

# Flutamide in the treatment of female androgenic alopecia

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*Female androgenic alopecia (FAA) is a common endocrine abnormality in premenopausal women. Evidence suggests that androgens are involved in this condition and that positive clinical response can be obtained by using antiandrogens to treat balding women. The following study investigates the effect of the pure antiandrogen flutamide on 13 female patients with androgenic alopecia.*

Baldness affects approximately 13% of women in their early 20s and 30s.<sup>1</sup> The most common type of hair loss, known as "diffuse alopecia," is not generally related to increased androgen production and does not present with frontoparietal recession.<sup>1,2</sup> The second type, known as "patterned androgenic alopecia," is associated with increased androgen production. This latter form of baldness usually coexists with other virilizing features, especially hirsutism, acne and seborrhea.<sup>3,4</sup> Despite these classifications, there is increasing evidence that a common etiology exists for female baldness, involving abnormalities in androgen metabolism and genetic factors.<sup>3,5,6</sup>

The response of balding women to antiandrogen therapy provides evidence

that male hormones play a role in FAA. Clinical trials<sup>7-10</sup> using cyproterone acetate and spironolactone have yielded a positive response rate of about 45%. Such a limited rate of success may be related to the lack of specificity of these antiandrogens and their undesirable side effects.<sup>11-13</sup>

We<sup>14</sup> have recently observed a dramatic positive response to the administration of the specific nonsteroidal antiandrogen flutamide in patients suffering from hirsutism and related symptoms. These positive effects, coupled with a lack of significant adverse effects from the drug, prompted us to conduct our own pilot study on the effects of similar treatment with flutamide on FAA.

## Subjects

Thirteen premenopausal women aged between 20 and 39 years (mean = 28 years) met the criteria for FAA and were included in the study. Informed consent was obtained from all patients, who had generally good health and received no medication for two months before the start of the study.

## Study protocol

To evaluate the degree of androgenic alopecia in patients, the following arbitrary rating score (0-4) was used, based on the criteria of Rook and Ludwig:<sup>1,15</sup>

- 0: no hair loss
- 1: perceptible thinning of scalp hair
- 2: obvious thinning of hair on the crown area
- 3: pronounced rarification of hair on the crown
- 4: full baldness, total denudation.

All patients were evaluated monthly by a dermatologist who was unaware of the medication used by the patients. The sum of the individual scores were then used to evaluate the degree of alopecia in the study group. Other hair loss problems such as iron deficiency, alopecia areata and hypothyroidism were ruled out. Ten patients had concomitant hirsutism, while nine had seborrhea and two had acne; these conditions were all evaluated according to Cremonici et al.<sup>16</sup>

Each patient underwent a complete endocrine baseline evaluation between day 20 and 25 of their menstrual cycle,

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Table 1: Clinical data of patients with androgenic alopecia at start of therapy

Patient (number)	Age (years)	Ideal Body weight (%)	Associated symptoms <sup>†</sup>	LH/FSH	Pelvic ultrasound ovaries	Previous therapy	Menses <sup>‡</sup>
1	29	+65	H,A,S	0.96	Normal	Oral contraceptive	H
2	25	+85	H	2.40	Normal	Spironolactone	O
3*	31	+15	H	2.58	Increased volume bilaterally	Oral contraceptive, dexamethasone	A
4	21	+140	H, S	1.80	Normal	Nil	A
5	33	+5	H, A, S	0.5	Normal	Spironolactone	N
6*	25	+2	H, S	2.16	Normal	Nil	N
7	23	+47	H, S	2.49	Cystic bilateral	Nil	A
8*	20	+60	H, S	0.26	Normal	Nil	N
9	39	+12	H, S	1.37	Normal	Nil	N
10	28	-10	H, S	0.90	Normal	Nil	N
11*	26	+2	S	0.26	Normal	Minoxidil	N
12*	36	-8	Nil	0.12	Normal	Nil	N
13	29	-8	Nil	1.15	Follicular cyst	Nil	N

\*family history of female pattern androgenic alopecia

<sup>†</sup>H = hirsutism, A = acne, S = seborrhea

<sup>‡</sup>N = normal, O = oligomenorrhea, A = amenorrhea, H = hypomenorrhea

in those patients with cycles. Patients were assessed for hair loss, hirsutism, acne and seborrhea, as well as for plasma Beta human chorionic gonadotropin (βhCG), luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin (PRL), sex hormone binding globulin (SHBG) and ovarian as well as adrenal steroid levels. These tests were performed at monthly intervals for 12 months. In addition, patients had a

complete medical examination with hematologic, hepatic and renal function analyses. Ten ovulatory nonalopecia control subjects were used as controls for steroid serum and SHBG levels during their late luteal phase. Patients were identified by the above clinical criteria and not according to serum androgen concentration levels. One to three days after the initial evaluation, patients started taking 250 mg of

oral flutamide<sup>17</sup> (Euflex®, Schering) twice daily in combination with an oral contraceptive (Ortho 1/35®, Ortho).

#### Hormone assays

All blood samples were collected at 8 a.m. Serum levels of the following total steroids were measured by radioimmunoassay: progesterone, estradiol, androstenedione,

testosterone, androstane-3 $\alpha$ ,17 $\alpha$ -diol (3 $\alpha$ -diol), androstane-3 $\beta$ ,17 $\beta$ -diol (3 $\beta$ -diol), dehydroepiandrosterone (DHEA) and its sulfate, (DHEA-S).<sup>18</sup> Serum  $\beta$ hCG, LH, FSH and PRL were also measured by double-antibody radioimmunoassay,<sup>19</sup> while SHBG levels were measured with an immunoradiometric assay (Farnos-Diagnostics). The intra-assay coefficients of variation at low (20 nmol/L) and high (100 nmol/L) SHBG serum concentrations were  $4.1 \pm 0.9$  standard deviations (SD) and  $2.6 \pm 0.5$  SD respectively.

### Calculations

Radioimmunoassay data were analyzed using a program based on model II of Rodbard and Lewald.<sup>20</sup> Statistical significance was measured according to a multiple-range test of Duncan-Kramer.<sup>21</sup> Results are presented as mean  $\pm$  standard error of means (SEM) unless otherwise indicated.

### Results

Table 1 illustrates the initial clinical and laboratory evaluation of the 13 patients with androgenic alopecia. The mean duration of symptoms of alopecia was 5.6 years. Patients 3 and 7 had LH/FSH ratios and ultrasonic findings consistent with polycystic ovarian disease. Five women had an history of abnormal menses and five had received some previous treatment; another five had a family history of female pattern androgenic alopecia.

The overall changes in the androgenic alopecia score during the 12 months of therapy is illustrated in Figure 1. A rapid improvement in androgenic alopecia score was seen

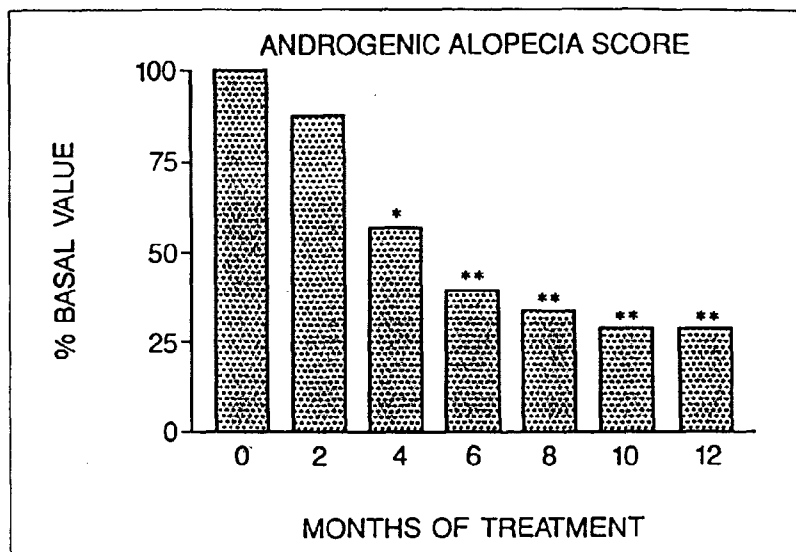


Figure 1: Androgenic alopecia score during 12 months of therapy with flutamide and an oral contraceptive in women with female androgenic alopecia. Results are expressed in % of basal values at time 0.

\*P < 0.05

\*\*P < 0.01

during the antiandrogenic therapy with a 40% ( $P < 0.05$ ) decrease at four months and an almost maximal inhibition at six months of therapy ( $P < 0.01$ ). At the eight-month interval, an approximate 75% inhibition of alopecia score was obtained with a regrowth (increased hair density) of cosmetically suitable scalp hair in 10 of 13 patients. Only one subject (patient 4) in the alopecia and associated hirsutism group failed to respond to antiandrogen therapy. In contrast, only one of the three patients with no associated hirsutism (patient 11) had a favorable response. An example of the remarkable improvement in androgenic alopecia after eight months of therapy is illustrated in Figure 2A and 2B.

Patients suffering from seborrhea and acne were completely relieved of

their symptoms within four to six months of therapy respectively (Figure 3). As shown in Figure 3, the score for hirsutism was improved to approximately 50% of initial values after six months of therapy. This represents only a 10% higher score than that found in normal (nonhirsute) premenopausal women. By the end of the 12 months of antiandrogen administration, the body hair distribution of the study group was within the normal range for premenopausal nonhirsute women.

Figures 4 and 5 show the effect of the combination therapy on ovarian and adrenal serum steroid levels. A highly significant ( $P < 0.01$ ) maximal inhibition of serum progesterone was already seen after one month of therapy (Figure 4A). The serum estradiol concentration was

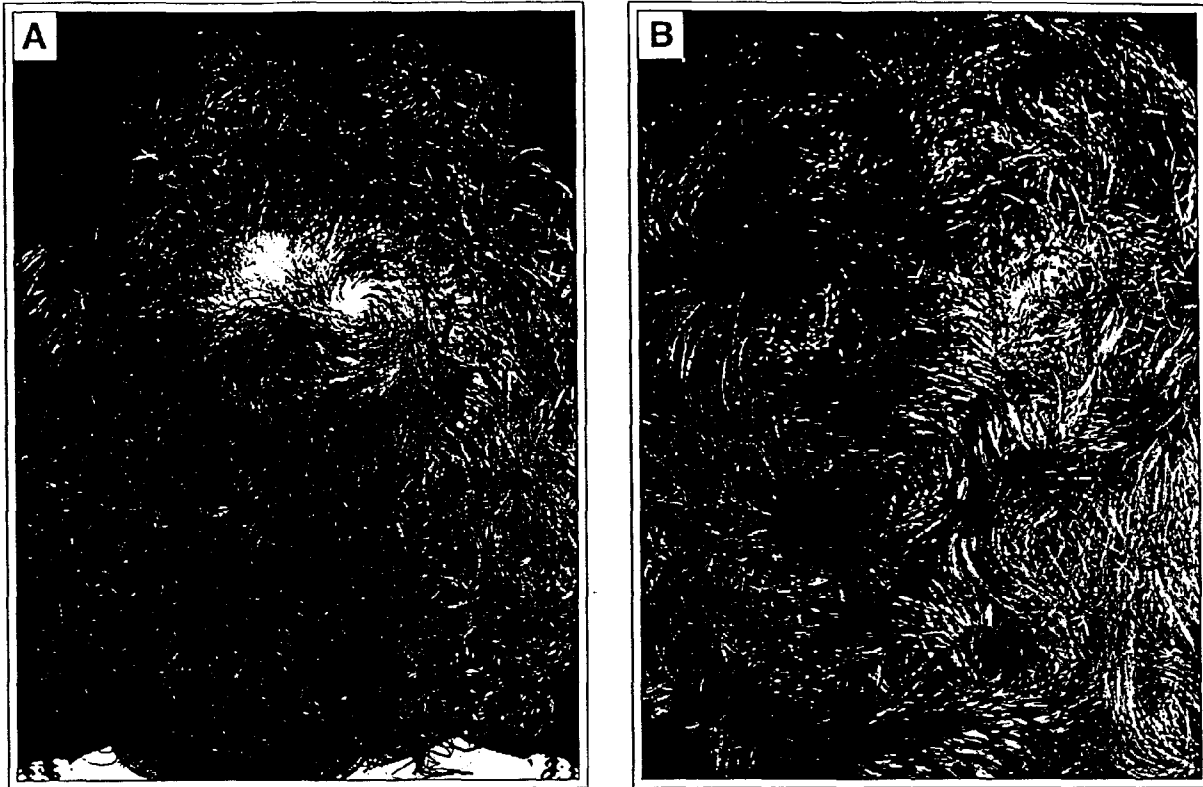


Figure 2: Patient #7 is shown with androgenic alopecia before (A) and after (B) eight months of therapy with flutamide and an oral contraceptive pill

decreased by 60% ( $P < 0.01$ ) at one month, followed by a continuous progressive decline to 10% ( $P < 0.01$ ) at 12 months (Figure 4B). On the other hand, serum androstenedione decreased ( $P < 0.05$ ) by 25% to 35% at one, two and three months of treatment (Figure 4C). Serum testosterone values progressively decreased throughout treatment with a significant inhibition ( $P < 0.05$ ) at six months of therapy and at longer periods (Figure 4D).

There was no significant effect of treatment observed on serum DHEA, DHEA-S, 3 $\alpha$ -diol and 3 $\beta$ -diol basal

levels (Figure 5A, 5B, 5C and 5D respectively). When comparing the steroid values found in normal luteal phase premenopausal women at time 0 (Figures 4 and 5), the patients suffering from androgenic alopecia had significantly higher ( $P < 0.05$ ) serum levels of androstenedione, 3 $\alpha$ -diol and 3 $\beta$ -diol, except for estradiol, which was significantly lower.

Table 2 illustrates the SHBG plasma concentration through treatment in patients with alopecia compared to normal controls at time 0. Untreated patients with androgenic alopecia had

much lower SHBG values compared to normal controls ( $21 \pm 9$  and  $60 \pm 7$  nM plasma respectively,  $P < 0.01$ ). The treatment regimen caused an almost five-fold increase in pretreatment SHBG values after only one month of therapy. Such an effect is probably due to the well-known estrogenic stimulatory effect of the oral contraceptive on hepatic synthesis of the binding globulin. Although plasma LH levels were maximally inhibited after only one month of therapy (from  $25 \pm 2.2$  mIU/mL at time 0, to  $6.4 \pm 1.5$  mIU/mL at one month), no

significant change was seen on plasma FSH and PRL levels (data not shown). The treatment had no significant effect on hepatic, renal and hematologic function tests. The side effects most frequently reported by patients were dry skin and increased appetite.

**Discussion**

This study shows for the first time that female pattern androgenic alopecia responds well to therapy with the antiandrogen flutamide. Such therapy caused a rapid and marked reduction in androgenic alopecia score and induced hair regrowth in 10 of 13 patients.

The hair follicles on the scalp differ from all other hair, in that its growth is not androgen-dependent.<sup>6</sup> On the contrary, in genetically predisposed male and female individuals, androgens are responsible for the progressive replacement of terminal by vellus hair.<sup>22,23</sup> Although no related functional hyperandrogenism can be identified in many cases of FAA, evidence now supports the proposal that hair loss can be due to alteration in the enzymatic activity of the pilosebaceous unit. The pilosebaceous unit possesses the enzymatic capability for converting testosterone as well as other C-19 steroid precursors into 5 $\alpha$ -DHT via 5 $\alpha$ -reductase.<sup>23-25</sup> Additionally, there is evidence that bald scalp tissue has a greater capacity than nonbald scalp to convert testosterone into 5 $\alpha$ -DHT in vitro.<sup>23,25</sup> The critical factors involved in female alopecia may be related to the androgen biosynthetic ability and the response of the target organ, and not to the circulating steroid hormone levels. It should be mentioned, however, that serum androstenedione levels were elevated in women suffering from andro-

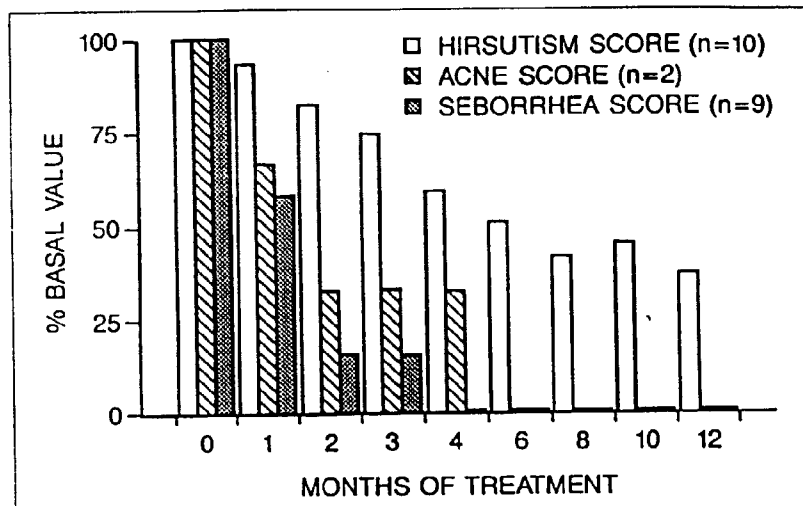


Figure 3: Hirsutism, acne and seborrhea score during 12 months of therapy with flutamide and an oral contraceptive in women with androgenic alopecia. Results are expressed in % of basal values at time 0.

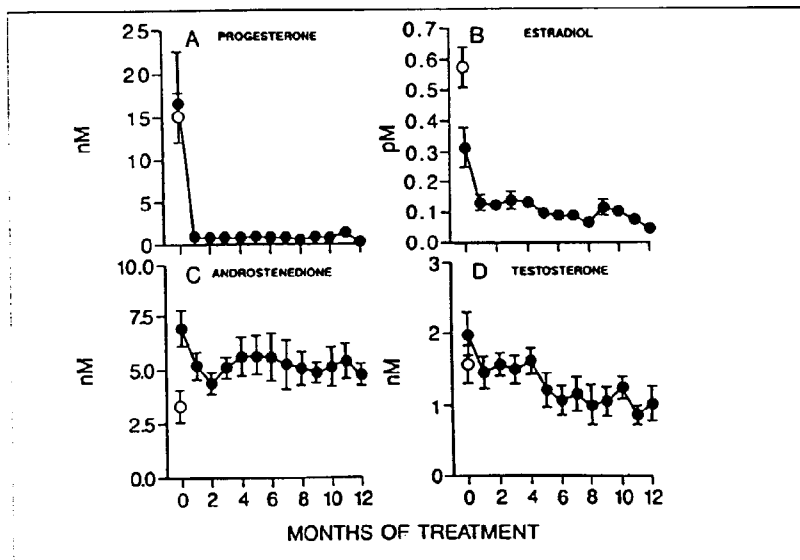


Figure 4: Mean serum values of progesterone (A), estradiol (B), androstenedione (C) and testosterone (D) during 12 months of therapy with flutamide and an oral contraceptive in women with androgenic alopecia (solid circles). Serum steroid levels of nonhirsute control women are also presented at time 0 (open circles). \* means  $\pm$  SEM

**Table 2: Plasma concentration of SHBG during therapy with flutamide and an oral contraceptive in patients with female alopecia**

Months of treatment	Study group						No treatment
	0	1	2	4	8	12	
SHBG (nM)	21 ± 9	93 ± 25	120 ± 25	141 ± 36	119 ± 19	159 ± 12	60 ± 7

values represent means ± SD

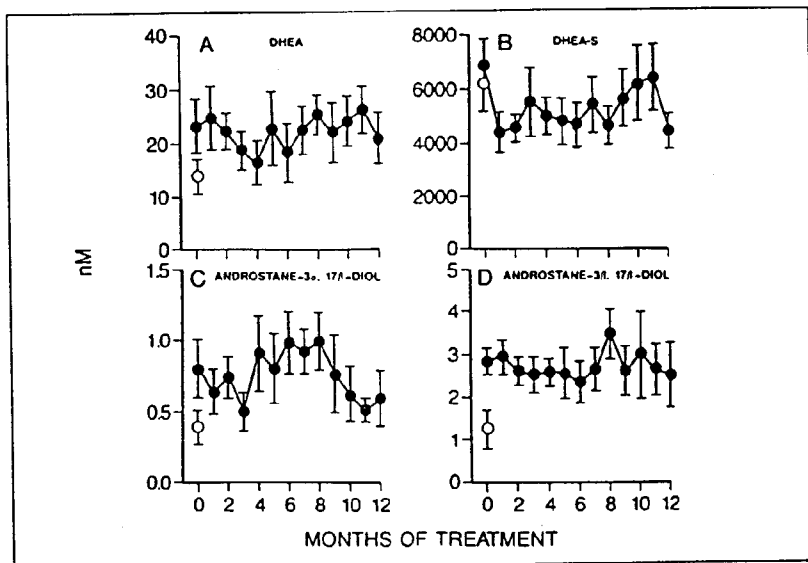
genic alopecia (Figure 4). With the evidence for a role of androgens in this disease, it seems logical to propose that the ideal means to alleviate androgenic alopecia could be treatment with a

specific antiandrogen. Androgenic alopecia could well be an example of an intracrine disease<sup>26</sup> or excess local formation of androgen.

Flutamide has no androgenic,

progestagen, glucocorticoid or mineralocorticoid activities, as opposed to the other clinically available antiandrogens like spironolactone or cyproterone acetate.<sup>11,12,27-30</sup> Flutamide acts exclusively by competitively preventing endogenous androgens from binding on the androgen receptor.<sup>17</sup> The results obtained in this study indicate that more than 75% of women suffering from FAA experience a cosmetically acceptable hair regrowth when treated with this drug in combination with a contraceptive pill. Most importantly, the beneficial effects have been obtained without significant adverse side effects. It should also be emphasized that 10 of the 13 women studied had concomitant hirsutism, which responded favorably to treatment. The role of androgen in this disease is further supported by the finding of increased serum androstenedione, 3 $\alpha$ -diol and 3 $\beta$ -diol levels, as well as decreased SHBG in these women. It should be mentioned that one of the three women with alopecia (but no hirsutism) responded well to therapy, despite previous failure with topical minoxidil.

An interesting aspect of combining



**Figure 5:** Mean serum values of DHEA (A), DHEA-S (B), androstane-3 $\alpha$ , 17 $\beta$ -diol (C) and androstane-3 $\beta$ , 17 $\beta$ -diol (D) during 12 months of therapy with flutamide and an oral contraceptive in women with androgenic alopecia (solid circles). Serum steroid levels of nonhirsute women are also presented at time 0 (open circles). \* means  $\pm$  SEM

flutamide with oral contraceptives is the possibility of creating a state of hypoandrogenism by a dual mechanism of action. The antiandrogen provides an androgen receptor blockade, thereby decreasing the action of DHT at the level of the pilosebaceous unit; meanwhile, a marked increase in SHBG levels induced by the estrogen causes a reduction in the free biologically-active testosterone fraction.<sup>14</sup> These two combined effects should be beneficial in correcting hyperandrogenic symptoms in women suffering from androgenic-related diseases such as hirsutism, alopecia, seborrhea and acne of various etiologies. The effects should also benefit the treatment of polycystic ovaries, partial adrenal enzymatic deficiencies and idiopathic diseases. This conclusive preliminary observation on the inhibitory effects of flutamide on FAA paves the way for further clinical investigation in the form of randomized double-blind placebo trials. □

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