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DHEA supplementation may improve IVF outcome in poor responders: a proposed mechanism

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ABSTRACT

Objective: Dehydroepiandrosterone (DHEA) supplementation for poor responders may improve ovarian response and IVF treatment outcome. This study aimed to determine the mechanism of action of DHEA, and specifically, the stage of folliculogenesis influenced by DHEA.
Study design: This is a prospective, self-controlled study of poor responders to IVF treatment, comparing day 3 biochemical (anti-Mullerian hormone (AMH), inhibin B and FSH) and ultrasound (antral follicle count (AFC)) ovarian reserve markers and IVF treatment outcome before and after DHEA supplementation of at least 3 months duration.
Results: Thirty-two women were included. Following DHEA, there was a significant increase in AFC ($P = 0.0003$) without significant changes in the baseline biochemical parameters AMH, inhibin B, or FSH. The enhanced response comprised increased peak estradiol levels ($P = 0.0005$), number of follicles > 15 mm, oocytes, MII oocytes and embryos ($P = 0.004$, $P = 0.00001$, $P = 0.0004$ and $P = 0.0006$, respectively) and oocytes number/total FSH dose ($P = 0.0009$). The proportion of cancelled cycles due to very poor response decreased significantly ($P = 0.02$).
Conclusions: DHEA does not appear to exert influence via recruitment of pre-antral or very small antral follicles (no change in AMH and inhibin B) but rather by rescue from atresia of small antral follicles (increased AFC).

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1. Introduction

Poor responders to ovarian stimulation continue to pose a clinical challenge: expected pregnancy rates range from 2% to18% per in vitro fertilization (IVF) cycle [1,2]. Several markers indicate reduced ovarian reserve: rise in early follicular serum FSH, decrease in serum inhibin B, decrease in serum anti-Mullerian hormone (AMH), and low antral follicle count (AFC) [3–5]. These markers predict ovarian stimulation outcome, while AMH may also indicate oocyte quality and likelihood of pregnancy [6–9].

Historically, many alternative protocols for poor responders have been suggested, including low dose gonadotropin-releasing hormone (GnRH) agonist, short GnRH-agonist (flare), antagonist, combination clomiphene citrate-gonadotropins, and novel therapies such as testosterone, letrozole, luteal phase estradiol, recombinant LH, arginine, and aspirin [9–19]. The Cochrane review of interventions for poor responders concluded that no particular treatment offered clear benefit, or could be recommended [20].

Dehydroepiandrosterone (DHEA) supplementation has been proposed as a potential intervention for poor responders [21]. DHEA is a steroid hormone secreted by the adrenal glands, theca cells of the ovarian follicle, and central nervous system [22]. In the ovarian follicle, DHEA is converted to androstenedione and estrone, the source of testosterone and estradiol according to the two-cell theory [22]. DHEA has been marketed as a "wonder drug" for aging women, with reported benefit to physical and psychological well-being [23].

DHEA for poor responders gained favor following the publication of several case reports demonstrating improved ovarian response and increased oocyte number [24–26]. Case–control studies revealed improved oocyte and embryo quantity and quality, and higher pregnancy and live birth rates [27–31]. A

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recent small randomized controlled study showed significantly improved live birth rate following DHEA [32]. Additional possible benefits include reduced spontaneous miscarriage [33] and increased euploid embryos [30,34]. Review of existing data suggests that DHEA supplementation may improve pregnancy and live birth rates in women with diminished ovarian reserve [35,36].

Despite reported benefits, the mechanism of action of DHEA in improving reproductive outcome in poor responders remains elusive. One proposed mechanism is that DHEA acts as a precursor for sex steroid hormones in the ovarian follicle [37,38]. Also, improved reproductive function due to DHEA may be related to induction of FSH receptors by androgens in the granulosa cells, as described with aromatase inhibitors for poor responders [14]. DHEA may induce a temporary "polycystic-like" state [27], mediated by hyperandrogenism, an increase in IGF-1 levels and decrease in IGFBP-1 [37,39] which has been reported following DHEA supplementation.

This study seeks to evaluate the stage of folliculogenesis influenced by DHEA, and establish its mechanism of action in improving IVF treatment outcome for poor responders. During folliculogenesis, AMH is secreted from primary and secondary pre-antral immature follicles and small 2–6 mm antral follicles [40], while inhibin B is secreted subsequently from small- and medium-sized antral follicles [41,42]. Accordingly, we assessed serum and ultrasound markers for various stages of follicular maturation: AMH, inhibin B and antral follicle count, as well as the number and quality of oocytes and embryos, before and after DHEA supplementation.

2. Materials and methods

2.1. Patients

Forty-three women treated in the IVF Unit of Shaare Zedek Medical Center were recruited. All women had undergone at least one IVF cycle, where despite treatment with high dose gonadotropin (minimal FSH starting dose 450 IU/day), no more than 4 oocytes were collected. The mean number of previous failed cycles was 2.0 ± 1.3 (median = 3, range 1–6). Inclusion criteria were: age up to 45 years, normal BMI (20–27 kg/m^2) and day 3 FSH less than 20 IU/L. Patients who had undergone oophorectomy were excluded.

2.2. Design

The study was a prospective single arm study, in which patients were their own controls. Patients with previous poor response to controlled ovarian hyperstimulation received DHEA supplementation of 75 mg/day for at least 3 months. During this period IVF treatment was suspended. The 3-month treatment period was based on previous studies [27,28,31], suggesting that between 2 and 4 months of treatment are required to significantly improve ovarian reserve and treatment outcome. Following DHEA treatment, women underwent an IVF cycle with the same starting FSH dose and the same ovarian stimulation protocol. Markers of ovarian reserve and response to treatment, before and after DHEA supplementation, were compared. The study was approved by the Institutional Review Board of Shaare Zedek Medical Centre.

Markers of ovarian reserve included day 3 AFC, FSH, inhibin B and AMH. Serum DHEA was also measured to verify compliance. Response to treatment was evaluated by peak serum estradiol (E2), maximal endometrial thickness, number of follicles with diameter of >15 mm on day of hCG administration, number of oocytes and metaphase II (MII) oocytes retrieved, number of oocytes per total FSH dosage, and number and quality of embryos. The clinical outcomes of IVF cycles were compared, including clinical pregnancy rate, miscarriage rate, and live birth rate.

2.3. Protocol

Study subjects were treated with a long down-regulation protocol with triptorelin acetate (Decapeptyl, 0.1–0.05 mg daily, Ferring Ltd., Herzliya, Israel), then stimulation with recombinant FSH (Gonal F, Merck Serono, Herzliya, Israel) and/or hMG (Menogon, Ferring Ltd.) with doses starting at a minimum of 450 IU. After the first 3–5 days, the dose was adjusted according to follicular development and serum estradiol. Alternatively, the flexible GnRH antagonist protocol was employed, with recombinant FSH, and introduction of GnRH antagonist (Cetrotide 0.25 mg/day, Merck Serono) when the lead follicle reached 14 mm. When at least 2 follicles with mean diameters of 17 mm were observed, ovulation was triggered with recombinant hCG (Ovitrelle 250 μg, Merck Serono, Israel). The criteria for cancellation were fewer than two 17 mm follicles after 14 days of FSH stimulation.

2.4. Methods

Blood samples were obtained on day 2–4 of the menstrual cycle between 07:30 a.m. and 09:00 a.m., centrifuged for 5 min at 2000 cycles/min, and preserved frozen at maximum −20 °C. Serum AMH and inhibin-B levels were measured by ELISA, using enzymatically amplified two site immunoassay kits (Diagnostic Systems Laboratory, Inc., USA). The limit of sensitivity of the AMH assay was 0.017 ng/ml. The minimum detection of inhibin B was 7 pg/ml. Serum DHEA was determined by enzyme immunoassay (EIA) kit (Diagnostic Systems Laboratory, Inc., USA), which uses competitive binding. Theoretical sensitivity was 0.1 ng/ml and the maximal concentration detectable was 27 ng/ml. The expected value range for adult females was 1.3–9.8 ng/ml. Serum concentrations of E2 and FSH were measured using DxI 800 (Beckman Coulter Instruments Inc., USA). Assay sensitivities were 150 pmol/L and 0.1 IU/L, respectively.

Embryo quality before transfer was evaluated according to the accepted principles [43,44]. A high-quality embryo was defined as an embryo with at least 6 cells and no more than 10% fragments on the third day after oocyte retrieval.

Transvaginal ultrasound utilizing Voluson 730 Expert RIC 5–9 MHz transducer or Voluson E8 RIC 6–12 MHz transducer (GE Healthcare, Milwaukee, WI, USA) was performed in all patients by a single observer (R.R.) to preclude inter-observer bias [45]. This observer performed all AFC measurements for the IVF Unit (3–5 daily) and was blinded to patients' treatment. Total number of follicles measuring 2–10 mm (AFC) in both ovaries was recorded.

2.5. Statistical analysis

Statistical analysis was performed using paired Student's *t*-test (values with normal distribution, according to Kolmogorov–Smirnov test) and Wilcoxon Signed rank test (variables not displaying normal distribution), followed by the Bonferroni post hoc test. All variables, except serum inhibin B, showed normal distribution before and after DHEA. All tests applied were two-tailed, with P value < 0.05 considered statistically significant.

3. Results

Forty-three women met the inclusion criteria and were recruited. All reported compliance with DHEA treatment. Completed data were obtained for 32, and partial data for the others (not included). Table 1 provides background data. Advanced female age and diminished ovarian reserve were the main or

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