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Effect of Pretreatment with Coenzyme Q10 and DHEA before ART in Patients with Diminished Ovarian Reserve

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Abstract

Objective (s): *Aim of this study was to explore the efficacy of pretreatment with a combination of coenzyme Q10 (CoQ10) and dehydroepiandrosterone (DHEA) in comparison to that of DHEA alone before IVF-ICSI cycles in patients with diminished ovarian reserve.*

Methods: *This retrospective case control study was conducted in Infertility Care and Research Center (ICRC) Ltd Dhaka, Bangladesh between January 2018 and December 2023. One hundred and forty (140) patients who had AMH level <1ng/ml and underwent ART after pre-treatment by micronutrients were the candidates of this study. Among these patients fifty-six were treated with DHEA 75 mg /d and eighty-four patients were treated with combination of CoQ10 (600mg/d) and DHEA (75mg/d) for 90 days prior to IVF-ICSI cycles. Patients of combination of CoQ10 and DHEA group was considered as case (study) and only DHEA group as control. Main outcome measures were ovarian response to gonadotropin, amount and duration of gonadotropin needed to get optimum response, cycle cancellation, number of mature follicles ³18 mm, number of oocytes retrieved, fertilization and cleavage rate, number of good-quality embryos, number of embryo transferred, embryo freezing, clinical pregnancy and miscarriage rate. A p-value of < 0.05 was considered significant.*

Result: *All patients' baseline parameters were similar. There was no statistically significant difference of age, AMH, D3 FSH, E2, TSH and prolactin level. Ten patients (11.90%) of case and nine patients (16.07%) of control group did not develop any follicle in-spite of highest dose (450 IU/d) of gonadotropin and cycle was cancelled. Cancellation rate is more in control group though statistically was not significant (p=.480). The number of mature follicles ³18mm and oocytes retrieved was higher in the CoQ10+DHEA group compared to DHEA alone group (4.71±2.57 versus 3.7±2.5, p<0.005). A significantly lower amount of total gonadotropin dosages was needed in the Coq10+DHEA group compared to the DHEA group (3185±659 IUs versus 3642±1190 IUs, p=0.004). Fertilization rate, cleavage rate, and good quality embryo were significantly higher in women treated with Coq10 and DHEA than only DHEA group (3.73±2.19 versus 2.1±1.52, 3.65±2.17 versus 2.05±1.39, 2.35±1.45 versus 1.17±1.01 respectively, p<0.05). The rate of clinical pregnancy was also found significantly higher in CoQ10 and DHEA group than the only DHEA group (27.38% versus 8.9%, p=.0.007). A p value of <0.05 was considered significant.*

Conclusion: *Pretreatment with CoQ10 and DHEA before ART increases ovarian responsiveness, number of oocytes, good-quality embryos, and pregnancy rates in patients with decreased ovarian reserve. Further large-scale study is required to establish the therapeutic effect of CoQ10 and DHEA.*

Keywords: *Co-enzyme Q10, DHEA, Ovarian reserve, IVF*

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Introduction:

Fecundity is declining worldwide, and ovaries are aging fast. Nowadays, more patients seek fertility treatment with decreased ovarian reserve at younger ages. Despite significant advancements in assisted reproductive technology, diminished ovarian reserve (DOR) or poor ovarian response (POR) is still considered one of the major challenges in reproductive medicine. The condition is frustrating for infertile couples due to treatment-related low conception rates, higher cycle cancellation rates, and high treatment expenditures.

Diminished ovarian reserve is defined as a decrease in the number and quality of oocytes. Reproductive potential decreases and fertility outcomes are poor even when assisted reproductive techniques (ART) are used in patients with diminished ovarian reserve[1,2].

Increased oxidative stress and mitochondrial dysfunction have been linked to premature decline in ovarian function and poor ovarian response. Co-enzyme Q10 can mitigate the negative effects of oxidative stress. This lipid-soluble coenzyme, a crucial part of the inner mitochondrial membrane, is involved in oxidative phosphorylation, which produces energy, and electron transport in the mitochondrial respiratory chain[3,4].

Tissue levels of CoQ10 decrease with age leading to lipid oxidation, ROS generation, and cell death[5]. Oocyte mitochondrial function declines with maternal age, CoQ10 supplementation can enhance oocyte quality and contribute to the preservation of the ovarian follicle pool[6,7]. By preventing lipid peroxidation and DNA damage, CoQ10 acts as an antioxidant[8,9]. In clinical settings, CoQ10 supplementation before IVF procedures resulted in decreased aneuploidy and higher pregnancy rates compared to placebo[10.-13].

DHEA is another adjuvant demonstrated by various studies for the improvement of ovarian markers and pregnancy rate in patients with DOR and POR in IVF cycles[14-16]. DHEA stimulates the initiation of primordial follicles, promotes granulosa cell proliferation, and develops gonadotrophin-responsive preantral and early antral follicles[17,18]. DHEA plays a role in early follicular development by enhancing the expression of the FSH receptor and preventing follicular atresia by lowering apoptosis[19].

Multiple interventions including different adjuvant treatments are proposed to improve ovarian response and reproductive outcomes in diminished ovarian reserve, but evidence-based therapeutic strategies are still lacking. On the basis of positive findings of individual drug CoQ10 and DHEA we tried to explore the efficacy of combined therapy of coenzyme CoQ10 and DHEA in comparison to single drug DHEA before IVF-ICSI cycles in patients with diminished ovarian reserve.

Materials and methods:

This retrospective case control study was conducted in Infertility Care and Research Center (ICRC) Ltd Dhaka, Bangladesh between January 2018 and December 2023. One hundred and forty (140) patients who had AMH level <1.1ng/ml and underwent ART after pre-treatment by micronutrients were the candidates of this study. Bologna criteria[20] and Poseidon classification [21] defined POR or DOR differently. According to Reig et al. DOR or POR is defined when AMH is less than 1.1 ng/mL and antral follicle count is less than 5, which is closer to POSEIDON criteria [22].

The women whose AMH level was ≥1.1 ng/ml were excluded from this study.

Diminished ovarian reserve is usually associated with less number and oxidative stress related to poor-quality eggs. So, patients with diminished ovarian reserve were treated with different micronutrients to improve number and quality of eggs. Among these patients fifty-six (56) were treated with DHEA 75 mg / d and eighty-four (84) patients were treated with combination of CoQ10 (600mg/d) and DHEA (75mg/ d) for 90 days prior to IVF-ICSI cycles. Patients of combination of CoQ10 and DHEA group was considered as case (study) and only DHEA group as control. All patients were treated by GnRH antagonist protocol and ovarian stimulation was given by recombinant FSH (150-300 IU) and recombinant LH (75-150 IU) (Pergoveris, Serono 1-2 ampuls) according to patients' age and AMH level. Ovulation was triggered by recombinant hCG (Ovedril, Serono) 250 microgram stat, when at least one good sized (≥18 mm) follicle with good triple line (≥8mm) of endometrium and E2 level (≥100 pg/ml) achieved on the day of monitoring, and which was considered as minimum response to proceed. OPU was scheduled between 34-36 hours after triggering.

Main outcome measures were ovarian response to gonadotropin, amount and duration of gonadotropin

needed to get optimum response, cycle cancellation, number of mature follicles ³18 mm, number of metaphase II oocytes retrieved, fertilization and cleavage rate, number of good-quality embryos, number of embryos transferred, embryo freezing, clinical pregnancy and miscarriage rate and live birth rate. Quality of embryo was evaluated and graded on D3 embryos by blastomere size and fragmentation. Embryos exhibiting equal blastomere size and no fragmentation were considered G1. G2 embryos had blastomeres of equal size with slight fragmentation (<20%), while G3 embryos had blastomeres of unequal size but no fragmentation. G4 embryos had blastomeres of equal or unequal size and moderate fragmentation (20%–50%), and G5 grade embryos were those with unrecognizable blastomeres and severe fragmentation (>50%) [23].

Data analysis was done by statistical package for the social science (SPSS). Student t test and chi-square (c^2) test were done for test of significance. A p-value of < 0.05 was considered significant.

Results:

All patients' baseline parameters were similar. There was no statistically significant difference of mean age, AMH, D3 FSH, E2, TSH and prolactin level of both groups (Table 1). Ten patients (11.90%) of case and nine patients (16.07%) of control group did not develop any follicle in-spite of highest dose (300IU rFSH and 150 IU rLH/d) of gonadotropin and cycle was cancelled. Cancellation rate is more in control group though statistically was not significant (p=.480). The number of mature follicles ³18mm and metaphase II oocytes retrieved was higher in the CoQ10+DHEA group compared to DHEA alone group (4.71±2.57 versus 3.7±2.5, p<0.005) (Table 2). A significantly lower amount of total gonadotropin dosages was needed in the CoQ10+DHEA group compared to the DHEA group (3185±659 IU versus 3642±1190 IUs, p=0.004). Fertilization rate, cleavage rate, and good quality embryo were significantly higher in women treated with CoQ10 and DHEA than only DHEA group (3.73±2.19 versus 2.1±1.52, 3.65±2.17 versus 2.05±1.39, 2.35±1.45 versus 1.17±1.01 respectively, p<0.05). The rate of clinical pregnancy was also found significantly higher in CoQ10 and DHEA group than the only DHEA group (27.38% versus 8.9%, p=.0.007) (Table 2). Though there was no difference in miscarriage rate, both ongoing pregnancy (p=0.035) and delivery (p=0.051) were significantly higher in study group. Clinical pregnancy, miscarriage, ongoing pregnancy and live birth of both groups are shown in Fig 1.

Table-I

Characteristics of the patient compared between pretreatment with combined CoQ10 & DHEA supplements versus DHEA alone before IVF cycles.

Variable	Study N=84 Mean±SD	Control N= 56 Mean±SD	P value
Pre-Stimulation assessment			
Age	34.10±4.1	36.66±3.66	.000
AMH	.49±.26	.58±.25	.035
FSH (D3)	10.24±5.32	10.05±4.90	.340
E2 (D3)	34.25±16.64	32.54±12.14	.510
TSH	3.21±1.87	3.40±2.13	.570
Prolactin	21.59±8.70	24.89±14.90	.101

CoQ10 + DHEA - Study
DHEA-Control

Table-II

The treatment outcome compared between combined CoQ10 & DHEA supplements and DHEA alone during IVF cycles.

Variable	Study N=84 Mean±SD	Control N= 56 Mean±SD	P value
Ovarian response			
Total dose of Gn (IU)	3185.06±659.40	3642.20±1190.30	.004
Duration of stimulation (days)	11.06±1.60	11.54±2.50	.172
Number of mature follicles	4.71±2.58	3.75±2.54	0.31
Oocyte retrieved	4.01±2.27	3.16±1.96	.024
Fertilization rate	3.74±2.19	2.18±1.53	.000
Cleavage rate	3.65±2.171	2.05±1.39	.000
Cycle cancelled N (%)	10 (11.90%)	9 (16.07%)	.480
Embryo			
Gr1	2.36±1.45	1.18±1.01	.000
Gr2	.82±.85	.50±.57	.015
Gr3	.35±.63	.16±.37	.050
Gr4	.07±.26	.20±.40	.027
Reproductive outcome			
Clinical pregnancy n (%)	26 (30.95)	9(16.07)	0.046
Miscarriage n (%)	3 (3.57)	2(3.57)	1.000
Ongoing pregnancy n (%)	23 (27.38)	7(12.5)	0.035
Delivery Live birth n (%)	18 (21.42)	5(8.92)	0.051

CoQ10 + DHEA - Study
DHEA-Control

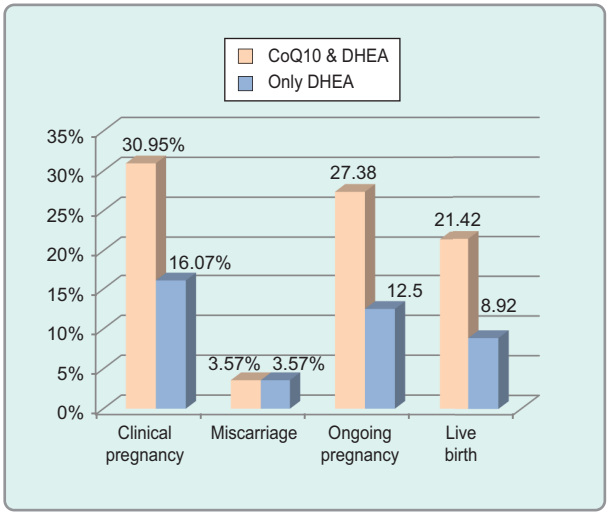

Figure 1: Reproductive outcome

Discussion:

This retrospective study examined 140 IVF-ICSI cycles with pretreatment by CoQ10 and DHEA and DHEA only. There was a lower gonadotropin requirement and a higher number of mature follicles, oocyte retrieval, good quality embryos, pregnancy and live birth and lower cancellation rate with combined supplementation of CoQ10 and DHEA than DHEA alone suggesting an improved ovarian response and fertility outcome by combined therapy in women with low AMH.

In the study of Yangying Xu et al. CoQ10 pretreatment compared with placebo before IVF cycles resulted in significantly lower gonadotrophin requirements, an increased number of retrieved oocytes (4, IQR 2–5), higher fertilization rate (67.49%), and better-quality embryos [(1, IQR 0-2), pÂ0.05]. Findings were similar to our study suggesting that adding CoQ10 preceding IVF cycles improves ovarian response and reproductive outcome[3].

A systematic review and network meta-analysis evaluated different adjuvant treatments in poor responders and diminished ovarian reserve using the Bologna criteria. The meta-analysis revealed DHEA and CoQ10 adjuvant pretreatment before IVF, both groups resulted in significantly higher clinical

pregnancy rates [odds ratio (OR) 2.46,95% CI 1.16 to 5.23; 2.22,1.08-4.58, respectively] compared to control and CoQ10 pretreatment resulted in higher number of oocytes retrieved, number of embryos transferred were more and there was lowest cycle cancellation rate compared to control[24].

Itai Gat et al. conducted a large retrospective study that compared the effect of CoQ10 and DHEA versus DHEA only in 253 IVF cycles and 797 IUI cycles. The study demonstrated lower gonadotropin requirement with combined supplementation compared to DHEA only (3414 ± 1141 IUs vs 3877 ± 1143 IUs respectively). This result was similar to our study. Pre-stimulation AFC was found higher in the CoQ10 and DHEA group than DHEA alone after supplementation. But in their study, there was no difference between the two groups regarding the number of mature follicles, oocytes retrieved, and fertilization rate (5.9±4.6 vs 5.5±3.5, 8.4±7.1 vs 8.5±5.6, 4.7±4.5 vs 5.3±4.1 respectively). In the same study, C clinical pregnancy and ongoing pregnancy rates were higher in CoQ10 and DHEA groups compared to the DHEA group (29.5%, 23.1% vs 25.1%, 21.1% respectively), but the differences did not reach statistical significance[7]. Itai Gat et al. reported that combined supplementation resulted in a significantly higher number of AFC pre-stimulation and mature follicles on the day of trigger in IUI cycles[25].

In our study, CoQ10 and DHEA pretreatment significantly increased the fertilization rate and the number of good-quality embryos. Clinical pregnancy and live birth rate were also found higher with combined CoQ10, and DHEA compared with DHEA only. The number of cycle cancellations was less with combined supplementation compared with DHEA only, but these differences failed to achieve significance.

Bentov et al. conducted a randomized controlled trial and reported that the use of CoQ10 supplementation in women undergoing IVF resulted in reduced aneuploidy and increased pregnancy rates compared with placebo[10].

CoQ10's ability to combat oxidative stress and boost oocyte energy generation improves reproductive outcomes. Reduced oxidative phosphorylation and decreased ATP generation are the results of mitochondrial dysfunction in oocytes. Excessive levels of reactive oxygen species, emitted during mitochondrial aerobic respiration, can lead to DNA mutations and deletions in the mitochondria and accelerate cell death. These all have an impact on the results of reproduction, including low-quality oocytes and embryos, diminished ovarian reserve, and reduced fertilization rate. CoQ10 contributes to oxidative phosphorylation, ATP synthesis, and electron transport in the respiratory chain of the mitochondria. Therefore, CoQ10 enhances mitochondrial function in oocytes and functions as an antioxidant system inside the cell.[3,9,26]

Limitations of this study are the absence of a control group without adjuvant pretreatment and a retrospective study without randomization. Poseidon group 3 and 4 (Poseidon 3; age Â35, AMH Â1.2 ng/ml; Poseidon 4: age Ã35, AMH Â1.2 ng/ml) both were included in the two groups and there was heterogeneity among the included population.[27]

Conclusion:

Pretreatment with CoQ10 and DHEA before ART increases ovarian responsiveness, the number of oocytes, good-quality embryos, and pregnancy rates in patients with diminished ovarian reserve. A further large-scale study is required to establish the therapeutic effect of CoQ10 and DHEA.

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