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ARTICLE

Role of dehydroepiandrosterone in improving oocyte and embryo quality in IVF cycles

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Abstract The purpose of this study was to evaluate the role of dehydroepiandrosterone (DHEA) on the number and quality of oocytes and embryos in poor responders undergoing IVF cycles. A total of 50 patients with a history of poor ovarian response in the previous cycle(s) were enrolled in a prospective cohort study. They were treated with oral micronized DHEA 25 mg three times a day for 4 months. Oocyte and embryo number and quality were recorded before and after treatment. The results were analysed using Student's paired t-test. After treatment with DHEA, a significant increase in number of mature follicles was seen in the post treatment period (≤35 years $P < 0.001$; ≥36 years $P = 0.002$). There were significant increases in numbers of oocytes retrieved, fertilization rates and, consequently, the total number of embryos available. More embryos were vitrified among patients ≤35 years ($P < 0.001$) post treatment, and clinical pregnancy rate in this group was 26.7%. DHEA treatment resulted in a higher number of oocytes retrieved, oocytes fertilized, embryos overall and of grade-I embryos. It can help in increasing pregnancy rate in poor responders.

KEYWORDS: dehydroepiandrosterone, embryos, infertility, in vitro fertilization, oocytes, ovarian reserve

Introduction

Infertility is defined as a disease of the reproductive system resulting in failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse (Zegers-Hochschild et al., 2009). Out of the various causes of female infertility, diminished ovarian reserve has become an increasingly recognized cause.

A woman's ability to respond to ovulation-inducing medication declines with increasing age, so that fewer follicles are produced and fewer mature oocytes are yielded when exposed to maximal gonadotrophin stimulation with

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IVF cycles. This change in ovarian responsiveness is known as diminished ovarian reserve (Barad and Gleicher, 2006).

There is a wide inconsistency in the definition of poor responders, but most reports characterize patients with low oocyte yield (fewer than four or five oocytes retrieved) and low oestradiol concentrations (<500 pg/ml) on the day of human chorionic gonadotrophin (HCG) administration (De Placido et al., 2005) or day-3 FSH concentration >15 mIU/ml (Cheung et al., 2005).

Dehydroepiandrosterone (DHEA) is an endogenous steroid that originates from the zona reticularis of the adrenal cortex and the ovarian theca cells in women (Burger, 2002). While DHEA is an essential prohormone in ovarian follicular steroidogenesis (Casson et al., 2000) it is an important step in the production of testosterone, oestradiol and androstenedione. Low DHEA concentration is expected to cause low concentrations of these hormones as well (Burger, 2002). DHEA is said to increase follicular insulin-like growth factor I (IGF-I), which can promote the gonadotrophin effect (Casson et al., 1998). DHEA has also been reported to suppress apoptosis and thus increasing the oocyte and embryo numbers and overall improves the quality of embryos produced in each cycle (Kaipia, 1997). The effects of DHEA increase over time, reaching peaks during 4–5 months of supplementation and may also persist up to 4 months after cessation of treatment (Barad and Gleicher, 2005). The present study is aimed to evaluate the effect of DHEA in patients undergoing IVF who have demonstrated poor response to ovarian stimulation with less than five oocytes retrieved in previous IVF cycle(s).

Materials and methods

This prospective cohort study was conducted in the Assisted Reproductive Technology Centre, Department of Obstetrics and Gynaecology, AIIMS, New Delhi from January 2012 to December 2012. The subjects were poor responders in prior IVF cycles. Ethical approval was obtained from the institutional review board before the commencement of the study (IRB reference no. IEC/T-180/30.03.2011, approved 5 November 2012). Fifty patients with a history of previous failed IVF who fulfilled the inclusion criteria were recruited after obtaining written informed consent. The inclusion criteria were age <42 years, with fewer than five oocytes retrieved in previous IVF cycles, day-2 FSH 10–20 mIU/ml and willingness to participate. The exclusion criteria were women with FSH >20 mIU/ml, single ovary, grade 3 and 4 endometriosis or with abnormal uterine cavity contraindicating IVF as uterine synechiae or thin endometrium. These patients were evaluated with detailed history, examination and investigations for infertility. Prior to commencing treatment in these infertile women, baseline hormonal markers were done, which included serum FSH, LH and anti-Müllerian hormone (AMH).

On the second or third day of the spontaneous menstrual cycle, an ultrasound was performed for antral follicle count. On investigation of their partners, three were found to have nonobstructive azoospermia; these women had had IVF with donor spermatozoa in the previous cycle. Tablet DHEA (micronized) 25 mg three times a day was administered for 4 months and was continued during the next stimulation cycle till the day of oocyte retrieval. After 4 months, serum FSH, LH and AMH measurements were repeated and the patients were then recruited for the next IVF cycle. Thirty patients had undergone stimulation by agonist protocol and 20 patients by antagonist protocol in the previous cycle, and the same protocol for ovarian stimulation was used as in the previous IVF cycle. Follicle growth was monitored by transvaginal ultrasound and HCG injection was administered when at least two or three follicles >18 mm were seen. Serum oestradiol and endometrial thickness were measured on the day of HCG injection. Oocyte retrieval was done 34–36 h after HCG injection. The number of oocytes retrieved and metaphase-II oocytes were calculated.

Fertilization was done with donor spermatozoa in the three cases with azoospermia in husband where surgical method of sperm retrieval (percutaneous epididymal sperm aspiration) had also failed. After fertilization, number of embryos cleaved, total number of embryos formed and number of grade-I embryos were noted. Subsequent embryo transfer was done on day 3–5 depending on the embryo status. Serum βHCG was measured on day 16 of embryo transfer to detect conception and clinical pregnancy was confirmed by the presence of fetal cardiac activity on transvaginal ultrasound in patients with raised βHCG.

Statistical analysis

Descriptive statistics such as mean, standard deviation and range were computed for continuous variables. After ensuring that the data followed approximate normal distribution, mean values computed during prior and post treatment periods on the same subjects were compared using Student's independent t-test. McNemar's test was used to assess the significance of the difference between two correlated proportions. For all the statistical tests level of significance was taken as $P < 0.05$.

Results

Age and duration of infertility among the 50 patients were (mean ± SD) 34.06 ± 4.0 years and 5.2 ± 1.4 years, respectively. Of these 50 patients, 40 had primary and 10 had secondary infertility. The baseline characteristics of the patients are presented in **Table 1**.

To investigate the effect of patient age on study parameters, the patients were divided into two groups: ≤35 years and ≥36 years. The effect of age on outcome measures before and after treatment were tested using Student's paired t-test (**Table 2**). A significant increase in AMH concentration was seen post treatment in both age groups ($P < 0.001$). There was a significant decrease in FSH concentration in both groups ($P < 0.001$); decrease in LH was seen only in the younger age group ($P = 0.015$). A significant increase in the number of mature follicles was seen in the post-treatment phase (≤35 years $P < 0.001$; ≥36 years $P = 0.002$). There was a significant increase in the number of oocytes retrieved (≤35 years $P = 0.001$; ≥36 years