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Research Article

DHEA Supplementation Prevents Follicle Depletion due to Chemotherapy-Induced Ovarian Damage

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Abstract

The aim of this study was to investigate the protective effect of Dehydroepiandrosterone-sulfate (DHEA-S) on chemotherapy-induced ovarian damage (CIOD). Twenty one adult female Wistar albino rats were equally divided in three groups with 7 rats in each group: The groups consisted of a vehicle-treated control group (group 1), chemotherapy-treated rats followed by intraperitoneal DHEA-S injection (group 2) or chemotherapy-treated rats followed by CoQ10 (group 3). The rats were given daily intraperitoneal injections of cisplatin during ten days for rat model of CIOD. The cisplatin was administered intraperitoneally once daily at doses of 2.0 mg/kg for 10 days. Rats in group 2 and 3 were given DHEA (6 mg/kg, s.c) and CoQ10 (20 mg/kg, per oral) respectively. Treatment with DHEA-S and CoQ10 were started at the 1th day of chemotherapy and continued for 10 days during chemotherapy. The animals were sacrificed two weeks later, and their ovaries were excised for histopathological analysis. Serum levels of anti-Mullerian hormone (AMH), body weight and ovarian weight of animals were also monitored. Significantly higher mean follicle count was detected in the group 2 compared to the group 3. The ovaries of the rats in the control group showed follicles in all stages of development. The ovaries of the rats in the DHEA-S showed increased numbers of primary and antral follicles. Group 2 had higher serum AMH levels than those in the group 3. DHEA-S administration improve follicle survival and AMH production in chemotherapy-induced ovarian damage.

Keywords: *DHEA-S; CoQ10; Ovarian Damage; Oocyte*

Introduction

Chemotherapy drugs are widely applied treatment of many cancer types including gynecological malignancies. Most of this agents have a deleterious effect on ovarian follicles and total ovarian reserve. The risk of follicle damage is directly correlated with the mechanism of action of the agent used, the cumulative dosage, the duration of the treatment and the age of the patients [1].

Dehydroepiandrosterone sulfate (DHEA-S) is a steroid hormone produced mainly by the adrenal cortex and thecal layer of ovary [2]. By increasing the insulin like growth factor-I (IGF-1) DHEA treatment via oral supplementation improves follicular development and quality. It has been reported that DHEA supplementation to increase ovarian reserve in women with low ovarian reserves [2,3]. CoQ10 has a critical role on energy production in mitochondrial electron transport chain and has antioxidant properties [4]. By blocking membrane peroxidation and free radical production CoQ10 may have a role in prevention of follicle depletion. Despite the widespread use of DHEA and CoQ10 in reproductive biology possible protective impact of DHEA and CoQ10 on ovarian damage induced by chemotherapy remained

speculative. There is no study investigating the possible effect of DHEA and CoQ10 supplementation on follicle count and anti-Mullerian hormone (AMH) levels in cases with chemotherapy-induced ovarian damage (CIOD). This experimental study was, therefore, planned for the purpose of determining the influence of DHEA and CoQ10 supplementation on ovarian reseve and serum AMH levels of animal with cisplatin induced ovarian damage.

Materials and Methods

Twenty one adult female Wistar albino rats were equally divided in three groups with 7 rats in each group: The groups consisted of a vehicle-treated control group (group 1), chemotherapy-treated rats followed by intraperitoneal DHEA-S injection (group 2) or chemotherapy-treated rats followed by CoQ10 (group 3). The rats were given daily intraperitoneal injections of cisplatin during ten days for rat model of CIOD. The cisplatin was administered intraperitoneally once daily at doses of 2.0 mg/kg for 10 days. The rats residing in the group 2 received 6 mg/kg/day DHEA (dissolved in 0,1 ml sesame seed oil) subcutaneously. Rats in group 3 were given CoQ10 (20 mg/kg, per oral). Treatment with DHEA-S and CoQ10 were started at the 1th day of chemotherapy and continued for 10 days during chemotherapy. The animals were sacrificed two weeks later, and their ovaries were excised for histopathological analysis. Serum levels of anti-Mullerian hormone, body weight and ovarian weight of animals were also monitored. Mann-Whitney U and ANOVA tests were used for comparisons of results. Data were given as mean ± standard deviation. *P* values < .05 were considered to indicate statistical significance.

Follicle count and AMH assay

Venous blood of animals were used for assay of AMH. All samples were analysed using an ultra-sensitive AMH Gen II ELISA kit (Beckman-Coulter, Inc., Webster, USA). The lower limit of AMH detection was 0.16 µg/l. Inter-assay variation was 10% at 0.27 µg/l. All values are expressed in ng/mL. The ovaries of the rats were fixed in paraformaldehyde and embedded in parafin. Average of 8 sections was obtained 5 µm in thickness. Follicle counts were performed on representative sections from seven rats from each group, and the mean count per section was calculated.

Results

Rats were given DHEA showed vaginal smears with parabasal cells showing an androgenic effect. Increase in total body weight and ovarian weight were observed at 2 weeks in control animals. Insignificant decrease was detected in body weigh of animals on DHEA compared to control group. Significant decrease was found in body weight of animals on CoQ10 compared to control and DHEA groups (P < .05). H-score evaluation of the ovaries demonstrated a higher mean follicle count in animal receiving DHEA compared to the animals receiving CoQ10. Significantly higher mean total follicle count was detected in the group 2 compared to the group 3. The ovaries of the rats in the control group showed follicles in all stages of development. The ovaries of the rats in the DHEA-S showed increased numbers of primary and antral follicles. As shown in table 1, compared to control group (4.16 ± 0.22 ng/mL) rats in DHEA group showed insignificant decrease in serum levels of AMH (3.89 ± 12.2 ng/mL, P <. 06). When compared to control group, significant decrease in AMH levels occured in rats were given CoQ10 (3.01 ± 2.76 ng/mL, P < .02).

Groups	Total follicle count	Serum AMH levels (ng/mL)	Total body wight
Vehicle treated control	14.4 ± 0.34	4.16 ± 0.22	280.1 ± 2.33
CIOD plus DHEA	10.11 ± 0.39	3.89 ± 12.2	260.4 ± 44.12
CIOD plus CoQ10	4.12 ± 7.98	3.01 ± 2.76	201.1 ± 0.11
P value			
1 vs 2	P < .05	P < .06	P < .07
1vs 3	P < .05	P < .02	P < .05
2 vs 3	P < .05	P < .05	P < .05

Table 1: *Follicle count, serum levels of AMH and total body weight of animals in each groups.*

Discussion

Gonadotoxic treatments with anti-cancer drugs is the conditions in which the fertility needs to be preserved. Undesired adverse effects of chemotherapy drugs on growing follicle that may cause premature ovarian failure due to follicle loss. To prevent chemotherapy-induced follicle loss many chemical agnets or plant derived polyphenols have been used for their chemopreventive features [5].

Subcutaneous DHEA administration cisplatin-induced follicle loss. Ovaries of rats in DHEA group showed increased numbers of early growing follicles. In good agreement with this, insignificant decrease was detected in the serum levels of AMH in animals were given DHEA. Moreover, animals on DHEA showed insignificant weight loss. Although DHEA treatment improves follicle recruitment, potentialized gonadotropin effects, reduces follicle apopitosis, how DHEA exerts fertility-promoting effects in animals with ovarian damage [5]. The improvement of ovarian reserve after DHEA supplementation might be explained through the positive effect of this pro-hormone on ovarian microenvironment. Preserved follicle count and AMH levels in rats were given DHEA may be due to induction of IGBP-1 production by DHEA administration.

DHEA may also exerts its oocyte protecting function at the level of granulosa cell mitochondrial membrane. As supportive, apoptotic pathway located in mitochondria has been reproted responsible for cancer cell death. By inhibiting mitochondrial apopitosis, DHEA may protect granulosa cell death and then improve ovarian reserve of animals with cisplatin induced POF. Relatedly, a beneficial effect of DHEA on peak serum estradiol level was reported among women with diminished ovarian reserve [6]. The second possibility of positive effect of DHEA on serum AMH and follicle count might be the substitution of drug-related decline in serum and ovarian tissue levels of androgens and estrogens with exogenous DHEA. Both circulating androgen and estrogen decrease with advancing age with ovarian damage. Another possible target for DHEA action is the insulin-like growth factor-I [7]. Decreased IGF-1 levels have been reported in women with poor responders. Subcutaneous DHEA administration increases IGF-1 levels and up-regulates the expression of IGF-I and its receptors in follicle [8].

Both follicle count and AMH levels of animals on CoQ10 were found to be decreased significantly. Despite its antioxidant properties, CoQ10 did not prevent follicle loss due to chemotherapy. This may be due to the fact that CoQ10 can not be easily diffused into the oocyte. Because chemotherapy disturb the mitochondrial function of oocyte CoQ10 can be ineffective for restoration of follicle.

Conclusion

High circulating androgen levels have been reported in reproductive aged women and women with benign ovarian tumors [9]. In a recent study, Chern., *et al.* showed that DHEA supplementation improves *in vitro* fertilization outcomes of poor ovarian responders, especially in women with low serum concentration of DHEA-S [10]. Likewise, Fuentes., *et al.* [11] demonstrated the decreased serum and follicular fluid androgens levels of women with poor responders undergoing controlled ovarian stimulation. We concluded that while DHEA administration does not prevent primordial follicle loss significantly, DHEA protect primary antral follicles depletion. DHEA supplementetion may be use an effective oocyte preservetion method particularly among young cancer patients undergoing chemotherapy. By inducing IGBP and some cell cycle regulatory enzymes, DHEA may facilitate the removal of toxic metabolites of chemotherapeutic agents from the ovary and preserve ovarian reserve.

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