Does adding coenzyme Q10 to dehydroepiandrosterone sulphate positively impact fertility outcomes in young, poor responder infertile women undergoing antagonist protocol for IVF/ICSI cycles?

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Background. One of the biggest issues in reproductive medicine is treating women with low ovarian reserves or a poor ovarian response (POR) to stimulation. Oxidative stress was suggested as one of the major contributors to POR. However, the pathophysiology remains unknown. Focusing on certain subpopulations within the diverse group of poor responders may help determine the best therapy for these patients.
Objective. To investigate the effect of adding coenzyme A Q10 to dehydroepiandrosterone (DHEA) in young, poor responder infertile females undergoing in vitro fertilisation (IVF)/intracytoplasmic sperm injection (ICSI) cycles.
Methods. One hundred and sixty-eight females with poor ovarian response (Poseidon Group 3) from multiple centres were randomly divided into two groups. The first group received DHEA orally along with coenzyme 10, while the second group received only DHEA. Both groups underwent controlled ovarian stimulation.
Results. There was a significant improvement in the quality of oocytes and the number and quality of embryos transferred in the coenzyme A Q10 group. However, no significant differences were observed in other parameters between the groups.
Conclusion. In young, poor-responder women with decreased ovarian reserve, pretreatment with CoQ10 enhances oocyte and embryo quality and boosts ovarian response to stimulation. An improvement in clinical pregnancy and live birth rates may be possible.
Keywords. Coenzyme Q 10, dehydroepiandrosterone sulphate, flexible antagonist protocol, IVF/ICSI cycles.

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One of the primary issues with assisted reproductive technology (ART) therapies is patients' poor response to controlled ovarian hyperstimulation (COH). 'Poor or low responders' refers to women who react insufficiently to gonadotropins. These women are more likely to have cycle cancellation, fewer oocytes at retrieval, worse egg quality and fewer embryos available for transfer. This causes recurrent failure of ART cycles, which is upsetting for patients and those treating them. The different criteria used in the literature make it difficult to determine the precise incidence, with estimates varying from 5.6 - 35.1% of ART cycles.[1] Numerous therapies have been suggested to improve the reproductive outcomes of women with poor ovarian response (POR). However, randomised intervention trials and meta-analyses yielded inconsistent findings.[2,3] There are few evidence-based therapy approaches to increase ovarian response and reproductive outcomes in POR-affected women. Doctors often recommend empirical therapies supported by little clinical data.[4]

Furthermore, it is becoming more widely accepted that pregnancies after assisted conception cannot be predicted by the ovarian reserve tests now in use. The addition of dehydroepiandrosterone (DHEA), a steroid hormone primarily released by the adrenal glands[5] and converted to androstenedione and estrone in the ovarian follicle (precursors to testosterone and oestradiol, respectively),[6] has produced mixed results. Initial retrospective case-controlled studies[7-9] and one randomised controlled study,[10] showed encouraging improved outcomes with DHEA. These studies' data interpretation and analysis, as well as the little amount of evidence they provided, were questioned.[11,12] DHEA's impact on fertility still needs to be clarified despite the publication of more recent research with superior methods.[13-15] While some studies have shown significantly higher implantation and pregnancy rates and a significant improvement in ovarian markers following DHEA supplementation,[14,15] other studies[13,16] failed to show a favourable outcome among treated patients compared with controls. Despite this debate, a global survey of in vitro fertilisation (IVF) doctors in 45 countries indicated that 26% use DHEA in their stimulation regimens for patients with POR.[4] Coenzyme Q10 (Co Q10) is another supplement for treating POR sufferers. This fat-soluble coenzyme functions as an antioxidant and electron transporter that takes part in the mitochondrial respiratory chain.[17] According to Bentov *et al.*,[18] supplementing with CoQ10 before IVF treatments decreases aneuploidy and boosts pregnancy rates compared with placebo.

Additionally, luteinisation (mid-luteal progesterone), endometrial thickness, ovulation and, most crucially, pregnancy rate were all considerably improved in patients with clomiphene-resistant polycystic ovary syndrome (PCOS) using CoQ10.[19] According to Turi *et al.*,[20] mature oocytes and excellent-grade embryos have greater amounts of CoQ10/protein and CoQ10/cholesterol in their follicular fluid than immature eggs and bad-grade embryos, respectively. This study aims to assess the effect of adding coenzyme A Q10 to DHEA on the administrated dose of gonadotropins and on improving the

clinical pregnancy rate in young, poor responder infertile females undergoing flexible antagonist protocol for IVF/intracytoplasmic sperm injection (ICSI) cycles.

Methods

This multicentre study was conducted from June 2018 - April 2020 and included the ART unit at the Obstetrics and Gynecology Department, Faculty of Medicine, Cairo University and private IVF centres. Ours was a prospective randomised double-blind clinical trial.

Inclusion criteria

Young POR (Poor Ovarian Responders) infertile female patients scheduled for an IVF/ICSI cycle were recruited for the study according to POSEIDON criteria (Group 3): age <35 years**,** AMH (Anti-Mullerian Hormone)<1.2 ng/mL, AFC (antral follicular count) <5 and history of poor response in a previous ICSI (intracytoplasmic sperm injection) cycle.

Exclusion criteria

The exclusion criteria were patients younger than 35 years, previous ovarian surgery, previous treatment with adjuvant therapy over the past 6 months, endocrine or autoimmune disease (e.g., diabetes, thyroid disease or presence of anti-thyroid antibodies or PCOS), chromosomal abnormality, uterine malformations or allergy to coenzyme Q10 and DHEAS.

Allocation concealment and randomisation

Recruited patients were randomised into a 1:1 ratio and divided into two arms.

Group 1: received DHEA orally in a dose of 25 mg twice daily along with 200 mg of Co Q10 three times daily for 8 weeks.

Group 2: received DHEA orally at 25 mg twice daily and three placebo tablets (similar to Co Q10) for 8 weeks.

A third party (nurse practitioner) who was not directly engaged in patient treatment or the randomisation procedure performed the randomisation using computer-generated randomisation codes before placing them in sealed, opaque sequentially numbered envelopes. Each patient selected one of the two groups by drawing from sealed envelopes containing a random number after completing the preoperative investigations, clinical examination and providing their medical histories. Patients received a thorough description of the care plan and provided informed consent.

Intervention

The study participants and the investigators (health providers) were blinded to the patient grouping. The patients enrolled in either group received treatment by DHEA and coenzyme Q Group 1) or DHEA alone (Group 2) (full 8 weeks before starting the ICSI cycle), followed by ovarian stimulation, oocyte retrieval and embryo transfer. The flexible antagonist protocol was used in the ovarian stimulation cycles. Human menopausal gonadotropin 150 IU (IBSA pharmaceutical, Switzerland) and highly purified follicle-stimulating hormone (FSH) I50 IU (IBSA pharmaceutical, Switzerland) were used. Stimulation started on day 2 of the cycle; the starting dose was 300 IU, which was further adjusted on day 7 of the cycle (day 6 of stimulation) according to the response. Gonadotrophin-releasing hormone (GnRH) antagonist Cetrorelix 0.25 mg SC injection (Cetrotide 0.25 mg, Merck Serono, Germany) was administered when the leading follicle reached 12 mm and continued daily until the day of human chorionic gonadotropin (HCG) trigger. The response was monitored using follicular size and serum oestradiol levels. HCG trigger was administered when at least one follicle reached 18 mm. The cycle was cancelled when there were no follicles with a diameter >14 after 8 - 9 days of gonadotropin therapy and peak E2 levels were less than 250 pmol/L. Oocytes were retrieved 34 - 36 hours after the HCG trigger (10 000 IU) (IBSA pharmaceutical, Switzerland) via the transvaginal route. Mature oocytes were confirmed by the presence of a second polar body. Fertilisation was assessed 18 hours after injection and was confirmed by the presence of two nuclei and two polar bodies. The resulting embryos were transferred to a culture medium for 48 hours before being transferred.

Primary outcome

The total dose of human menopausal gonadotrophins (HMG) and FSH used during stimulation and clinical pregnancy rate (presence of intrauterine gestational sac by ultrasound 30 days after embryo transfer).

Secondary outcome

Chemical pregnancy rate (positive Quantitative BHCG 15 days after embryo transfer), number and quality of transferred embryos, cycle cancellation rate, ovarian response parameters (i.e., basal hormonal parameters (FSH and luteinising hormone (LH)) at the start of stimulation, number of expected oocytes, total E2 levels and the endometrial thickness and pattern on the day of HCG trigger and other embryological parameters (i.e., number and quality of oocytes retrieved and fertilisation rate).

Data analysis

Data was gathered, coded to enable data processing and double-entered into Microsoft Access. The Statistical Package of Social Science (SPSS) software version 18 running on Windows 7 was used to analyse the data. Simple descriptive analysis using percentages and numbers for qualitative data, arithmetic means as a measure of central tendency, and standard deviations (SD) as a measure of dispersion for quantitative parametric data are all acceptable. Inferential statistical tests were used after the one-sample Kolmogorov-Smirnov test in each group was used to check the normality of the quantitative data included in the study. Regarding parametric quantitative data, an independent Student *t*-test was used to evaluate measurements between two sets of quantitative data for qualitative data to compare two or more qualitative groups using the χ^2 test. $P<0.05$ was considered significant.

Results

There was no statistically significant difference between study groups regarding age, baseline hormonal profile, AFC, dose of hormonal treatment used for ovarian stimulation and duration of stimulation (Table 1).

Significant differences were observed between the groups regarding the quality of oocytes (M2, M1, G1 and G2), with group 1 (received DHEA with Co Q10) displaying a high mean of M2 and G1 and a low mean of M1 and G2 ($p<0.05$). In contrast, no statistically significant differences were noted between the groups in terms of the number of expected oocytes, number of embryos, cycle cancellation rate and germinal vesicle (GV) level (Table 2).

There was no statistically significant difference between groups regarding the level of E2 after treatment, which indicated both groups had the same effect on the E2 level (Fig. 1). Furthermore, no statistically significant differences were observed regarding the rate of clinical pregnancy, which indicated both groups had a similar pregnancy rate (Fig. 2).

Table 1. Baseline characteristics of included patients

Variables	DHEA (*n*=84), mean (SD)	DHEA + Co Q10 (*n*=84), mean (SD)	*p*-value
Age (years)	31.2 (2.9)	31.1 (3.5)	0.8
AMH (ng/mL)	0.64 (0.31)	0.66 (0.35)	0.7
AFC	3.67 (0.47)	3.52 (0.50)	0.6
FSH (IU/mL)	8.6 (4.0)	8.45 (3.6)	0.8
LH (IU/mL)	5.53 (3.5)	5.56 (3.8)	0.9
Fostimon (IU)	2308.9 (1 028.5)	2092.3 (1 041.1)	0.2
Metrional (IU)	1982.4 (1 027.5)	1889.9 (1 041.7)	0.6
Total dose (IU)	4243.8 (1 083.2)	3982.1 (1 237.4)	0.1
Duration of stimulation (days)	12.4 (1.5)	12.2 (1.7)	0.2

DHEA = dehydroepiandrosterone; SD = standard deviation; AMH = anti-mullerian hormone; AFC = antral follicular count; FSH = follicle-stimulating hormone; LH = luteinising hormone.

Table 2. Study outcomes

Variables	DHEA (*n*=84), mean (SD)	DHEA + Co Q10 (*n*=84), mean (SD)	*p*-value
Expected oocytes (*n*)	3.17 (0.83)	3.31 (0.81)	0.3
Quality of oocytes			
M2	1.26 (0.73)	1.95 (0.95)	<0.001***
M1	0.56 (0.62)	0.33 (0.59)	0.02*
GV	0.45 (0.7)	0.45 (0.8)	0.9
Number of embryos	1.27 (0.8)	1.56 (0.9)	0.03*
Cycle cancellation rate	0.06 (0.2)	0.06 (0.2)	0.9
Quality of oocytes			
G1	0.89 (0.58)	1.3 (0.85)	<0.001***
G2	0.42 (0.52)	0.24 (0.43)	0.02*

*$P<0.05$
***$P<0.001$
DHEA = dehydroepiandrosterone; SD = standard deviation; Co = coenzyme; M = metaphase; GV = germinal vesicle; G = grade.

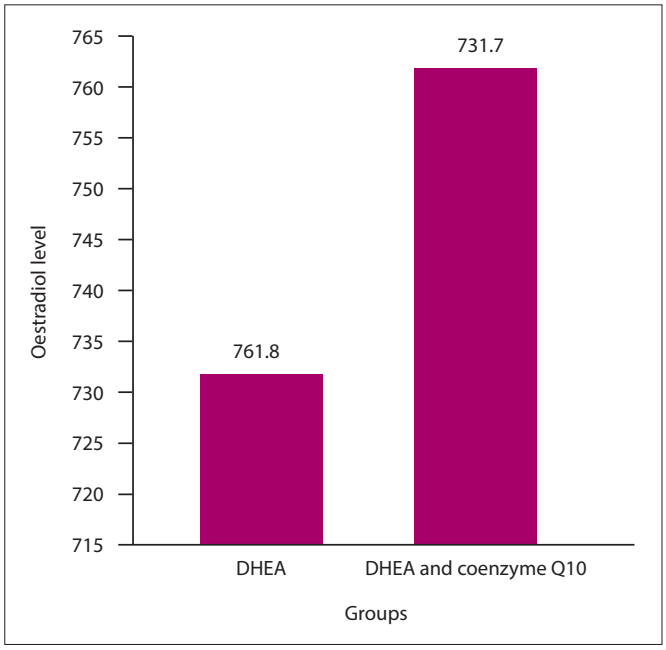

Fig. 1. Mean oestradiol levels for the two groups.

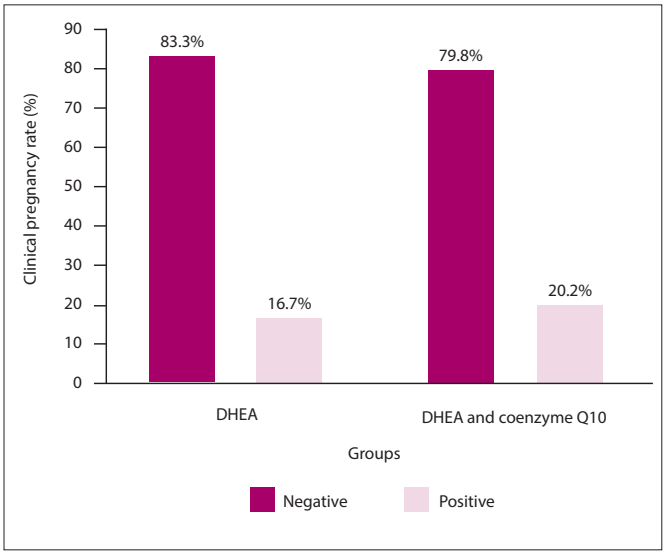

Fig. 2. Comparisons of clinical pregnancy rate in the two study groups. (DHEA = dehydroepiandrosterone.)

Discussion

Our study did not find between-groups differences in cycle cancellation (p=0.9) and pregnancy (p=0.5) rates. Gat *et al.*[21] Performed a retrospective study to evaluate the potential benefit of using Co Q10 and DHEA during intrauterine insemination (IUI) and IVF cycles in patients with decreased ovarian reserve (DOR). In their study, 175 patients treated with DHEA were included in IVF cycles. Seventy-eight patients treated by DHEA and Co Q10 were included in IVF cycles. The average age in that study was higher than in our study (mean 39 (3.6) years in the control group v. 39.2 (2.7) in the study group), whereas the mean age in the intervention v. control group was 31.1 (3.5) v. 31.2 (2.9) in our study.

Our study had equal pre-stimulation AFC and hormonal treatment doses, whereas the study by Gat *et al.*[21] reported differences between the two groups examined in terms of AFC (p=0.0001) before hormonal stimulation, which in turn caused a difference in the dose of hormonal treatment in favour of the Co Q10 group (p=0.003). According to Gat *et al.*,[21] the disparity in pre-stimulation AFC was treated with a greater hormonal dosage, which prevented the two groups from differing significantly in the quantity and quality of oocytes and embryos. The absolute rates of biochemical, clinical and continuing pregnancy were greater in the study group compared with the control group (30.8%, 29.5% and 23.1% v. 27.4%, 25.1% and 21.1%, respectively); however, these were not statistically significant.[21] To determine whether pretreatment with Co Q10 enhances ovarian response and embryo quality in low-prognosis young women with poor ovarian reserve (POR), Xu *et al.*[22] conducted a prospective randomised controlled research. This paper enrolled 186 consecutive POR patients from group 3 of the POSEIDON categorisation. The patients were split into two groups (76 treated for 60 days with Co Q10 and 93 untreated controls). That study reported contrasting prior ovarian response parameters to stimulation to our findings.[22] Nevertheless, the authors confirmed that Co Q10 had a beneficial impact on the quality of the embryos since the Co Q10 group had a considerably greater mean number of high-quality embryos than the control group (p=0.03). Furthermore, the women receiving Co Q10 treatment had a clinical pregnancy rate of 34.85% compared with 25% in the controls.[22] This difference is not statistically significant, consistent with our findings.

Consequently, we may conclude from both our work and that of Xu *et al.*[22] that combining DHEA with Co Q10 has similar effects as Co Q10 alone, but only in young POR. A prospective randomised controlled trial by Caballero *et al.*[23] Investigated the role of adding coenzyme Q in a dose of 600 mg twice daily for 12 weeks and compared it to no treatment. They concluded that coenzyme Q addition confers no additional benefit to the treatment.

A systematic review and meta-analysis that included 5 randomised controlled trials evaluating the role of adding coenzyme Q on cumulative pregnancy rates concluded that coenzyme Q addition was associated with higher pregnancy rates compared with the placebo.[24]

Conclusion

In young, poor-responder women with decreased ovarian reserve, pretreatment with CoQ10 enhances oocyte and embryo quality and boosts ovarian response to stimulation. Clinical pregnancy and live birth rates may be positively impacted. However, larger randomised controlled trials are required to validate this finding. Further research is needed to determine the best course of therapy, timing and dosage, and to assess the therapeutic impact of Co Q10 supplementation in additional subgroups of POR patients with poor prognoses.

Declaration. None.

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Author contributions. AT contributed to data collection, and MD and SH contributed to the study protocol. AO was involved in the writing of the manuscript. AE assisted with data collection. FAH was involved in the revision of the manuscript.

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Data availability statement. The datasets generated and analysed in the current study are available from the corresponding author upon reasonable request.

Conflicts of interest. None.

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