoQ10 intake on the expression of PPAR-γ, glucose transporter 1 (GLUT-1), LDLR as well as metabolic profiles such as insulin metabolism and lipid profiles in infertile women with PCOS candidates for IVF.

Methods

Trial design

A randomized, double-blinded, parallel, placebo-controlled clinical trial was used in this investigation. The study was carried out by the Helsinki Declaration. Each participating patient provided their written informed consent before the intervention.

Participants

Forty infertile women with PCOS diagnosed with Rotterdam criteria[22], 18–40 years old who were scheduled for IVF, were included in the research. The subjects were recruited from December 2018 to March 2019 (recruitment date: December 2018–January 2019 and intervention date: January 2019–March 2019). Exclusion criteria were: subjects with malabsorptive, cardiovascular diseases, neoplastic syndromes, anti-obesity and anti-diabetic medications, and previous or current use of any type of hormonal therapy.

Interventions

Participants took either 100 mg CoQ10 ($n = 20$) or placebo ($n = 20$) daily for eight weeks. Placebos and CoQ10 were completely alike in colour, shape, and other design characteristics. The respondents were asked to return the supplement containers, and a brief daily message was sent to their cellphones to remind them to take the supplements. Patients were requested not to alter their ordinary physical activity and not to consume any nutritional supplements that might affect their nutritional status during the 8-week intervention.

Outcomes

The secondary outcomes were FPG and lipid profiles, whereas the primary endpoints were HOMA-IR and serum insulin.

Assessment of anthropometric measures

A trained midwife took anthropometric measurements at baseline and after the 8-week intervention. The Seca 713 scale was used to measure weight and height without shoes and in light clothing to the nearest 0.1 kg and 0.1 cm, respectively. BMI was computed as the current body weight/(height)^2 ratio [kg/m^2].

Biochemical assessment

Fifteen millilitres of fasting samples were gathered from the subjects before and after 8 weeks of intervention. FPG and lipid profiles (except LDL cholesterol) were determined utilizing commercially available kits (Pars Azmoun Co.) with coefficient variances (CVs) of lower than 5%. LDL cholesterol values were calculated using the available formula. Serum insulin concentrations were determined by an ELISA kit (DiaMetra) with inter-assay and intra-assay CVs of 3.6 and 5.2%, respectively. The homoeostasis model of assessment-insulin resistance (HOMA-IR) is defined as [fasting glucose (mmol/l) × fasting insulin (μmol/l)/22.5]. The quantitative insulin sensitivity check index (QUICKI) is determined as $QUICKI = 1/[\log(I_0) + \log(G_0)]$, where I_0 is fasting insulin (μU/ml), and G_0 is fasting glucose (mg/dl).

RNA extraction and real-time polymerase chain reaction (RT-PCR)

Lymphocyte cells were extracted from blood samples using 50% percoll (Sigma-Aldrich). Trypan blue, RNA, and DNA extraction were used to perform cell count and viability tests[23]. RNA was isolated from blood samples using the Cinnacolon RNX-plus kit (Tehran, Iran). The RNA suspension was kept frozen at – 20°C until cDNA was extracted. Total RNAs were extracted from each sample and quantified using a UV spectrophotometer. Each sample's OD 260/280 ratio was considered to be between 1.7 and 2.1, indicating no contamination with protein or DNA[23].

Using moloney murine leukaemia virus reverse transcriptase (RT), the extracted RNA was reverse transcribed to a cDNA library[24,25]. PPAR-γ, LDLR, and GLUT-1 gene expressions[26–29] were measured in peripheral blood mononuclear cells (PBMCs) using SYBR green detection and the Amplicon Kit, as well as quantitative RT-PCR and Light Cycler

Table 1

Specific primers used for real-time quantitative PCR

Gene	Primer	Product size (bp)	Annealing temperature (C)
GAPDH	F: AAGCTCATTTCCTGGTATGACAACG R: TCTTCCTCTTGTGCTCTTGCTGG	126	61.3
PPAR-γ	F: ATGACAGACCTCAGACAGATTG R: AATGTTGGCAGTGGCTCAG	210	54
GLUT-1	F: TATCTGAGCATCGTGGCCAT R: AAGACGTAGGGACCACACAG	238	62.1
LDLR	F: ACTTACGGACAGACAGACAG R: GGCCACACATCCCATGATTC	223	57

GAPDH, glyceraldehyde-3-Phosphate dehydrogenase; GLUT-1, glucose transporter 1; LDLR, low-density lipoprotein receptor; PCR, polymerase chain reaction; PPAR-γ, peroxisome proliferator-activated receptor gamma.

technology (Roche Diagnostics) (Table 1). As a housekeeping gene, primers for glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were utilized. Primer Express software (Applied Biosystems) and Beacon designer software (Takaposizt) were used to create the primers. The Pffafi technique was used to calculate relative transcription levels.

Sample size

To determine the sample size for this investigation, we considered type one error (α) of 0.05, type two error (β) of 0.20, and the power of 80%. Mean difference (d) of HOMA-IR equal to 2.0 and SD of 2.0 were used for the calculation[30]. Therefore, each group needed 16 members. After taking into account the potential dropout of four participants per group, a final sample size of 20 was chosen for each intervention group.

Randomization and treatment allocation

First, women with PCOS candidates for IVF were stratified according to block randomization based on two criteria: age (<30 and ≥ 30 years) and BMI (<25 and ≥ 25 kg/m^2). Subjects were allocated randomly to take either CoQ10 supplements or a placebo (containing starch without an active ingredient) at random. The following intake of placebo capsules did not see any potential impact on the outcomes. Randomization was done by applying computer software. Randomization and allocation were concealed from the researchers and subjects until the final analyses were completed.

Implementation

A trained staff at the clinic, who was not involved in the trial and not aware of assignments, assigned numbered packages of CoQ10 and placebos to the participants.

Blinding

This study was double-blind (both participants and researchers).

Statistical methods

The Kolmogrov–Smirnov test was performed to determine if the study outcomes were normally distributed or not. An independent-sample *t*-test was used to compare changes in anthropometric measurements, metabolic profiles, and gene expression linked to insulin and lipids across the two intervention groups. All data were presented as means ± standard deviation. Within-group differences were detected using a paired-sample *t*-test. To see if the magnitude of the difference was affected by baseline values of variables, age, or baseline BMI, we conditioned all analyses on age, baseline values of variables, and baseline BMI. The analysis of covariance (ANCOVA) was used to make these modifications. The Cohen's d effect size was employed to validate our finding. *P* values less than 0.05 were considered statistically significant.

Results

Participant flow and recruitment

At first, 50 participants were recruited for the study. There were three and four cases pulled out of the CoQ10 supplementation and placebo group due to personal reasons, respectively, and 33 patients [infertile subjects' candidate for IVF taking CoQ10 ($n=17$) and placebo ($n=16$)] fulfilled the trial (Fig.1). Compliance rate in both groups ranged 90–100% in this study.

Baseline data and numbers analyzed

The study's two groups' [CoQ10 ($n=17$) and placebo ($n=16$)] mean ages, weights, heights, and BMI were statistically comparable (Table 2).

Outcomes and estimation

In comparison to the placebo, CoQ10 supplementation significantly reduced blood insulin levels (-0.3 ± 1.0 vs. 0.5 ± 0.7, $P=0.01$) and insulin resistance (-0.1 ± 0.2 vs. 0.1 ± 0.2, $P=0.01$), and increased PPAR-γ expression ($P=0.01$) (Table 3). In infertile PCOS patients' candidates for IVF, CoQ10 supplementation showed no appreciable impact on other metabolic profiles. Also, CoQ10 supplementation revealed no significant impact on GLUT-1 ($P=0.30$), or LDLR ($P=0.27$) expression. Within-group changes of insulin levels ($P=0.01$) and HOMA-IR ($P=0.01$) showed a significant elevation in the placebo group.

Ancillary analyses

When we adjusted the analysis for baseline BMI, baseline values of variables, and age, our findings did not affect (Data not shown).

Harms

There were no reports of any side effects since receiving CoQ10 supplements among infertile PCOS patients throughout this trial.

Discussion

Generalisability

This trial showed that 100 mg/day CoQ10 for 8 weeks had positive consequences on glycemic control among women candidates for IVF but did not significantly affect lipid profiles. This suggests that CoQ10 intake may confer advantageous therapeutic potential for women candidates for IVF. Further research is needed in other patients and for longer periods to determine the safety of CoQ10 intake.

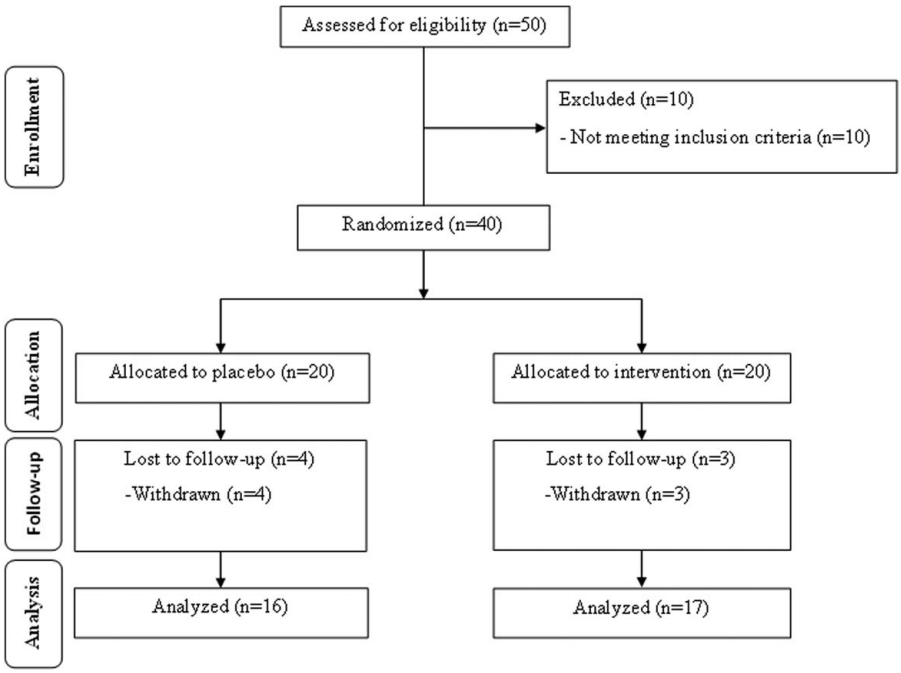

Figure 1. Summary of patient flow diagram.

Interpretation

Hyperinsulinemia, dyslipidemia, and inflammation are observed in most PCOS patients[31,32,] and the risk of cardiovascular diseases and diabetes is high in this syndrome[33]. This study showed that women candidates for IVF received CoQ10 supplementation for 8 weeks and saw substantial reductions in blood insulin, HOMA-IR, and PPAR-γ expression. However, there was no significant change in GLUT-1 expression. We have previously reported the beneficial effects of nutritional supplements in subjects with PCOS[31,34,35]. Congruous with our findings, Zhang *et al*.[36] showed that the intake of 120 mg CoQ10 daily for 24 weeks significantly decreased HOMA-IR in dyslipidemic subjects and improved glycemic profiles. Moreover, 100 mg/d CoQ10 supplements for twelve weeks in subjects with diabetic nephropathy significantly improved PPAR-γ expression, but no significant effects were observed on GLUT-1 expression[37]. Also, it was reported that a dose of 200 mg/d CoQ10 for 12 weeks significantly increased insulin sensitivity in people with T2DM[38]. Further, the intake of 100 mg CoQ10 supplements for eight weeks significantly reduced insulin values and HOMA-IR in people with metabolic syndrome[39]. Conversely, there are studies with discordant results. Mehrdadi *et al*.[40] reported that there were no significant changes in insulin levels and HOMA-IR by receiving 200 mg CoQ10 daily for 12 weeks in overweight and obese T2DM patients. Insulin resistance, independent of obesity, has a high prevalence in women with PCOS and is related to reproductive difficulties of the disease[41]. As we mentioned, cardiovascular diseases, diabetes, and metabolic syndrome are the complications of PCOS[42]. Superoxide/hydrogen peroxide production through complex II is increased by reduction of mitochondrial CoQ10, and as a result, insulin resistance can occur in adipocytes[43]. Hyperinsulinemia would result in excessive androgen secretion, contributing to greater ovarian sensitivity to luteinizing hormone (LH)[44]. In addition, granulosa cell dysfunction due to follicle-stimulating hormone inhibition possibly contributes to androgen excess; which in turn, hyperandrogenism stimulates the growth of small antral follicles but damages ovulation by inhibiting the growth of the dominant follicle[45]. Also, in subjects with PCOS, adiponectin levels in adipose tissue were found to be reduced, and this could play a main role in the progress of insulin resistance-dependent hyperandrogenism[46]. A possible mechanism by which insulin resistance could induce fertility impairment is the advanced glycation end-product accumulation[47]. Certainly, the key mechanism underlying the correlation between diabetes and infertility lies in the hyperinsulinemia discussed previously[48]. Interestingly, when it comes to IVF outcomes in women with PCOS, they tend to conduct better than subjects with no PCOS, whereas women with dysmetabolic infertility and obesity have poorer outcomes compared to normal-weight subjects[49]. Therefore, improved metabolic profiles in women with PCOS would result in improved clinical outcomes[49]. Supplements of CoQ10, as the major form of CoQ10 in humans, may improve insulin sensitivity via different mechanisms including regulation

Table 2

General characteristics of study participants

	Placebo group ($n=16$)	Q10 group ($n=17$)	P*
Age (year)	31.7 ± 2.3	29.6 ± 5.4	0.15
Height (cm)	161.2 ± 2.4	162.1 ± 7.0	0.63
Weight at study baseline (kg)	66.9 ± 10.6	69.5 ± 8.3	0.45
Weight at end-of-trial (kg)	67.0 ± 10.4	69.7 ± 8.2	0.43
BMI at study baseline (kg/m^2)	25.7 ± 3.9	26.6 ± 3.9	0.53
BMI at end-of-trial (kg/m^2)	25.8 ± 3.8	26.7 ± 3.9	0.52

Data are means ± SDs.
*Changes between groups obtained from paired *t*-test.

Table 3

Changes in the levels of metabolic profiles in two groups of patients with polycystic ovary syndrome candidate for in-vitro fertilization

	Placebo group ($n=16$)				Q10 group ($n=17$)					
	Baseline	End-of-trial	Change	P*	Baseline	End-of-trial	Change	P*	Effect size	P†
FPG (mg/dl)	92.0 ± 6.4	92.1 ± 5.9	0.1 ± 2.2	0.91	89.5 ± 8.7	88.8 ± 7.9	− 0.7 ± 4.7	0.54	0.07	0.55
Insulin	10.5 ± 4.1	11.0 ± 4.1	0.5 ± 0.7	0.01	9.2 ± 3.2	8.9 ± 3.1	− 0.3 ± 1.0	0.20	0.20	0.01
HOMA-IR	2.4 ± 0.9	2.5 ± 0.9	0.1 ± 0.2	0.01	2.1 ± 0.8	2.0 ± 0.8	− 0.1 ± 0.2	0.20	0.20	0.01
QUICKI	0.33 ± 0.01	0.33 ± 0.02	− 0.001 ± 0.005	0.27	0.34 ± 0.02	0.35 ± 0.02	0.002 ± 0.007	0.26	0.05	0.11
Triglyceride (mg/dl)	106.0 ± 33.7	106.8 ± 33.6	0.8 ± 6.8	0.66	118.3 ± 35.3	120.1 ± 37.7	1.7 ± 9.3	0.44	0.008	0.72
Total cholesterol (mg/dl)	161.8 ± 33.1	165.5 ± 37.2	3.7 ± 9.4	0.13	183.4 ± 33.8	181.4 ± 39.2	− 2.0 ± 12.7	0.52	0.10	0.15
LDL cholesterol (mg/dl)	99.6 ± 35.6	103.8 ± 36.6	4.2 ± 9.6	0.10	113.2 ± 29.7	109.6 ± 35.3	− 3.5 ± 13.5	0.29	0.09	0.06
HDL cholesterol (mg/dl)	41.0 ± 7.3	40.4 ± 6.6	− 0.6 ± 3.1	0.43	46.5 ± 7.7	47.7 ± 9.4	1.2 ± 6.4	0.45	0.03	0.31

All values are means ± SDs.

*P values represent within-group differences (paired-sample t-test).

†P values represent independent t-tests.

FPG, fasting plasma glucose; HDL, high-density lipoprotein; HOMA-IR, homoeostasis model of assessment-estimated insulin resistance; LDL, low-density lipoprotein; QUICKI, quantitative insulin sensitivity check index.

of insulin and adiponectin receptors, glucose transporters, and also improvement of redox system and lipid profile[50].

Moreover, we found that 8 weeks of CoQ10 intake had no discernible impacts on the blood lipid profiles or the expression of LDLR. Similar to our findings, 100 mg/d CoQ10 supplements given to individuals with diabetic nephropathy for 12 weeks showed no significant effects on ox-LDL gene expression[37]. Sangouni *et al*.[51] found that 60 mg CoQ10 daily for 12 weeks had no significant difference in lipid profiles in people with metabolic syndrome. Also, CoQ10 supplementation for 3 months had no significant effects on lipid profiles in T1DM[52]. Moreover, Lee *et al*.[53] observed that 200 mg/day CoQ10 for 12 weeks in obese subjects did not significantly influence lipid parameters and ox-LDL levels. Gholami *et al*.[54] reported that taking 100 mg CoQ10 daily for 12 weeks decreased total- and LDL-cholesterol, and increased HDL-cholesterol levels in women with T2DM. Moreover, 150 mg/day CoQ10 for 8 weeks significantly decreased total- and LDL-cholesterol values in people with T2DM[55]. According to a recent meta-analysis result, patients with PCOS had increased total cholesterol levels and decreased HDL-cholesterol concentrations, and the risk of non-fatal cerebrovascular diseases is high among them[56]. Low concentrations of CoQ10 in plasma among hypercholesterolemic cases are associated with arterial stiffness, and CoQ10 supplementation can be useful in improving this condition[57,58]. CoQ10 consumption may also reduce endothelial oxidative damage induced by ox-LDL by attenuating ROS production[59].

Limitations

This work had few limitations. We did not evaluate outcomes of IVF, such as the number of fertilized oocytes, oocytes retrieved and embryo, fertilization rate, and pregnancy rate. In the current study, the sample size is small which limits statistical power to detect differences between groups. We suggest that future studies with a cross-over design and a bigger sample size are needed to confirm the validity of our findings. Also, in our study, the duration of intervention was short. We suggest that future studies with a longer timescale confirm the validity of our findings. In addition, possible confounding variables like sperm health and oocyte quality should be assessed or controlled for in the analysis.

Conclusions

The findings of this trial showed that CoQ10 supplementation for 8 weeks had beneficial effects on insulin, PPAR-γ, and HOMA-IR among infertile women candidates for IVF but did not influence lipid profiles.

Ethical approval

The research was approved by the ethics committee of AUMS. Ethics committee reference number: IR.ARAKMU.REC.1397.245. Approval date: 2018-12-16. IRCT code: IRCT20170513033941N52. IRCT record: https://www. IRCT20170513033941N52. https://www.irct.ir/trial/38393

Consent

Before any procedures were performed, all subjects signed an informed consent form.

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Author contribution

S.A.A., R.A., E.A. and M.J. involved in drafting and data collection. All authors accepted the final version.

Conflicts of interest disclosure

The authors declare no conflict of interest.

Research registration unique identifying number (UIN)

Registry used: IRCT20170513033941N52 Unique Identifying number or registration ID: IRCT20170513033941N52 Hyperlink to your specific registration: https://www.irct.ir/trial/38393.

Guarantor

Guarantor is Mehri Jamilian.

Data availability statement

The datasets analysed and/or used during the present study are obtainable from the corresponding author on rational request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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