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A randomized, controlled, pilot trial on the effect of dehydroepiandrosterone on ovarian response markers, ovarian response, and in vitro fertilization outcomes in poor responders

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Objective: To evaluate whether pretreatment dehydroepiandrosterone (DHEA) supplementation improves ovarian response markers, ovarian response to standard low-dose gonadotropin stimulation, and in vitro fertilization (IVF) outcomes in poor responders.
Design: Randomized, double-blind, placebo-controlled pilot study.
Setting: Tertiary reproductive medicine unit.
Patient(s): Thirty-two women with anticipated poor ovarian response.
Intervention(s): Randomization into DHEA group (n = 16) receiving GNC (25 mg three times a day) or placebo (n = 16) starting from at least 12 weeks before the scheduled IVF treatment according to a computer-generated randomization list.
Main Outcome Measure(s): Measurement of monthly ovarian response markers, including antral follicle count (AFC), serum antimüllerian hormone (AMH), and follicle-stimulating hormone (FSH) levels; comparison of ovarian response to a standard dose of gonadotropin stimulation at week 8 and IVF outcomes; and AFC after 12 weeks (primary outcome).
Result(s): The DHEA supplementation resulted in statistically significantly higher serum DHEA-S, free androgen index, and follicular DHEA-S levels. No statistically significant differences in the ovarian response markers (AFC, AMH, or FSH), the ovarian response to standard-dose gonadotropin stimulation, or IVF outcomes were found between the two groups.
Conclusion(s): No statistically significant improvement in ovarian response markers, ovarian response to standard dose gonadotropin stimulation, or IVF outcomes was found in poor responders receiving pretreatment DHEA.
Clinical Trial Registration Number: HKCTR-1149 (www.hkclinicaltrials.com) and NCT01915186 (www.ClinicalTrials.org). (Fertil Steril® 2014;■:■–■. ©2014 by American Society for Reproductive Medicine.)
Key Words: DHEA, in vitro fertilization, ovarian response markers, poor responders

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Dehydroepiandrosterone (DHEA) is an endogenous steroid produced mainly in the zona reticularis of adrenal cortex and ovarian theca cells in women. Androgens have been implicated in ovarian follicular steroidogenesis and are believed to increase follicular insulin-like growth factor-1 (IGF-1), which promotes folliculogenesis (1), potentiates the effects of gonadotropin (2), and reduces follicular arrest (3).

Previous observational studies have reported preliminary success in using DHEA in poor responders, leading to improved ovarian response, increased oocyte yield, improved embryo quality, reduced miscarriage rates, and higher pregnancy rates after assisted reproductive treatments (2, 4–7). A recent meta-analysis that included three randomized controlled trials (RCTs) (8–10) using transdermal testosterone and one RCT using DHEA (11) showed increased

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ongoing pregnancy/live-birth rates (relative risk 2.08; 95% confidence interval, 1.10, 3.93; $P=.002$) when adjuvant androgen (DHEA or testosterone) pretreatments were given to poor responders (12). A worldwide survey conducted in 2010 revealed that over a quarter (26%) of IVF clinicians added DHEA as an adjuvant to IVF treatment protocols in poor responders (13). Even in women with primary ovarian insufficiency, our group has previously demonstrated improvements in antral follicle count (AFC), ovarian volume and follicular activity after DHEA supplementation in an RCT (14).

Despite the wider use of DHEA in poor responders, there are still considerably diverse views among many clinicians. Most of the published studies were based on retrospective and/or observational data, and the results were not free from bias. Our study assesses the effect of DHEA on ovarian response markers, ovarian response to standard gonadotropin stimulation, and the number of oocytes obtained in poor responders in an RCT setting.

MATERIALS AND METHODS

Study Design and Protocol

Consecutive women attending the Subfertility Clinic at the Department of Obstetrics and Gynaecology, University of Hong Kong, who were indicated for IVF treatment were screened and recruited. The inclusion criteria included [1] age $\leq$40 years, [2] subfertility $>$1 year, and [3] expected poor ovarian response defined as AFC $<$5. Patients were excluded if they [1] had a history of ovarian cystectomy or oophorectomy, [2] had received cytotoxic chemotherapy, [3] had received pelvic irradiation, or [4] had a history of taking testosterone or DHEA supplementation.

The study was approved by the institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster and was registered under Hong Kong Clinical Trial Center (HKCTR-1149) and ClinicalTrials.gov (NCT01915186). All women were fully counseled, and written consents were obtained.

Baseline assessments were performed on the second day of the menstrual cycle 12 weeks before the scheduled IVF treatment. Ovarian response markers including AFC and serum antimüllerian hormone (AMH) and follicle-stimulating hormone (FSH) levels were measured. Serum estradiol (E_2), testosterone, DHEA-S, sex hormone-binding globulin (SHBG), insulin-like growth factor-1 (IGF-1), complete blood picture and liver enzymes were also checked.

Assignment and Masking

Women were randomized in a 1:1 ratio according to a computer-generated randomization list generated by a research nurse not involved in the subjects' clinical management and were allocated in sealed, opaque, sequentially numbered envelopes. The hospital pharmacy packaged the DHEA and identical placebo capsules according to the randomization list and labeled the drug packs with subject numbers only. The physicians and research nurses involved and the study participants were all blinded to the assignment.

Treatment and Monitoring

Pretreatment and monitoring. Either DHEA (GNC LiveWell), one 25 mg capsule, three times a day (i.e., 75 mg per day), or matching placebo capsules were started after baseline investigations. The patients were evaluated at four intervals at weeks 0, 4, 8, and 12. Transvaginal scans were performed by gynecologists experienced in pelvic scanning using a 7 MHz vaginal probe (Voluson 730; GE Healthcare) to determine the AFC (2–9 mm) in both ovaries. The intraobserver coefficient of variation for AFC was 7%. Blood was collected for serum AMH, FSH, E_2, testosterone, DHEA-S, SHBG, IGF-1 measurements and the complete blood picture and liver function tests.

Standard low-dose ovarian stimulation. At week 8, low-dose gonadotropin stimulation using 75 IU of human menopausal gonadotropin (hMG, Menogon; Ferring Pharmaceuticals) was given on days 2 to 8 as a standardized test for ovarian response. Ovarian response was assessed on day 10 by the number of follicle(s) $>$10 mm and serum E_2 levels (15).

IVF treatment. At week 12, the women were treated with ovarian stimulation under the fixed antagonist protocol. The hMG injections were started at 450 IU for 2 days followed by 300 IU daily. Ovarian response was monitored by serial transvaginal scanning with or without hormone monitoring. Further dosage adjustments were based on the ovarian response. When the leading follicle was $\geq$18 mm, human chorionic gonadotropin (hCG, Pregnyl; Organon) at 10,000 IU was given intramuscularly to trigger final maturation of oocytes. Cycles were canceled if the follicles remained $<$10 mm after 14 days of stimulation. Transvaginal ultrasound-guided oocyte retrievals were scheduled 36 hours later. A maximum of two embryos were transferred 2 days after retrieval. Excess good-quality embryos were frozen for subsequent transfer.

Serum samples were stored at -20°C until assayed as a whole batch. Follicular fluid was collected from dominant follicles during the oocyte retrieval. Samples were assayed for AMH, FSH, E_2, progesterone, DHEA-S, testosterone, and IGF-1. Serum and follicular AMH levels were measured using AMH Gen II ELISA (Beckman Coulter); IGF-1 levels were measured using Quantikine ELISA human IGF-1 (R&D Systems); and E_2, progesterone, testosterone, DHEA-S, and SHBG were measured using the Beckman Coulter Access 2 Immunoassay system.

The intra-assay coefficients of variation were 3.4% to 5.4% for AMH, 3.5% to 4.3% for IGF-1, 12% to 21% for E_2, 7.51% to 9.57% for progesterone, 1.67% to 3.93% for testosterone, 1.6% to 8.3% for DHEA-S, and 4.5% to 4.8% for SHBG. The interassay coefficients of variation were 4.0% to 5.6% for AMH, 7.5% to 8.1% for IGF-1, 12% to 21% for E_2, 6.11% to 11.19% for progesterone, 4.22% to 7.08% for testosterone, 3.7% to 11.3% for DHEA-S, and 5.2% to 5.5% for SHBG. The detection limits were 0.08% to 22.5 ng/mL for AMH, 0.007–6 ng/mL for IGF-1, 73–17,621 pmol/L for E_2, 0.25–127.2 nmol/L for progesterone, 0.1–16 ng/mL for testosterone, 2–1000 μg/dL for DHEA-S, and 0.33–200 nmol/L for SHBG.

Statistical Analysis

We used AFC at week 12 as the primary outcome measure. We aimed at assessing any improvement in functional

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