

# USE OF SPIRONOLACTONE IN COMBINATION WITH AN ORAL CONTRACEPTIVE IN TREATMENT OF HIRSUTISM

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## ABSTRACT

**Objective:** To assess the clinical and endocrinological efficacy of a combination of spironolactone and oral contraceptive pills in the treatment of hirsutism.

**Methods:** Thirty-six hirsute women were involved in our study; all patients were evaluated clinically and by laboratory investigation before and after six months of treatment with spironolactone (100 mg/day) and Microgynon 30 tablets (levonorgestrel 0.15 mg and ethinylestradiol 0.03) from day 5 to day 26 of the cycle. Each patient recorded her subjective assessment of hair growth and any side effects. The results for the group were expressed as means  $\pm$  standard deviation.

**Results:** Out of the 36 patients, 32 completed 6 months of treatment; while 4 patients withdrew from the study due to persistent nausea. Of the 32 patients, 25 had both subjective and objective improvement. Serum level of (testosterone, androstenedione and 17 hydroxyprogesterone) were significantly reduced and sex hormone binding globulin (SHBG) levels were significantly higher after treatment. LH, FSH levels were suppressed in all patients to levels of less than 0.9 i.u/l and less than 0.5 i.u/l after treatment.

**Conclusion:** Spironolactone in combination with oral contraceptive is effective and well tolerated for the treatment of hirsutism.

**Key words:** Hirsutism, Spironolactone, Contraceptive pills.

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## Introduction

Hirsutism is a troublesome cosmetic problem, may also be a sign of serious systemic disease, most patients with functional hirsutism have elevated production rates of testosterone, elevated metabolic clearance rates of testosterone, depressed levels of sex hormone binding globulin, and elevated levels of serum free testosterone and hair follicle sensitivity<sup>(1)</sup>. Pharmacological therapy consists of anti - androgens and includes the androgen receptor blockers, spironolactone and cyproterone acetate<sup>(2)</sup>. Other drugs reducing androgen expression include oral contraceptives and corticosteroids. A new follicular 5-alpha reductase inhibitor (finasteride) is currently under evaluation as an anti - androgen. Flutamide<sup>(2-4)</sup> gonadotrophin, by releasing hormone agonists suppresses the pituitary, decreases androgen and estradiol secretion, improves severe hirsutism and shows early promise in the treatment of hirsute<sup>(2,4,5)</sup>.

A major action of spironolactone is to inhibit androgen-binding receptor molecules in the cytosol or of the nucleus of target tissues, such as the skin; it inhibits steroidogenesis by interfering with ovarian enzymatic activity and inhibits 5- $\alpha$  reductase activities in pilo sebaceous unit<sup>(6)</sup>. Cyproterone acetate in combination with estrogen has been widely advocated<sup>(7,8)</sup> but it is associated with a number of side effects. The diuretic spironolactone, has been demonstrated to be useful<sup>(9,10,11)</sup> but when given alone it is not as effective as the cyproterone acetate/estrogen combination<sup>(12)</sup> or in combination with oral contraceptive<sup>(13,14)</sup>.

Furthermore, nearly 56% of women experienced the problem of polymenorrhea and other side effects such as urticaria, and scalp hair loss<sup>(15,16)</sup>. To overcome this problem and to produce an elevation of sex hormone binding globulin (SHBG)<sup>(17)</sup> we have assessed the effect of adding estrogen in the form of oral contraceptive to the spironolactone (100 mg daily).

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## Methods

Thirty-six premenopausal hirsute women were involved in our study between 1997 and 2000 at Queen - Alia Military hospital. None of these patients used any medications in the previous six months. The patients were advised to avoid pregnancy during the study period. A complete medical and gynecological examination was performed for each patient. A 20 ml sample of blood was obtained in the follicular phase in patients with regular menses. Seven patients had irregular cycles more prolonged than 35 days. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone, androstenedione, dehydroepiandrosterone sulphate (DHA-S) and sex hormone binding globulin (SHBG) were measured.

After 6 months of treatment with spironolactone (100mg) and microgynon 30 from day 5 to 26 of the cycle, all the above mentioned investigations were repeated. Patients with hyperprolactinemia, ovarian or adrenal neoplasm, drug - induced hirsutism, cushing disease, and thyroid disease were excluded. Distributions of patients according to age, and weight were shown in Table I and II.

Ferriman - Gallwey (F-G) scoring system <sup>(16)</sup> was used to assess hair growth before and after treatment, the hair score was assessed on all occasions by the same observer.

Paired t- test was carried out to detect the significance of hormonal profile changes, which were expressed as means and standard deviation values.

## Results

Of the 36 patients, 32 completed 6 months of treatment. Four patients withdrew due to persistent nausea.

Breast tenderness occurred in two patients and intermenstrual spotting in three. No changes in blood pressure were demonstrated.

Two reported polyuria in the first few days of treatment. After 6 months of treatment, 25 of the 32 patients showed an improvement on the basis of a reduction of more than 3 points in the score Ferriman and Gallwey hair. No patient had a higher score after the treatment, and the hair scores fell from a mean of 17.3 ( $\pm$  2.8) to 11.1 ( $\pm$  2.7), ( $p < 0.01$ ). LH and FSH were suppressed in all patients to levels of  $< 0.7$  i.u./L and  $< 0.2$  i.u./L after treatment. Serum levels of testosterone, androstenedione, and 17-OHP were significantly reduced and SHBG levels were significantly higher after treatment (Table I).

Serum levels of testosterone were suppressed from

$3.2 \pm 0.3$  n mol /L to  $2.3 \pm 0.2$  n mol /L ( $p < 0.05$ ), androstenedione from  $8.7 \pm 0.3$  n mol /L to  $4.5 \pm 0.4$  n mol /L ( $p < 0.01$ ), 17 hydroxyprogesterone from  $7.4 \pm 0.7$  to  $3.1 \pm 6.3$  ( $p < 0.01$ ), and SHBG raised from  $48 \pm 3$  to  $102 \pm 8$  ( $p < 0.005$ ), no significant change of Dehydroepiandrosterone sulphate before and after treatment  $5.2 \pm 0.3$  n mol /L to  $4.3 \pm 0.3$  n mol /L.

## Discussion

Spironolactone blocks androgen receptors and its effectiveness in hirsutism is dosage - dependent, Low dosages are less active than other antiandrogens, whereas high dosages (200 mg /day) are very effective at the cost of several adverse effects particularly dysfunctional uterine bleeding <sup>(2,15,16)</sup>.

Spironolactone when given alone is not as effective as in combination with oral contraceptive <sup>(13,14)</sup>.

The addition of oestrogen increase, therapeutic effectiveness by suppressing gonadotrophin - mediated ovarian androgen secretion and by increasing sex hormone binding in plasma, this reduce the free, biologically androgen in the circulation <sup>(2)</sup>.

GnRH agonist, suppressing the pituitary, decrease androgen and oestradiol secretion and improve severe hirsutism, to avoid estrogen deficiency problem, (add back) therapy with estrogen -progestogens or combined oral contraceptives is advised, this method of treatment is complicated and expensive limiting its use to severe form of ovarian hyperandrogenism with hyperinsulinemia <sup>(2,5)</sup>. Cyproterone acetate with ethinyl oestradiol is effective and better tolerated but much expensive than the combination of spironolactone and the oral contraceptive pills <sup>(19)</sup>. Bassaw *et al* <sup>(20)</sup> showed no significant change in hirsutism index, and measurement of serum testosterone, androstenedione, Dehydroepiandrosterone sulphate and sex hormone binding globulin (binding Capacity).

Although spironolactone has a known diuretic effect, this was not a long term problem in any of our patients, two reported polyuria in the first few days of treatment. No changes in blood pressure were demonstrated during treatment. In our study combination of spironolactone and microgynon produced an improvement in hirsutism as assessed by Ferriman and Gallwey score in 78% of the patient who completed treatment also produced significant change in serum androgen concentration including serum levels of testosterone, androstenedione, 17-hydroxy progesterone and sex hormone binding globulin so spironolactone in combination with oral oestrogen are effective and well tolerated agents for the treatment of hirsutism.

**Table I.** Distribution of patients according to age

Age (year)	Number of patients
< 20	4
21 – 25	12
26 – 30	9
31 – 35	8
36 – 40	3

**Table II.** Distribution of patients according to weight.

Weight (kg)	Number of patients
< 50	3
50 – 60	7
61 – 70	15
71 – 80	8
>80	3

**Table III.** Serum androgen concentrations before and after 6 months of treatment with spironolactone 100 mg plus Microgynon 30.

	Pre-treatment	Post-treatment	Significance of difference (P)
Testosterone	3.2 ( $\pm$ 0.3)	2.3 ( $\pm$ 0.2)	< 0.05
Androstenedione (n mol/L)	8.7 ( $\pm$ 0.8)	4.5 ( $\pm$ 0.4)	< 0.01
Dehydroepiandrosterone Sulphate ( $\mu$ mol/L)	5.2 ( $\pm$ 0.3)	4.3 ( $\pm$ 0.3)	NS
17- hydroxy progesterone (n mol/L)	7.4 ( $\pm$ 0.7)	3.1 ( $\pm$ 6.3)	< 0.01
Sex hormone binding globulin (Binding Capacity)	48 ( $\pm$ 3)	102 ( $\pm$ 8)	< 0.005

Results are means  $\pm$  SD.

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