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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.

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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