COMBINED COENZYME Q10 AS AN ADJUVANT FOR OVULATION INDUCTION IN POLYCYSTIC OVARY SYNDROME

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Abstract

Objective: To evaluate the effect of combination of oral Coenzyme Q10 (CoQ10), with clomiphene citrate (CC) for ovulation induction in CC-resistant polycystic ovary syndrome (PCOS).

Patients and method: A prospective controlled randomized trial which comprised of 110 infertile women with PCOS resistant to CC. Patients were randomized to either combined CC/CoQ10 (51 patients, 82 cycles) or CC 150 mg/day alone (50 patients, 71 cycles) for ovulation induction in patients with CC-resistant PCOS. The main outcome measures were number of follicles, serum E2, serum P, endometrial thickness, and pregnancy rate (PR) and miscarriage rate.

Results: Combination of CC and coenzyme Q10 significantly increased both ovulation ($p < 0.001$) and pregnancy rates ($p < 0.001$) in women with CC-resistant PCOS compared with CC only, (65.9% vs.15.5% and 39.2% vs. 6%, respectively). No women reported side effects.

Conclusion: Combination of CoQ10-CC in the treatment of CC-resistant PCOS patients improves the ovulation and pregnancy rates. It is an effective, safe option and should be considered before gonadotropin therapy or laparoscopic ovarian drilling.

Key Words: Coenzyme Q10, polycystic ovary syndrome, clomiphene-citrate resistance, pregnancy

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive age women. It is now well evidenced that PCOS is associated with obesity, insulin resistance, hyperandrogensim, abnormal lipid profile and an oxidative stress (OS) (1, 2). Recently, PCOS was reported to be associated with mitochondrial dysfunction which has a negative impact on oocyte quality, compromise meiotic spindle configuration, chromosomal misalignment and eventually caused oocyte death (3, 4). About 20–25% of PCOS women failed to ovulate with incremental doses of CC (5). Ovulation induction with gonadotrophins is the standard treatment for CC-resistant women. However, this approach is associated with complications and has the added disadvantage of high cost and need for careful monitoring. Hence, there is a clear need for an alternative less expensive therapy.

Coenzyme Q10 (CoQ10) is a fat-soluble coenzyme, found in the inner mitochondrial membrane and plays a crucial role in the production of cellular energy and act as an antioxidant. It has been used as a dietary supplement in the treatment of many disorders as cardiovascular diseases, high cholesterol levels, diabetes mellitus, improve immune function in people with HIV or AIDS and act as anticancer agent in breast cancers. It is also widely used as an ingredient in cosmetic products as some shampoos and conditioners (6, 7). Evidence has been accumulating for a role of CoQ10 in

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the treatment of mitochondrial disorders, from animal studies as CoQ10 can profoundly rejuvenate eggs in old aged mice (8). It is unknown if this improvement in eggs demonstrated in mice may occur in humans or not. The present prospective randomized controlled study was conducted to evaluate the effect of combination of coenzyme Q10 with clomiphene citrate in CC-resistant PCOS.

Patients and methods

The study comprised of 110 women (153 cycles) with CC-resistant PCOS among those attending the Fertility Outpatient Clinic in Mansoura University Hospitals, Mansoura University, Egypt, and a private practice setting in the period from January 2010 to January 2013. Diagnosis of PCOS based on the revised 2003 consensus on diagnostic criteria and long-term health risks related to PCOS (9). All women were previously treated with 100 mg of CC daily for 5 days per cycle, for two to three cycles with persistent anovulation or ovulate with very thin endometrium <5 mm at the time of hCG administration. Exclusion criteria included patients with hyperprolactinaemia, hypercorticism and thyroid dysfunction. Patients receiving medications such as cholesterol lowering drugs, beta-blockers, and tricyclic antidepressants were also excluded. All patients had patent Fallopian tubes proved by hysterosalpingography and normal semen analysis for their partners according to the modified criteria of World Health Organization (2010). The study was approved by the departmental ethical committee and all participants gave informed consent before inclusion in the trial.

Patients were randomly allocated using a computer-generated random table and sealed envelopes into two treatment groups: Coenzyme Q10 (CoQ10) and clomiphene citrate (CC) group (55 patients, 82 cycles) and clomiphene citrate alone group (55 patients, 71 cycles). Allocation process was done by a third party (nurse). Withdrawal bleeding was achieved using 10 mg of dydrogesterone tablets for 10 days before stimulation. Patients in CoQ10/CC group received CC (Global Napi, Cairo, Egypt) 150 mg/day from cycle days 2-6, and CoQ10 (Mepaco, Enshas Elraml, Sharkia, Egypt), in a dose of 60 mg capsules orally 3 times daily starting on day 2 of the cycle and till the day of human chorionic gonadotropin (hCG) administration. Patients in the CC alone received CC (Global Napi, Cairo, Egypt) 150 mg/day from the day 2 of the cycle for 5 days.

All patients were monitored by transvaginal ultrasound for the mean follicular diameter and endometrial thickness in the days 10, 12, and 14 of the cycle. The physicians monitoring the cycles were blinded to the protocol of each group. Serum E2 (pg/mL) was measured at the time of hCG injection by RIA using direct double antibody kits (Pantex, Santa Monica, CA) and serum P (ng/mL) was measured on days 21–23 of the cycle by RIA using antibody coated-tube method (Coat-A-Count; Diagnostic Product Corporation, Los Angeles, CA). Human chorionic gonadotropin injection (5,000–10,000 IU IM, Pregneyl; Organon, Oss, Holland) was given when at least one follicle measured 18 mm was found. Patients were advised to have intercourse 24–36 hours after hCG injection. Serum hCG was determined 2 weeks after hCG injection in the absence of menstruation for diagnosis of pregnancy.

Tnanche primary outcome measures were the number of growing and mature follicles, serum E2 (pg/ml), serum P (ng/mL), and endometrial thickness (mm). Secondary outcome measures were the occurrence of pregy and miscarriage.

Statistical Analysis

Before starting the study, sample size calculation was done. Fifty cases were needed in each arm to gain a significant difference of 22% in pregnancy rate at a significant level of 5% and a study power of 80%. Data obtained were statistically analyzed using SPSS computer package (SPSS Inc., Zonguldak Karaelmas University, Zonguldak, Turkey). Proportions were analyzed using the Chi Square test while means and standard errors of the mean were analyzed by Student's t-test. The differences were considered significant when $p<0.05$.

Results

The study comprised 110 patients (153 cycles) in total. There were no statistical significant differences between the two groups with regard to age, parity, duration of infertility, body mass index (BMI), the presenting symptoms and signs and hormonal profile (Table 1).

The number of follicles >14mm and >18 mm were significantly higher in the CoQ10 group (Table 2). The endometrial thickness at the time of hCG administration was significantly more in the CoQ10 group (8.82 ± 0.27 mm vs. 7.03 ± 0.74 mm). Ovulation occurred in 54/81 cycles (65.9%) in the CoQ10 group and 11/71 cycles (15.5%) in the CC alone group with significant difference between two groups. Serum E2 and P were higher in the CoQ10 group with a statistical significant difference (Table 2). Pregnancy occurred in 15/51 cycles in the CoQ10 group (29.4%) and 3/50 cycles (6%) in the CC alone group and the difference was statistically significant. One twin pregnancy occurred in the

CoQ10 group and none in the other group. No higher order pregnancies or OHS occurred in both groups.

Discussion

To our knowledge, this is the first report of the potential reproductive effects of CoQ10 in human females. Animal studies reported that CoQ10 increases the reproductive lifetime of female mice by about 30%, and the animals that got the CoQ10 produced more and healthier eggs, improves the ovarian response and variable changes in hormonal levels (8).

The oocyte has the largest number of mitochondria of any cell, (approximately 2x105 copies). The functional status of the mitochondria contributes to the quality of oocytes and plays an important role in the process of fertilization and embryo development (11). Failure of the oocyte to increase the number of mitochondria during maturation may lead to a poor embryo outcome (4). Mitochondrial dysfunction, may contribute to the onset of metabolic syndrome including obesity, insulin resistance, abnormal lipid profile and an increased risk of coronary heart diseases later in life (12).

he results of the present study demonstrated that combined therapy with CoQ10-CC significantly improves ovulation rates in CC-resistant PCOS women. There are a number of potential mechanisms by which CoQ10 improves the ovarian functions in CC-resistant PCOS. Firstly, CoQ10 acts directly on the mitochondria, probably related to, electron transfer in the respiratory chain and plays a crucial role in the production of cellular adenosine triphosphate (6, 9). Secondly, CoQ10 is the only lipid-soluble antioxidant that is synthesized in human bodies, it could reduce oxidative stress within the ovary, and protects DNA from free radical induced oxidative damage. CoQ10-treated mice had significantly higher CoQ10 levels within their ovaries and ovarian veins and their ovaries contained less reactive oxygen species (12). CoQ10 acts as antioxidant by itself, and in its reduced form, Ubiquinol which inhibits lipid peroxidation in biological membranes and in low-density lipoprotein, and it also protects membrane proteins against oxidative damage. Ubiquinol can regenerate the vitamin E from its oxidized form; this interaction with vitamin E is thought to be particularly important for the protection of LDL and other lipoproteins from oxidative damage (7, 13). Thirdly, it protects the stability of the plasma membranes to remain flexible. The fluidity of the membranes is crucial to proper physical performance since membrane fluidity affects membrane receptors, carriers and enzymes (14). Fourthly, CoQ10 is a micronutrient, the extent of tissue uptake of CoQ10 correlates with the degree of tissue deficiency. Finally, it act as antiapoptotic, it is well known that apoptosis is the main mechanism involved in follicular cohort atresia. Microinjection of small numbers of mitochondria into mouse oocytes prevents the onset of apoptosis (15).

In this study, the mean endometrial thickness was significantly increased ($p< 0.001$) in CoQ10-CC group versus CC group; probably it was related to higher E2 levels as a result of better ovulatory response. The results of the present study demonstrated that combined therapy with CoQ10-CC significantly improves the pregnancy rates in CC resistant PCOS women. The discrepancy between ovulation rate and pregnancy rate among CoQ10-CC may be due to adverse effects of CC on the endometrium as well as on the cervical mucus. The improved pregnancy rate is probably related better ovarian response, the use of CoQ10 in the in vitro culture of bovine embryos results in superior rate of early embryo cleavage, blastocyst formation, percentage of expanding blastocysts and a larger inner cell mass (16,17). Also, the potential for embryo implantation is correlated with the ATP content of the embryo (18). CoQ10 was well tolerated by all the patients and no adverse effects were observed.

The results of this study were encouraging, however, the proper dosage of CoQ10 and the optimal duration of treatment needs to be revised. Moreover, the effects of CoQ10 therapy on the hormonal and metabolic profiles, symptoms of hyperandrogenism, and cardiovascular risk factors need further assessment, whether it may modify these risk factors particularly in PCOS or not. Comparing CoQ10 with other medical methods of ovulation induction in cases of CC-resistant PCOS, CoQ-10 is not time consuming as metformin which require duration from 1-6 months, and it is not as expensive as gonadotrophins and does not need intensive monitoring during and after treatment. So, it may be a valuable alternative in developing countries, it may be ideal for women aged more than 35 years and who require more rapid treatment protocols.

In conclusion, CoQ10 seems to be a promising adjuvant to the oral ovulatory agents such as CC. Combination of C0Q10 and CC is proved to be effective, inexpensive and safe for stimulating follicular development in CC-resistant PCOS and can be tried successfully before a more complicated lines such as gonadotrophins and laparoscopic ovarian drilling.

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