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Is dehydroepiandrosterone more efficient in diminished ovarian reserve patients with higher FSH levels?

Hikmet Hassa[1], Yunus Aydin[1*], Tufan Oge[2], Vehbi Yavuz Tokgoz[2]

[1]*Eskisehir Osmangazi University Medical Faculty, Obstetrics and Gynecology Department, Reproductive Medicine Unit, Eskisehir, Turkey*

[2]*Eskisehir Osmangazi University Medical Faculty, Obstetrics and Gynecology Department, Eskisehir, Turkey*

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ABSTRACT

Objective: To investigate the effects of dehydroepiandrosterone (DHEA) on FSH and estradiol levels, as markers of ovarian reserve. **Methods:** A total of 32 DOR and/or POF patients received DHEA. We measured hormone profiles of FSH, LH, estradiol, before and after the DHEA treatment. Patients with pre-treatment FSH levels between 15-29 mIU/mL were classified as group 1, patients with FSH levels between 30-49 mIU/mL were defined as group 2, and patients with FSH levels above 50 mIU/mL were categorized as group 3. **Results:** The mean FSH values decreased when the pooled patients' results were analyzed (58.5±6.3 *vs*. 31.5±4.9, $P<0.01$), but this reduction was most impressive in group 3 patients, who exhibited pre-treatment FSH values above 50 μIU/mL (93.4±10.7 *vs*. 38.9±7.7, $P<0.01$). **Conclusions:** In all patients who used DHEA, FSH levels decreased; however, the decrease was more impressive when patients´ FSH levels were initially >50 μIU/mL. Further studies are necessary to provide possible explanations of optimized treatment responses when patients have higher FSH levels.

1. Introduction

Ovarian reserve, a widely used and poorly understood term, is sometimes used incorrectly. It represents the follicle pool that women have from the time of embryonic life. In practice, the functional loss of ovarian reserve starts from menarche. In addition to a genetically determined low ovarian reserve, increasing age is also a contributing factor in the diminished functional ovarian reserve, resulting in a decreased chance of spontaneous pregnancy and a decreased response to infertility treatments[1] .

POF (premature ovarian failure) is a clinical entity that describes a low functional ovarian reserve, characterized by high gonadotropin and low estrogen concentrations, as well as amenorrhea before the age of 40. Although the prevalence of POF in the general population is 1%, it is 10%-28% in patients diagnosed with primary amenorrhea and 4%-18% in patients with secondary amenorrhea [2]. The main feature distinguishing POF from menopause is that ovarian function can come back intermittently with POF, and a slight chance of pregnancy remains. As much as 10% of POF patients may become pregnant. Similarly, diminished ovarian reserve (DOR) patients are characterized by high gonadotropin concentrations and decreased AMH and antral follicle counts, and they also have a decreased chance of pregnancy, as observed in POF cases[3] . Dehydroepiandrosterone (DHEA) indirectly affects peripheral target organs by its conversion to estrogen and androgen or its conversion to neurosteroids in the brain. Externally applied DHEA may cause ovarian cysts and follicular atresia in a developmental polycystic ovary-like rodent model. It was first shown by Casson *et al*. that DHEA supplementation may increase the response to ovarian stimulation [4]. In another promising study, Barad *et al*. reported that, with DHEA supplementation, the DOR patients primarily show increased oocyte and embryo numbers[5]. Subsequently in another case control study, it was found that patients who received DHEA supplementation demonstrated shorter pregnancy durations and higher pregnancy rates [6].

It was largely believed that DHEA supplementation

*Corresponding author: Yunus Aydin, Eskisehir Osmangazi University Medical Faculty, Obstetrics and Gynecology Department, Eskisehir, Turkey Eskisehir Osmangazi Universitesi-Kadin Hastaliklari ve Dogum ABD, 26000, Eskisehir, Turkey.
Tel: +90 222 2292002
Fax: +90 222 2393772
E-mail: aydin. yunus@yahoo.com

increases the ovarian response to gonadotropins through a synergistic effect. Although the mechanism is currently poorly understood, DHEA may increase the response by improving the ovarian reserve [7].

In this study, we aimed to investigate the effects of DHEA on FSH and estradiol levels, as they are the typical markers of ovarian reserve. In addition, we also aimed to determine whether there is any relationship between the impact of DHEA and differing FSH levels.

2. Materials and methods

A prospective observational study was conducted between March 2010 and April 2011. Fifty DOR and/or POF patients were referred to our reproductive endocrinology department. The diagnosis of POF was confirmed in 15 patients who exhibited the classical triad of symptoms: <40 years old age, ≥4 month's amenorrhea and two FSH measurements >40 mIU/mL[8]. The diagnosis of DOR was confirmed in 35 patients, defined as basal FSH measurements >12 mIU/mL and a basal antral follicle count ≤4[2]. Five patients were excluded from the study by pretreatment evaluations because of their increased liver function test results, which is a contraindication for DHEA treatment. Thirteen patients refused participation, as they preferred Assisted Reproduction Technique (ART) treatment, which was discussed with all patients in relation to its low chance of success.

The patients were systematically evaluated based on their complaints. The age of first menstruation and menstruation patterns were assessed. They were also examined according to their fertility desire. Blood FSH, LH, estradiol, prolactin and TSH levels were obtained. The patients were categorized according to their FSH levels: patients with pre-treatment FSH level of 15-29 mIU/mL were defined as group 1, patients with FSH levels between 30-49 mIU/mL were classified as group 2, and patients with FSH levels ≥50 mIU/mL were categorized as group 3.

Oral DHEA 75 mg/day was provided to all patients in three divided doses. The chance of spontaneous pregnancy was explained to patients, and based on the patients' complaints and laboratory values, the DHEA treatment was continued after 2 months of usage, if appropriate.

At the end of the study, we checked the laboratory values of FSH, LH, and estradiol. We evaluated the decrease of FSH in patients, according to the previously defined groups. Paired sample *t*-tests were used to test for statistical significance. All statistical analyses were carried out using the SPSS 15 software (Chicago, IL). Probability values of <0.05 were considered to be statistically significant.

3. Results

The mean age of patients was (31.0±1.3) years. The mean age of menarche was (13.3±0.3) years, the mean body mass index (BMI) was (24.9±1.7) kg/m^2 and the mean DHEA usage period was (4.0±0.4) months. According to the patients' complaints, infertility and menstrual irregularity (such as oligomenorrhea) were diagnosed most frequently. When we evaluated patients' menstrual cycles, we diagnosed oligomenorrhea in 22 patients (68%). Fifteen patients (46%) who started the treatment had infertility complaints. Additionally, 7 patients (22%) were amenorrheic. In our study, the mean FSH value was 58.5 μIU/mL before DHEA treatment. The TSH and prolactin values of patients were within normal limits. After the DHEA treatment, the mean FSH value decreased to 31.5 μIU/mL, and the mean value of LH decreased from 26.3 μIU/mL to 16.7 μIU/mL. In contrast, the mean estradiol value increased from 41.2 μIU/mL to 52.2 μIU/mL following treatment. When we compared the mean values of FSH before and after treatment, a statistically significant decrease in FSH values from 58.5 μIU/mL to 3.5 μIU/mL was observed (P<0.01). The FSH values decreased to below 15 μIU/mL in 8 patients (25%) (Table 1). According to the three previously defined FSH groups, these patients showed different responses to DHEA treatment. Although the mean FSH value decreased when the entire sample's results were analyzed (58.5±6.3 *vs*. 31.5±4.9, P<0.01), this reduction was most pronounced in the group 3 patients who had pre-treatment FSH values above 50 μIU/mL (93.4±10.7 *vs*. 38.9±7.7, P<0.01) (Table 1). Furthermore, 3 of the patients (11%) from group 3 became spontaneously pregnant following DHEA treatment. In our study, the mean FSH value of the three pregnant women before 4 months of treatment with DHEA was >50 μIU/mL.

Table 1
Changes in FSH in the entire sample and in FSH subgroups(μIU/mL).

FSH values	Mean FSH value		*P*
	before treatment	after treatment	
All patients	58.5±6.3	31.5±4.9	<0.01
Group 1	20.2±1.9	16.4±6.5	>0.05
Group 2	39.8±1.8	32.7±9.1	>0.05
Group 3	93.4±10.7	38.9±7.7	<0.01

Paired sample *t*-test was used, Data were expressed as mean±SEM.
SEM, Standard error of mean.

4. Discussion

DOR and POF are two of the most common problems among infertile couples. In those patients, infertility treatments, including ART, have mostly failed due to a low follicular number and the subsequent cancellation of their cycles. The field continues to search for alternatives to offering oocyte donations, which have become a routine approach for these types of couples after unsuccessful treatment trials.

Casson *et al*. first showed that DHEA supplementation may improve the ovarian response in controlled ovarian hyperstimulation cycles[4]. This was the first report that demonstrated the improvement of oocyte yield with DHEA treatment. Subsequently, Barad and Gleicher reported that DHEA pre-treatment with IVF cycles may result in a significant increase in fertilized oocytes, day-3 embryos, transferred embryos and average embryo scores per oocyte[5]. In a subsequent case-controlled study, 89 DOR patients with 4 months of DHEA pre-treatment before IVF exhibited significantly higher cumulative clinical pregnancy rates, as

compared to a control group (28.1% *vs*. 11.9%; 95% CI 1.2–11.8; $P<0.05$)[6].

Physiological DHEA levels generally decrease with aging, as well as in cases of diminished ovarian reserves [9]. DHEA is usually a source for steroidogenesis [10]. Consequently, DHEA is a prehormone for 48% of the follicular fluid testosterone, which is a precursor of estradiol in the follicular development process[11]. At the same time, DHEA contributes to the maturation and selection of follicles with FSH by binding to the androgen receptors [12]. It is obvious that androgens stimulate the follicular differentiation with FSH [13]. Furthermore, androgens have led to the increase of follicular selection and insulin-like growth factor-1 (IGF-1) levels [14]. It was confirmed that DHEA improves the response to ovulation induction through the IGF-1 pathway[15].

It is speculative to suggest that DHEA may increase the ovarian reserve or whether it only acts on the intraovarian androgen milieu to subsequently increase the response to gonadotropins. Our study was not designed to show an improvement in the response to ovarian stimulation with DHEA treatment, if it is present. We aimed to determine whether FSH levels are altered with DHEA supplementation. According to our results, we demonstrated a significant decrease in FSH levels with 4 months of DHEA supplementation (58.5 ±6.3 *vs*. 31.5±4.9, $P<0.01$). In a subgroup analysis, we also observed that the DHEA response was more pronounced in patients with higher pre-treatment FSH levels. It is unclear whether DHEA supplementation increased the ovarian reserve or whether it only affected the intraovarian androgen environment. However, we observed a direct decline in the FSH values, as well as 3 (11%) spontaneous pregnancies. In a related study, Gleicher *et al*. demonstrated that AMH concentrations significantly improved after the DHEA supplementation in 120 DOR patients ($P=0.002$) [16]. In our clinic, we do not use AMH routinely; as a result, we did not check AMH levels for the evaluation of the ovarian reserve.

In summary, we used DHEA treatment, similar to recent studies, in patients who had DOF and/or POF. We determined that the DHEA treatment significantly resulted in the improvement of ovarian function. According to these results, the most important consequence of our study was the improved treatment response observed in patients with higher basal FSH levels. In all patients who used DHEA, FSH levels decreased; however, this reduction was greater when patients showed pre-treatment FSH levels of ≥50 μIU/mL. Furthermore, this group included spontaneous pregnancies. However, we did not obtain outcome data about the precise dosage and duration of DHEA treatment. The statistical power in our study may not be sufficient, given the small population. However, we believe that further studies are necessary to provide possible explanations for these improved treatment responses when patients have higher pre-treatment FSH levels.

Declare of interest statement

As a corresponding author I state that all of the authors report no conflicts of interest.

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