

Dehydroepiandrosterone supplementation in women undergoing assisted reproductive technology with poor ovarian response. A prospective case-control study

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Abstract

Objective: The effects of dehydroepiandrosterone (DHEA) supplementation in Saudi Arabian women with poor ovarian response (POR) is presently unknown. The present study aimed to assess the benefits of DHEA supplementation in women undergoing in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI).

Methods: This was a prospective case-control study involving 62 women who were diagnosed with POR and underwent IVF/ICSI between January 2012 and June 2016. The positive influence of DHEA in 34 women, compared with 28 women without supplementation, was defined as improvements in the number of oocytes retrieved, the fertilization rate, the number of grade I embryos generated and the pregnancy rate.

Results: Both groups were evenly matched for age, body mass index and laboratory test parameters. There were statistically significant differences between the groups with and without DHEA supplementation for oocyte yield (6.35 ± 2.41 versus 3.98 ± 3.2), Grade I embryos generated (55% versus 30%), positive pregnancy rate (21/34 versus 10/28), and live birth rate (18/34 versus 4/28).

Conclusion: DHEA supplementation in women with POR had a positive effect on hormonal profiles, the quality of the endometrium, the number of oocytes retrieved, the quality of embryos, and the pregnancy and live birth rates.

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Introduction

Poor ovarian response (POR) is common among women attending infertility clinics worldwide, including Saudi Arabia. The incidence of POR among Saudi Arabian women is unknown but the worldwide incidence is 9%–24%, which has increased further recently.¹ Many causes for POR have been proposed, but a genetic influence has now been suggested as a probable cause.^{2,3} Various protocols for ovarian stimulation with the additions of androgen modulating agents have been tried to increase ovarian response, with mixed results.^{4–6} One such agent is dehydroepiandrosterone (DHEA) which has shown some beneficial effects in the management of women with POR.^{7–9}

DHEA is secreted mainly by the adrenal cortex and is known to influence changes in cardiovascular tissues, female fertility and central nervous system functions.¹⁰ A recent meta-analysis of use of DHEA in POR showed improvement in the indices in women undergoing in vitro fertilization (IVF) that could succeed in a pregnancy and healthy outcome. Routine use of DHEA is not recommended by the US Food and Drug Administration as a treatment for women with POR. However, it is allowed to be sold as a dietary supplement¹² and is, therefore, easily available in Saudi Arabia. The use of DHEA in Saudi Arabia and its effects on women with POR has not been reported. This prospective case-control study was carried out with the aim of finding any positive effects in women with POR.

Materials and methods

After the approval of the Institutional Review Board of the Imam AbdulRahman Bin Faisal University, Dammam, this prospective case-control study was carried out at the King Fahd Hospital of the University and the Dr. Samir Abbas Infertility Center. Patients were counseled and written informed consent was obtained from all participants enrolled in the trial. Only Saudi Arabian women were included in the study, aged between 25 and 40 years. They were diagnosed with POR and had previously experienced failed IVF cycles. The study was conducted between January 2012 and June 2016. POR was defined according to the Bologna criteria,⁴ with at least two features to be present: low serum anti Müllerian hormone (AMH) levels and low antral follicular count (AFC) of <7 (diameter 2–10 mm), with or without high levels of follicle-stimulating hormone (FSH) > 15 IU/l. The AFC and endometrial thickness were assessed in all patients using transvaginal ultrasonography (TVU; GE Healthcare, Chicago, IL, USA), retrieval of oocytes and transfer of embryos. The embryos were cultured by a single embryologist at the Dr. Samir Abbas Infertility Center. All enrolled women underwent IVF or intracytoplasmic sperm injection (ICSI). The rationale for using DHEA was explained in detail to the women. The study group consisted of 34 women (Group I) who decided to take the DHEA supplement. The control group was 28 women (Group II) who did not take DHEA. Patients in Group I were instructed to take DHEA at 50 mg daily

(nonmicronized and phyto-derived; Natrol Inc., Chatsworth, CA, US) for 3 months prior to the trial. On the day of oocyte retrieval, DHEA was discontinued.

Patients had serum levels of FSH, estradiol (E2) and AMH measured, and vaginal ultrasonography for AFC on day 3 of the menstrual cycle. The positive influence of DHEA was defined as improvements in the number of oocytes retrieved, the fertilization rate, the number of embryos produced and the pregnancy rate.

Treatment protocol

After the initial assessment, the groups were separated into those with and without DHEA supplementation. A standard GnRH antagonist protocol for stimulation was used. Patients were started on day 2 or 3 of the cycle with recombinant FSH injections (Gonal F[®], Merck-Serono SA, Aubonne, Switzerland). On day 5 in the evening an antagonist (0.25 mg subcutaneously) was added. Patients were followed by serial TVU for folliculometry in addition to measuring serum estradiol (E2) levels. As soon as three follicles reached 17 mm in diameter, a triggering human chorionic gonadotropin (hCG) 10,000 iu injection (Merck & Co., Kenilworth, NJ, USA) was given and oocyte aspiration was performed after 36 h. Fertilization was assessed the day after IVF or ICSI and embryo quality was graded.¹³ On day 3, embryos were transferred. The luteal phase was supported by use of micronized progesterone at 400 mg/day at 12-h intervals. A positive pregnancy was confirmed by measuring ascending serum levels of β -hCG.

Clinical pregnancies were monitored by TVU and were considered positive when a fetal heart beat was noted. To avoid type I and II statistical errors in a randomized trial, a sample size between 36 and 63 is suggested to be adequate.¹³⁻¹⁴ Data were entered into

the database daily and finally analyzed and compared using IBM SPSS Statistics (v. 21.0; IBM Corp., Armonk, NY, USA). Student's *t*-tests were used; continuous measurements are presented as the mean \pm standard deviation and $P \leq 0.05$ was considered statistically significant.

Results

Sixty-two women participated in the study; 34 took DHEA supplements and the remaining 28 opted to try another cycle without supplementation. The age, body mass index (BMI), FSH and AMH levels, and AFC in both groups were similar without any statistically significant differences. (Table 1). Women who used DHEA showed promising improvements in most parameters compared with the untreated control group. The endometrial thickness, numbers of oocytes, E2 levels, and number of grade I embryos were all significantly different in the DHEA group ($P < 0.001$ to $P < 0.05$; Table 2). The only nonsignificant parameter was of grade II embryos and the numbers of embryos transferred. The overall successful pregnancy rate was 50% and the rate was higher in the DHEA group at 62% versus 34%. Table 3 shows patients in Group I (with DHEA) aged 30 years compared with those aged 31–40 years. Patients aged 20–30 years fared better than those aged 31–40 years.

Discussion

We found that DHEA supplementation had a positive impact on women with POR undergoing IVF/ICSI cycles. The benefits observed were in nearly all the parameters tested. Moreover, women who were younger had better results. Previous studies have shown improvements in E2 levels, AMH levels, and oocyte retrieval numbers.^{15–17} In contrast, Yeung et al.¹⁸ reported a meager

improvement after DHEA supplementation. In contrast, our results support the findings of Yilmaz et al.¹⁹ and Tsui et al.²⁰ Those authors found robust improvements in ovarian response and ovarian reserve markers with the use of DHEA supplementation.

Most studies on the effect of DHEA on women with POR put the cutoff age for

treatment as aged ≤ 40 years. In this study, we also studied women aged < 40 years but in a post hoc analysis we observed that the effect was more pronounced in women aged < 30 years when compared with those aged ≥ 31 years. Jirgi et al.⁹ did not find any significant difference between younger and older patients (≤ 40 years) in terms of oocyte yield and total numbers of embryos. Our results suggest that DHEA works better in younger patients with POR.

Since Casson et al.²¹ first observed that DHEA supplementation in women with POR led to an enhanced ovarian response, many studies have reported its beneficial effect.²²⁻²⁶ In contrast, a recent meta-analysis found no beneficial effect.²⁷ Our rationale for using DHEA is that it is a precursor of androgens; animal studies have confirmed that androgens are essential to normal follicle maturation and female fertility.²⁸ Tsui et al.¹⁷ suggested that the lack of benefit of DHEA could arise from bias caused by clinical heterogeneity, different populations and varied protocols and durations of treatment.^{26,29-30} To bypass this issue, we studied DHEA supplementation in a single

Table 1. Baseline comparisons between Group I (DHEA 50 mg daily) and Group II (without DHEA).

Variables	Group I	Group II
Number of patients	34	28
Age, years	34.7 \pm 4.37	33.9 \pm 5.1
BMI (kg/m ²)	21.7 \pm 1.4	22.2 \pm 1.1
FSH (IU/l)	11.25 \pm 2.62	10.96 \pm 1.3
AMH (ng/ml)	0.84 \pm 1.1	1.03 \pm 0.06
AFC	3.2 \pm 1.3	3.4 \pm 1.9
Failed cycles (no pregnancy)	2.9 \pm 0.85	2.22 \pm 0.7

AFC, antral follicle count; AMH, anti-Müllerian hormone; BMI, body mass index; FSH, follicle-stimulating hormone. No statistically significant difference was observed between groups for any parameter.

Table 2. Patient outcomes in Group I (DHEA 50 mg daily) and Group II (without DHEA).

Parameter	Group I (34)	Group II (28)	P
Endometrial thickness (mm)	10.7 \pm 2.4	8.76 \pm 1.9	<0.008
hCG Day	9.1 \pm 0.6	12.8 \pm 1.1	<0.001
E level on hCG day (pc/ml)	3196 \pm 547	1927 \pm 692	<0.001
Oocytes retrieved (n)	6.35 \pm 2.41	3.98 \pm 3.2	<0.002
Metaphase II oocytes (n)	4.9 \pm 1.8	3.16 \pm 2.5	<0.003
Grade I embryos (%)	55	30	<0.05
Grade II embryos (%)	29	28	NS
Embryos transferred (n)	2.7 \pm 0.4	2.4 \pm 0.3	NS
Positive pregnancy (n)	21	10	<0.05
Abortions (n)	1	3	<0.05
Ectopic pregnancies (n)	2	0	<0.07
Live birth (n)	18	4	<0.01
NVD	10	1	<0.001
Cesarean Section	8	2	NS

NVD, normal vaginal delivery.

Table 3. Comparison of patients in Group I (DHEA 50 mg daily) aged 20–30 or 31–40 years.

Parameter	20–30 (<i>n</i> = 14)	31–40 years (<i>n</i> = 20)	<i>P</i>
Endometrial thickness (mm)	11.7 ± 2.4	8.16 ± 1.1	<0.006
hCG day of cycle	9.2 ± 0.4	7.8 ± 0.51	<0.001
E2 level on hCG day (pc/ml)	4205 ± 647	3651 ± 552	<0.01
Oocytes retrieved (<i>n</i>)	7.41 ± 1.2	5.54 ± 2.2	<0.003
Metaphase II oocytes (<i>n</i>)	5.8 ± 1.2	3.96 ± 2.4	<0.005
Grade I Embryos (%)	66	42	<0.02
Grade II Embryos (%)	16	13	<0.1
Embryos transferred (<i>n</i>)	2.1 ± 0.8	1.9 ± 0.7	<0.2
Positive pregnancies (<i>n</i>)	14	7	<0.001
Abortions (<i>n</i>)	1	0	<0.1
Ectopic pregnancies(<i>n</i>)	2	0	<0.1
Live birth (<i>n</i>)	11	7	<0.06
NVD	8	2	<0.03
Cesarean section (<i>n</i>)	3	5	<0.2

NVD, normal vaginal delivery.

population group with a standard protocol; one IVF consultant and one embryologist completed the study, and our study indicates a positive influence of DHEA. Although there is much published data in support of the positive effects of DHEA in women with POR, only 25% of IVF practitioners use DHEA on a routine basis and some question whether DHEA treatment is justified in the absence of sound overall evidence.³¹

The limitation of our study is the small sample size because of the low number of patients attending our facility. The strengths of our study are that we could compare treatment with another group of women with POR from the same ethnic group who did not accept supplementation. Further, although a bias of any study could be the involvement of different physicians and embryologists—which could affect oocyte retrieval, embryo culture and transfer—this was not the case here.

In conclusion, we found that DHEA supplementation had a positive effect on hormonal profiles, the quality of endometrium, the number of oocytes retrieved, the

quality of the embryos, and ultimate pregnancy and live birth rates. Second, younger women (aged ≤30 years) who took the supplementation fared better than did those aged ≥31 years. Third, although studies involving multiple centers and patients from various backgrounds have been inconclusive, our study of a single homogeneous ethnic group showed benefits of DHEA supplementation in Saudi Arabian women with POR.

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Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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