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*Original Article*

# Comparison of the Efficiency of Anti-Androgenic Regimens Consisting of Spironolactone, Diane 35, and Cyproterone Acetate in Hirsutism

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**The aim of the present study was to evaluate the effects of three different anti-androgenic drug-therapy regimens, Diane 35 (cyproterone acetate (CPA) [2 mg] and ethinyl estradiol [35 μg]) plus CPA, Diane 35 plus spironolactone, and spironolactone alone, in patients with hirsutism. In this prospective, randomized clinical study, 79 subjects with idiopathic hirsutismus were studied. The patients were divided into 3 groups. Group I patients (n = 32) were treated with Diane 35 plus CPA, group II patients (n = 25) with Diane 35 plus spironolactone [100 mg], and group III patients (n = 22) with spironolactone [100 mg] alone. Serum FSH, LH, testosterone (T), and DHEAS levels were analyzed before and after treatment at 6 and 12 months. Hirsutism scores were graded according to the Ferriman-Gallwey scoring system, and side effects were monitored. All treatment regimens were found to be efficient and well-tolerated, and none of the patients stopped therapy due to any adverse event. However, in hormone screening, only patients on the Diane 35 plus CPA regimen revealed a decrease in serum T levels after therapy. As such, treatment of each hirsute patient should be planned individually, but with regard to both cost-efficiency and potential side effects, we recommend spironolactone alone in the treatment of hirsutismus.**

**Key words:** hirsutism, Diane 35, spironolactone, cyproterone acetate

The presence of increasing numbers of terminal hairs on the face, chest, back, lower abdomen, and inner thighs is referred to as hirsutism in women. Hirsutism, in combination with increased circulating levels of androgenic hormones, is accompanied by menstrual dysfunction, usually oligomenorrhea but sometimes amenorrhea.

The pharmacological therapy for androgen excess is directed at interrupting one or more of the steps in the pathway leading to its expression: (1)- suppression of adrenal and/or ovarian androgen production; (2)- alteration of the binding of androgens to their plasma proteins; (3)- impairment of the peripheral conversion of androgen precursors to active androgen; and (4)- inhibition of androgen action at the target tissue level. For the most part, such treatment has a limited effect on terminal hairs previously formed, since the cycle of hair growth ordinarily occurs only every 6 months to 2 years. Consequently, an effective approach to the management of hirsutism usually consists of both medical and cosmetic treatment, including plucking, bleaching, depilatory creams, electrolysis, waxing, and shaving.

In the present study we evaluated the efficiency of 3 anti-androgenic treatment regimens among premenopausal women with idiopathic hirsutismus.

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## Materials and Methods

In this prospective, randomized study, 79 premenopausal hirsute women that were diagnosed at our outpatient clinic were studied. Patients with Cushing's syndrome, androgen-secreting tumors, prolactinoma, congenital adrenal hyperplasia, or any other disease were not included in the study. Those patients who had taken any medication known to affect pituitary-gonadal function within at least 6 months of application to clinic were also not included. Patient histories regarding hirsutism and menstrual cycles were recorded. Each patient underwent a complete medical examination as well as an endocrine profile and hematological, hepatic, and renal function analysis. The degree of hirsutism was graded according to the Ferriman Gallwey scoring system [1] by the same physician during the study period. This physician was not informed of the given treatment regimen. A total score of $> 8$ was considered to confirm a diagnosis of hirsutism. Ultrasonography was performed for ovaries. Diagnosis of polycystic ovary syndrome (PCO) was based on the pelvic ultrasonography findings and a LH/FSH ratio $> 2$, obesity, and irregular menstrual cycles. Only patients with idiopathic hirsutism were included in the study. At the onset of study, the patients who would be coming to the outpatient clinic during the subsequent 3-month period were divided into 3 groups. Patients coming in the first month were assigned to group I ($n = 32$) and administered Diane 35 on days 1–21 of the cycles, plus 50 mg CPA on the first 10 days of the cycles. The subjects in the second month were assigned to group II ($n = 25$) and given Diane 35 plus spironolactone [100 mg/daily], and those in the third month were assigned to group III ($n = 22$) and administered spironolactone [100 mg daily] alone. The mean age of subjects in the 3 groups was $23.6 \pm 5.3$, $21.9 \pm 4.7$, and $24.3 \pm 7.2$ years, respectively, and the mean body mass index was $24.9 \pm 6.1$, $24.1 \pm 4.7$, $25.3 \pm 4.9$ kg/m$^2$, respectively. The Ferriman-Gallwey scores of hirsutism were $11.7 \pm 3.2$, $12.5 \pm 3.1$, and $12.3 \pm 4.5$ respectively, in groups I, II, and III at baseline. None of these parameters were significantly different among the groups. Blood levels of total T (Immunotech-Immunoradiometric assay kit), DHEAS (Immunotech-Radioimmunoassay kit), FSH, and LH (FSH IRMA and LH IRMA -Immunotech-Radioimmunoassay kit) were screened before and after at 6 and 12 months of therapy. Blood samples were drawn from the women after an overnight fasting in midfollicular phase of the menstrual cycle, or on a convenient day in those with amenorrhea. The efficacy of drug therapy regimens was assessed regarding clinical and laboratory findings. Clinically, patient information regarding the frequency of shaving, hot waxing, electrolysis, and thinning and paling of the colors of the terminal hairs as well as the Ferriman-Gallwey scores were recorded for each control. Response to the anti-androgen therapy was also assessed regarding the androgen levels (T and DHEA) at the 6 th and 12 th treatment months.

Statistics: SPSS for Windows, release 6.0 was used for the statistical analysis. The values are expressed as means $\pm$ SD. Determination of the level of significance was achieved using a Student's unpaired $t$-test for the laboratory data.

## Results

All patients had decreased their complaints of hirsutism at the end of the study. Clinical improvement was observed in all patients ($P < 0.05$, Table 1). The hormone results before and after treatment and the compari-

**Table 1** Ferriman-Gallwey scoring and shaving or hot-waxing frequency before and after treatment regimens

| Regimens (n) | Baseline | | At 6 months | | At 12 months | |
|---|---|---|---|---|---|---|
| | Ferriman-Gallwey scoring | Shaving or hot waxing frequency a month | Ferriman-Gallwey scoring | Shaving or hot waxing frequency a month | Ferriman-Gallwey scoring | Shaving or hot waxing frequency a month |
| Group I (32) | $11.7 \pm 3.2$ | $5.9 \pm 0.9$ | $9.6 \pm 2.9$* | $3.3 \pm 0.7$** | $8.7 \pm 2.1$* | $2.4 \pm 0.5$** |
| Group II (25) | $12.5 \pm 3.1$ | $5.5 \pm 1.0$ | $10.7 \pm 2.5$* | $3.2 \pm 0.6$** | $9.5 \pm 2.7$* | $2.4 \pm 0.5$** |
| Group III (22) | $12.3 \pm 4.1$ | $5.6 \pm 1.1$ | $10.5 \pm 2.8$* | $3.4 \pm 0.7$** | $9.3 \pm 3.1$* | $2.6 \pm 0.6$** |

*$P < 0.05$, **$P < 0.001$, comparison to baseline parameters.

son with basal levels are summarized in Table 2. There was no significant difference between groups I, II, and III with respect to baseline serum T, DHEAS, FSH, and LH levels ($P > 0.05$). At the end of the treatment, T levels were significantly decreased in group I ($0.77 \pm 0.39$ *vs.* $1.05 \pm 0.67$ ng/ml, $P < 0.001$). There was no significant decrease in T levels of groups II and III after the treatment period ($P > 0.05$) (Table 2). LH levels in groups I and II decreased significantly at 12 months, although the LH levels of group III showed no significant difference ($P > 0.05$) (Table 2). FSH and DHEAS levels of the three groups were not changed at the end of the therapy, compared with their baseline values ($P > 0.05$). Serum biochemistry (fasting blood glucose, AST, ALT, LDH, ALP, BUN, creatinin, Na, K, Cl levels) and CBC values of all patients were found in normal ranges before and after therapy. The frequency of hot waxing or shaving of the subjects a month before and after therapies is given in Table 1. There were no side effects requiring cessation of therapy in the patient groups. However, transient nausea was observed in 3 patients (2 in group II, 1 in group III) in the first 3 months.

## Discussion

In clinical practice, therapy for hirsutism, especially for the idiopathic type, includes oral contraceptives (OC), Cyproterone acetate (CPA), and antiandrogens such as spironolactone, flutamide, and finasteride [2–5]. Among these drugs, spironolactone, as an antiandrogen, acts primarily at the periphery to inhibit 5-$\alpha$ reductase activity and to interfere with the interaction of dihydrotestosterone and its intracellular receptor. CPA competitively inhibits the binding of T and dihydrotestosterone to androgen receptors. As a synthetic progestin, it inhibits gonadotropin secretion, thereby reducing ovarian androgen production. CPA increases the metabolic clearance rate of T by inducing hepatic enzymes and decreasing sex hormone-binding globulin (SHBG) levels [6]. Various drug combinations have been used for treatment of hirsutism with some success.

**Table 2** Hormonal parameters of patients with hirsutism before and after therapy

| Parameters | Baseline | 6 Months | 12 Months |
|---|---|---|---|
| FSH (IU/L) | | | |
| Group I | $6.53 \pm 4.5$ | $4.21 \pm 3.7$* | $5.54 \pm 509$* |
| Group II | $4.73 \pm 3.2$ | $5.22 \pm 3.4$* | $6.48 \pm 5.2$* |
| Group III | $6.21 \pm 4.3$ | $6.36 \pm 3.2$* | $5.28 \pm 3.4$* |
| LH (IU/L) | | | |
| Group I | $10.41 \pm 9.0$ | $5.94 \pm 5.6$** | $4.23 \pm 3.27$** |
| Group II | $9.15 \pm 7.9$ | $6.71 \pm 7.0$** | $4.92 \pm 3.5$** |
| Group III | $8.15 \pm 5.9$ | $12.6 \pm 8.15$** | $7.21 \pm 6.5$* |
| Testosterone (ng/ml) | | | |
| Group I | $1.05 \pm 0.67$ | $0.52 \pm 0.28$** | $0.77 \pm 0.39$** |
| Group II | $0.94 \pm 0.77$ | $0.95 \pm 0.96$* | $1.09 \pm 0.84$* |
| Group III | $0.94 \pm 0.54$ | $0.86 \pm 0.74$* | $0.74 \pm 0.43$* |
| DHEAS (mg/dl) | | | |
| Group I | $274.80 \pm 95.6$ | $282.66 \pm 111.2$* | $250.71 \pm 79.3$* |
| Group II | $308.59 \pm 129.8$ | $278.88 \pm 159.8$* | $348.26 \pm 125.4$* |
| Group III | $273.58 \pm 162.4$ | $219.73 \pm 95.6$* | $238.27 \pm 68.1$* |

Values are means $\pm$ SD. **$P < 0.001$; *$P > 0.05$. Basal compared with 6- and 12- month values.

The results of the present study show that all 3 group regimens are efficacious in treating hirsutism with respect to both patient complaints and clinical observation. However, only the serum T and LH levels of the patients in group I showed a significant decrease at 12 months of therapy in comparison with the basal levels. None of the patients stopped treatment, and side effects appeared to be acceptable in the 3 groups.

The efficiency of spironolactone, CPA, and OC in the treatment of hirsute patients is well known. However, there have been several comparative studies of combination treatments of hirsutism attempting to show which drug or combination is more cost-effective and produces fewer side effects. O'Brian *et al.* [7] and Erenus M *et al.* [8] have also compared a treatment of 100 mg spironolactone combined with OC versus 50–100 mg CPA for 10 days combined with OC regimens. They have shown these drug combination to be equally effective in the treatment of hirsutism with comparable side effects.

In other comparative studies including mono and/or combined anti-androgen drug treatments in which the effects of Diane 35, Diane 35, plus spironolactone, CPA plus E2, spironolactone plus E2, CPA plus E2, and spironolactone plus E2 at similar doses in the treatment of hirsutism, it has been concluded that these drug regimens are significantly effective in the treatment of hirsutismus treatment and are well-tolerated. They have also demonstrated a decrease in T levels after treatment, with no particular drug combination demonstrating a particular advantage over the other [9, 10].

Consistent with these studies, the current study showed that drug regimens including Diane 35 plus CPA 50 mg, Diane 35 plus spironolactone 100 mg, and spi-

ronolactone 100 mg alone are significantly effective in improving the symptoms of idiopathic and PCO hirsutism at 12 months of therapy. We observed no significant clinical differences among the 3 groups in response to therapy. Nevertheless, only the Diane 35-plus-CPA group achieved a significant reduction in plasma T levels after the end of treatment.

As it is well known that the main reason hirsute women go to a physician is their physical appearance; many women with idiopathic hirsutism have normal T and DHEAS levels, and they usually have regular menses. Correspondingly, although T and LH levels were decreased after therapy only with the group I regimen, all 3 treatment regimens were found to be effective. Therefore, considering the cost-effectivity, side effects, and easy usage, we recommend that hirsute patients use spironolactone alone, and if the patients develop menstrual problems, then OC may be added to the therapy regimen.

In conclusion, the present data demonstrate that Diane 35 plus CPA and Diane 35 plus spironolactone, and spironolactone alone are effective and safe in the treatment of hirsutism.

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