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Effect of dehydroepiandrosterone administration in Chinese women over 37 years undergoing assisted reproductive techniques

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ABSTRACT

Objective: To evaluate the effect of DHEA supplementation on in vitro fertilization (IVF) parameters and pregnancy outcomes in patients older than 37 years with normal ovarian reserve.
Study design: A retrospective cohort study was conducted to evaluate the impact of DHEA supplementation on IVF outcome of infertile women over 37 years with normal ovarian reserve between January 2012 and July 2014. 243 patients (study group) received 75 mg of DHEA daily (25 mg three times daily) before the IVF cycle. Another 243 patients (control group) received infertility treatment, but did not receive DHEA. The IVF outcome parameters in each group were compared.
Results: Both groups did not show statistically significant differences in terms of patient demographics characteristics, mean numbers of oocytes retrieved and mature oocytes rate. While patients in the DHEA group have the significantly higher implantation rate and live birth rate compared with controls (30.13% versus 22.70%, 43.33% versus 28.26%). We also found that the cycle cancellation rate and miscarriage rate were lower in the DHEA group (1.23% versus 5.34%, 13.33% versus 28.89%).
Conclusion: DHEA supplementation may significantly improve IVF outcomes in infertile women over the age of 37.

Introduction

Age is an important factor influencing woman's ability to conceive, as ovarian reserve and oocytes quality decrease with age. Beginning the age of 32, the women fertility significantly declines, and more rapidly after the age of 37 [1,2]. In China, the number of women seeking fertility treatment at the advanced reproductive age is constantly increasing with the implementation of the two-child policy. The advanced women often have poor reproductive outcomes, but there is still no effective treatment. Therefore, how to improve in vitro fertilization (IVF) outcomes in infertile women with advanced reproductive age remains a significant challenge in assisted reproductive techniques.

Dehydroepiandrosterone (DHEA) is an endogenous steroid from adrenal cortex and ovarian theca cells [3] and an essential pro-hormone in ovarian follicular steroidogenesis [4]. Evidence showed that DHEA levels decreased with age [5]. So DHEA supplementation may "rejuvenate" the aged ovarian environments as women grow older to improve pregnancy outcomes. In the last few years, a number of studies have suggested that DHEA treatment may be effective in infertile women with poor ovarian response [6–14]. Because DHEA may enhance the follicular microenvironment to improve follicular development and oocyte quality and diminish aneuploid embryo rates [15,16] and miscarriage rates [1,17,18] to improve IVF outcome, it is now widely used in poor responders. Recently, a world-wide survey showed that approximately one third of IVF clinicians in 45 countries added DHEA as an adjuvant to IVF treatment protocols in women with poor ovarian response [19]. In addition, the beneficial effects of DHEA supplementation might be even greater in patients with normal ovarian reserve undergoing IVF treatment [1,20]. However, the clinical evidence for DHEA on improvement of IVF parameters and pregnancy outcomes in women with advanced reproductive age and normal ovarian reserve is very limited. Therefore, we decided to retrospectively review the data from our centre to observe the impact of DHEA supplementation on IVF outcome for infertile women older than 37 years.

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Materials and methods

Study design

This was a retrospective cohort study. We have retrospectively reviewed the data of all patients over 37 years, who were treated at Yantai Yuhuangding Hospital between January 2012 and July 2014. The study conformed to the "Declaration of Helsinki for Medical Research involving Human Subjects". Also, approval was obtained from the Ethical Committee of the Yantai Yuhuangding Hospital. Each of the patients has given written authorization at the time of treatment for the future use of their clinical data.

Study participants

After we reviewed the data of all patients, a total of 486 patients undergoing IVF/ICSI treatment were enrolled. Each patient was included with only one treatment cycle. At that time, all patients were thoroughly informed about the novelty and unknown efficacy of DHEA in improving IVF parameters and pregnancy outcomes. The patients have received DHEA supplementation according to their own choice. 243 patients (study group) received 75 mg of DHEA daily (25 mg three times daily) for 3 months before the IVF cycle. Another 243 patients (control group) only received IVF treatment, but did not receive any pre-treatment.

Inclusion criteria were as follows: age older than 37 years, BMI 19–30 kg/m^2, basal FSH <10 IU/L, regular menstrual cycles of 25–35 days, normal uterine cavity as assessed through hysterosalpingogram or hysteroscopy, normal thyroid stimulating hormone (TSH) level. Exclusion criteria as the following: primary ovarian failure, previous poor response, history of severe ovarian hyperstimulation syndrome (OHSS), polycystic ovarian syndrome (PCOS), hydrosalpinx if it has not been surgically removed or ligated, any contraindication to pregnancy, thyroid or adrenal dysfunction, neoplasia, severe impairment of renal or hepatic function, and use of medications that might interfere with study evaluations (e.g. hormonal medication, prostaglandin inhibitors, psychotropic agents).

Protocol for COH

All patients of both groups underwent a standard down-regulation long protocol with GnRH analogue hormone (triptroline 0.03 mg/day, Ipsen, France). Ovarian suppression was assessed by the hormonal profiles (E_2 and LH) and the ultrasound (US) scan of the ovaries. When suppression was confirmed (E_2 <30 pg/mL, LH <3 IU/L, endometrial thickness ≤5 mm and no follicles of mean diameter ≥10 mm), all patients received a starting dose 300 IU urinary FSH (Fostimon, IBSA, Switzerland). After 5 days, the dose of FSH was adjusted dependent on the individual response of each patient. If there were follicles ≥14 mm in diameter after administered 7 days FSH, all patients in both groups were administrated recombinant LH (lutrophin alpha, Serono, Italy), 75 IU/day, subcutaneously until the end of ovarian stimulation. Daily gonadotropin and triptroline were continued until the day of human chorionic gonadotropin (hCG) injection. Recombinant hCG (250 mg; Ovidrel, Serono, Italy) was given to trigger ovulation when two leading follicles reached a mean diameter of 18 mm. Oocytes were retrieved transvaginally 34–36 h after hCG administration. IVF or ICSI was performed as appropriate, with taking semen quality into account. Fewer than three embryos were transferred on the third day after oocyte retrieval, and excess viable embryos were cryopreserved for subsequent frozen embryo transfer (FET) cycles. The obtained embryos were graded according to published criteria [20]. The embryos of grade 1 or 2 were considered of high quality. All transfer procedures were performed by the same physician to avoid inter-operator variability. The embryologist was blinded to the medication assignment. The luteal phase was supported with 200 mg progesterone (Utrogest^{TM} 200, Besins-Iscovesco, France) vaginal medication three times daily from the day of oocyte retrieval. A quantitative pregnancy test (serumβ-hCG based) was taken on the 14th day after embryo transfer. In case of pregnancy, a transvaginal ultrasound was performed after 4 weeks from the embryo transfer and repeated as required. Clinical pregnancy was confirmed if the fetal heartbeat was observed by transvaginal ultrasound.

Study end-points

The clinical pregnancy rate was considered as the primary outcome for this study, with the live birth rate, implantation rate and miscarriage rate assumed as correlated parameters of the primary outcomes. Secondary outcomes were standard IVF parameters, such as duration of ovarian stimulation, mean cumulative gonadotrophin dose, mean E_2 levels on hCG-day, endometrial thickness, number of retrieved oocytes, metaphase II oocytes rate, two-pronuclear (2PN) zygotes rate, high quality embryos rate and total testosterone levels before and after DHEA supplementation.

Statistical analysis

The data were analyzed by use of the SPSS-12.0 software. The data were presented as mean ± SD or percentages. Differences between groups of continuous variables were analyzed with *T*-test and the chi-square test was used to assess differences in proportions. $P < 0.05$ was considered to be statistically significant.

Results

486 ART cycles were analyzed in the present investigation. DHEA group and control group consisted of 243 patients respectively. The study patients took DHEA for an average of 90 days before entry into their IVF cycles. In this study, the medication was well tolerated by all patients. No patient dropped out of treatment because of side effects attributed to DHEA use. The patient characteristics and basal ovarian reserve assessment were similar between both the groups. No significant differences were observed between the two groups in terms of age, number of failed cycles, body mass index (BMI), duration of infertility, basal FSH, antral follicle count (AFC) and causes of infertility (Table 1).

In women, DHEA mostly converts to testosterone. Therefore, we assessed the total testosterone levels before and after

Table 1
Patient characteristics in the DHEA and control groups.

Parameter	DHEA group	Control group	*P* value
Number of cycles	243	243	
Age (years)	39.05 ± 1.59	38.86 ± 1.66	0.21
Number of failed cycles	0.69 ± 0.90	0.61 ± 0.99	0.34
Body mass index (kg/m^2)	24.30 ± 2.99	24.16 ± 3.05	0.64
Duration of infertility (years)	7.76 ± 4.95	7.37 ± 4.85	0.39
Basal FSH (IU/L)	6.91 ± 1.83	6.98 ± 1.69	0.66
Antral follicle count (AFC)	10.60 ± 4.16	10.10 ± 4.46	0.19
Cause of sterility			
Tubal factor	51.90%	53.50%	0.79
Male factor	4.50%	4.10%	1.00
Mixed	35.00%	31.70%	0.50
Endometriosis	4.50%	5.40%	0.84
Unexplained	4.10%	5.30%	0.53

Note: Values are expressed as mean ± SD or percentages.