

Original Article

Q10 Co-enzyme Effect on Fetus Implantation in ART Cycles

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ABSTRACT

Background and Aim: Infertility is a common condition that affects many couples. Although current cutting-edge therapeutic methods have been found promising in this regard, their success still is not sufficiently high. Accordingly, researchers are working to develop new methods to augment the likelihood of successful results of Assisted Reproductive Technology (ART). Recently, coenzyme Q10 has been recognized an important and influential factor in the process of reproduction and some scarce studies have been along favorable results in this regard. This study aims to examine the effect of oral administration of coenzyme Q10 on embryo implantation in ART cycles. **Methods and Materials:** In this randomized, placebo-controlled clinical trial, a total of 128 infertile females who were candidates for ART were randomized in two groups receiving either a daily capsule of coenzyme Q10 by the commencement of gonadotropin through to pregnancy test result (case group, 64 patients), or placebo (control group, 64 patients). Finally, oocyte count, fertilization rate, embryo count, quality of embryos, transferred embryo count, implantation rate and pregnancy rate were compared between the two groups. **Results:** The mean age of the patients was 32.77 ± 6.01 years (20-41) in the case group and 32.45 ± 5.93 years (20-42) in the case group, with no significant difference between the two groups ($p=0.77$). In comparison between the case and control groups, in spite of better results in the case group, no significant difference was found in terms of oocyte count (10.47 ± 7.16 and 9.38 ± 7.52 , respectively; $p=0.40$), fertilization rate (66.88 ± 16.08 % and 66.73 ± 21.50 %, respectively; $p=0.96$), embryo count (7.03 ± 4.78 and 5.84 ± 4.85 , respectively; $p=0.17$), quality of embryos (71.9% grade I and 28.1% grade II in cases, 68.8% grade I and 31.3% grade II in controls; $p=0.70$) transferred embryo count (10.9% one, 56.3% two-three and 32.8% more than three in cases, 14% one, 56.3% two-three and 29.7% more than three in controls; $p=0.84$), implantation rate (8.39 ± 12.73 % and 7.22 ± 12.80 %, respectively; $p=0.60$), and pregnancy rate (34.4% and 26.6%, respectively; $p=0.34$). **Conclusion:** Although using coenzyme Q10, in comparison with placebo, was along with better results in terms of outcome variables of ART, the difference was statistically insignificant possibly because of a small sample size and short duration of the intervention.

INTRODUCTION

The role of Q10 coenzyme has been positively detected in biologic energy induction. This coenzyme has its role as two electron carrier in the mitochondrial membrane lipid phase and is necessary for creating energy resulted from the pairing of protons (1-4). In various previous studies the effective role of Q10 coenzyme has been proven for growth of cells in the extracellular medium (5). Even it has been shown in some studies that some oncogenes show malignant behaviour in cells after reduction of this coenzyme, in a way that by increasing the level of this coenzyme the

incidence of adenocarcinoma has been decreased in human cells (1,3).

Treatment of infertile couples has improved during recent decades and addition of various assisted reproduction techniques has led to reduction in infertility rate for these couples. Despite of appropriateness of this method and its high success rate, some complications and disadvantages have been mentioned about it. For example, multiple pregnancy rate, preterm delivery, placenta previa, gestational diabetes, cesarean delivery, low birth weight, and neonatal mortality have been higher in people who get pregnant with assisted reproductive techniques. One of the problems

in using assisted reproduction methods is failure of the implemented method even in advanced centres. Different reasons have been proposed for this issue such as rejection of the embryo by endometrial, occurrence of adverse implantation, inappropriate division of embryonic cells in vitro prior to implantation. Furthermore, although fetal chromosomal abnormalities affect incidence of insufficient cell divisions, this problem appears more when using assisted reproduction methods (6,7).

Considering the mentioned characteristics for Q10 coenzyme in controlling cellular growth and proliferation, it seems useful to use it for preventing failure in assisted reproduction methods. In one of the scarce studies conducted in this field has been that of Stojkovic et al. (1999) in animal model. In that study the role of industrial Q10 coenzyme and an ineffective similar constructional material on growth rate of embryonic cells was investigated and compared, and results showed the growth in the number of primary embryonic cells and higher success in implantation for case group rather than control group (7). As it was mentioned, that study was not conducted on human sample and extracted cells were from bovine fetal. Furthermore, this study was conducted in vitro and the obtained results were only true for outside environment of body and it is not possible to generalize them to live human sample. Therefore, in this study we tried to measure the role of Q10 coenzyme in improving the results of assisted reproduction methods and decreasing their failure rate.

MATERIALS AND METHODS

In this randomized, controlled clinical trial study 128 females of 19-42 years old who were candidates for ICSI or IVF therapy in infertility ward of Tabriz Alzahra Educational-Therapeutic Centre during 13 months (July 2014 to August 2015) underwent randomized treatment either with oral Q10 coenzyme supplement or placebo and their ART associated variables were compared. Written consent was acquired from all under-study patients prior to study. This study has been approved by Ethics Committee of Tabriz University of Medical Sciences and has been registered on IRCT.org with registration code of IRCT2015102724746N1.

Inclusion criteria is to have a high number of newly transferred embryo (maximum 2 or 3 transferred embryo in cycles of ovulation induction, fresh embryo) and exclusion criteria were considered personal factors such as age over 42, low embryo number, underlying disorders like patients with gastrointestinal disorders, patients with liver dysfunction, gynecological diseases such as endometriosis, genital anomalies such as disorders of the fallopian tubes, and uterine anatomic abnormalities.

In the first group (intervention or case) a daily capsule of coenzyme Q10 was received by the commencement of gonadotropin through to pregnancy test result. In the second group (control) ineffective placebo was used with similar shape and schedule. It should be mentioned that intervention has been done besides routine therapeutic protocols. The consequence of this study was considered as the number and quality of oocyte and embryo and pregnancy rate. To do

so, after approval of follicular growth by ultrasonography monitoring and serum hormone tests, patient underwent IVF or ICSI for ovarian puncture and oocytes retrieval and based on this, the number of oocyte and embryo, quality of embryo (based on the cell numbers, granulation, and meiosis) and rate of fertilization and implantation were registered. Pregnancy has been estimated via BHCG measurement.

Statistical Analysis

Mean age of patients in intervention group was 32.77 ± 6.01 (20 to 41) and that of control group was 32.45 ± 5.93 (20 to 42) ($p=0.77$). In intervention group 14 patients (21.9%) and in control group 17 patients (26.6%) had children ($p=0.54$). Mean infertility period in patients of intervention group was 5.18 ± 3.28 years (1 to 16) and that of control group was 5.30 ± 4.02 years (1 to 20) ($p=0.86$). In intervention group the infertility type was primary in 46 cases (71.9%) and secondary in 18 cases (28.1%), while in control group there were 44 primary cases (68.8%) and 20 secondary cases (31.3%) ($p=0.59$). In intervention group the infertility reason was feminine in 35 cases (54.7%), masculine in 22 cases (34.4%), and unjustifiable in 7 cases (10.9%), while in control group there were 37 feminine cases (57.8%), 23 masculine cases (35.9%), and 4 unjustifiable cases (6.3%) ($p=0.64$).

Variables associated to intervention and its results in two groups have been summarized and compared in Table 1. Based on this, statistically significant difference was not observed between two groups.

DISCUSSION

In this study the effect of Q10 coenzyme on fetus implantation in ART cycles was investigated. Based on this, although in intervention group there were better conditions in terms of the number of oocytes, the number of embryo, the quality of embryo, the number of transferred embryo, the rate of implantation, and the rate of pregnancy comparing with the group receiving placebo, in none of the cases observed difference was not statistically significant. The studies in this field are rare:

In an investigation by Burstein et al (2009) in human model, female mice received Q10 coenzyme or placebo for 18 weeks before superovulation. Comparing with control group, administering Q10 coenzyme significantly increased the number of fertilized oocytes and production of mitochondrial ATP of oocytes and simultaneously led to significant decrease in ROS levels of oocytes (8). As it is observed, although the results of this study in terms of the positive effect of Q10 on the number of fertilized oocytes correspond with the findings of our study, as it mentioned, against these results this difference is not statistically significant in current investigation. In justification of this difference in results, the most important point is type of studies, that is, in the mentioned study it has been on mice, while in this study it has been on humans. It has been shown that there are major differences between these two models in terms of Q10 coenzyme impact. For example, lifetime of mouse and human is very different, which makes it impossible to compare direct-

Table 1. Variables associated to intervention and its results in two intervention and control groups

Variable	Intervention group (64 patients)	Control group (64 patients)	P value
Number of IVF/ICSI cycle	1.34±0.62 (1 to 3)	1.19±0.47 (1 to 3)	0.11
Number of oocyte	10.47±7.16 (2 to 37)	9.38±7.52 (1 to 38)	0.40
Rate of fertilization	66.88±16.08 (33 to 100)	66.73±21.50 (17 to 100)	0.96
Number of embryo	7.03±4.87 (1 to 24)	5.84±4.85 (1 to 26)	0.17
Quality of embryo	(71.9) 46 (28.1) 18	(68.8) 44 (31.3) 20	0.70
Number of transferred embryo	10.9) 7 (56.3) 36 (32.8) 21	(14.1) 9 (56.3) 36 (29.7) 19	0.84
Implantation rate (%)	8.39±12.73 (0 to 50)	7.22±12.80 (0 to 50)	0.60
Transfer period (day)	16.84±0.72 (16 to 19)	16.72±0.83 (16 to 19)	0.36
Pregnancy	(34.4) 22	(26.6) 17	0.34

Data have been shown as SD±mean (minimum and maximum) and frequency (%)

ly. Furthermore this difference in lifetime affects administration time, in a way that 12 to 16 weeks of Q10 coenzyme treatment in mouse is equivalent with a decade of treatment in human. Therefore it is not clear that if a short intervention such as administration of mitochondrial factor like Q10 coenzyme could reverse the effect of environmental factors for decades (9). In fact, one of the major limitations in human studies on administration of Q10 coenzyme for improving pregnancy status is inadequacy of administration period to achieve tangible clinical results (10). In another study in this field by Gendelman and Roth (2012) conducted *in vitro*, it has been shown that adding Q10 coenzyme to medium of bovine oocytes could significantly increase mitochondrial performance and ATP production (11). Here again the difference between the type of studies is the most important distinction point of two studies. In an investigation by Turi et al. (2012) existence and content of Q10 coenzyme in human follicular fluid and its role were studied. To do so, in 20 infertile women undergoing ovarian stimulation program for IVF, Q10 coenzyme level in follicular liquid was measured by chromatography method and modified based on cholesterol and protein levels. Based on this, it has been shown that in mature oocytes comparing with dysmorphic cases level of Q10 coenzyme is significantly higher. Also direct relationship between Q10 coenzyme level and embryo quality was seen. Finally it was concluded that in order to reach tangible clinical results, some studies should be conducted based on administration of Q10 coenzyme in these patients (12). Conducting current study was to respond to the limitations of previous studies including the study mentioned above. In fact it should be noted that lack of adequate studies in terms of advantages and disadvantages of administering Q10 coenzyme is considered as one of the major limitations of clinical use of this material. In the study of Bentov et al (2014) the incidence level of oocyte aneuploidy after meiosis in patients under IVF and ICSI under therapy with Q10 was investigated. To do so, in that double-blind trial study, patients ranging from 35-43 years old were studied. Patients in intervention group (27 patients) received daily 600 mg Q10 coenzyme and patients of control group (27 patients) received

placebo. The rate of aneuploidy was significantly lower in intervention group. Simultaneously, the rate of pregnancy in intervention group was reported insignificantly higher (33% vs. 26.7%). Finally it was concluded that lack of statistically significant difference could have been due to low impact of the study after implementing low sample size (10). As it is observed, results of this study are in full accordance with findings of our study in terms of the most important outcome variable, i.e. pregnancy (in our study: 34.4% in intervention group vs. 26.6% in control group). Although in our study determining sample size has been conducted based on available standards, it seems because of novelty of the subject and its findings, such as above mentioned study, possibly future studies with higher sample sizes would lead to statistically significant differences in this field. In a study by Ben-Meir et al. (2015) it has been shown that aging of the female reproductive cells alongside with mitochondrial dysfunction is associated with reduction of oxidative phosphorylation and ATP level. Reduction in incidence of enzymes affecting production of Q coenzyme in oocytes of older females was observed both in mouse and human. Therefore it was concluded that procedure of quality and quantity loss of oocyte with aging could be reversed by administering Q10 coenzyme (9). The findings of our study have partly approved this suggestion.

Complex process of oocyte maturation before ovulation includes nucleus, cytoplasmic, and epigenetic changes resulting to meiotic spindle. All these processes need energy, which is provided through mitochondria mainly by oxidative phosphorylation (13). The reason for this, is limitation of alternative energy producing processes of glycolysis in oocytes due to limited expression of phosphofructokinase (14). Bioenergetic status of oocyte affects its growth adequacy; A status which itself affects implantation ability, ATP content, and potential of mitochondrial membrane. Furthermore, intervention with oxidative phosphorylation or mitochondrial performance leads to suspension of oocyte maturation, chromosomal displacement, and impaired embryo development (15). Various studies such as those conducted by Kalen et al. (1989) and Miles et al

(2004) have shown tissue-specific reduction in the levels of Q coenzyme alongside with aging (16,17). Bentov and Casper (2013) in their review study also concluded that one of the main reasons of reduced fertility in women with aging is mitochondrial dysfunction and the impact of oxygen radicals in aging process. Based on this, shortage of Q10 coenzyme was proposed as underlying cause in this case (18). In a study by Meldrum et al. (2016) it was concluded that mitochondria function and energy production decrease correlated with aging which can adversely affect ovarian reserve, chromosomal separation, and the adequacy of the embryos. In a study on old mice it has been shown that Q10 coenzyme administration could prevent lots of these adverse changes. Primary studies on human have also been hoping, but as it was mentioned, investigations in this field are scarce and in terms of quality they suffer some shortcomings such as low sample size and short intervention interval (19). Based on this, maybe one of possible causes of failure in reaching statistically significant results in current study, alongside with sample size and short interval of administration, is attendance of patients with average age (32.8 years old in intervention group and 32.5 years old in control group). Therefore it is possible to suggest inclusion of older patients in future studies, since based on the mentioned points the impact of prescribing Q10 coenzyme for infertility would be more obvious in women of older ages (see suggestions).

One of the points which should be considered in this field, is proper dose of administering Q10 coenzyme. As it was mentioned, in the study of Bentov et al (2014) daily 600 mg of Q10 coenzyme was administered for patients in intervention group (10). In our study also one Q10 coenzyme capsule was administered. However, the ideal dose to be administered in these patients is not clear and needs further studies. While, it has been shown that ovaries have high power and adequacy to absorb externally administered Q10 coenzyme (20). All in all, this study has clinical importance due to limitation of similar investigations and in spite of lack of statistically significant differences between two groups, apparent differences specially in terms of rate of pregnancy makes further research with higher sample size necessary. On the other hand, considering lack of complications related to Q10 coenzyme administration in this type of patients in current study and similar studies, it seems that it is possible to consider administration of Q10 coenzyme if it acquires acceptable results in cost-effectiveness studies.

CONCLUSION

Considering the obtained results, although administering Q10 coenzyme did not lead to statistically significant differences for improving variables related to ART comparing with placebo, there were differences supporting administration of Q10 coenzyme when comparing both groups. Based on this and considering safety of this supplement it is still possible to administer it for this type of patients.

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