

## HIRSUTISM AND TREATMENT

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Gazi Medical Journal 3 : 47-52, 1992

**SUMMARY :** *Hirsutism is a common clinical condition in women characterized by the excessive growth at terminal hair in a male pattern as a result of excessive production of androgen. Testosterone is the principal circulating androgen in normal women.*

*Hirsutism's spectrum varies from mild forms with dominating pshyctic component to severe forms associated with virilisation.*

*The cause of the increased androgen secretion in idiopathic hirsutism is poorly understood, several hypothesis have been proposed.*

*The treatment for hirsutism is determined by the underlying pathophysiological conditions. When the diagnosis is idiopathic hirsutism, however the best treatment is uncertain and several available regimens are possible.*

**Key Words :** *Hirsutism, Androgen, Medical Treatment.*

Hirsutism is a common clinical condition in women characterized by the excessive growth of terminal hair in a male pattern as a result of excessive production of androgens (Ehrman and Rosenfield, 1990; Killinger, 1981; Rittmaster and Loriaux, 1987; Siegel et al. 1990). Hair must be bigger than 0.5 cm. coarse and pigmented (Greenspan, 1991).

The androgen production in the female depends upon direct secretion by the ovaries and the adrenals and upon peripheral conversion of androgen precursors and finally on the metabolic clearance rate which may be regarded as a function of androgen production. More than 98 % of the androgens circulating in the blood are bound to specific plasma proteins such as sex hormone binding globulin (SHBG) (Breckwoldt et al. 1989).

The major circulating androgens in women are testosterone, dihydrotestosterone, androstenedione, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S). Testosterone is the principal circulating androgen in normal women.

A woman is considered to have hirsutism when she has a score of 8 or more on the Ferriman and Gallwey scale, in which hair growth in each of the eight androgen sensitive areas is graded from 0 (none) to 4 (Frankly virile).

The eight hair growth areas on the Ferriman and Gallwey scale are :

1- Upper lip

- 2- Chin
- 3- Chest
- 4- Abdomen
- 5- Back
- 6- Sacroiliac region
- 7- Upper sides of the extremities
- 8- Lower sides of the extremities (Ferriman and Gallwey, 1961).

Hirsutism's spectrum varies from mild forms with dominating psychic component to severe forms associated with virilization (Erkkola and Ruutuinen, 1990). Virilism divides into 2 groups. 1- Defeminization, 2- Masculinization.

Signs of Defeminization :

- 1- Amenorrhoea
- 2- Menstrual disturbance
- 3- Breast atrophy
- 4- Lack of woman behavior
- 5- Lack of woman lipid deposition.

Signs of Masculinization.

- 1- Clitoris hypertrophy
- 2- Deep voice
- 3- Acne
- 4- Alopecia
- 5- Male type body appearance
- 6- Male type behavior

Causes of hirsutism (Rittmaster and Loriaux, 1987).

#### **I-Androgen mediated :**

- 1- Ovarian
  - a) Polycystic ovarian syndrome
  - b) Insulin resistance
  - c) Ovarian tumors
- 2- Adrenal
  - a) Cushing syndrome
  - b) Androgen producing tumors
  - c) Congenital adrenal hyperplasia

- i) 11-Hydroxylase deficiency
- ii) 21-Hydroxylase deficiency
- iii) 3 Beta - hydroxysteroid dehydrogenase deficiency

#### **3- Combined ovarian and adrenal**

- a) Idiopathic hirsutism (mostly ovarian)
- b) Polycystic ovarian syndrome secondary to adrenal hyperandrogenism

#### **4- Exogenous medications**

- a) Androgens
- b) Birth control pills

#### **II- Androgen Independent :**

- 1- Drugs : Minoxidil, diazoxide, phenytoin, glucocorticoids, cyclosporine
- 2- Hyperprolactinemia

**Pathogenesis :** The intracellular reduction of testosterone to dihydrotestosterone has to be considered as a basic requirement for the androgen mediated growth of the hair follicle in sexual skin areas (Breckwoldt et al. 1989).

Hirsutism is caused by increased androgen production or sensitivity increase of hair follicles to androgen in sexual areas.

In patients suffering from hirsutism, the conversion rate of testosterone to dihydrotestosterone is significantly increased, almost reaching male levels. Dihydrotestosterone causes androgen dependent hair growth (Breckwoldt et al. 1989; Greenspan, 1991; Rittmaster and Loriaux, 1987).

The cause of the increased androgen secretion in idiopathic hirsutism is poorly understood. Several hypothesis have been proposed (Rittmaster and Loriaux, 1987).

a) Hypothalamus : Some women with polycystic ovarian syndrome have an altered gonadotropin secretory pattern in which the ratio of plasma luteinizing hormone to follicle stimulating hormone is high and the midcycle gonadotropin surge is absent. The abnormalities in luteinizing hormone secretion have been offered as evidence for a primary hypothalamic defect in this condition. Other authors however, have shown that women with adrenal hyperandrogenism or an ovarian tumor may have this abnormality.

b) Adrenal : Iodocholesterol uptake by the adrenal cortex is increased in women with polycystic ovarian syndrome, suggesting adrenal hyperfunction. Levels of DHEA and DHEA-S, androgen precursors that are almost entirely of adrenal origin, are elevated in patients with idiopathic hirsutism and polycystic ovarian syndrome. These patients differ from women with classic congenital adrenal hyperplasia in that the proposed enzyme deficiency is mild and results in only modest elevations of the appropriate steroid intermediates.

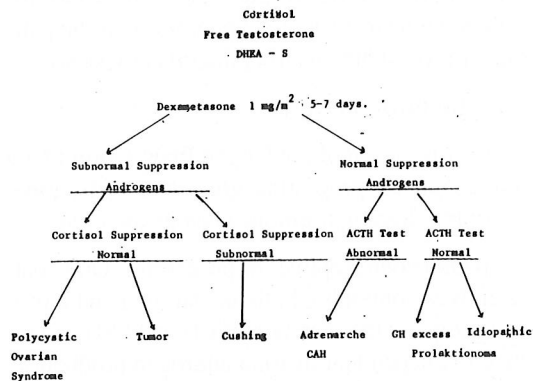
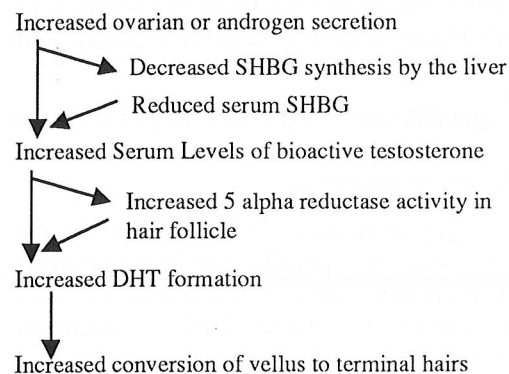
c) Insulin : There is an association between hyperinsulinism and androgen excess. Women with polycystic ovarian syndrome often have hyperinsulinemia, even in the absence of obesity.

d) Obesity : Many hirsute women, especially those with polycystic ovarian syndrome are obese. In some, weight loss reverses the hyperandrogenism and menstrual disturbance. Adipose tissue can convert preandrogens into testosterone. Obesity is also associated with reduced plasma concentrations of sex hormone binding globulin, this may serve to amplify the biologic effect of an increased testosterone production rate. Obesity is associated with insulin resistance. This sequence of events, however, has never been documented experimentally.

e) Prolactin : Increased plasma prolactin levels is often associated with elevated plasma DHEA and DHEA-S levels.

f) Sex hormone binding globulin : In hirsutism the plasma concentrations of SHBG are decreased resulting in elevated levels of free androgens (Breckwoldt et al. 1989).

Hypothyroidism, androgen treatment, corticosteroids, obesity and acromegaly decrease SHBG. Hyperthyroidism, pregnancy, estrogen therapy and cirrhosis increase SHBG.



Differential Diagnosis of Hyperandrogenemia (Ehrmann and Rosenfield, 1990)

Development factors of androgen dependent hirsutism (Greenspan, 1991).

**Treatment :** The treatment for hirsutism is determined by the underlying pathophysiologic conditions. When the diagnosis is idiopathic hirsutism, however the best treatment is uncertain and several available regimens are possible.

Medical treatment involves suppressing adrenal or ovarian androgen production or blocking the action of androgens at terminal hairs to have a shorter active growth phase and become finer and less pigmented. The response to medical treatment however is slow and does not always produce satisfactory results. This treatment has limited effect on terminal hairs previously formed since the cycle of hair growth ordinarily occurs only every 6 months to 2 years. Therefore hirsutism therapy divides into 2 groups.

- 1- Mechanic (Cosmetic) therapy.
- 2- Medical therapy.

**1- Mechanic therapy :**

- a) Bleaching and mechanical hair removal.
- b) Electrolysis.
- c) Thermolysis.

Generally 6 to 12 months are needed to judge the efficacy of a given therapy (Ritmaster and Lorrux, 1987). In this period mechanic treatment is

applied. Electrolysis and thermolysis are popular and medically proven electrochemical and electro-surgical techniques for permanent hair removal (Richards et al. 1986; Wagner, 1990). In an electro-epilation (electrolysis) treatment 93 % of the patients improved but electroepilation is expensive.

## 2- Medical therapy:

**1- Suppression of Androgen Production :** Oral contraceptives, progestins, glucocorticoids, gonadotropin releasing hormone analogs are used.

a) Oral contraceptives or progestins : Oral contraceptives containing both an estrogen and a progestin suppress the secretion of LH and FSH and reduce LH dependent ovarian androgen production. The progestin component also increases the metabolic clearance rate of testosterone, while the estrogen component stimulates the production of SHBG. Although treatment with a progestin alone suppresses the secretion of LH and increase the metabolic clearance rate of androgens there is no concomitant increase in SHBG levels. Progestins are therefore generally less effective than combination oral contraceptives. They may be useful when estrogens are contraindicated (Greenspan, 1991). This treatment has been clinically helpful in up to 75 % of women with idiopathic hirsutism (Rittmaster and Loriaux, 1987).

b) Glucocorticoids : If increased androgen production is predominantly or entirely of adrenal origin such as occurs in adult onset adrenal hyperplasia treatment with glucocorticoids is indicated. In these cases dexametasone 0.5-0.75 mg/day or prednisone 5-7.5 mg/day has been used to reduce the production of adrenal androgens (Greenspan, 1991). This treatment is effective in reducing hair growth up to 50 % of women (Rittmaster and Loriaux, 1987).

c) Gonadotropin releasing hormone analogues : GnRH analogues (Nafarelin) are effective in the management of hirsutism due to excessive ovarian androgens. They inhibit pituitary FSH and LH secretion and thus decrease ovarian androgen production. Since ovarian estradiol production will also be reduced, treatment with GnRH analogues will produce symptoms and other changes of estrogen deficiency. These can be prevented by concurrent low dose estrogen replacement.

In one research nafarelin was used 1000 microgram/day for 6 months. Serum gonadotropin, tes-

tosterone, free testosterone and androstenedione concentrations decreased significantly during treatment. The clinical response was very good, hair growth was slower and new hair was less coarse compared to the pretreatment period (Andreyko et al. 1986).

## 2- Antiandrogens:

a) Cimetidine : Cimetidine is a weak antiandrogen and has not been used widely to treat hirsutism.

b) Spironolactone : Spironolactone increases testosterone metabolism, reduces testosterone production and decreases peripheral conversion of testosterone to estradiol. Spironolactone competes with dihydrotestosterone for androgenic receptors in target tissues. It also decreases 17 alpha hydroxylase activity and thus reduce serum levels of testosterone and androstenedione (Greenspan, 1991).

Doses ranging from 50 to 200 mg/day have been used to treat hirsutism.

Aldactone 50 mg/day had little effect on hormone concentrations, only LH was significantly reduced after 12 months of treatment but hair growth reduced after 5 months of treatment.

Very good clinical results were observed in 80 % of the patients who were under study for a minimum of 3 to 4 years (Lunde and Djoseand, 1987; Tremblay, 1986).

When the drug is used 100 mg. spironolactone twice daily on days 4-21 of menstrual cycles metrorrhagia, nausea, fatigue, headache, urticaria, scalp hair loss were seen frequently. Therefore 50 mg spironolactone twice daily on days 4-21 of the menstrual cycle is recommended. Alternatively one may consider adding cyclically estrogen / progesterone therapy to continuous spironolactone therapy (Helfer et al. 1988).

Studies with spironolactone in our country showed that hirsutism reduced 50 % (Arslan et al. 1989; Hatemi et al. 1985) and 71 % (Özata et al. 1990).

Spironolactone is especially useful for therapy in women in whom oral contraceptives are contraindicated or ineffective.

c) Cyproteron acetate : It suppresses the secretion of LH, with a subsequent decrease in ovarian androgen production, and blocks the binding of androgens to receptors in the hair follicles (Greenspan, 1991).

Used dosage is 50 mg/day on days 5-14 of each menstrual cycle. Reaches maximum effect at 9<sup>th</sup> month. At 10<sup>th</sup> month dosage is reduced 1/4 tablet on days 5-14 of the menstrual cycle. The treatment is continued to 2 years.

At the end of the first month of treatment acne improves and at the end of the third month hair becomes thin, pale and fall out.

Since endogenous estrogen production is also reduced during treatment, estrogen is usually administered concurrently. A commonly used dosage is 2 mg of cyproterone acetate plus 50 microgram of ethinyl estradiol daily on days 5-25 of each menstrual cycle.

Side effects includes nausea, weight gain, breast tenderness, breakthrough bleeding, headache, decreased libido and depression.

In our country, studies with cyproterone acetate showed that hirsutism improved 80 % and indicated as an important agent in hirsutism treatment (Kologlu et al. 1982; Özata et al. 1990).

### 3 - New Drugs :

a) Flutamide : Flutamide is a potent, nonsteroidal, selective antiandrogen without progestational, estrogenic, corticoid or antigonadotrophic activity (Ehrmann and Rosenfield, 1990). Treatment with flutamide 250 mg twice daily and an oral contraceptive resulted in a particular rapid and marked decrease in the total hirsutism score, which reached the normal range at 7 months. Treatment was associated with a decrease in plasma luteinizing hormone, progesterone and estradiol levels. Plasma sex hormone binding globulin levels were increased significantly during therapy. No clinically significant side effects were observed (Cusan et al. 1990).

b) Topical antiandrogens : Topical antiandrogens hold promise as safe and effective treatments for women with localized hirsutism (Rittmaster and Loriaux, 1987).

c) Ketoconazole : It is an antifungal drug. It reduces steroid biosynthesis in testicular and adrenal tissue. This inhibitory action on cytochrome p-450 dependent enzymes is the basis for the use of ketoconazole in the treatment.

Used dosage is 400-1200 mg/day for 1-6 months (Martukainen et al. 1988). High dose (800-1200 mg/day) ketoconazole treatment decreased

serum androstenedione, dehydroepiandrosterone and testosterone concentrations, while that of 17 alpha hydroxyprogesterone, estradiol, ACTH, LH, FSH, cortisol increased (Venturoli et al. 1990).

Several side effects and complications arise during treatment, such as headache, nausea, loss of scalp hair, abdominal pain, dryness of the skin, decreased libido, increased SGOT, SGPT and alkaline phosphatase levels, increased triglyceride, cholesterol levels, polymenorrhea, oligomenorrhea, and anovulatory cycle (Venturoli et al. 1990). Increased in SGOT, SGPT levels return to normal within 2 months after the drug is stopped.

Studies about the role of ketoconazole in polycystic ovarian syndrome and hirsutism treatment in our country indicated that this drug decreases androgen levels but here is no satisfactory effects on hirsutism (Kologlu et al. 1990).

In our country, in the other study with ketoconazole, androgen levels significantly decreased and clinically improvement was observed (Akalin, 1991).

d) 5 alpha reductase inhibitors : It is expected that, in the near future 5 alpha reductase inhibitors will be tested in the clinic as a treatment for hirsutism (Brooks, 1986). Azasteroid "finasteride" is a 5 alpha reductase inhibitor (Gillman et al. 1990).

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