Dexamethasone during ovulation induction for in-vitro fertilization: a pilot study

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The purpose of the present study was to determine whether adrenal androgen suppression with dexamethasone (DEX) during ovulation induction improves the outcome of in-vitro fertilization (IVF) cycles. A total of 25 patients with serum dehydroepiandrosterone sulphate (DHEAS) concentrations >2.5 µg/ml were randomized to receive either 0.5 mg DEX daily or placebo during ovulation induction with leuprolide acetate down-regulation plus human menopausal gonadotrophins (HMG). Nine patients undergoing a subsequent IVF cycle were crossed over to the other treatment group. Ovarian responsiveness and IVF outcome variables analysed included number of follicles >12 mm in diameter, serum oestradiol concentrations on the day of human chorionic gonadotrophin (HCG) administration, number of ampoules of HMG administered, number of oocytes retrieved, percentage of oocytes fertilized, number of embryos transferred, implantation rate and numbers of clinical pregnancies and live birth pregnancies. The 31 randomized IVF cycles revealed a trend towards a higher implantation rate for the placebo-treated group compared to the DEX-treated group (24 versus 10%; P = 0.07). The remainder of the IVF cycle variables revealed no statistically significant differences. In conclusion, the suppression of adrenal androgens with DEX in women with DHEAS concentrations >2.5 µg/ml appears to have no beneficial effects on ovarian responsiveness or clinical or live birth pregnancy rates.

Key words: dexamethasone/IVF/ovulation induction

Introduction

The effects of adrenal androgens on ovarian follicular development remain poorly understood. However, elevated adrenal androgens appear to adversely influence folliculogenesis and perhaps ovarian responsiveness during ovulation induction. Several studies suggest that suppression of adrenal androgens with glucocorticoid therapy may be beneficial in patients previously unresponsive to conventional ovulation induction with clomiphene citrate or human menopausal gonadotrophins (HMG) (Lobo et al., 1982; Evron et al., 1983; Daly et al., 1984). Daly et al. (1984) reported a significantly higher rate of ovulation and conception in patients treated with clomiphene plus glucocorticoids versus clomiphene alone if the baseline dehydroepiandrosterone sulphate (DHEAS) concentrations were >2.0 µg/ml. Clinical studies evaluating the endocrine effects of flutamide (Petermann et al., 1993) and laparoscopic electrocautery of the ovarian surface (Naether et al., 1994) offer additional support for a beneficial effect of adrenal androgen suppression in hyperandrogenaemic women. The potential benefit of adrenal androgen suppression on the ovulation induction regimens used for in-vitro fertilization (IVF) has not been published. The purpose of the present study was to determine whether adrenal androgen suppression by dexamethasone (DEX) during ovulation induction improves ovarian responsiveness and the outcomes of IVF cycles for patients with serum DHEAS concentrations >2.5 µg/ml.

Materials and methods

The present study utilized a prospective, randomized, double-blind, placebo-controlled, crossover design. The clinical trial was approved by the Brigham and Women's Hospital Human Research Committee. Between 1991 and 1993 a total of 618 patients underwent at least one cycle of IVF at Brigham and Women's Hospital, Boston, MA, USA and 1063 IVF cycles were initiated. These cycles resulted in a live birth rate of 19% per cycle initiated. During this period, all patients were required to have serum DHEAS concentration analysed as part of our routine screening, and 81 eligible patients were identified with DHEAS concentrations >2.5 µg/ml. The normal range for DHEAS in our laboratory is 0.35–4.3 µg/ml.

Ovarian responsiveness and IVF outcome variables analysed included number of follicles >12 mm in diameter, serum oestradiol concentrations on the day of human chorionic gonadotrophin (HCG) administration, number of ampoules of HMG administered, number of oocytes retrieved, percentage of oocytes fertilized, number of embryos transferred, implantation rate and numbers of clinical pregnancies and live births. The implantation rate was defined as the number of gestational sacs at 6 weeks gestation per number of embryos transferred. Clinical pregnancy was defined as the presence of an intrauterine gestational sac by ultrasound.

A total of 25 patients with serum DHEAS concentrations >2.5 µg/ml agreed to participate in the study and were randomized to receive either 0.5 mg DEX daily or placebo during ovulation induction for IVF. Three patients enrolled in the study decided to undergo gamete intra-Fallopian transfer (GIFT) rather than IVF during their initial cycle, and were selectively excluded from the analyses of fertilization, embryos transferred, implantation and pregnancy rates. Nine patients undergoing a subsequent IVF cycle were crossed over to the other treatment group. However, one patient underwent GIFT during her initial cycle and was excluded from the analyses of crossover cycles. A total of 34 cycles were available for data analysis. The randomization scheme was based on computer-generated...
permuted blocks and the assignment of DEX or placebo was determined by the hospital’s investigational pharmacy. The clinical investigators and patients remained blinded to the treatment group throughout the duration of the study. Compliance with the study medications was confirmed by our nurse coordinator (P.T.).

Ovulation induction consisted of standard leuprolide acetate down-regulation and HMG as previously reported (Jackson et al., 1992). Administration of DEX or placebo was initiated on the first day of HMG stimulation and discontinued the day after human chorionic gonadotrophin (HCG) administration. This protocol was based on the previous work of Daly et al. (1984). Patients underwent transvaginal ultrasound-guided oocyte retrieval ~34 h after HCG administration. Fertilization was assessed 12–18 h after insemination, and embryo transfer was performed 48–54 h after oocyte retrieval.

Differences between the groups for the randomized cycles were determined by either the Mann–Whitney rank sum or Fisher exact tests. Differences between the groups for the crossover cycles were determined by the Wilcoxon signed rank test. Data are expressed as means ± SEM. Power analyses were performed on each of the outcome variables to assess the likelihood of not detecting a significant difference when a significant difference really exists.

Results

Demographic data for both groups are reported in Table I. The mean age of the patients was 34 ± 0.91 years in both groups. The patients’ mean DHEAS concentration was 3.28 ± 0.72 μg/ml (range 2.51–4.90). The distribution of fertility diagnoses was not significantly different between the groups. The 31 randomized IVF cycles revealed a trend towards a higher implantation rate for the placebo-treated group compared to the DEX-treated group which approached statistical significance (24 versus 10%; P = 0.07; Table II). The initial 22 randomized IVF cycles, i.e. prior to crossover, similarly revealed a trend towards a higher implantation rate for the placebo-treated group compared to the DEX-treated group (20.6 versus 10.8%; P = 0.17). The remainder of the IVF cycle variables revealed no statistically significant differences between the groups for serum oestradiol concentrations, number of follicles, number of ampoules of HMG, number of oocytes retrieved, percentage of oocytes fertilized, embryos transferred, or number of clinical pregnancies and live births (Table II). The results of the matched crossover cycles also revealed a trend towards higher implantation rates for the placebo-treated group, but there were no statistically significant differences between the groups (Table III). The relatively low fertilization rates in both groups were likely to have been due to the diagnosis of severe male factor in six cycles.

The sample size determination estimates showed that, with an α error of 0.05 and a β error of 0.20, a total of 96 patients would be necessary to detect a statistically significant difference in the implantation rate and 137 patients would be necessary to detect a statistically significant difference in the clinical pregnancy rate. The power analyses for the remainder of the non-statistically significant variables revealed type II, β errors ranging from 0.93 to 0.95.

Discussion

The purpose of the present study was to test the hypothesis that adrenal androgen suppression may be beneficial during IVF. This is the first published randomized, placebo-controlled clinical trial utilizing glucocorticoid suppression of adrenal androgens during IVF. In the present study patients treated with DEX demonstrated a trend towards a lower rate of implantation and a lower number of clinical and live birth pregnancies. Willman et al. (1992) presented the results of a similar study of 52 women and 13 crossover cycles at a Pacific Coast Fertility Society Meeting. They similarly demonstrated
no improvement in the clinical pregnancy rate for patients taking DEX and concluded that adrenal androgen suppression may be less beneficial when combined with leuprolide acetate down-regulation.

In contrast, previous studies have suggested a potentially beneficial role for DEX in patients undergoing ovulation induction with clomiphene citrate or HMG. Lobo et al. (1982) added DEX to the treatment regimens of 12 women with polycystic ovaries in whom 250 mg of clomiphene citrate for 5 days failed to induce ovulation. Six of the 12 patients subsequently ovulated and one conceived. In a prospective randomized crossover trial, Daly et al. (1984) demonstrated significantly higher rates of ovulation and conception in anovulatory patients with elevated concentrations of DHEAS treated with a combination of clomiphene and DEX when compared to patients treated with clomiphene alone. A total of 45 anovulatory patients were assigned to receive either clomiphene citrate alone or clomiphene citrate with 0.5 mg of DEX. The significantly higher rates of ovulation and conception noted in the clomiphene + DEX group were correlated with elevations of serum DHEAS >2.0 µg/ml. Finally, Evron et al. (1983) treated 27 patients with DEX and HMG who had previously failed to conceive with clomiphene or HMG alone. A total of 22 patients ovulated and 20 conceived. These authors also demonstrated that the combination of DEX and HMG resulted in a significant reduction in the amount of HMG required to induce ovulation. In summary, earlier studies suggested that adrenal androgen suppression with glucocorticoids is beneficial in patients previously unresponsive to ovulation induction with clomiphene citrate or HMG.

There are several potential reasons for the difference in results between the present study and the previous publications. First, the previous studies did not evaluate patients treated with leuprolide acetate down-regulation plus HMG. Second, whereas the previous studies were limited to patients with anovulation and/or polycystic ovaries, the current study selected subjects solely on the basis of DHEAS concentration. Third, two of the three previous studies were case series lacking adequate control groups. Finally, the present and previous studies were limited by relatively small sample sizes. Although the present study involved a prospective randomized placebo-controlled study design, the small sample size clearly limits definitive conclusions. Nevertheless, our data suggest that there is no beneficial effect of DEX (0.5 µg) during ovulation induction with leuprolide acetate and HMG for patients with concentrations of DHEAS >2.5 µg/ml. Moreover, our findings lend support to the studies of Haning et al. (1985) which suggest that DHEAS is an important substrate for the ovary.

There are also certain disadvantages of the crossover design in infertility trials (Daya, 1993). The major problem with the crossover design is that the subject who conceives during the first cycle does not have the opportunity to be exposed to the second treatment. A similar problem exists when a subject drops out of the study during the first cycle. Thus, in this study both the statistical power and the adequacy of the control group were limited by the small number of patients who completed a second cycle.

The decision to discontinue patient recruitment was based on the trend towards lower rates of implantation, clinical pregnancies and live births with DEX therapy. Although increasing the sample size might demonstrate a statistically significant adverse effect of DEX on implantation rate or live births, our overall conclusions would remain unchanged. Thus, our data seem to suggest that the addition of DEX to standard leuprolide down-regulation and ovarian stimulation with HMG appears to have no beneficial effect on ovarian response or IVF outcome. In addition, DEX (0.5 mg) should not be recommended as an adjuvant therapy during ovulation induction with leuprolide acetate down-regulation during IVF in patients with DHEAS concentrations >2.5 µg/ml. However, the potential efficacy of different doses of glucocorticoids during IVF for other indications clearly warrants additional clinical trials, since higher doses of glucocorticoids are often prescribed when micromanipulation is used for assisted fertilization and hatching.

References


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