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.


Keywords: Polycystic ovary, DHEAS, clomiphene citrate, dexamethasone.

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
Dexamethasone plus Clomiphene in PCOS

causes.1,2 Women with hyperandrogenism may have nor­
mal 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.3,4 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 ap­
pars to be effective in inhibiting adrenal androgens,
other mechanisms may also exist. LH activity and ova­
rian 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 en­
duced ovulatory function under acute stress could be
due to corticosteroid enhancement of folliculogenesis,16
and short course treatment with DEX during the follicu­
lar 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 follicu­
lar phase, in CC-resistant women with PCOS and nor­
mal 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 Univer­
sity of Medical Sciences. The Shiraz University of Medi­
cal Sciences Ethics Review Committee for Human Re­
search approved the study. Informed consent was ob­
tained 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 his­
tory of amenorrhea or oligomenorrhea, presence of el­
evated 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 (con­
tral group) in a double-blind, randomized format. DEX
was stopped without tapering.

A person who did not participate in this study by as­
signing odd numbers to treatment and even numbers
to control group performed random allocation when the
patient entered the study. The copies 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 treat­
mation 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
in treatment. If menstruation occurred after 2 weeks of ad­
ministration 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 deter­
mined 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 (α =
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 dif­
ference was not statistically significant. Most of the pa­
tients 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 co­nsumption
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be oligomenorrheic prior to treatment. The mean diam­
eter of dominant follicle±SD of the treatment group was
18.4124±2.4314 mm, while the mean diameter of domi­
nant follicle in the placebo group was 13.8585±2.0722
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.

### DISCUSSION

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

<table>
<thead>
<tr>
<th>Menstrual status</th>
<th>Before treatment (No. of patients)</th>
<th>After treatment (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligomenorrhea</td>
<td>75</td>
<td>78.7% Regular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.3% Minimal changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8% No change</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>18</td>
<td>61.1% Regular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27.8% Minimal change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.1% No change</td>
</tr>
<tr>
<td>Polymenorrhea</td>
<td>2</td>
<td>100% Regular</td>
</tr>
<tr>
<td>NL Menstruation</td>
<td>16</td>
<td>100% Regular</td>
</tr>
<tr>
<td>Oligomenorrhea</td>
<td>72</td>
<td>8.2% Regular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21.9% Minimal change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>69.9% No change</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>23</td>
<td>8.2% Regular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21.9% Minimal change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>69.9% No change</td>
</tr>
<tr>
<td>Polymenorrhea</td>
<td>10</td>
<td>4.3% Regular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34.8% Minimal change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60.9% No change</td>
</tr>
<tr>
<td>NL Menstruation</td>
<td>14</td>
<td>100% Regular</td>
</tr>
</tbody>
</table>

*Minimal change: Slight change from the basic status (2 month interval to 42 days interval).*
traditional alternatives for CC-resistant patients include gonadotropin therapy and laparoscopic ovarian dianetherapy. 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 and Edward et al. 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, 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.

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 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. DHEAS has been shown to act as a prehormone for T, 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.

DEX therapy during the follicular phase has been described without any side effects or serious sequelae. 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.

REFERENCES

4- Bidzeniska B, Tworowska U, Demissie-M, Milewicz A: Modified dexamethasone and gonadotropin releasing hor-

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

<table>
<thead>
<tr>
<th>Group</th>
<th>DHEAS Mean ± SD</th>
<th>FSH Mean ±SD</th>
<th>LH Mean ±SD</th>
<th>LH/FSH Mean ±SD</th>
<th>P Mean ± SD</th>
<th>PRL Mean ±SD</th>
<th>T Mean ±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat B</td>
<td>321.92 ± 83.17</td>
<td>7.18 ± 3.22</td>
<td>14.29 ± 5.27</td>
<td>2.19 ± 1.00</td>
<td>3.21 ± 1.49</td>
<td>254.21 ±95.69</td>
<td>1.1 ± 0.35</td>
</tr>
<tr>
<td>Treat A</td>
<td>248.97 ± 85.33</td>
<td>7.08 ± 2.26</td>
<td>9.98 ± 3.62</td>
<td>1.46 ± 0.55</td>
<td>8.98 ± 4.92</td>
<td>247.04 ±78.52</td>
<td>0.35 ± 0.23</td>
</tr>
<tr>
<td>Cont B</td>
<td>325.29 ± 105.28</td>
<td>6.61 ± 3.22</td>
<td>14.09 ± 5.27</td>
<td>2.29 ± 0.79</td>
<td>3.26 ± 1.77</td>
<td>258.29 ±87.97</td>
<td>0.92 ± 0.24</td>
</tr>
<tr>
<td>Cont A</td>
<td>321.16 ± 87.98</td>
<td>6.76 ± 2.78</td>
<td>14.23 ± 5.27</td>
<td>2.33 ± 0.68</td>
<td>3.43 ± 1.85</td>
<td>268.33 ±80.76</td>
<td>0.86 ± 0.27</td>
</tr>
</tbody>
</table>

P-values: *0.001, 0.001, 0.001, 0.001, 0.272, 0.026, 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
mone-agonist (Dexa-GnRha) test in the evaluation of androgen source in hirsute women. Przegl Lek 57(7-8): 393-6, 2000.