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A PROSPECTIVE, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED CLINICAL TRIAL OF DEXAMETHASONE DURING THE FOLLICULAR PHASE IN CLOMIPHENE RESISTANT PATIENTS WITH POLYCYSTIC OVARY SYNDROME AND NORMAL DHEAS

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ABSTRACT

In order to evaluate the effects of short course administration of dexamethasone (DEX) combined with clomiphene citrate (CC) in CC-resistant patients with polycystic ovary syndrome (PCOS) and normal DHEAS, a prospective, double blind, placebo controlled, randomized study was undertaken at referral university hospitals.

Two-hundred and thirty women with PCOS and normal DHEAS who failed to ovulate with a routine protocol of CC received 200 mg of CC from day 5 to 9 and 2 mg of DEX from day 5 to 14 of the menstrual cycle. The control group received the same protocol of CC combined with placebo.

Follicular development, hormonal status, ovulation rate, and pregnancy rate were evaluated.

Mean follicular diameters were 18.4124±2.4314 mm and 13.8585±2.0722 mm ($p<0.001$) for treatment and placebo group respectively. Eighty-eight percent of treatment and 20% of the control group had evidence of ovulation. The difference of cumulative pregnancy rate in treatment and control groups was statistically significant ($p<0.0001$).

Hormonal levels, follicular development and cumulative pregnancy rate improved with the addition of DEX to CC in CC-resistant patients with PCOS and normal DHEAS.This regimen is recommended before any gonadotropin therapy or surgical intervention.

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INTRODUCTION

Approximately 40% of subfertile women have disorders of ovulation and PCOS is the most common cause of anovulatory infertility accounting for over 70% of

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causes.[1,2] Women with hyperandrogenism may have normal total serum androgen levels.[3] The serum level of SHBG in women with PCOS is significantly lower than weight matched controls. This implies that for a given level of serum testosterone (T) in PCOS, the target tissues are exposed to a higher concentration of free T than in non-PCOS.[3,5] By virtue of it's efficacy, safety and ease of administration, clomiphene citrate (CC) is the first line of therapy, although 20% to 30% of patients do not respond to this medication.[6-8] Patients most likely to not respond to CC are those who are most hyperandrogenic and overweight.[2] Although administration of DEX appears to be effective in inhibiting adrenal androgens, other mechanisms may also exist. LH activity and ovarian steroidogenesis may be affected.[9-14] There are some reports that in the female rat, short course treatment with DEX can induce a significant elevation of serum FSH levels.[15,16] It is speculated that previous reports of enhanced ovulatory function under acute stress could be due to corticosteroid enhancement of folliculogenesis,[16] and short course treatment with DEX during the follicular phase is expected to facilitate folliculogenesis and thereby to enhance the effectiveness of CC to induce ovulation. This regimen may have beneficial effects in those groups of PCOS who have normal DHEAS and are CC resistant. This study was designed to evaluate the effects of addition of DEX to CC during the follicular phase, in CC-resistant women with PCOS and normal DHEAS.

MATERIAL AND METHODS

Between May 1994 and January 2000, 230 women with PCOS, all of whom complained of infertility and were resistant to CC were studied in the Infertility and Reproductive Endocrinology Division of Shiraz University of Medical Sciences. The Shiraz University of Medical Sciences Ethics Review Committee for Human Research approved the study. Informed consent was obtained from each individual. Hormonal assessment was completed before inclusion in the study on cycle days 3 to 5. The diagnosis of PCOS was made based on a history of amenorrhea or oligomenorrhea, presence of elevated basal LH and androgen levels, and ultrasound findings of enlarged ovaries with multiple small cysts scattered around the periphery and highly echogenic stroma. Serum DHEAS levels, HSG, post-coital test and semen analysis were normal in all cases.

CC resistance was considered when ovulation and a normal luteal phase were not achieved in patients treated with the highest dose of CC for 5 days and at least for 5 cycles. Women had failed to ovulate during treatment with 250 mg of CC for 5 days combined with 10000 IU of HCG. A total of 1150 cycles of ovulation had been induced previously. Subjects were given CC, 200mg from cycle days 5 to 9 and DEX, 2 mg from cycle days 5 to 14 (treatment group) or the same protocol of CC combined with 4 tablets of placebo from cycle days 5 to 14 (control group) in a double-blind, randomized format. DEX was stopped without tapering.

A person who did not participate in this study by assigning odd numbers to treatment and even numbers to control group performed random allocation when the patient entered the study. The codes of randomization were broken after completion of the study. Folliculometry was done on cycle day 16 or 17 (7 days after the last dose of CC). HCG was administered intramuscularly on cycle day 15 or 16 (7 days after completion of CC therapy and the time of endogenous LH surge in a CC treatment cycle), and hormonal assessment was repeated one week after injection of HCG. Hormonal assay was performed only for one cycle in each group to assess the effects of treatment. If menstruation occurred after 2 weeks of administration of HCG, the next cycle of treatment was started, and continued for a maximum of 6 cycles. If menstruation was delayed and a negative HCG assay was observed, β-HCG assay was repeated after 10 days and 100 mg of progesterone was injected intramuscularly to induce menstrual bleeding. Any patient who became pregnant and lost to FU in both groups was excluded and the remainder started the new cycle. BMI was determined in both groups.

Normal values of hormonal levels

FSH=3-13 MIU/mL, LH=1.5-12 MIU/mL, Prolactin=80-500 MIU/mL, Testosterone=0.2-0.9 ng/mL, Progesterone=1.87-28 ng/mL, DHEAS=80-350 μg/dL, TSH=0.35-5 μU/mL.

Statistical methods

Survival analysis with Kaplan-Meier and Log Ranks test and Two-Sample-Test were used in this study ($\alpha = 0.05$).

RESULTS

The mean age of women in the treatment group was 23.56 and in the control group was 24.66 years. The difference was not statistically significant. Most of the patients were in the age range of 21-25 in both groups. The mean length of infertility was 4 years (range 2 to 14 years) and 4.25 years (range 3 to 14.5 years) in treatment and control groups respectively. Menstrual status (pre and post-treatment) is shown in Table I. Sixty-seven percent of treatment and 61% of control groups were found to be oligomenorrheic prior to treatment. The mean diameter of dominant follicle±SD of the treatment group was 18.4124±2.4314 mm, while the mean diameter of dominant follicle in the placebo group was 13.8585±2.0722

mm. The serum DHEAS levels and T levels were within normal limits in all 230 patients (Table II). In women who received DEX, 88% ovulated as evidenced by progesterone (P) levels, whereas 20% of women ovulated when placebo was used in combination with CC. As shown in Table II, a significant decrease in serum DHEAS, LH and T levels and LH/FSH ratio was observed in the treatment group ($p<0.01$).

Forty-six pregnancies (40.5%) resulted following the combined use of CC and DEX, while only 5 women (4.2%) in the control group conceived. The cumulative conception rate in treatment and control groups is shown in Figure 1; the difference was statistically significant ($p<0.0001$).

The means and SD of the BMI of the treatment and placebo group were 30.33±4.11 and 29.82±4.35 respectively, which was not statistically significant ($p= 0.48$). None of the women treated with DEX showed any side effects.

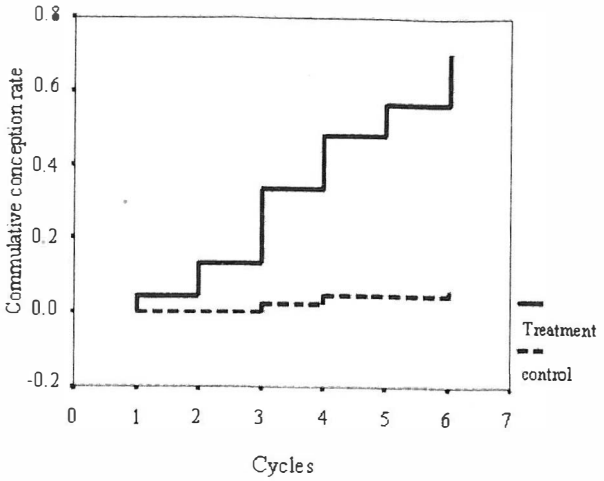

Fig. 1. The cumulative conception rate in treatment and control groups.

DISCUSSION

Ovulation induction in women with PCOS who present with CC-resistant anovulatory infertility remains a major challenge in gynecologic endocrinology. The

Table I. Menstrual status before and after therapy in treatment and control groups.

	Menstrual status	Before treatment (No. of patients)	After treatment (% of patients)
Treatment	Oligomenorrhea	75	78.7% Regular 13.3% Minimal changes 8% No change
	Amenorrhea	18	61.1% Regular 27.8% Minimal change 11.1% No change
	Polymenorrhea	2	100% Regular
	NL Menstruation	16	100% Regular
Control	Oligomenorrhea	72	8.2% Regular 21.9% Minimal change 69.9% No change
	Amenorrhea	23	8.2% Regular 21.9% Minimal change 69.9% No change
	Polymenorrhea	10	4.3% Regular 34.8% Minimal change 60.9% No change
	NL Menstruation	14	100% Regular

*Minimal change: Slight change from the basic status (2 month interval to 42 days interval).

Table II: Hormonal level before and after therapy in treatment and control groups (mean±SD).

Group	DHEAS Mean ± SD	FSH Mean ±SD	LH Mean ±SD	LH/FSH Mean ±SD	P Mean ± SD	PRL Mean ±SD	T Mean ±SD
Treat B	321.92 ± 83.17	7.18 ± 3.22	14.29 ± 5.27	2.19 ± 10.0	3.21 ± 1.49	254.21 ±95.69	1.1 ± 0.35
Treat A	248.97 ± 85.33	7.08 ± 2.26	9.98 ± 3.62	1.46 ± 0.55	8.98 ± 4.92	247.04 ±78.52	0.35 ± 0.23
P-value	*0.001	0.634	*0.001	*0.001	*0.001	0.272	*0.001
Cont B	325.29 ± 105.28	6.61 ± 3.22	14.09 ± 5.27	2.29 ± 0.79	3.26 ±1.77	258.29 ±87.97	0.92 ± 0.24
Cont A	321.16 ± 87.98	6.76 ± 2.78	14.23 ± 5.27	2.33 ± 0.68	3.43 ± 1.85	268.33 ±80.76	0.86 ± 0.27
P-value	0.168	0.301	0.528	0.267	0.508	0.030	0.080

B= Before treatment, A= After treatment, Treat=Treatment, Cont=Control.

*Significant difference

*T= ng/mL, PRL= mIU/mL, P= ng/mL, LH= mIU/mL, FSH= mIU/mL, DHEAS= µg/dL

traditional alternatives for CC-resistant patients include gonadotropin therapy and laparoscopic ovarian diathermy. However because of the cost and risk inherent to these therapies, alternative treatments are attractive. Our experience with a regimen of high dose DEX during the follicular phase resulted in a high rate of ovulation (88%) with a pregnancy rate of 40%. Our findings are similar to those seen by Lisse[22] and Edward et al.[23] who reported an ovulation rate of 80% and a pregnancy rate of 38. These results contrast sharply with the low ovulation (20%) and pregnancy rate (4.2%) seen in placebo groups.

In spite of hyperandrogenism, androgen levels are normal in most cases of PCOS. This may be due to the increase of free or unbound T. The increase of free T has been described by some authors,[3,17,18] so the total T level may not be used to predict ovulation in women receiving CC. Corticosteroids have been reported as primary therapy in women with elevated DHEAS.[19]

Although our study was not designed to examine the mechanism involved in establishing ovulation, some known responses of the hypothalamic-pituitary-ovarian axis to DEX may be beneficial in CC-resistant patients. DEX reduces circulating DHEAS, T, LH and LH/FSH ratio[9,14,20] that were observed after 2 weeks of DEX therapy in the treatment group. Previous reports of similar hormonal improvement stimulated our interest in this regimen.[15,16] DHEAS has been shown to act as a prehormone for T,[21] and the reduction in this prehormone led to a decrease in T level.

Post-treatment hormonal changes can improve folliculogenesis and follicular maturation.

As mentioned previously mean±SD of the diameter of the dominant follicle in the treatment group was significantly higher than the placebo group.

Pregnancy rate was 40% while 88% of patients ovulated during treatment cycles. The low rate of conception in contrast to the high rate of ovulation may be due to other infertility factors and antiestrogenic effects of CC on the cervix and endometrium.[24]

DEX therapy during the follicular phase has been described without any side effects or serious sequelae.[22,23] Our results provide a potential new avenue for successful intervention in CC resistant anovulatory patients. Although the mechanism underlying the beneficial effects of DEX is not exactly understood, it is speculated that DEX therapy during the follicular phase can enhance follicular development, and ovulation.

We concluded that DEX therapy combined with a high dose of CC in the follicular phase can improve folliculogenesis, ovulation and pregnancy rates. This regimen is recommended before gonadotropin therapy or any surgical intervention.

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