European Review for Medical and Pharmacological Sciences 2020; 24: 9104-9111

Dehydroepiandrosterone supplementation improves ovarian reserve and pregnancy rates in poor responders

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Abstract. – OBJECTIVE: We investigated whether DHEA supplementation had an impact on ovarian reserve parameters and pregnancy rates in patients with poor ovarian response (POR) and primary ovarian insufficiency (POI).

PATIENTS AND METHODS: A total of 34 people, 6 patients with POI and 28 patients with POR, were included in the study. The patients in the POR group consisted of two different groups: diminished ovarian reserve (DOR) and premature ovarian failure (PMOF). Patients in the POI and POR group were given 50 mg DHEA supplementation daily for 5 months. The primary outcome was to determine spontaneous clinical pregnancy rates. The monthly changes in the serum hormone levels and AFC were recorded for five months. AMH levels were also measured before and after treatment.

RESULTS: The total follow-up time was 152 cycles. The number of pregnancies during the follow-up period was 9. The ratio of pregnancies to the number of patients was 26.5% and the rate per cycle was 5.9%. While 8 of 9 pregnancies resulted in a live birth, one resulted in a miscarriage. The rate of abortion was 11.1%. The mean AFC was 0 to 5 before treatment. Following DHEA administration, a significant increase was detected in 30.8% of the patients. There was an increase in AMH levels after DHEA, but this was not significant. The live birth rate and pregnancy rate per cycle were significantly higher in POR patients than those in POF. Patients with POF had no pregnancy. Although the PMOF patients were younger than the DOR patients, the rate of pregnancy (36% vs. 29%), and pregnancy rates per cycle (8.5% vs. 6.35%) were higher in the DOR group. The rates of live birth were the same in the PMOF and DOR groups (29% vs. 29%).

CONCLUSIONS: Oral DHEA supplementation improves both ovarian reserve and pregnancy rates in women with POR.

Key Words:
DHEA, POR, POI, Ovarian reserve, Pregnancy rates.

Introduction

A trend for postponement of pregnancy due to marriage at an older age has increased the ratios of infertile couples in society. The decrease in ovarian reserve with advancing age has led to new approaches in the treatment of infertile patients. The main causes of premature ovarian aging and diminished ovarian reserves are; endometriosis, genetics, stress, obesity, past mumps infection, chemotherapy, radiotherapy, smoking, alcohol use, pesticides, chemical toxins, autoimmune diseases, idiopathic, ovarian induction agents, systemic diseases, long-term analog or antagonist use and diabetes mellitus. Many treatment modalities have been attempted to improve the reduced ovarian reserve. Dehydroepiandrosterone (DHEA) has been used in approximately 25% of *in vitro* fertilization (IVF) centers for the treatment of infertile patients with poor ovarian response (POR)[1].

DHEA is naturally found in the Jerusalem artichoke, and in the human body is secreted by the adrenal gland (zona reticularis) and from the theca interna cells of the ovaries. DHEA has a role as precursor hormone in the synthesis of estradiol and testosterone[2]. It has a weak androgenic effect. After peaking between the ages of 20 and 30, DHEA levels decrease by about 2% each year down to 10-20% of the peak at around the age of 80 years[3]. The purpose of DHEA supplementation is to replace DHEA in patients with reduced ovarian reserves. The substitution of DHEA may correct the substrate pool of steroidogenesis. Androgens have been shown to increase steroidogenesis and insulin-like growth factor 1 (IGF-1) in primate ovaries[4,5]. IGF-1 levels in preantral and early antral follicles have been reported to be elevated in DHEA-treated mouse ovaries[6]. Casson et al[7] reported that DHEA supplementation was useful in intrauterine insemination (IUI) treatment

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in patients with poor response to ovarian stimulation. This benefit of DHEA is attributed to an increase in serum-free IGF-I concentration, which in turn increases the gonadotropin response in the target organ[7]. In 2005, it was shown that oocyte production was increased, and 9 healthy embryos were obtained after DHEA supplementation in a 43-year-old IVF patient with DOR[8]. However, several studies have reported conflicting results of DHEA supplementation on ovarian reserve markers and pregnancy outcomes in infertile patients with diminished ovarian reserve (DOR) or premature ovarian failure (PMOF)[9-15]. The aim of this study was to investigate the effect of DHEA supplementation on ovarian reserve parameters and pregnancy rates in infertile patients with POR or primary ovarian insufficiency (POI).

Patients and Methods

A total of 34 women, 6 patients with POI and 28 patients with POR, were included in the study. The patients in the POR group consisted of two different patient groups: diminished ovarian reserve (DOR) and premature ovarian failure (PMOF). Patients who met at least two of the Bologna criteria were accepted as poor ovarian reserve[16-18]. These criteria were: (1) advanced maternal age (≥40 years) or other risk factors for poor ovarian reserves; (2) history of previous POR (≤3 oocytes with conventional over stimulation protocols); and (3) an abnormal ovarian reserve test [i.e., an antral follicular count: AFC, < 5-7 follicles or < 0.5-1.1 ng/ml of Anti-Mullerian Hormone (AMH)]. Serum AMH levels were analyzed by using AMH Gen II ELISA kit (Beckman-Coulter, Inc., Brea, CA USA). Values are expressed in ng/mL. Primary ovarian insufficiency (POI, primary ovarian failure, POF) was defined as a 4-month period of amenorrhea, serum FSH levels > 40 IU/L at one-month intervals, and a decrease in sex steroids in women younger than 40 years. Patients in the POI and POR group were given 50 mg DHEA (Interpharm, Konya, Turkey) supplementation daily for 5 months. This time interval was chosen because of early follicular growth induced by DHEA occurs within et least 2 months of treatment. The primary outcome was to determine spontaneous clinical pregnancy rates. Pregnancy was evaluated in all patients with serum β-HCG levels after menstruation delay. Patients with a positive β-HCG result underwent TV-USG at 6 weeks after the last menstruation. Clinical pregnancy was considered with the presence of a fetal heartbeat. Serum Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), and Estradiol (E_2) levels were measured at baseline and monthly during 5 months after DHEA supplementation. Fasting blood samples of the patients were collected with venipuncture. All samples were centrifuged at 1500 g for 10 min, at 4°C. Serum FSH, LH, E2 and progesterone levels were evaluated with the electrochemiluminescence method (ADVIA Centaur XP, Siemens Diagnostics, Los Angeles, CA, USA). The AFC (2-10 mm follicles) as determined by transvaginal ultrasonography (General Electric RTX 200, Boston, MA, USA).

Patients were excluded if they had a history of a malignant or borderline ovarian tumor, metabolic disease, a chromosomal disease in either of the partners, male factor infertility, or hysterosalpingography revealing defective female genitalia. Genetic disorders such as Turner syndrome, patients using alkylating agents or radiotherapy, patients who underwent ovarian surgery, patients with hyper or hypothyroidism, patients with type I diabetes, those with Cushing disease or Addison disease, excessively obese cases and extremely weak cases were also not included in the study. The study was approved by the Ethics Committee of Mustafa Kemal University School of Medicine (Protocol No: 2017/157-27.10.2017-183). Informed consent was obtained from all the patients.

Statistical Analysis

Statistical analyses were performed with the SPSS 20.0 software (IBM Armonk, NY, USA). Data were shown as mean ± standard deviation (SD) values or percentage. The effect of DHEA on ovarian reserve parameters was evaluated. Percentages of serum hormone levels before and after treatment were compared using the Paired *t*-test. Percentages of AFC in the groups were compared using the Chi-square test. The pregnancy outcome was compared according to age, infertility status and the type of ovarian pathology. A $p < 0.05$ was considered as statistically significant.

Results

The demographic and follow-up characteristic of 34 participants during DHEA supplementation is summarized in Table I and Figure 1. The mean age of the patients was 35.8 ± 7.6 years. 24 out of the 34 patients were primary infertile. The remaining ten patients were secondary infertile.

Table I. General characteristics and pregnancy outcomes of patients with POR and POF given DHEA supplementation.

Age (year, mean± SD)		**35,8 ± 7.6**
Infertility status	Primary infertility (n, %)	24 (70.5%)
	Secondary infertility (n, %)	10 (29.5%)
Type of ovarian dysfunction	POF (n, %)	6 (17.6%)
	PMOF (n, %)	14 (41.1%)
	DOR (n, %)	14 (41.1%)
Total follow up period (cycles, n)		152
Total number of pregnancies achieved and percent based on number of patients (n, %)		9 (26.4%)
Total number of pregnancies achieved and percent based on number of cycles (n, %)		9 (5.9%)
Total number of pregnancies delivered in term (n, %)		8 (23.5%)
Total number of abortions (n, %)		1 (11.11%)

POF: Primary Ovarian Failure; **PMOF:** Premature Ovarian Failure; **DOR:** Diminished Ovarian Reserve; **SD:** Standard Deviation; **N:** Patient number.

The total follow-up time of patients was 152 cycles. The total number of pregnancies during the follow-up period was 9. Ovulation was detected in 16 of 28 patients with poor ovarian response (57%). The ratio of pregnancies to the number of patients was 26.5% and the rate per cycle was 5.9%. While 8 of 9 pregnancies resulted in a live birth one resulted in a miscarriage. The rate of abortion was 11.1% per pregnancy.

The monthly changes in the serum hormone levels and AFC in patients with POR or POF were shown in Table II. At the end of 5th month, a significant decrease in the levels of FSH and LH (32.4 ± 24.7 mIU/ml to 14.7 ± 6.6 mIU/ml, p<.004 and 13.7 ± 11.1 mIU/ml to 7.7±7.6 mIU/ml, p<.001) were detected. On the other hand, an insignificant increase was detected in E_2 levels (34.6 ± 13.4 pg/ml to 42.9 ± 23.4 pg/ml, p<.093). There was an increase in AMH levels after DHEA, but this was not significant (0.89±1.2 *vs.* 1.01± 1.6 ng/mL). The number of mean AFCs ranged from 1 to 5. Following DHEA administration, a significant increase was detected in 30.8% of the patients. The pregnancy rate (PR), live pregnancy rate (LPR), live birth rate (LBR), and pregnancy rate per cycle (PRPC) were significantly higher in POR patients than those in POF (Table III). The pregnancy rate per cycle was highest in patients younger than 35 years (7.4% for 35-39 years, 6.7% for 40-44 years, and smaller than 6.7% for over 45 years (Figure 2). The PR per patient, LBR, and PRPC were significantly higher in patients with secondary infertility (SI) than in primary infertility (PI) group (Table IV, Figure 3). Patients with POF had no pregnancy although they were younger. Although the PMOF patients were younger than the DOR patients, the rate of pregnancy (36% *vs.* 29 %), and pregnancy rates per cycle (8.5% *vs.* 6.35%) were higher in the DOR. The rates of live birth were the same in the PMOF and DOR groups (29% *vs.* 29%).

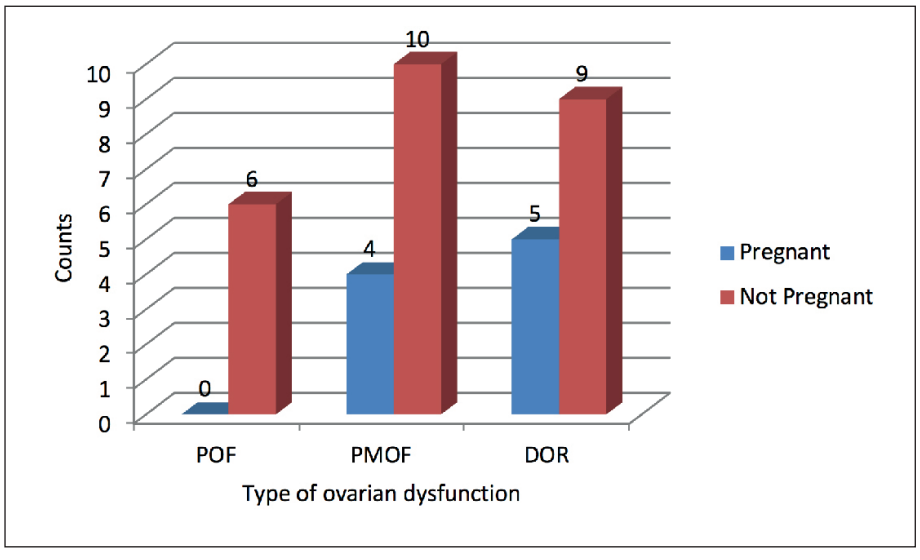

Figure 1. Distribution of pregnancies group based upon type of ovarian dysfunction in patients with poor ovarian response or POF given DHEA supplementation.

Table II. Monthly changes in ovarian reserve test and counts of achieved pregnancy in patients with poor ovarian response and POF given DHEA supplementation.

DHEA	FSH (mIU/ml)	LH (mIU/ml)	E2 (pg/ml)	TvUSG 0-5 AFC		6-10 AFC		Achieved pregnancy counts per month	Total pregnancy counts
				n	%	n	%		
Before	32.4±24.7	13.6±11.1	34.6±13.4	34	100	0	0	0	0
1 month after	14.1±10.2	6.7±6.9	58.9±45.0	25	73.5	9	26.5	3	3
2 month after	21.9±14.6	9.9±7.2	46.8±30.2	25	83.3	5	16.7	1	4
3 month after	12.1±7.4	5.9±4.5	48.3±41.6	23	82.1	5	17.9	1	5
4 month after	19.8±16.2	9.7±5.7	54.7±51.4	19	76.0	6	24.0	1	6
5 month after	14.7±6.6	7.7±7.6	42.9±23.4	18	69.2	8	30.8	3	9

FSH: Follicle Stimulating Hormone; **LH:** Luteinizing Hormone; **E2:** Estradiol; **TvUSG:** Transvaginal Ultrasonography; **AFC:** Antral Follicle Counts.

Table III. Pregnancy rates and pregnancy outcomes based upon infertility status in infertility patients with poor ovarian response and POF given DHEA supplementation.

	Infertility Status		*p*
	Primary infertility n: 24	Secondary infertility n: 10	
Age (years, mean±SD)	35.0±8.2	37.8±5.9	0.352
Clinical pregnancy rate (n/N; %)	3/24; 12.5%	6/10; 60%	0.004*
Live birth rate (n/N; %)	3/24; 12.5%	5/10; 50%	0.019*
Abortion rate (n/N; %)	0; 0%	1/10; 10%	0.772
Clinical pregnancy rate per cycles (n/N; %)	3/112; 2.7%	6/40; 15%	0.001*

*$p \leq 0{,}05$: Significant according to statistics, n: Case count, N: Total case count.

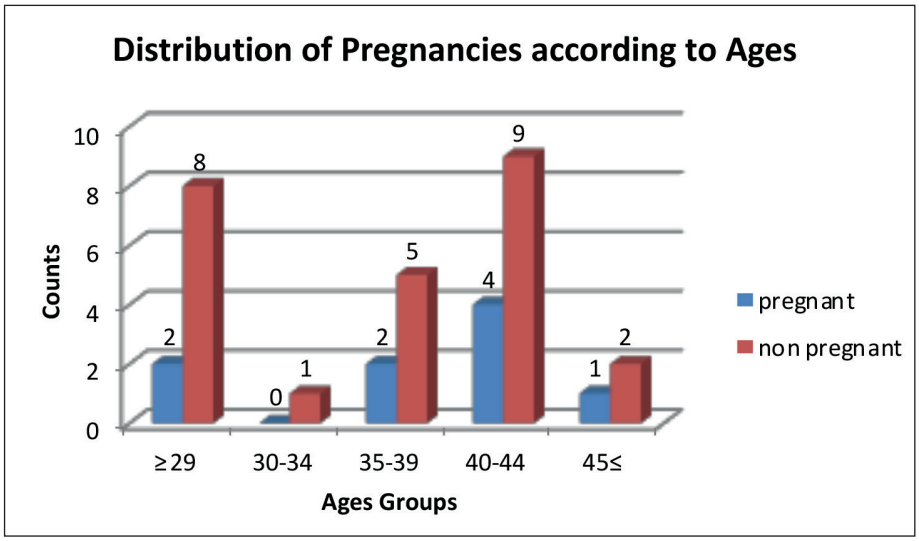

Figure 2. Distribution of pregnancies based upon patient's age groups in patients with poor ovarian response or POF given DHEA supplementation.

Table IV. Pregnancy rates and pregnancy outcomes based upon type of ovarian dysfunction in patients with POR and POF given DHEA supplementation.

	Patient number	Age (years, mean±SD)	Clinical pregnancy rate (n/N; %)	Live birth rate (n/N; %)	Abortion rate (n/N; %)	Clinical pregnancy rate per cycles (n/N; %)
POF	6	31.3±8.8	0/6; 0%	0/6; 0%	0; 0%	0/40; 0%
PMOF	14	31.1±5.4	4/14; 29%	4/14; 29%	0; 0%	4/63; 6.35%
DOR	14	42.5±2.6	5/14; 36%	4/14; 29%	1/5; 20%	5/59; 8.5%

POF: Primary Ovarian Failure; **PMOF**: Premature Ovarian Failure; **DOR**: Diminished ovarian reserve.

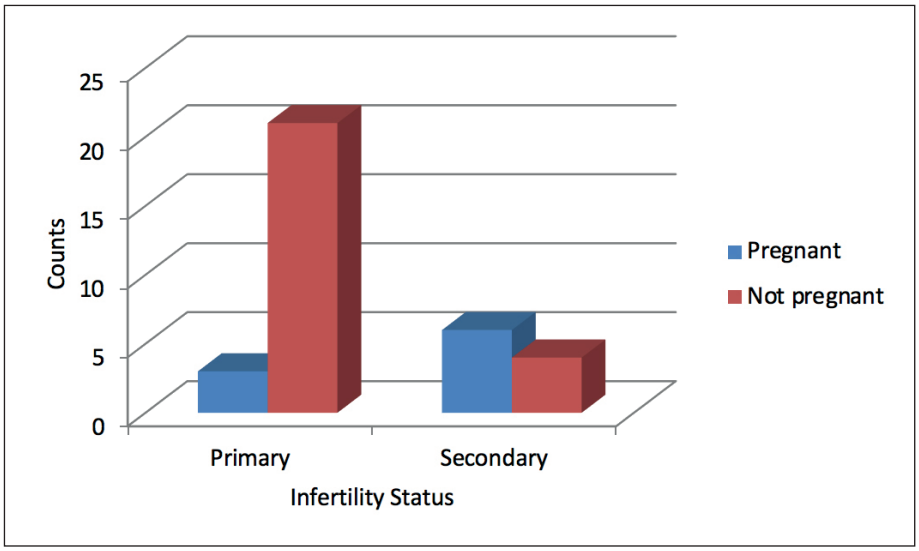

Figure 3. Distribution of pregnancies based upon infertility status in patients with poor ovarian response or POF given DHEA supplementation.

Discussion

In some infertile patients with DOR, androgen deficiency has been suggested to be the main underlying problem[19-21]. Androgen supplementation with testosterone or DHEA may stimulate early follicle development and improve functional ovarian reserve in this patients[22-24]. To obtain more mature oocytes at the time of oocyte collection, ovarian stimulation focuses on the last 2 weeks, characterized by the presence of antral follicles. Unlike conventional ovarian stimulation protocols, stimulation and synchronization of follicles in the earlier period of the maturation process will improve outcomes in patients with POR[25]. Recent animal studies have shown that androgens induce follicles in the preantral and antral stages through granulosa cells[22,23]. Furthermore, in the early stages of follicular maturation, androgens and FSH have been shown to exhibit synergistic effects on granulosa cells[22,23]. In the present study, we clearly demonstrated that DHEA supplementation markedly improved the ovarian-reserve markers in patients with POR. Pregnancy outcomes were better in patients with secondary infertility than in those with primary infertility. No pregnancy was achieved in the POF group. Patients with DOR have good pregnancy outcomes compared to POF group. High pregnancy rates were achieved in patients older than 35 years compared to those younger than 35 years. The present research has shown that DHEA supplementation in POR subjects at least 5 months increased the AFC in 30.8% of patients. Our results are incompatible with those of previous studies. Casson et al[7] reported that DHEA supplementation at a dose of 80 mg/day for 2to 5 months could improve ovarian response to gonadotropins by increasing IGF-1 activity in patients with POR. Likewise, Gleicher et al[9] reported that DHEA supplementation at a dose of 75 mg/day for

1-4 months in POR women increases serum AMH levels. Yilmaz et al[10] showed that serum levels of AMH, Inhibin B and AFC increased after supplementation with 25 mg/day DHEA for at least 6 weeks while the FSH and E2 levels decreased. On the contrary Yeung et al[11] reported that there was no positive effect of DHEA on ovarian reserve markers in patients with POR. Differences in these studies might be explained by possible clinical heterogeneity in respect of the low number of cases, variation in age, variation in patient's demographic features and variation in treatment duration[18,26]. The positive effect of DHEA supplementation on ovarian reserve markers in patients with poor ovarian response has been demonstrated. A recent meta-analysis showed that DHEA increases the AMH level and the AFC[27]. However, most of these studies consist of heterogeneous patient groups. In addition, DHEA application periods vary from 6 weeks to a year. In the present study, we did not find significant changes in AMH values before and after treatment. In line with our research, some reports show that DHEA has no effect on AMH levels. Only a few isolated studies have reported an increase in AMH levels after DHEA[10]. Narkwichean et al[28] experimentally on sheep reported that DHEA stimulated the development of primordial follicles, improved gonadotropin response, triggered granulosa cell proliferation, increased AMH production, and delayed ovarian aging. Likewise, Tsui et al[29] attributed the positive effect of DHEA supplementation on ovarian reserve to markedly altered gene expression in the ovaries. Celik et al[30] reported, for the first time, DHEA supplementation improves endometrial HOXA-10 mRNA expression in poor responders. It has been reported that DHEA supplementation reduces the rate of spontaneous abortion when compared to patients who did not receive DHEA. Gleicher et al[31] showed the mean rate of miscarriage as 15.1% after DHEA treatment. Other researchers have also shown that DHEA reduces abortion rates in patients with poor ovarian response[11,32]. In contrast, a meta-analysis in 2017 determined that DHEA supplementation did not improve miscarriage rates in patients with poor ovarian response[27]. In the current study, the miscarriage rate was at a reasonable level of 2.9% per patient and 11.1% per pregnancy.

Earlier studies have shown that DHEA supplementation increases clinical and cumulative pregnancy rates in patients with poor ovarian response. The clinical pregnancy rate in poor responders receiving DHEA supplementation was 28.1% in a study by Barad et al[12], and 23.5% in a study by Wiser et al[13]. The rate of clinical pregnancy rates in patients with poor ovarian response receiving DHEA supplementation was found to be 32% in a study by Kara et al[14], 2.1% by Vlahos et al[15], and 18.8% by Yeung et al[11]. In our study, there was no group of patients who did not receive DHEA supplementation, so it was not possible to evaluate the effect of DHEA on clinical pregnancy rate and live-birth rates. The clinical pregnancy rate in our patients cohort was 26.5% per patient and the live-birth rate was 23.5%.

After dividing the patients with a poor ovarian response or POF receiving DHEA supplementation into two groups, according to infertility status, the clinical pregnancy rate, live pregnancy rate and pregnancy rate per cycle were found to be higher in the secondary infertility group compared to the primary infertility group. None of the previous studies had compared the efficacy of DHEA supplementation in primary and secondary infertility groups. Better pregnancy outcomes in patients with secondary infertility may be due to less severe ovarian dysfunction, which is more difficult to treat in patients with primary infertility.

The ability of women to conceive is known to decrease with aging. This decrease starts around the age of 32 years and accelerates after 37 years[33,34]. No previous study could be found which had evaluating pregnancy outcomes by age in patients with POR who received DHEA supplementation. Nonetheless, Gleicher et al[9] showed that DHEA supplementation improved the ovarian reserve markers, especially in younger patients. Better pregnancy outcomes might be expected in younger patients with better improvement of ovarian reserves. However, similar results were not found in the present study.

Conclusions

The main limitation of this study was the lack of a control group that did not receive DHEA supplementation. It is another handicap to measure AMH levels only before and after treatment and not to test monthly and the inclusion of patients with POF who have a more severe ovarian impairment. Together, significant improvements in ovarian reserve markers were observed in patients with poor ovarian response receiving DHEA supplementation. Pregnancy outcomes were better in patients with secondary infertility. Likewise, patients with DOR, PMOF as well as patients over 35 years of age had good preg-

nancy outcome. No clinical pregnancy was observed in patients with POF. As a result, we recommend using DHEA for at least 5 months to improve clinical pregnancy rates in patients with poor responders undergoing spontaneous or ART cycles. Further prospective and randomized controlled trials with larger populations are needed to clarify the effects of DHEA supplementation on ovarian reserves and pregnancy outcomes in patients with diminished ovarian response and POI.

Disclosures

The authors declare that they have no conflict of interests to declare..

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