Reproductive BioMedicine Online (2015) **30**, 191–196

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ARTICLE

Dehydroepiandrosterone administration before IVF in poor responders: a prospective cohort study

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Abstract The use of dehydroepiandrosterone (DHEA) may improve ovarian stimulation outcomes in women of advanced reproductive age and could reduce embryo aneuploidy. In this prospective study, 48 women diagnosed with poor ovarian response received DHEA supplementation for at least 12 weeks. These women were compared with a group of poor responders ($n = 113$) who did not receive supplementation. During the study period, patients taking day 2 FSH and oestradiol were measured monthly before and after treatment. Stimulation characteristics, stimulation outcome and clinical outcome (clinical pregnancy and live birth rates) were reported. Evaluation of anti-Müllerian hormone (AMH) was carried out before initiation of treatment and immediately before the subsequent stimulation. Supplementation with DHEA for at least 12 weeks resulted in a modest, but statistically significant, increase in AMH levels and decrease in baseline FSH ($P < 0.001$ and $P = 0.007$, respectively). Administration of DHEA had no effect on any of the stimulation parameters nor was there any difference in clinical pregnancy rates and live birth rates between the two groups. Supplementation with DHEA significantly affects women with poor prognosis undergoing ovarian stimulation for IVF. Patients should be counselled about the uncertain effectiveness, potential side-effects and cost of this treatment.

http://dx.doi.org/10.1016/j.rbmo.2014.10.005
1472-6483/

KEYWORDS: AMH, DHEA, IVF, ovarian response, ovarian stimulation

Introduction

The definition of poor response to ovarian stimulation (POR) varies. Advanced age, previous poor response to gonadotrophin stimulation, retrieval of less than three oocytes in a previous stimulation cycle, and serum oestradiol of less than 300 pg/ml on day 5 of stimulation are some of the criteria used to define poor responders. In a resent systematic review of 47 trials, 41 different definitions of poor responders were used (Polyzos and Devroey, 2011). According to the recently published European Society of Human Reproduction and Embryology criteria (Ferraretti et al., 2011), the definition of a poor responder includes at least two of the following: advanced maternal age or any other risk factor for POR; a previous poor ovarian response; and an abnormal ovarian reserve test (ORT). Two episodes of poor ovarian response after maximal stimulation are sufficient to define a patient as poor responder in the absence of advanced maternal age or abnormal ORT. Patients of advanced age with an abnormal ORT may be classified as poor responders, as both advanced age and an abnormal ORT may indicate reduced ovarian reserve and act as a surrogate of ovarian stimulation cycle outcome (Ferraretti et al., 2011).

Pregnancy and delivery rates in IVF are closely correlated to the number of retrieved oocytes, and less than an optimal number is associated with a poor outcome. Several strategies have been used to improve pregnancy rates after assisted reproduction techniques for patients responding poorly to ovarian stimulation. Such methods include the use of oral contraceptives before stimulation, low doses of gonadotrophin-releasing hormone analogues (microflare protocols), and the addition of growth hormone or recombinant LH to the stimulation regimen (Alviggi et al., 2006; De Placido et al., 2006; Madani et al., 2012; Pandian et al., 2010; Sunkara and Coomarasamy, 2011; Vollenhoven et al., 2008).

Several years ago, it was suggested, that supplementation with dehydroepiandrosterone (DHEA) could improve ovarian function, increase oocyte production and improve pregnancy rates in poor responders (Barad and Gleicher, 2005, 2006). Subsequent publications from the same group provided support for the use of DHEA in poor responders (Gleicher and Barad, 2008; Gleicher et al., 2009, 2010a); nevertheless, this approach never gained wide acceptance. Recently, a review by Urman and Yakin (2012) raised several issues about the use of DHEA as a miracle drug for those patients. Moreover, a meta-analysis conducted by Sunkara et al. (2011) showed no significant difference in the number of oocytes retrieved and ongoing pregnancy and live-birth rates with androgen supplementation compared with the control groups.

The purpose of this study was to evaluate the effect of DHEA supplementation on surrogate markers of ovarian reserve as well as on stimulation characteristics and pregnancy outcome.

Materials and methods

Between June 2008 and July 2012, patients diagnosed with poor response were included in the prospective study. The definition of poor response was based on the presence of at least two of the following criteria: age over 40 years, day 2 FSH greater than 9.5 mIU/ml, anti-Müllerian hormone (AMH) less than 2 ng/ml, at least one previous cycle of ovarian stimulation with less than three oocytes retrieved, at least one cancelled attempt owing to poor response and oestradiol less than 500 pg/ml on the day of HCG administration. This threshold level of AMH was selected as a surrogate marker of poor response in study population, according to the experience of the centre. In the study population, AMH levels less than 2 ng/ml were associated with frequent cancellations, no more that two to three oocytes obtained and pregnancy rates of less than 5%. All patients were counselled about their prognosis. Other treatment options, including oocyte donation and adoption, were also presented and discussed in detail. All patients were aware that the use of DHEA was experimental and informed consent was obtained for those agreeing to use the medication. Women in the DHEA group received 25 mg of DHEA (Solgar 90 DHEA; Solgar Inc., Leonia NJ,USA) three times a day for at least 12 weeks. All patients used the same formulation of DHEA, which was obtained from the same source. During this period, women underwent monthly measures of early follicular phase FSH and oestradiol. Anti-Müllerian hormone was measured before starting treatment and at the end of the observation period. All patients were stimulated with a fixed gonadotrophin-releasing hormone (GnRH) antagonist protocol. Briefly, all women had measurements of serum FSH and oestradiol and a pelvic sonogram on the second day of their cycle. Providing that serum FSH was less than 17 mIU/ml and oestradiol was less than 70 pg/ml on day 2, ovarian stimulation was initiated with 450 IU of gonadotrophins either in the form of a combination of highly purified urinary FSH and LH (Menopur; Ferring Pharmaceutical Hellas AE) or with a combination of recombinant FSH and recombinant LH (Gonal and Luveris, Serono Hellas AE). All patients were re-evaluated on day 5 of stimulation, when dosage adjustments were made and the fixed GnRH antagonist protocol (Cetrorelix; Cetrotide, Merck Serono Hellas AE) or ganirelix (Orgalutran; Merck Sharp Dohme Ltd. 0.25 mg/day) were initiated. When at least two follicles reached an average diameter of 17 mm, final oocyte maturation was triggered with 10,000 IU of HCG (Pregnyl; Organon, Greece Inc.). Oocyte retrieval was carried out 34–36 h later. All patients underwent intracytoplasmic sperm injection to reduce the chance for fertilization failure. Patients with successful fertilization underwent embryo transfer under sonographic guidance on day 3 after retrieval. A soft catheter (Ultrasoft Frydman set echo; C.C.D International, Paris, France) was used. Embryos were evaluated and scored according to criteria established by the Istanbul consensus workshop on embryo assessment (Alpha Scientists in Reproductive and

Table 1 Demographic and stimulation characteristics of the study groups.

	Dehydroepiandrosterone use				
	Yes		*No*		
	n	*Mean (Mean SEM)*	n	*Mean (Mean SEM)*	*Mean difference (95% CI)*
Age (years)	48	39.67 (0.54)	113	39.07 (0.34)	0.60 (−0.68 to 1.87)
Body mass index	48	22.3 (0.60)	113	23.7 (0.80)	−1.40 (−3.947 to 1.147)
FSH before treatment (mIU/ml)	48	13.19 (0.33)	113	12.46 (0.22)	0.73 (−0.06 to 1.53)
Anti-Müllerian hormone before treatment (ng/ml)	48	1.47 (0.10)	113	1.32 (0.06)	0.15 (−0.08 to 0.38)
Previous IVF attempts	48	2.71 (0.26)	113	2.21 (0.14)	0.50 (−0.09 to 1.08)
Total gonadotrophin consumption (IU)	48	3936.67 (127.8)	113	3742.04 (93.9)	194.42 (−120.33 to 509.17)
Duration of stimulation (days)	48	9.17 (0.37)	113	9.20 (0.22)	−0.03 (−0.89 to 0.82)
Number of oocytes	40	3.90 (0.49)	92	3.64 (0.21)	0.26 (−0.81 to 1.33)
Number of metaphase II oocytes	39	3.00 (0.41)	88	2.78 (0.16)	0.22 (−0.67 to 1.10)
Embryos transferred	38	1.87 (0.19)	88	1.81 (0.11)	0.06 (−0.37 to 0.49)

Independent samples *t*-test indicated no statistically signifcant differences between the two groups.

Embryology ESIGo, 2011). Micronized progesterone (Utrogestan; Angelini Pharma Hellas ABEE) 200 mg three times daily vaginally was used for supplementation of the luteal phase. A serum beta-HCG was measured 12 days after the stimulation. Clinical pregnancy was confirmed by ultrasound visualization of fetal heart beat 2 weeks later.

Outcome measures

The primary outcome measured was live birth rate. Secondary outcomes were total amount of gonadotrophins used, duration of stimulation, number of oocytes retrieved, number of metaphase II (MII) oocytes, fertilization rates and embryo quality, biochemical pregnancy rate and clinical pregnancy rate.

Endocrine assays

Circulating concentrations of AMH, FSH and oestradiol were analysed in serum samples collected on day 2 of the cycle. A commercially available kit (Gen 2 ELISA; Beckmann-Coulter) with a sensitivity of 0.079 ng/ml was used for AMH measurements. Electro-chemiluminescence immunoassay kit (ECLIA; Roche Diagnostics) were used to measure FSH and oestradiol, with a sensitivity of 0.10 IU/L and 4.9 pg/ml, respectively The intra-assay and inter-assay coefficient of variation (%) for AMH, FSH, and oestradiol were 5.7 and 4.6, 3.0 and 3.8, 3.9 and 5.6, respectively.

Statistical evaluation

A commercially available statistical package (SPSS 17.0, Chicago, IL. Inc) was used for statistical evaluation. The Student's t-test was used for comparison of means between the two groups and the chi-squared or the Fisher's exact test when appropriate, for comparisons between proportions. Numerical data were evaluated for normality with the Shapiro–Wilk test. The study was approved by the University of Athens, Aretaieion University Hospital ethics committee on 24 September 2013; reference number: B-08/24-09-2013.

Results

During the study period, 161 patients with a diagnosis of poor ovarian response underwent ovarian stimulation for IVF. Of those, 48 were treated with DHEA 25 mg three times daily for at least 12 weeks. The remaining patients ($n = 113$) who did not receive DHEA served as the control group. The demographics of the two groups as well as the stimulation characteristics are shown in Table 1. Overall, no differences were found between the two groups in age, day 2 FSH and AMH levels, and number of previous IVF attempts. No differences were found between the two groups in the total amount of gonadotrophins used as well as in the duration of the stimulation. No differences were found between the two groups in the total number of oocytes and the number of MII oocytes per retrieval. The number of transferred embryos was similar between the two groups (mean: 1.87 versus 1.81; median: 2, range 1–4).

Primary outcome

Six live births took place in the control group (5.3%) and no live births in the DHEA group (Table 2). This difference, however, was not statistically significant. Similarly, no differences between the two groups were found in biochemical or clinical pregnancy rates. The cancellation rates were similar between the two groups (Table 2). Eight patients (16.7 %) in the DHEA group had no oocytes retrieved and 10 in total (20.8%) had no available embryos for transfer. In the control group, 21 patients (18.6%) had no oocytes retrieved and 25 in total (22.1%) had no embryos available for transfer. Thirty-eight patients (79.2%) in the DHEA group and 88 (77.9%) in the control group proceeded to transfer.

We also evaluated the changes in day 2 FSH as well as in AMH levels, before and after treatment, in the group treated

with DHEA (Table 3). A statistically significant reduction occurred in FSH levels from 13.4 to 12.6 ($P = 0.007$) at the end of the 3-month treatment period, which was accompanied by an increase in AMH levels from 1.47 to 1.63 ($P < 0.001$).

Discussion

In this study, the effects of DHEA administration in women with a prior poor response to controlled ovarian stimulation was investigated. In contrast to previous investigators (Gleicher and Barad, 2011; Gleicher et al., 2010a, 2010b), a significant benefit could not be demonstrated in any of the stimulation characteristics (gonadotrophin requirements, duration of stimulation oocyte and embryo yield) or pregnancy rates (biochemical and clinical pregnancy and live birth rates) in women treated with DHEA. Our results are in agreement with recent meta-analysis published on the subject (Narkwichean et al., 2013), which found no significant difference in the clinical pregnancy rate between women pre-treated with DHEA compared with those without DHEA pre-treatment. In contrast, we have documented a small but statistically significant improvement in two surrogate markers of ovarian reserve (AMH and Day-2 FSH).

The use of DHEA in ovarian stimulation has been reported as early as 2005 (Barad and Gleicher, 2005), when it was shown that supplementation of DHEA improved ovarian stimulation outcomes in a woman of advanced reproductive age who had multiple stimulation cycles for embryo cryopreservation and aneuploidy screening. According to that report, administration of DHEA was associated with a profound improvement in stimulation outcome. It was hypothesized that DHEA, as an androgen precursor, could increase intrafollicular levels of androgens. In primates, increased androgen concentration in the follicular environment could improve recruitment and initiation of primordial follicular growth (Vendola et al., 1998, 1999; Weil et al., 1999). Androgens may also increase the number of primary and preantral follicles by up-regulating insulin-like growth factor-I (Vendola et al., 1998, 1999).

Subsequently, Barad and Gleicher (2006) in a group of 25 women with poor ovarian response who received a daily dose of 25 mg of DHEA three times daily for an average period of 18 weeks, a significant increase in fertilization rates was demonstrated ($P < 0.001$), normal day 3 embryos ($P = 0.001$) and increased average embryo scores per oocyte ($P < 0.001$) after DHEA treatment. The same group also suggested that use of DHEA could reduce embryo aneuploidy (Gleicher et al., 2010b). In that study, 22 women with decreased ovarian reserve, treated with DHEA, underwent pre-implantation genetic screening (PGS) for chromosomes X, Y, 13, 16, 18, 21 and 22. Each patient was age-matched with two control IVF cycles without DHEA supplementation ($n = 44$). A significant reduction in aneuploid embryos resulted from DHEA supplementation for 4–12 weeks. Although these findings were impressive and could explain improvements in clinical outcome, the authors did not provide any explanation on the exact mechanism by which DHEA could reduce the incidence of aneuploidy.

Recently, in a small prospective randomized trial (Wiser et al., 2010), 17 patients that received DHEA (75 mg /day for at least 6 weeks) were compared with a control group of 16 patients that underwent two rounds of ovarian stimulation for IVF. Patients in the study group completed a total of 26 cycles and there were six live births (23.1%), whereas patients in the control group underwent 25 stimulation cycles and there was only one live birth. The authors concluded that DHEA treatment was associated with an increased chance for successful conception per cycle (23.1% versus 4.0%; $P = 0.05$). This study however, was heavily criticized for the use of inappropriate statistical methods; therefore, their results are questionable (Kolibianakis et al., 2011).

In the present sutdy, no improvement was detected in any of the stimulation characteristics, number of retrieved oocytes, number of mature oocytes, fertilization rates and number or quality of embryos available for transfer after administration of DHEA. Both groups required similar amounts of

Table 2 Pregnancy outcomes between the two groups.

	Dehydroepiandrosterone use	
	Yes (n = *48*) n *(%)*	*No* (n = *113*) n *(%)*
Number of women with no oocytes retrieved	8 (16.7)	21 (18.6)
Number of women with no embryos available for transfer[a]	10 (20.8)	25 (22.1)
Biochemical pregnancies	3 (6.3)	10 (8.8)
Clinical pregnancies	1 (2.1)	8 (7.1)
Preterm deliveries	0 (0.0)	1 (0.9)
Term deliveries	0 (0.0)	5 (4.4)
Live birth rates	0 (0.0)	6 (5.3)

Fisher's exact test indicated no significant differences between the two groups.
[a]No embryo transfer owing to no oocytes during retrieval or no available embryos.

Table 3 Changes in ovarian reserve markers before and after treatment for the group treated with dehydroepiandrosterone.

	Dehydroepiandrosterone use (n = *48*)				P-*value*[a]
	Before treatment Mean (SE)	*After treatment Mean (SE)*	*Mean difference (SE)*	*95% CI*	
FSH (mIU/ml)	13.4 (2.45)	12.6 (2.45)	0.79 (0.28)	0.222 to 1.36	0.007
Anti-Müllerian hormone (ng/ml)	1.47 (0.68)	1.63 (0.76)	-0.163 (0.04)	−0.246 to 0.0793	<0.001

[a]Repeated measures t-test.

gonadotrophins, for a similar period of time and produced similar numbers and quality of embryos (Table 1). Cancellation rates caused by poor response were the same between the two groups as well as the chance of not having embryos available for transfer (**Table 2**). Pregnancy rates were disappointing in both groups despite treatment with DHEA. One clinical pregnancy occurred in the DHEA group and no live birth. As mentioned previously, few randomized controlled trials have produced sufficient evidenced to support the use of androgen supplementation or modulation to improve live birth outcome in poor responders undergoing IVF and intracytoplasmic sperm injection treatment (Sunkara et al., 2011).

After DHEA treatment in the present study, however, a statistically significant improvement was detected in two of the most commonly used surrogate markers of ovarian reserve: day 2 FSH and AMH. This is in agreement with findings from Gleicher et al. (2010a) in a cohort of 120 women with poor ovarian reserve treated with DHEA over a period of 34–119 days (mean 73 ± 27 days). In contrast, in a recently published randomized controlled trial (Yeung et al., 2013) of 22 women with premature ovarian failure, treatment with DHEA did not improve any of the surrogate markers for ovarian reserve; nevertheless, a significant increase in ovarian volume took place after 20 weeks of treatment. In our study, day 2 FSH decreased from 13.4 mIU/ml to 12.6 mIU/ml and AMH increased from 1.47 ng/ml to 1.63 ng/ml after treatment with DHEA. Although statistically significant, whether those changes in AMH and FSH after DHEA treatment have any clinical significance, remains unclear.

Some weaknesses in the present study are worth mentioning. The study is not randomized and, as such, it suffers from all the inherent problems studies of this kind face. Nevertheless, the two arms were of an appropriate size and similar in demographics and baseline characteristics. Both groups were stimulated according to the same protocol, and most retrievals and transfers were carried out by the same physician, using a similar technique (NV). Furthermore, it has to be mentioned that as no DHEA formulations have been approved either by the US Food and Drug Administration or its European counterpart, the European Medicines Evaluation Agency, the true standardization of the formulations used cannot be guaranteed.

One can also argue that patients in the present study had worse prognosis than the patients reported in the trial by Wiser et al. (2010). The mean FSH levels were 9.4 mIU/ml for the study group and 9.6 mIU/ml for the control group. In the present study, mean baseline FSH levels were 12.46 and 13.2 mIU/ml, and AMH levels, 1.47 and 1.32 ng/ml for the study and the control groups, respectively. It is true that patients in the present study could have a significantly worse prognosis; however, we believe that the efficacy of DHEA should be investigated precisely in this type of population.

It may also be argued that no differences in rates could be detected between the two groups because of power limitations, and therefore the possibility for a type II error could not be eliminated. Despite the fact that no power calculation was made in our study, the probability of type II error seems quite small. When comparing the size of our samples with previous reports (Gleicher et al., 2010b; Hyman et al., 2013; Wiser et al., 2010), we believe that our sample size was adequate to demonstrate any clinically significant improvement in pregnancy rates. According to Wiser et al. (2010), in the DHEA treatment group, seven clinical pregnancies were achieved in 26 cycles for a clinical pregnancy rate of 26.9% per cycle and a live birth rate of 23%. In the control group, three pregnancies were achived in 25 cycles for a clinical pregnancy rate of 12% and a live birth rate of 4%. Although no statistically significant difference in the clinical pregnancy rates were found, an improvement was reported in live birth rate, which barely reached statistical significance ($P = 0.05$). On the basis of these data, and assuming a pregnancy rate of 12% for the control group and 20% for the treatment group, according to post-hoc calculations the sample size required to document a difference in clinical pregnancy rates for an alpha error level of 5% and a beta error level of 50% would be 114 cycles for both groups in total.

Looking at live birth rates, and assuming that the live birth rate for the control group is 5% and 15% for the treatment group, then the required sample size would be 49 for both samples. In our study, the total sample size was 161, which was adequate to detect any difference between the two groups in live birth rates but also in clinical pregnancy rates if there was one. The fact that our study had adequate power to detect miniscule changes in FSH and AMH between the two groups also supports our arguments.

In conclusion, no benefit was found in the administration of DHEA in women with a previous poor response to ovarian stimulation. Patients should be counselled adequately about the uncertain effectiveness and potential side-effects and cost of this treatment.

Acknowledgements

The authors would like to thank Dr Bulent Urman, Professor and Head Obstetrics and Gynecology and Assisted Reproduction Unit, American Hospital, Istanbul Turkey, for the critical review of the manuscript and his suggestions. This research was supported by Research Network for the evaluation of DHEA administration in poor responders and the 2nd Department of Obstetrics and Gynecology, 'Aretaieion' Hospital, University of Athens, Greece.

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Declaration: The authors report no financial or commercial conflicts of interest.

Received 5 April 2014; refereed 22 September 2014; accepted 9 October 2014.