Increased oocyte production after treatment with dehydroepiandrosterone

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Objective: To describe a case of dramatically improved ovarian reserve in a 42.7-year-old woman who was using the dietary supplement dehydroepiandrosterone (DHEA) as well as acupuncture.
Design: Case report.
Setting: Private IVF center.
Patient(s): A 42.7-year-old patient with initial severely decreased ovarian reserve.
Intervention(s): Serial ovulation induction with concomitant use of DHEA dietary supplementation as well as acupuncture.
Main Outcome Measure(s): Peak E_2 concentration, oocytes retrieved, and cyropreservable embryos.
Result(s): In her first treatment cycle peak E_2 was 1,211 pmol/mL. After seven months of DHEA supplementation her peak E_2 in cycle 8 was >18,000 pmol/mL. Because of fear of hyperstimulation we reduced her gonadotropin stimulation by 25%. In the ninth cycle peak E_2 was 9,178 pmol/mL, resulting in retrieval of 17 oocytes (16 embryos). In the last 11 months the patient has undergone nine treatment cycles while continuously and dramatically improving her ovarian response and banking of 66 embryos overall.
Conclusion(s): This case illustrates the possibility that ovarian function may be salvaged, even in women of advanced reproductive age. (Fertil Steril® 2005;84:756.e1–3. ©2005 by American Society for Reproductive Medicine.)

Key Words: Ovarian reserve, aging, DHEA, in vitro fertilization, cryopreservation

Ovarian reserve declines with age (1). When attempting IVF, older women produce few oocytes (2) and yield few normal embryos, even when exposed to maximal gonadotropin stimulation (3). In this report we present a unique case which raises the possibility that ovarian function may be salvaged, even in a woman of advanced reproductive age.

CASE REPORT

This 43-year-old single woman was seeking embryo cryobanking for postthaw aneuploidy screen (4) to preserve an option for future pregnancy. She was of northern European background. Her menarche occurred at age 11 years. She had a history of lifelong regular 28- to 30-day menstrual cycles with 5 to 6 days of bleeding. She used oral contraceptives intermittently throughout her adult life. She had no history of obesity or hirsutism. She never previously attempted to become pregnant. Her body mass index (BMI) at first visit was 21.8; over the one year of treatment her BMI increased to 23.2. Her endocrine work-up was unremarkable with PRL of 13.42 ng/mL (0.583 pmol), TSH of 2.48 mIU/mL, and cycle day two E_2 of 67.6 pmol/L, FSH of 6.29 IU/L, and LH of 4.64 IU/L. During her 11 months of treatment her peak cycle day 3 serum FSH was 15 IU/L. Ovulation induction was accomplished in each cycle using norethindrone acetate tablets (10 mg) for 10 days, starting on day two of menses, followed three days later by 40 μg of leuprolide acetate, twice daily, and, after another three days, by either (cycle 1) 600 IU of FSH (Ares-Serono, Geneva, Switzerland), (cycle 2–8) 450 IU of FSH and 150 IU of hMG (Ares-Serono), or (cycle 9) 300 IU of FSH plus 150 IU hMG. When the lead follicle diameter was 18 to 20 mm, follicular maturation was triggered with injection of 10,000 IU hCG, with oocyte retrieval 34 hours later. After her first cycle, the patient independently began self-administration of 75 mg per day of oral micronized dehydroepiandrosterone (DHEA) and also initiated weekly acupuncture treatment.

We divided the cycles into four progressive groups and used one-way ANOVA with a polynomial linear term to test for a linear increase of oocyte counts and cryopreserved embryos across treatment cycles. Outcomes are presented as mean ± 1 SD. Statistics were performed using SPSS for Windows, Standard version 10.0.7 (SPSS, Chicago, IL). Assay of E_2 and FSH were performed using the ACS 180 chemoluminescence system (Bayer Health Care, Tarrytown,

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NY). Ten of this patient's embryos were analyzed using blastomere biopsy and seven-probe fluorescence in situ hybridization (FISH) for chromosomes X, Y, 13, 16, 18, 21, and 22.

A total of 66 embryos have been cryopreserved. Results of each treatment cycle are presented in Figure 1. Progressively more oocytes were retrieved with each cycle (linear trend, F = 102, *df* 1, *P*<.001). The number of embryos available for cryopreservation increased steadily across cycles following initiation of DHEA supplementation (linear trend, F = 35, *df* 1, *P*<.01).

Peak E_2 in cycle one was 1,211 pmol/L. Peak E_2 in cycle eight was 18,557 pmol/L. In cycle nine, after we decreased the dose of gonadotropin to 300 IU FSH and 150 IU hMG, peak E_2 was 9,178 pmol/L and we retrieved 17 oocytes and were able to cryopreserve 16 embryos. Only 1 of 10 embryos analyzed by FISH technique was diploid for the seven chromosomes tested, the 9 remaining embryos analyzed were aneuploid. The single normal embryo was cryopreserved.

DISCUSSION

The present case report is evidence that an older woman with documented decreased ovarian reserve may dramatically improve her response to ovulation induction over successive cycles.

This patient's response may be due to an interaction of DHEA, gonadotropin stimulation, and acupuncture treatments and not an effect of DHEA alone. However, only DHEA, a weak androgen, offers considerable theoretical foundation for a beneficial effect on the ovary.

DHEA is secreted by the adrenal cortex, central nervous system, and the ovarian theca cells and is converted in peripheral tissue to more active forms of androgen or estrogen (5). At physiologic doses, DHEA increases serum levels of the insulin-like growth factor (6) and serves as a prohormone for estrogens (7). DHEA-exposed rats develop cystic changes similar to polycystic ovary syndrome (PCOS) (8) and have a higher percentage of meiotically active oocytes and less evidence of atresia (9). Women chronically exposed to androgens can also develop PCOS-like ovaries (10).

In general, older ovaries have few antral follicles, high rates of atresia (11), and increased "resistance" to ovulation induction (2, 12, 13). A "delay" of the atretic process has been noted among anovulatory women with PCOS, where increased follicular DHEA concentration was associated with increased aromatase activity (14). During IVF cycles day three, T levels ≤0.694 nmol/L are associated with poor IVF success rates.

Casson et al. (15) previously noted only a small increase in follicle number and E_2 response to ovulation induction after DHEA administration. They treated five women for only two months with DHEA (80 mg/day) administration. In contrast, our patient's dramatic increase in oocyte production began after four months of treatment. This treatment duration is in keeping with the interval required for normal follicular initiation of recruitment and growth (16) and raises the possibility that the previous study did not treat its subjects long enough to achieve maximum effect.

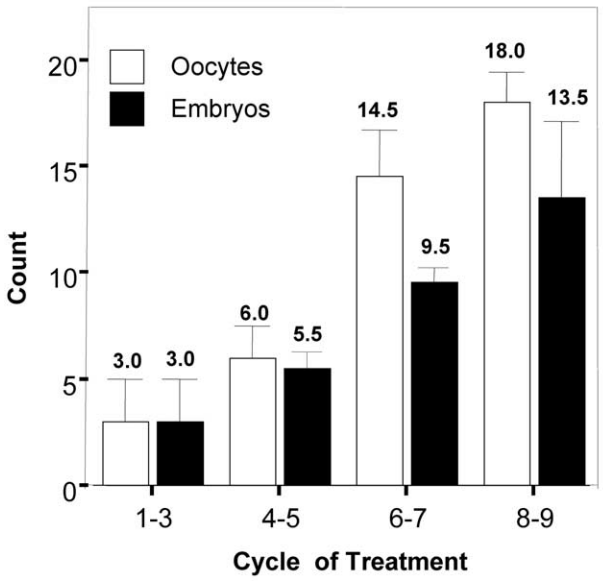
Aneuploidy is a known consequence of reproductive aging; however, the average woman of advanced reproductive age will produce too few viable embryos for preimplantation diagnosis. By increasing the number of embryos available for analysis, one may be able to increase the availability of at least a few normal embryos for transfer.

We have since used DHEA pretreatment for three additional patients undergoing IVF who had a history of poor ovarian function and elevated baseline FSH. One of these three patients was 45 years old and had a baseline FHS of 25 IU/mL. Not surprisingly, she demonstrated little improvement after DHEA treatment. The other two patients are 42 and 33 years old. They each had a previous unsuccessful IVF cycle with few healthy embryos. Both of these patients were able to establish continuing clinical pregnancies after IVF and are in their first trimester at the time of this submission.

The "aging ovary" represents the last frontier of human infertility treatment and is generally considered untreatable

FIGURE 1

Mean ± SD of embryos and oocytes produced over 9 cycles of treatment. Oocytes: cycles 1 to 3 (3 ± 2), 4 and 5 (6 ± 1.4), 6 and 7 (14.5 ± 2.1), 8 and 9 (18 ± 1.4) (linear trend, F = 102, *df* 1, *P*<.001). Embryos: cycles 1 to 3 (3 ± 2), 4 and 5 (5.5 ± 0.7), 6 and 7 (9.5 ± 0.7), 8 and 9 (13.5 ± 3.5) (linear trend, F = 35, *df* 1, *P*<.01).



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with current medical resources. The possibility that any intervention may significantly improve the response of the aging ovary is therefore potentially revolutionary.

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