

Addition of dehydroepiandrosterone (DHEA) for poor-responder patients before and during IVF treatment improves the pregnancy rate: A randomized prospective study

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BACKGROUND: The aim of this study was to evaluate the effect of dehydroepiandrosterone (DHEA) supplementation on *in vitro* fertilization (IVF) data and outcomes among poor-responder patients.

METHODS: A randomized, prospective, controlled study was conducted. All patients received the long-protocol IVF. Those in the study group received 75 mg of DHEA once a day before starting the next IVF cycle and during treatment.

RESULTS: Thirty-three women with significantly diminished ovarian reserves were enrolled, 17 in the DHEA group and 16 in the control group. The 33 patients underwent 51 IVF cycles. The DHEA group demonstrated a non-significant improvement in estradiol levels on day of hCG ($P = 0.09$) and improved embryo quality during treatment ($P = 0.04$) between first and second cycles. Patients in the DHEA group also had a significantly higher live birth rate compared with controls (23.1% versus 4.0%; $P = 0.05$), respectively. Six of seven deliveries were among patients with secondary infertility ($P = 0.006$).

CONCLUSION: Dehydroepiandrosterone supplementation can have a beneficial effect on ovarian reserves for poor-responder patients on IVF treatment.

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Key words: Dehydroepiandrosterone, DHEA / IVF outcome / long-protocol IVF / poor responder / recombinant LH

Introduction

Poor ovarian response presents a significant challenge in artificial reproductive treatment (ART). It is estimated that 5–18% of all *in vitro* fertilization (IVF) cycles are ended by poor ovarian response. However, there is currently no uniform definition of 'poor response' (Surrey and Schoolcraft, 2000). The criteria for defining poor response are based mainly on the total amount of FSH administered during ovulation induction; cycle cancellation due to poor response to ovarian stimulation when the gonadotrophin starting dose for induction of ovulation was at least 300 IU/day and/or the number of retrieved oocytes (Kailasam *et al.*, 2004; Frattarelli *et al.*, 2008). Despite the lack of a uniform definition, these patients have poor IVF outcome,

with successful pregnancy rates as low as 2–4% (Ulug *et al.*, 2003; Mohamed *et al.*, 2005; Schmidt *et al.*, 2005; Frattarelli *et al.*, 2008). The ideal stimulation regimen for poor responders is currently unknown. A number of randomized controlled trials (RCT) have compared different stimulation protocols; however, none has so far been demonstrated to be superior (Vollenhoven *et al.*, 2008). Casson *et al.* (2002) was the first to describe the beneficial effect of dehydroepiandrosterone (DHEA) supplementation on ovarian stimulation in poor-responder patients. Dehydroepiandrosterone is an endogenous steroid that originates from the zona reticularis of the adrenal cortex and from ovarian theca cells (Burger, 2002). Dehydroepiandrosterone is an essential prohormone in ovarian follicular steroidogenesis (Casson *et al.*, 2002). Barad and Gleicher (2005) reported

increased oocyte production after treatment with DHEA. A beneficial effect of DHEA on IVF outcome parameters (peak estradiol (E2) level, embryo numbers and quality) was reported among women with significantly diminished ovarian reserves (Barad and Gleicher, 2006). However, an RCT to evaluate the beneficial effects of DHEA supplementation on the outcomes of poor-responder patients during IVF treatment has not been performed. The aim of this study was to assess the potential benefit of DHEA supplementation for infertile, poor-responder patients in an ART program.

Materials and Methods

Study population

A poor response in a previous IVF cycle was defined as retrieval of fewer than five oocytes, poor-quality embryos, or cycle cancellation due to poor response to ovarian stimulation (Frattarelli *et al.*, 2008), whenever the gonadotrophin starting dose for induction of ovulation was at least 300 IU/day.

Patients with a prior poor response to ovarian stimulation in IVF were included in the study. Exclusion criteria were patients over the age of 42 and patients who received DHEA at any time before enrollment.

The study was approved by the local Institutional Review Board and written informed consent was obtained from each participant after a detailed explanation that included the meaning of poor response in previous IVF cycles and information about the possible beneficial effects of DHEA. In our explanation, we mentioned the lack of previous RCTs investigating the effect of DHEA on poor responders and that the purpose of the study was to evaluate the effects of DHEA because the lack of randomized studies prevented us from recommending this drug as a routine protocol for poor responders.

Study design

A prospective, randomized, open labeled, controlled study was conducted to evaluate the effect of DHEA administration in patients with a previous poor ovarian response to IVF treatment. The randomization was performed using computer generated random numbers. Each patient chose a sealed envelope containing the randomized assignment to either the study or the control group, after receiving a detailed explanation from the physician, agreeing to participate in the study and signing an informed consent form.

The study was registered with the National Institutes of Health (NIH) clinical trial site 98 (clinicaltrials.gov: NCT01145144).

Treatment protocol

The study was designed for two consecutive IVF cycles. The study group began taking 75 mg DHEA orally, once a day, at least 6 weeks before starting the first cycle of ovulation induction. Patients who did not conceive and continued to the second cycle took DHEA for at least 16–18 weeks. The decision to start IVF treatment after only 6 weeks was based on data about the cumulative effects of DHEA during treatment (Barad and Gleicher, 2005). The DHEA (a fine, crystalline powder, compounded by Super-Pharm Ltd., Herzliya, Israel) was dispensed by a single pharmacy to all study participants.

All patients were treated according to the standard long-stimulation protocol with GnRH agonist, triptorelin acetate (S.C Decapeptyl 0.1 mg, Ferring GmbH, Germany), started during the luteal phase. When down-regulation was achieved, 450 IU of rFSH (Gonal F, Merck, Serono SA, Aubonne, Switzerland) combined with 150 IU of rLH (Luveris, Merck, Serono SA, Switzerland) was administered. When the leading follicle(s)

achieved an 18-mm diameter, 500 µg of recombinant hCG (Ovitrel, Merck Serono SA, Bari, Italy) was administered. Ovum pick-up (OPU) was performed 36 h later. Fertilization was assessed 20 h after insemination by the appearance of two pronuclei. Embryos were graded from one to four, based on percent fragmentation and cell counts: grade 4, equal-sized symmetrical cells with no fragmentation; grade 3, equal-sized symmetrical cells with <10% fragmentation; grade 2, non-symmetrical blastomeres with 10–50% fragmentation and grade 1 >50% fragmentation. Up to three, best-quality embryos were transferred on Day 2 or 3, (according to the Israeli Fertility Association policy guidelines).

For luteal phase support, vaginal progesterone was commenced when fertilization was confirmed and continued until the pregnancy test. For patients with a positive pregnancy test, progesterone was continued for an additional 4 weeks. In addition, all patients received a single injection of 250 µg recombinant hCG (Ovitrel, Merck Serono SA, Bari, Italy) 3 days after OPU. A quantitative pregnancy test (serum β-hCG) was taken 12 days after hCG administration and if positive, it was repeated 2 days later. In case of pregnancy, a transvaginal ultrasound was performed 28–32 days after the embryo transfer and repeated as required. Clinical pregnancy was confirmed if a fetal heartbeat was observed by transvaginal ultrasound.

Study end-points

The primary outcome measures were peak estradiol levels, the number of retrieved oocytes, embryo quality and number of embryos reserved for transfer. Secondary outcome measures were pregnancy and live birth rates.

Power calculation

A power calculation was not undertaken, such analysis requires *a priori* knowledge of effect size. We conducted a thorough literature review to obtain information regarding the potential effect of DHEA on the rate of live births (PubMed search, conducted on 1 July 2007, using the following key words: dehydroepiandrosterone, DHEA, poor responder, birth and delivery). Nevertheless, such data do not exist. Thus, the lack of such information renders the power analysis highly speculative. Moreover, in the context of clinical studies, power analysis aims at ensuring that the sample size will not only be too small to detect a statistically significant difference between the study groups, on one hand, but also not too big to prevent unnecessary exposure of humans to a research intervention. We evaluated our results at this point and we found them statistically significant (there was no Type II error) and decided to end the study. Thus, our study had enough power to address the important outcome of live birth.

Statistical analysis

Data were analyzed using the SPSS-15.0 software. Fisher's exact test was used to compare proportions. Continuous variables were presented as mean and SD and tested by Student's *t*-test. All tests were two-tailed and a *P*-value of <0.05 was considered statistically significant.

Results

The study was conducted from January 2008 to July 2009. During this period, we identified 60 patients who met the criteria for poor response. Of these, 12 were older than 42 years of age, 13 were exposed to DHEA treatment before they came to our unit and 2 patients did not consent to participate. A total of 33 women were enrolled, 17 in the study (DHEA) group and 16 in the control group. There were no differences between the two groups regarding

Table I Demographic and IVF performance data during the cycle prior to study cycle.

	Study (n = 17)	Control (n = 16)	P-value
Age years (mean ± sd)	36.9 ± 4.7	37.8 ± 4.6	0.47
BMI kg/m ² (mean ± sd)	26.1 ± 5.5	25.7 ± 4.6	0.55
Primary infertility (number)	7	10	0.13
Secondary infertility (number)	10	6	
Basal FSH IU/ml mean (range)	9.4 (4.3–15.9)	9.6 (5.0–15.5)	0.73
Mean E2 ^a on hCG (pg/ml)	716 ± 329	817 ± 417	0.24
Mean progesterone on hCG (ng/ml)	0.5 ± 0.3	0.6 ± 0.3	0.63
Mean number of retrieved oocytes ^b	2.6 ± 1.9	1.7 ± 1.5	0.22
Mean no. of ET ^c	1.6 ± 1.3	1.0 ± 0.9	0.48

^aE2, estradiol.^bNine cycles cancelled: six study group, three control group.^cET, embryos transferred.

age, BMI, primary or secondary infertility and basal FSH (Table I). All 17 patients in the study group completed the first cycle. Nine patients completed a second cycle, for a total of 26 cycles. Of the remaining eight patients who did not continue to the second cycle, four conceived during the first cycle and four dropped out (one withdrew from the study and switched to another protocol, two decided to stop IVF treatments and consider egg donation and one went to another hospital). Among the control group, 16 patients completed the first cycle and 9 completed the second cycle. Of the remaining seven patients, two conceived during the first cycle and five dropped out (two decided to consider egg donation, one conceived, two stopped treatment altogether and one went to another hospital).

To evaluate the cumulative effect of DHEA during the study period, we compared the cycle outcomes between the first and second cycles of the patients in the DHEA group who completed two treatment cycles (Table II).

The study patients took DHEA for an average of 13.5 weeks. Patients who completed only the first cycle were exposed to DHEA for an average of 8.5 weeks, whereas patients who completed the second cycle received DHEA for an average of 21 weeks before OPU. In the DHEA study group, there was a non-significant increase in peak E2 levels from 572 pg/ml during the first cycle to 875 pg/ml in the second cycle ($P = 0.09$). The mean score of the leading embryo increased significantly from a mean of 2.7 in the first cycle to 3.4 in the second cycle ($P = 0.04$). This improvement was not observed in the control group.

A comparison between the two groups after the first cycle, revealed higher pregnancy and live birth rates among the study group patients; however, these findings did not reach statistical significance (Table III). When we summarized both cycles of the two groups, we found a significantly higher live birth rate among the

Table II Comparison between the two consecutive cycles of the study group.

Variables	First cycle	Second cycle	P-value
Mean E2 ^a on hCG (pg/ml)	572 ± 287	875 ± 354	0.09
Mean progesterone on hCG (ng/ml)	0.6 ± 0.4	0.6 ± 0.4	0.43
Mean endometrial thickness (mm)	9.8 ± 2.7	10.3 ± 2.3	0.68
Mean no. of retrieved oocytes	3 ± 1.7	3.5 ± 1.5	0.62
Fertilization rate (%)	68.0	53.0	0.55
Mean ET ^b no.	1.8 ± 1.0	2.3 ± 0.5	0.22
Mean score of leading embryo transfer	2.7 ± 0.5	3.5 ± 0.4	0.04

^aE2, estradiol.^bET, embryos transferred.**Table III** Study and control outcomes after the first treatment cycle.

	Study (n = 17)	Control (n = 16)	P-value
Mean E ₂ on hCG (pg/ml)	572 ± 287	964 ± 365	0.05
Mean progesterone on hCG (ng/ml)	0.6 ± 0.4	0.7 ± 0.3	0.83
Mean endometrial thickness (mm)	9.8 ± 2.7	10.9 ± 2.9	0.56
Mean no. of retrieved oocytes	2.8 ± 1.7	3.8 ± 1.9	0.34
Fertilization rate (%)	68.0	56.3	0.47
Mean embryo transfer no.	1.8 ± 1.0	2.1 ± 0.7	0.36
Mean score of leading embryo transfer	2.7 ± 0.5	3.2 ± 0.9	0.07
Clinical Pregnancy (%)	4 (23.5%)	2 (12.5%)	0.25
Live birth rate	3 (17.6%)	1 (6%)	0.20

DHEA group, 6 (23.1%) versus 1 (4.0%), respectively ($P = 0.05$; Table IV).

No significant differences were noted for the other IVF parameters. It should be noted that one patient in the study group conceived spontaneously 45 days after DHEA exposure, before starting IVF treatment and was included among the study group pregnancies.

Of the seven pregnancies in the DHEA group, six women delivered a live singleton infant and one patient had a missed abortion at 7-weeks gestation. Among the control group, two of the three pregnancies ended with an early spontaneous miscarriage before 12-weeks gestation and one patient delivered a live singleton infant. The patients in 8 of the 10 pregnancies that were achieved during the study had secondary infertility ($P = 0.05$), whereas two patients had primary infertility. Of the pregnancies that resulted in live infants, six of seven were among patients with secondary infertility ($P = 0.006$).

Table IV Comparison between the two groups for both treatment cycles.

Variables	DHEA (n = 26)	Control (n = 25)	P-value
Mean E2 ^a on hCG (pg/ml)	732 ± 337	917 ± 487	0.2
Mean E2 per retrieved oocyte (pg/ml)	239 ± 120	335 ± 150	0.35
Mean progesterone on hCG (ng/ml)	0.8 ± 0.6	0.7 ± 0.4	0.71
Endometrial thickness on hCG (mm)	10.5 ± 2.5	10.8 ± 2.8	0.74
Mean number of retrieved oocytes	3.2 ± 1.6	3.5 ± 2.4	0.65
Fertilization rate (%)	58.20%	56.30%	0.42
Mean no. of embryo transfer	2.1 ± 1.0	2.2 ± 0.7	0.73
Mean scoring of leading embryo transfer	3.1 ± 0.5	3.3 ± 0.4	0.42
Clinical Pregnancy (%)	7 (26.9%)	3 (12.0%)	0.07
Live birth rate	6 (23.1%)	1 (4.0%)	0.05

Discussion

Recently, there has been an increase in reports about the benefits of DHEA in improving ovarian function among poor ovarian responders (Barad and Gleicher, 2006; Barad *et al.*, 2007; Mamas and Mamas, 2009). Barad *et al.* described improved ovarian function among patients with poor ovarian response after DHEA supplementation (Barad and Gleicher, 2005, 2006; Barad *et al.*, 2007). In a case–control study, Barad *et al.* (2007) reported that DHEA treatment resulted in significantly higher cumulative pregnancy rates. Recently, Mamas and Mamas (2009) published promising findings related to DHEA administration in patients with ovarian failure. A decrease in FSH levels was noted after DHEA supplementation among these patients, with one spontaneous pregnancy reported during the administration period (Mamas and Mamas, 2009).

As far as we are aware, this is the first randomized controlled study to evaluate the contribution of DHEA to poor ovarian response. Although the sample size is a significant limitation of this study, our findings show a higher live birth rate among the DHEA-treated patients. These data support previous reports about the beneficial effects of DHEA. The DHEA supplementation group achieved six deliveries (23.1%) after two consecutive cycles of IVF compared with only one (4.0%) in the control group.

The mechanism of action of DHEA on the ovary remains speculative. Evidence shows that DHEA levels decrease with age (Harper *et al.*, 1999). Dehydroepiandrosterone can improve steroidogenesis, since it is a precursor of estradiol and testosterone (Hillier *et al.*, 1994). During ovarian induction with exogenous gonadotrophins, DHEA is the prohormone of the follicular fluid testosterone (Haning *et al.*, 1993). Androgens may influence ovarian follicular growth, not only by acting as a metabolic precursor for steroid production, but also by serving as ligands for androgen receptors (Dorrington *et al.*, 1975; Hillier *et al.*, 1994). Another possible mechanism was described

by Casson *et al.* (1998), who described a transient increase in insulin-like growth factor I (IGF-I) in patients undergoing exogenous gonadotrophin ovulation induction after pre-treatment with DHEA. This increase in IGF-I may have been due to an increase in androgen production. They later hypothesized that the beneficial effect of DHEA may have been mediated by an increase in IGF-I (Casson *et al.*, 1998, 2002). Barad and Gleicher (2006) postulated that the effect of DHEA was due to the creation of polycystic ovarian syndrome (PCOS)-like characteristics in the aging ovary. Polycystic ovaries have an alteration at the transition from primordial to primary follicle. Possible mechanisms that have been suggested for this observation are abnormal levels of growth factor, abnormally increased luteinizing hormone (LH) levels or increased ovarian androgens (Barad and Gleicher, 2006). Ovarian theca cells of the pre-antral follicle produce androstendione, testosterone and DHEA. Higher levels of these androgens were found in the serum and ovarian veins of patients with polycystic ovaries compared with controls (Amirikia *et al.*, 1986). Long-term androgen exposure can induce histological and sonographic changes in normal ovaries similar to PCOS (Amirikia *et al.*, 1986). The effect of DHEA is cumulative as more of the antral follicles become exposed to treatment, as described by Barad and Gleicher (2005). The theory of PCOS-like environment can explain the increase in response from cycle to cycle under DHEA exposure. Our findings also demonstrated an improvement between the first and the second treatment cycles in patients undergoing DHEA supplementation (Table II).

Women undergoing DHEA treatment may experience possible androgenic effects including acne, deepening of the voice and facial hair growth. These effects appear to be minimal with the therapeutic dose of 75 mg/day (Kroboth *et al.*, 1999). No androgenic or other side effects occurred among our patients.

The use of the long protocol for induction of ovulation could be considered a possible weakness of our study. It is possible that patients whose ovarian function did not improve despite DHEA supplementation would benefit from a 'softer' protocol instead of the GnRH agonist suppression. Some studies have suggested that women who have been down-regulated with GnRH agonist and then stimulated solely with r-FSH may experience low LH concentrations that compromise the parameters of IVF treatment (Humaidan *et al.*, 2004). According to the current concept in folliculogenesis, LH plays an essential role in the final stage of follicular maturation (Hillier, 2001). Owing to this evidence, we decided to include r-LH, in addition to r-FSH during the ovarian stimulation in our study protocol. Androgens are produced by the theca cells in response to LH. Elevation of intrafollicular androgen concentration in the early follicular phase resulted in a modest increase in the number of good quality embryos (Lossl *et al.*, 2006). As mentioned above, DHEA is precursor to androgens (Hillier *et al.*, 1994) and a prohormone for up to 48% of follicular fluid testosterone (Haning *et al.*, 1993). We speculate that the better results of the DHEA group were derived from the synergistic effect of both DHEA and r-LH that elevated the intrafollicular androgen concentration.

An important finding in our study was the fact that almost all clinical pregnancies (eight of nine) from both groups and six of seven deliveries were achieved among patients with secondary infertility ($P = 0.06$). This is an important message that patients with a previous pregnancy and poor ovarian response have a better prognosis than patients with primary infertility and poor ovarian response.

Conclusions

Dehydroepiandrosterone supplementation showed a beneficial effect on the live birth rate. This drug should be considered for poor-responder patients due to its simplicity of use and lack of side effects. Additional, larger studies, using different protocols are needed to reinforce our findings.

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