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Original Research Article

Can Co-enzyme Q10 improve the chances of conception after the age of 35?

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ABSTRACT

Background: ovarian follicular quality diminishes with age, Free radicals and oxidative stress begin to accumulate in cells, aging or slowing down the metabolic energy production centers in the cell- the mitochondria. When the mitochondria cannot generate a certain amount of energy, it slows growth and proper development of the follicle making it more prone to DNA damage, including chromosomal abnormalities resulting in poor fertilization patterns, and early miscarriage. Co-enzyme Q10 (CoQ10) is a major cellular antioxidant. its tissue levels gradually decrease with age. We attempt to evaluate its protective effect on ROS-induced ovarian damage, which is one of the most important and widely accepted patho- mechanisms underlying cell ageing.
Methods: 40 Participants from El Shatby hospital infertility clinic 35 to 38 years old, with history of bad response to ovulation stimulation, were divided into two equal groups (group A given (CoQ10) 3mg|kg body weight for three cycles prior to stimulation Serum anti- mullarian hormone level was measured before and after CoQ10 administration, group B= twenty cases as control). Participants were given gonadotrophins (150 IU to 375 IU). Follicular growth was monitored by trans- vaginal ultra- sonography and serum estradiol level (E2). Ovulation trigger was achieved using 10,000 IU of human chorionic gonadotrophin.
Results: The primary outcome was occurrence of normal pregnancy; secondary outcome was good response to stimulation (at least one mature follicle 18-22mm).
Conclusions: CoQ10 has no significant effect on response to ovulation stimulation or on pregnancy rates.

Keywords: Co- enzyme Q10, Ovarian reserve, Pregnancy

INTRODUCTION

Increased female age results in a decline in reproductive outcome and an associated increase in chromosomal aberrations.

Molecular pathways behind increased loss of germ cells in aged ovaries are poorly understood. Increased DNA damage due to less active DNA repair machinery is one possible trigger for oocyte loss.[1] The complex process of oocyte maturation prior to ovulation involves nuclear, cytoplasmic, and epigenetic changes culminating with the formation of the meiotic spindle. All of these processes require energy, which is provided by mitochondria.[2]

Therefore, the number of mitochondria markedly increases to provide adequate energy production to meet the metabolic requirements during the transition of a primordial follicle into a primary follicle. All energy-dependent mechanisms of human fertility are influenced by mitochondrial damage which is based on oxidative stress (Free radical theory, is the second most commonly

accepted theory and is strongly associated with ovarian ageing after physiological programmed ageing, which is the most commonly accepted theory.[3] Because mitochondrial damage results in an increased accumulation of reactive oxygen species (ROS) and mitochondrial DNA mutations, the increased release of intracellular ROS due to MD, which cannot be counteracted by antioxidant defences similar to those of ageing cells, induces damage to ovarian tissue.[4] The exposure to high levels of ROS may eventually contribute to granulosa cell apoptosis, follicular atresia, chromosomal abnormalities, oocyte ageing, and infertility.[5] Older cells tend to produce more oxidants and less ATP than younger cells from their mitochondria because of a positive correlation between the level of ROS production and chronological age. The potentially adverse effects of OS in most stages of human fertility can be counteracted by administration of several mitochondrial nutrients known as antioxidants, which have been demonstrated to increase energy production in mitochondria and to protect cells from OS. Alpha-lipoic acid (RALA), vitamin C, CoQ10, and resveratrol are the best and most commonly used antioxidants in current studies.[6]

Co-enzyme Q10 (CoQ10), a fat-soluble component of nearly all cell membranes, is located in the inner mitochondrial membrane. CoQ10 is an essential component for transporting electrons in the mitochondrial respiratory chain to produce cellular energy. Moreover, the reduced form of CoQ10, known as ubiquinol, acts as an antioxidant in cellular metabolism via inhibition of lipid peroxidation, protein, and DNA oxidation.[7,8]

Although CoQ10 is synthesised by virtually all normal tissues, the tissue levels of CoQ10 gradually decrease with ageing.[9]

The study attempted to evaluate the protective effect of CoQ10 on ROS-induced ovarian damage, which is one of the most important and widely accepted patho-mechanisms underlying cell ageing. This could also lead to biochemical alternatives for the management of women with poor ovarian reserve during IVF treatment.

METHODS

Patient enrollment into the study began in 1 August 2014 and was continued until 1 August 2016.

Participants were selected from El Shatby hospital infertility clinic their age ranged from 35 to 38 years, with history of bad response to ovulation stimulation. Participants fulfilling these criteria were forty in number, they were divided into two groups each of twenty cases (group A= they were given co-enzyme Q10 (CO- Q10) in a dose of 3 mg/kg body weight for three cycles prior to stimulation. Serum anti- mullarian hormone level was measured before and after COQ 10 administration, group B= twenty cases taken as control).

Serum AMH concentrations

Serum AMH levels were measured by USCN Life Science enzyme-linked immunosorbent assays (ELISA). The assay range was 0.31-20 ng/mL, and the minimum detectable dose of this assay was less than 0.078 ng/mL. The technician was unaware of the treatment allocation.

Participants were given gonadotrophins in doses ranging from 150 IU to 375 IU/ day (Purified FSH vials 75-150 IU Gonapure- Menapharm- Egypt, and LH vials 75- 150 IU Merional- IBSA- Switzerland) started on day 2 of the fourth cycle. Monitoring of follicular growth was done by trans- vaginal ultra- sonograhpy (Medison R-7, vaginal transducer 8-MZ). The dose of gonadotrophins was monitored according to the response. Follicular maturation was followed up untill at least one mature follicle of 18-20 mm diameter was obtained. Serum estradiol level (E2) was measured, CO Q10 was discontinued and ovulation trigger was achieved using 10,000 IU of human chorionic gonadotrophin HCG (choriomon 5000 IU, intra- muscular injection, IBSA-Switzerland). Vaginal progesterone (cyclogest 400mg) was used twice daily for luteal phase support for fourteen days then pregnancy test in serum was done. Positive cases were followed up till an intra- uterine gestational sac with positive cardiac pulsations was seen by trans-vaginal ultra- sonograhpy. During the trial, five cases from group B and one case from group A did not continue the follow up so they were excluded from the study.

The primary outcome was occurrence of normal pregnancy (intra- uterine gestational sac with positive cardiac pulsations on trans- vaginal ultra- sonograhpy), the secondary outcome was good responce to stimulation namely the presence of at least one mature follicle of diameter 18-22mm.

Statistical methodology

Data were collected and entered to the computer using SPSS (Statistical Package for Social Science) program for statistical analysis (version 21).[10] Data were entered as numerical or categorical, as appropriate.

When Kolmogorov-Smirnov test revealed no significance in the distribution of variables, parametric statistics was carried out, while in the not-normally distributed data the non-parametric statistics was carried out.[11]

Data were described using minimum, maximum, mean, standard deviation and 95% CI of the mean for the normally distributed data.

Data were described using minimum, maximum, median and inter-quartile range for not-normally distributed data.

Categorical variables were described using frequency and percentage of total.

Comparisons were carried out between two studied independent normally distributed subgroups using independent sample t test. When Levene's test for equality of variances is significant, Welch's t-test is used, which is an adaptation of Student's t-test, and is more reliable when the two samples have unequal variances and unequal sample sizes.[12,13]

Comparisons were carried out between two studied independent not-normally distributed subgroups using Mann-Whitney U test.[14]

Comparison between paired-variables in the same group was carried out using Wilcoxon Signed Ranks test.

Histograms with distribution curve, Box and Whiskers graph, bar chart and clustered bar chart were used accordingly. Chi-square test was used to test association between qualitative variables. Fisher's Exact test and Monte Carlo correction was carried out when indicated (expected cells less than 5).

An alpha level was set to 5% with a significance level of 95%, and a beta error accepted up to 20% with a power of study of 80%.

RESULTS

The two studied groups did not show any statistically significant difference as regards age (Table 1; p=0.286) neither did they as regards AMH levels (Table 2; p=0.349 according to Levene's Test, and p=0.123 according to independent samples t- test) AMH levels ranged from 0.8 to 1.9 ng/ml in the two groups.

No change was noticed in AMH level measured pre-and post COQ10 administration, where p=0.160 which is statistically not significant (Table 2).

Table 1: Age (years).

	Placebo group (n=15)	CoQ10 group (n=19)	All cases (n=34)
Minimum	35	35	35
Maximum	40	40	40
Mean	37.00	36.42	36.68
Std. deviation	1.603	1.426	1.512
Median	37.00	36.00	36.00
Inter-quartile range	36.00-38.00	35.00-38.00	35.00-38.00
KS test of normality	D=0.200 p=0.108 NS	D=0.248 p=0.003*	D=0.232 p=0.000*
Mann-Whitney U Test	Z=1.105 p=0.286 NS		

KS= Kolmogorov-Smirnov; *= statistically significant (p<0.05); NS: statistically not significant (p>0.05)

Table 2: AMH (ng/ml).

	Placebo group (n=15)	Co Q10 group (n=19)	All cases (n=34)
Basal line AMH level			
Minimum	0.80	0.90	0.80
Maximum	1.60	1.90	1.90
Mean	1.24	1.38	1.32
Std. deviation	0.219	0.293	0.269
Median	1.20	1.40	1.30
Inter-quartile range	1.10-1.40	1.20-1.60	1.20-1.45
KS test of normality	D=0.161 p=0.200 NS	D=0.163 p=0.200 NS	D=0.149 p=0.054 NS
Levene's test for equality of variances	F=0.903 p=0.349 NS		
Independent samples t test	$t_{(df=32)}$ =1.585 p=0.123 NS		
Post CO Q10 AMH level			
Minimum	0.90		
Maximum	1.90		
Mean	1.4105		
Std. Deviation	0.28847		
Median	1.4000		
Inter-quartile range	1.30-1.60		
KS test of normality	D=0.199 p=0.047*		
Wilcoxon signed Ranks Test	Z=1.406 p=0.160 NS		

KS= Kolmogorov-Smirnov; *= statistically significant (p<0.05); NS: statistically not significant (p>0.05)

Table 3: Doses of gonadotrophins (IU).

	Placebo group (n=15)	Co Q10 group (n=19)	All cases (n=34)
Minimum	150.00	150.00	150.00
Maximum	375.00	375.00	375.00
Mean	240.00	248.68	244.85
Std. deviation	76.063	75.218	74.564
Median	225.00	225.00	225.00
Inter-quartile range	150.00-300.00	150.00-300.00	150.00-300.00
KS test of normality	D=0.252 p=0.011*	D=0.226 p=0.012*	D=0.241 p=0.000*
Mann-Whitney U Test	Z=0.310 p=0.784 NS		

KS=Kolmogorov-Smirnov; *=statistically significant (p<0.05); NS: statistically not significant (p>0.05)

Doses of gonadotrophins used ranged from 150 IU TO 375 IU which did not show any statistically significant difference between the two groups (Table 3; p=0.784).

Duration of stimulation ranged from 12 to 15 days which was also statistically not significant between the two groups (Table 4; p=0.302).

Table 4: Days of stimulation (days).

	Placebo group (n=15)	Co Q10 group (n=19)	All cases (n=34)
Minimum	12.00	11.00	11.00
Maximum	15.00	15.00	15.00
Mean	13.00	12.63	12.79
Std. deviation	1.000	1.012	1.008
Median	13.00	12.00	12.50
Inter-quartile range	12.00-14.00	12.00-13.00	12.00-14.00
KS test of normality	D=0.241 p=0.019*	D=0.313 p=0.000*	D=0.284 p=0.000*
Mann-Whitney U Test	Z=1.113 p=0.302 NS		

KS= Kolmogorov-Smirnov; *=statistically significant (p<0.05); NS: statistically not significant (p>0.05)

Serum estradiol level (E2) measured prior to HCG trigger ranged from 939 to 1790 pmol/l which was statistically not significant between the two groups (Table 5; p=0.554NS).

Table 5: E2 level (pmol/l).

	Placebo group (n=15)	Co Q10 group (n=19)	All cases (n=34)
Minimum	990.00	939.00	939.00
Maximum	1790.00	1789.00	1790.00
Mean	1339.33	1330.10	1334.17
Std. Deviation	199.132	175.364	183.353
Median	1290.00	1290.00	1290.00
Inter-quartile range	1211.00-1480.00	1230.00-1478.00	1225.25-1478.50
KS test of normality	D=0.131 p=0.200 NS	D=0.128 p=0.200 NS	D=0.125 p=0.200 NS
Levene's Test for Equality of Variances	F=0.357 p=0.554 NS		
Independent Samples t Test	$t_{(df=32)}$ =0.144 p=0.887 NS		

KS=Kolmogorov-Smirnov; *=statistically significant (p<0.05); NS: statistically not significant (p>0.05)

Table 6: Pregnancy.

	Group		
	Placebo (n=15)	**CoQ10 (n=19)**	**All cases (n=34)**
Pregnancy	4 (26.67%)	5 (26.32%)	9 (26.47%)

The primary outcome (pregnancy) was achieved in only five cases in group A compared to four cases in group B which was statistically not significant (Table 6; p FE) =1.000).

DISCUSSION

Interest in coenzyme Q10 as a supplement to improve fertility was sparked when a report from Canada said fertility in mice was improved when the mice were given Co Q10. The mice that were given coenzyme Q 10 before they were given ovarian stimulation made more follicles and better eggs compared to mice that were not given Co Q10. According to the researchers, the Co Q10 seemed to cause the older mice to produce eggs that functioned more like eggs from younger mice.

This study suggests the possibility of a fertility benefit for women with low ovarian reserve. This study failed to find a benefit from using co- enzyme Q10 prior to ovulation stimulation. The study results matched with the results of a controlled randomised trial designed by Bentov et al. evaluating the effect of CoQ10 on post-meiotic oocyte aneuploidy rate in women undergoing IVF, in Sinai Hospital, Toronto, Canada, it was a double-blind placebo study that included IVF-ICSI patients 35-43 years of age.[15] The patients were treated with either 600 mg of CoQ10 or an equivalent number of placebo caps. Researchers compared the post-meiotic aneuploidy rate using polar body biopsy (PBBX) and comparative genomic hybridization (CGH). According to the power calculation, 27 patients were needed for each arm. But owing to safety concerns regarding the effects of polar body biopsy on embryo quality and implantation, the study was terminated before reaching the target number of participants.

A total of 39 patients were evaluated and randomized (17 CoQ10, 22 placebo), 27 were given the study medication (12 CoQ10, 15 placebo), and 24 completed an IVF-ICSI cycle including PBBX and embryo transfer (10 CoQ10, 14 placebo). Average age, base line follicle stimulating hormone (FSH), peak estradiol and progesterone serum level, as well as the total number of human menopausal gonadotropin (hMG) units did not differ between the groups. The rate of aneuploidy was 46.5% in the CoQ10 group compared to 62.8% in the control. Clinical pregnancy rate was 33% for the CoQ10 group and 26.7% for the control group. They concluded that there were no significant differences in outcome between the CoQ10 and placebo groups. However, the final study was underpowered to detect a difference in the rate of aneuploidy.

On the other hand, a prospective controlled randomised trial by El Refaeey et al. investigating the combination of oral CoQ10 and clomiphene citrate to improve ovulation induction response in women with clomiphene-resistant polycystic ovary syndrome proved that this combination is an effective and safe option for improving ovulation and clinical pregnancy rates.[16]

CONCLUSION

In light of the above-mentioned studies and our study results, we concluded that CoQ10 supplementation may protect ovarian reserve by improving mitochondrial function, counteracting both mitochondrial ovarian ageing and physiological programmed ovarian ageing although the certain effect of OS in female infertility is not clearly known, but it has no significant effect on response to ovulation stimulation neither does it improve pregnancy rates.

Recommendations

Further experimental studies need to be designed to define the optimum dosage and duration for CoQ10 supplementation to enhance its protective effects. Furthermore, future studies are needed to understand the effect of CoQ10 on ovaries and human reproduction.

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