

A Prospective Randomized Trial Comparing Low Dose Flutamide, Finasteride, Ketoconazole, and Cyproterone Acetate-Estrogen Regimens in the Treatment of Hirsutism

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ABSTRACT

Sixty-six hirsute women were randomized and treated with 1) flutamide (n = 15), 250 mg/day; 2) finasteride (n = 15), 5 mg/day; 3) ketoconazole (n = 16), 300 mg/day; and 4) ethinyl estradiol (EE)-cyproterone acetate (CPA; n = 20), 0.01 mg EE/day for the first week, 0.02 mg EE/day for the second week, and 0.01 mg EE/day for the third week, followed by a pause of 7 days, then 12.5 mg CPA/day added during the first 10 days of every month for 12 months. Hirsutism was evaluated by the Ferriman-Gallwey score, and hair diameter and hair growth rate were determined by a special image analysis processor in basal conditions and after 90, 180, 270, and 360 days of treatment. All treatments produced a significant decrease in the hirsutism score, hair diameter, and daily hair growth rate: flutamide, $-55 \pm 13\%$, $-21 \pm 14\%$, and $-37 \pm 18\%$; finasteride, $-44 \pm 13\%$, $-16 \pm 12\%$, and $-27 \pm 14\%$; ketoconazole, $-53 \pm 18\%$, $-14 \pm 12\%$, and $-30 \pm 21\%$; and EE-CPA, $-60 \pm 18\%$, $-20 \pm 11\%$, and $-28 \pm 21\%$.

Some differences existed among treatments with regard to effectiveness; EE-CPA and flutamide seem to be the most efficacious in improving hirsutism. For the hirsutism score, a greater decrease was seen with EE-CPA ($-60 \pm 18\%$) than with finasteride ($-44 \pm 13\%$; $P < 0.01$) and a greater decrease was seen with flutamide ($-58 \pm 18\%$) than with finasteride ($-44 \pm 13\%$; $P < 0.05$). Flutamide is the fastest in decreasing hair diameter; EE-CPA is the fastest in slowing down

hair growth, even though at the end of the treatment there was a significant difference between flutamide and finasteride only ($-41 \pm 18\%$ vs. $-27 \pm 14\%$; $P < 0.05$).

Flutamide, ketoconazole, and EE-CPA induced a significant decrease in total and free testosterone, 5α -dihydrotestosterone, dehydroepiandrosterone, dehydroepiandrosterone sulfate, and androstenedione plasma levels. During the EE-CPA treatment, gonadotropins were suppressed, and the sex hormone-binding globulin level increased. Finasteride induced a decrease in dehydroepiandrosterone sulfate and 5α -dihydrotestosterone and an increase in testosterone levels.

Very few side-effects were observed during treatment with low doses of flutamide, EE-CPA, and particularly finasteride. Flutamide induced a decrease whereas EE-CPA induced an increase in triglycerides and cholesterol, showing higher values within the normal range. Ketoconazole induced several side-effects and complications, and several people dropped out of the study.

Despite different modalities of action and significantly different effects on androgen levels, low doses of flutamide, finasteride, and EE-CPA constitute very satisfactory alternative therapeutic regimens in the treatment of hirsutism. (*J Clin Endocrinol Metab* 84: 1304-1310, 1999)

FLUTAMIDE (1-5), finasteride (6-10), ketoconazole (11-14), and cyproterone acetate (CPA) (15-20) are commonly employed in the treatment of hirsutism. Different therapeutic regimens have been used successfully; however, only a few randomized controlled trials exist, and subjective methods of evaluation are generally employed.

The aim of the present report was to compare, in a prospective, comparative, randomized study, as objectively as possible, the therapeutic efficacy as well as the endocrine and metabolic effects and reliability of low dose regimens of flutamide, finasteride, ketoconazole, and a combination of CPA and ethinyl estradiol (EE).

Subjects and Methods

Sixty-six premenopausal hirsute women (mean \pm SD age, 22.9 ± 4.7) were referred to the Reproductive Medicine Unit of the University of

Bologna (Bologna, Italy) for evaluation and treatment of hirsutism. The mean \pm SD body weight was 61 ± 10 kg, and the mean \pm SD height was 163 ± 6 cm. The mean body mass index (BMI) was 22.7 ± 2.7 (normal range, 18-24); 11 subjects (16%) were overweight (mean BMI, 27 ± 2.6).

Regular menses were reported by 29 of the 66 women; 32 had oligomenorrhea, 3 had amenorrhea, and 2 had polymenorrhea. Thirty-eight patients (58%) had ovulatory cycles (on the basis of typical progesterone levels in the premenstrual phase), and 28 (42%) had anovulatory cycles. Each patient underwent a complete medical and gynecological examination. In accordance with our codified parameters (21), all subjects had an etiological diagnosis of hirsutism. None of the women gave evidence of a hormonally active adrenal gland, an ovarian tumor, or Cushing's, PRL, or thyroid disorder. Twenty-seven patients (41%) had a diagnosis of polycystic ovary syndrome; 18 had anovulatory or oligoovulatory cycles, elevated plasma LH concentrations (LH/FSH ratio >2), high levels of testosterone and androstenedione, and ecographic evidence of enlarged polycystic ovaries. Nine patients had the concomitant presence of high dehydroepiandrosterone sulfate levels. Fourteen hirsute patients (21%) suffered from a mild form of nonclassic adrenal hyperplasia with high 17α -hydroxyprogesterone values, as diagnosed by ACTH test (21). Twenty-five patients (38%) were classified as having idiopathic hirsutism because they did not present any of the clinical features found in the other groups and had ovulatory cycles. In the entire population studied the hirsutism score ranged from 7-22.

Patients were randomized into four groups for treatment, indepen-

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dently of the diagnosis made. No significant differences were observed between groups regarding the prevalence of the diagnosis of hirsutism, clinical parameters, and menstrual rhythm or ovulatory/anovulatory cycles; thus, the patients were randomized into four comparable groups. Group 1 ($n = 15$; age, 22.6 ± 4 yr; BMI, 22.9 ± 2 kg/m²) received 250 mg/day flutamide, group 2 ($n = 15$; age, 23.2 ± 3 yr; BMI, 22.5 ± 3 kg/m²) received 5 mg/day finasteride, group 3 ($n = 16$; age, 23.2 ± 5 yr; BMI, 23.0 ± 3 kg/m²) received 300 mg/day ketoconazole, and group 4 ($n = 20$; age, 22.9 ± 4 yr; BMI, 22.6 ± 2 kg/m²) received a treatment regimen with low EE and CPA doses (the patients received 0.01 mg EE/day for the first week, 0.02 mg EE/day for the second week, and 0.01 mg EE/day for the third week, followed by a pause of 7 days, then 12.5 mg CPA/day administered in a reverse sequential regimen during the first 10 days of each treatment cycle). We planned a 12-month therapy period, and either the barrier method or intrauterine contraception was employed during the study in sexually active women to avoid any risk of conception.

Clinical and hormonal controls were performed in basal conditions and after 3, 6, 9, and 12 months. Each woman was studied during the early follicular phase of her menstrual cycle (3–6 days after the onset of a spontaneous menstrual flow) when present or at random in amenorrheic patients in basal conditions and after 180 and 360 days of treatment.

The study was approved by the ethical committee of the Institute of Obstetrics and Gynecology of the University of Bologna, and informed consent was obtained from each patient. All procedures followed in this study were in accordance with the Helsinki Declaration of 1975.

Hirsutism evaluation, clinical side-effects, endocrine and biochemical parameters [blood glucose, cholesterol, high density lipoprotein cholesterol, triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyltransferase, alkaline phosphatase, bilirubin, antithrombin III, and fibrinogen] were determined at each control visit.

Hirsutism and hair growth evaluation

Hirsutism was evaluated with a 2-fold criteria of control so as to have a method of analysis as objective as possible. 1) Hirsutism grading was codified by calculating the hirsutism score according to the modified Ferriman and Gallwey method (22), and the normal range was considered to be no higher than 8. Two patients with a total score of 7 were included because a severe regional (upper lip and thigh) hair growth, and the entry criteria for all patients was a score of 7 or greater. 2) As previously reported (12), hair parameters were codified using an IBAS image analyzer (Kontron Bildanalyse GmbH, Munich, Germany), a special image analysis processor with a sensitivity of 0.001 mm. First, all patients were shaved in a prefixed area of the right thigh. After 90 days, at least 20 hairs (basal hair growth) were cut from the same thigh area using curved scissors; then the area was reshaved, and treatments were started. This same procedure was repeated after 90, 180, 270, and 360 days of therapy. The mean diameter, hair length, and daily growth rate (obtained by dividing the length of each hair by the number of the days elapsed between shaving and the subsequent cut) were estimated. Considering that anagen hair growth on the thigh has a mean duration of 22 days and that the complete hair cycle is 84 days (23), a 90-day period of basal observation seems to be correct for establishing the mean basal hair growth in each group.

Self-reported evaluation

Patients' self-evaluation of the clinical outcome of the treatment was obtained. Each patient rated his appreciation as dissatisfied, satisfied, or highly satisfied.

Hormone assay

Blood samples were drawn at 0800 h; all samples from each subject were run in the same RIA. The RIA techniques used for hormonal measurements were: gonadotropins (FSH-LH) and PRL, rapid double antibody (kits purchased from Biodata, Rome, Italy); 17-hydroxyprogesterone (17-P) and progesterone (P), chromatographic separation on Sephadex LH-20 columns; dehydroepiandrosterone sulfate (DHAS) performed directly on diluted plasma, testosterone (T), 5 α -dehydrotestosterone (DHT), androstenedione (A), and 17 β -estradiol (E₂), TLC on silica

gel 60 F254; dehydroepiandrosterone (DHA), plasma extraction with ethyl ether, as previously described (24), using an ACTH kit purchased from CIS (Gif-Sur-Yvette, France) and a cortisol (F) kit purchased from Diagnostic Systems Laboratories (Webster, TX); free testosterone (Tf), the Coat-A-Count free testosterone procedure of Diagnostic Products (Los Angeles, CA); and sex hormone-binding globulin (SHBG), non-competitive liquid phase immunoradiometric assay (Farnos Diagnostic, Oulunsalo, Finland).

Statistical analysis

Paired and unpaired Student's *t* tests and ANOVA were used for statistical analysis, as needed. Values are expressed as the mean \pm sd.

Results

Hirsutism

Figure 1 shows the results of the different regimens of therapy during the entire treatment period. In each subject who finished the study, not less than 100 hairs were analyzed by IBAS, both under basal conditions and during the entire cycle of treatment. Under basal conditions, 1848 hairs were analyzed, and 6800 hairs were analyzed during the entire cycle of treatment.

In group 1 (flutamide), hirsutism improved in all subjects. The mean basal score (Fig. 1; 14.2 ± 4.5) progressively decreased and dropped to 6.4 ± 3.5 ($P < 0.001$; $-55 \pm 13\%$) after 12 months of treatment. The mean diameter (Fig. 1) fell from 0.169 ± 0.02 to 0.133 ± 0.02 mm ($P < 0.001$; $-21 \pm 14\%$), and the mean daily rate of hair growth (Fig. 1) fell progressively from 0.153 ± 0.03 to 0.084 ± 0.04 mm/day ($P < 0.001$; $-41 \pm 18\%$).

In group 2 (finasteride), hirsutism improved in all subjects. The mean basal score (Fig. 1; 12.4 ± 4.8) slowly dropped during therapy to 6.9 ± 3.5 ($P < 0.02$; $-44 \pm 13\%$) after 12 months of treatment. The mean diameter (Fig. 1) fell from 0.174 ± 0.02 to 0.147 ± 0.02 mm ($P < 0.001$; $-16 \pm 12\%$), and the mean daily rate (Fig. 1) of hair growth fell from 0.127 ± 0.05 to 0.095 ± 0.04 mm/day ($P < 0.005$; $-27 \pm 14\%$).

In group 3 (ketoconazole), 8 of 16 subjects who started the therapy stopped taking the drug within 180 days because of several side-effects and complications; hirsutism had improved in the 8 subjects who concluded the 12-month therapy period (mean basal score, 13.8 ± 4.4 ; 12-month therapy score, 6.5 ± 4.8 ; $P < 0.005$; $-53 \pm 18\%$; Fig. 1). The mean diameter (Fig. 1) fell progressively from 0.177 ± 0.01 to 0.148 ± 0.02 mm ($P < 0.005$; $-14 \pm 12\%$), and the mean daily rate of hair growth (Fig. 1) fell from 0.129 ± 0.03 to 0.090 ± 0.04 mm/day ($P < 0.005$; $-30 \pm 21\%$). Six of 8 hirsute subjects who interrupted the therapy had slower hair growth during the therapy on the basis of their subjective evaluations.

In group 4 (EE-CPA), hirsutism improved in all subjects. The mean basal score (Fig. 1; 13.3 ± 5.1) dropped to 6.1 ± 5.5 ($P < 0.001$; $-60 \pm 18\%$) after 12 months of treatment. The mean diameter (Fig. 1) fell from 0.164 ± 0.05 to 0.138 ± 0.02 mm ($P < 0.001$; $-20 \pm 11\%$). The mean daily rate (Fig. 1) of hair growth decreased during the first 90 days and fell from 0.127 ± 0.05 to 0.090 ± 0.03 mm/day ($P < 0.001$) ($-28 \pm 21\%$) after 12 months.

Comparative data among groups

There were no significant differences among groups with respect to their clinical basic data, endocrine parameters

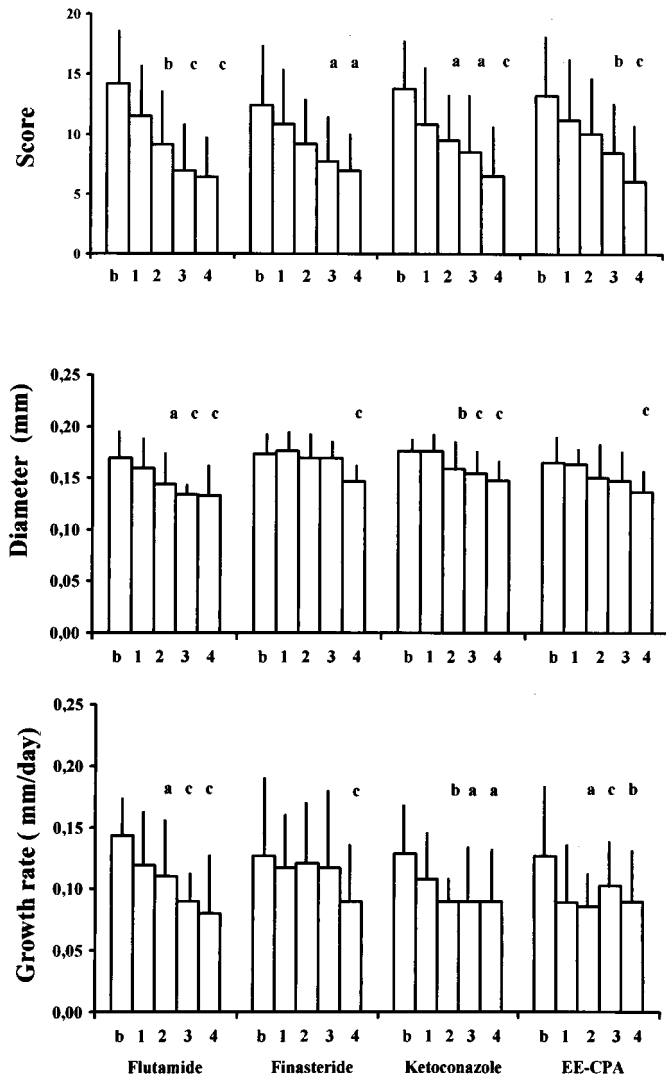


FIG. 1. Histograms representing the mean \pm SD hirsutism score, diameter, and daily growth rate of hair under basal conditions (b) and after 90 (1), 180 (2), 270 (3), and 360 (4) days of therapy with different treatment regimens. In the ketoconazole group, 2 patients of 16 dropped out during the first 90 days of therapy, and 6 patients dropped out during the first 180 days. At 180, 270, and 360 days of treatment, only 8 subjects were studied. a, $P < 0.05$; b, $P < 0.01$; c, $P < 0.005$ (vs. basal within each group). For hirsutism score: by ANOVA among groups in basal conditions, $P = \text{NS}$; by ANOVA among groups during treatment, $P = \text{NS}$. For hair diameter: by ANOVA among groups in basal conditions, $P = \text{NS}$; by ANOVA among groups during treatment, significant differences at 90 ($F = 3.9$; $P < 0.01$), 180 ($F = 3.9$; $P < 0.01$), and 270 ($F = 6.7$; $P > 0.01$) days. For hair growth: by ANOVA among groups in basal conditions, $P = \text{NS}$; by ANOVA among groups during treatment, significant differences at 90 ($F = 3.6$; $P < 0.02$) and 180 ($F = 5.1$; $P < 0.003$) days.

(Tables 1 and 2), hirsutism score, or basal hair characteristics (Fig. 1).

For the hirsutism score (Fig. 1), no differences (by ANOVA, $P = \text{NS}$) were observed among the groups during the control period, confirming the efficacy of all four treatments. However significantly higher differences were observed in the percentage of decrease (Fig. 2) at the end of treatment in the cases of flutamide vs. finasteride ($-55 \pm 18\%$

vs. $-44 \pm 13\%$; $P < 0.05$) and EE-CPA vs. finasteride ($-60 \pm 18\%$ vs. $-44 \pm 13\%$; $P < 0.01$).

For hair diameter (Fig. 1), significant differences were observed at 90 days ($F = 3.94$; $P < 0.01$), 180 days ($F = 3.6$; $P < 0.01$), and 270 days ($F = 6.7$; $P < 0.001$) among the groups. Flutamide induced the quickest decrease in hair diameter during treatment (at 90 days of treatment) even though the differences in the percent decrease disappeared at the end of treatment (Fig. 2).

For the hair growth rate (Figs. 1 and 2), significant differences among groups were observed at 90 days ($F = 3.6$; $P < 0.02$) and 180 days ($F = 5.1$; $P < 0.003$). Finasteride was the slowest in decreasing hair growth, whereas EE-CPA was the quickest. Flutamide acted progressively, and there was a significant difference between flutamide and finasteride ($-41 \pm 18\%$ vs. $-27 \pm 14\%$; $P < 0.05$) at the end of treatment (Fig. 2).

Hormone concentrations

Tables 1 and 2 show the mean hormonal values under basal conditions and during the different treatments. In group 1, flutamide induced a significant decrease in 17-P, Tf, T, DHT, A, DHAS, DHA, and F and an increase in E_2 levels. In group 2, finasteride induced a significant decrease in DHAS, E_2 , and DHT mean values and an increase in T and Tf mean values. In group 3, the mean plasma levels of T, Tf, DHT, DHA, DHAS, and A decreased progressively during ketoconazole treatment, whereas FSH, LH, E_2 , F, ACTH, and 17-P values increased. In group 4 during treatment with EE/CPA, there was a decrease in LH, E_2 , 17-P, T, Tf, A, DHA, and DHAS and an increase in F and SHBG plasma levels.

Side-effects, complications, and clinical and biochemical changes (Table 3)

In group 1, only a few, transient and slight side-effects occurred, and all subjects concluded the period of treatment. After 6 months of treatment, cholesterol (-11%) and triglycerides (-22%) values dropped significantly, with respect to the basal values. No changes were observed in the other parameters.

In group 2, no side-effects, complications, or biochemical changes were observed, even though two patients were dissatisfied.

In group 3, major side-effects and complications occurred during the first 90 days of treatment. A high number of patients dropped out within the first 180 days. Mean AST, ALT, and alkaline phosphatase levels increased progressively to the upper limit of the normal adult range. Two subjects had very high AST and ALT values. Triglycerides (-25%) and cholesterol (-17%) values decreased progressively. No changes were observed in the other parameters.

In group 4, some subjects experienced a mild weight gain (<2 kg) after 6–9 months of treatment and had mild transient side-effects. One subject suffered from irregular menstrual bleeding, and one dropped out because of persistent amenorrhea during the ninth month of therapy. Cholesterol mean values increased progressively ($+21\%$) up to the upper limit of normal values (<250 mg/dL), and mean triglycerides

TABLE 1. Endocrine mean \pm SD plasma values in basal conditions and after 180 and 360 days of therapy with different treatment regimens

	LH (IU/L; normal, 2–10)	FSH (IU/L; normal, 4–10)	PRL (μ g/L; normal, 6–28)	E ₂ (pmol/L; normal, 51.4–194.5)	ACTH (pmol/L; normal, 5–60)	17P (nmol/L; normal, 0.9–3.8)	SHBG (nmol/L; normal, 16–120)
Flutamide							
A	5.3 \pm 2.6	5.5 \pm 1.0	17 \pm 6	154 \pm 44	6.9 \pm 3.1	3.3 \pm 1.2	29 \pm 11
B	4.8 \pm 1.9	5.4 \pm 0.8	18 \pm 8	243 \pm 36 ^a	5.9 \pm 2.9	2.8 \pm 1.6	34 \pm 11
C	6.0 \pm 2.4	5.5 \pm 1.0	18 \pm 10	250 \pm 33 ^a	5.5 \pm 2.7	2.2 \pm 0.8 ^b	37 \pm 6
Finasteride							
A	6.0 \pm 2.2	5.7 \pm 1.6	15 \pm 8	130 \pm 37	6.1 \pm 0.4	2.7 \pm 0.9	38 \pm 15
B	6.0 \pm 2.1	6.0 \pm 1.4	11 \pm 5	130 \pm 41	5.2 \pm 0.5	2.2 \pm 0.8	38 \pm 12
C	5.1 \pm 1.9	5.5 \pm 1.2	13 \pm 4	55 \pm 31 ^a	7 \pm 0.4	2.7 \pm 0.8	43 \pm 16
Ketoconazole							
A	5.7 \pm 2.8	4.2 \pm 1.3	16 \pm 6	180 \pm 50	3 \pm 2.1	3 \pm 1.1	26 \pm 10
B	10.2 \pm 4.7 ^c	5.4 \pm 2.1	17.3 \pm 5	280 \pm 45 ^a	7 \pm 2 ^a	5 \pm 5.3	28 \pm 11
C	12.5 \pm 5.3 ^d	6.8 \pm 2.7 ^e	17 \pm 5	270 \pm 33 ^a	6 \pm 1.9 ^d	6 \pm 3.2 ^e	27 \pm 10
EE-CPA							
A	4.7 \pm 2.1	4.8 \pm 1.2	12 \pm 5	176 \pm 52	5.4 \pm 1.8	3.2 \pm 1.1	30 \pm 11.8
B	3.0 \pm 1.6 ^b	4.9 \pm 2.0	18 \pm 10	127 \pm 62 ^c	4.8 \pm 1.6	2.2 \pm 0.9 ^d	124 \pm 45 ^a
C	3.2 \pm 1.2 ^b	4.7 \pm 1.9	17 \pm 10	92 \pm 37 ^a	4.4 \pm 1.2	1.8 \pm 0.6 ^c	113 \pm 38 ^a

Normal hormonal ranges are reported in *parentheses*. In the ketoconazole group, at 180, 270, and 360 days of treatment, only eight subjects were studied. A, Basal; B, 180 days; C, 360 days. Significance is given for values within the same regimen.

^a $P < 0.001$ vs. basal.

^b $P < 0.05$ vs. basal.

^c $P < 0.05$ vs. basal.

^d $P < 0.005$ vs. basal.

^e $P < 0.02$ vs. basal.

TABLE 2. Endocrine mean \pm SD plasma values in basal conditions and during treatment after 180 and 360 days of therapy with four different treatment regimens

	T _f (pmol/L; normal, 2.4–12.5)	T (nmol/L; normal, 1–3.5)	DHT (nmol/L; normal, 0.3–1.1)	DHA (nmol/L; normal, 8.5–41.2)	DHAS (μ mol/L; normal, 1.9–10.3)	A (nmol/L; normal, 1.4–15.7)	F (nmol/L; normal, 193–662)
Flutamide							
A	8 \pm 3.1	1.7 \pm 0.6	0.8 \pm 0.2	40.8 \pm 14	9 \pm 2	10.8 \pm 2.5	510 \pm 57.9
B	8.7 \pm 5.2	1.8 \pm 0.7	0.7 \pm 0.2	31 \pm 10 ^a	6 \pm 1.8 ^b	7.5 \pm 2.9 ^c	455 \pm 49.6 ^d
C	5.8 \pm 2.7 ^a	1.1 \pm 0.2 ^b	0.6 \pm 0.1 ^c	26.7 \pm 10.7 ^c	5.9 \pm 1.8 ^b	7.4 \pm 1.6 ^a	480 \pm 55.1
Finasteride							
A	5.5 \pm 2.4	1.7 \pm 0.2	0.7 \pm 0.2	37.7 \pm 21.1	9 \pm 2	7.9 \pm 2.1	474 \pm 63
B	6.5 \pm 2.4	2.0 \pm 0.2 ^b	0.6 \pm 0.2	38.1 \pm 12.1	7 \pm 1.9 ^d	9 \pm 2.3	469 \pm 77
C	7.4 \pm 2.4 ^a	2.3 \pm 0.2 ^b	0.5 \pm 0.1 ^c	25.3 \pm 12.9	7 \pm 1.9 ^d	9.2 \pm 2.5	496 \pm 74
Ketoconazol							
A	7 \pm 2	1.6 \pm 0.7	0.7 \pm 0.3	32.1 \pm 14.5	9 \pm 2	7.5 \pm 3	500 \pm 200
B	5 \pm 3	1.2 \pm 0.2 ^b	0.5 \pm 0.2	20.5 \pm 8 ^a	7.5 \pm 2.1	4.4 \pm 3.1 ^a	850 \pm 197 ^b
C	5 \pm 2 ^a	1.2 \pm 0.1 ^b	0.4 \pm 0.1 ^c	20.6 \pm 7.5 ^a	6.2 \pm 1.9 ^c	4.4 \pm 2.7 ^a	800 \pm 255 ^d
EE-CPA							
A	5.8 \pm 2.4	1.8 \pm 0.5	0.7 \pm 0.3	35 \pm 15.2	9 \pm 1.8	9.1 \pm 2.2	518 \pm 102
B	4.1 \pm 2.0 ^c	1.1 \pm 0.5 ^b	0.8 \pm 0.3	29.1 \pm 15.4	7 \pm 2 ^c	7.1 \pm 2.7 ^e	596 \pm 80 ^e
C	3.8 \pm 1.7 ^c	1.3 \pm 0.5 ^c	0.8 \pm 0.3	19.4 \pm 6.5 ^b	6 \pm 2 ^b	6.4 \pm 1.8 ^b	626 \pm 55.1 ^b

A, Basal; B, 180 days; C, 360 days. See Table 1 legend. Significance is given for values within the same regimen.

^a $P < 0.05$ vs. basal.

^b $P < 0.001$ vs. basal.

^c $P < 0.005$ vs. basal.

^d $P < 0.01$ vs. basal.

^e $P < 0.02$ vs. basal.

values increased progressively (+38%), but they remained within the normal range (20–175 mg/dL).

Discussion

A very long treatment period is always required to improve hirsutism and prevent or delay its relapse; the use, as much as possible, of low doses of antiandrogens may be a suitable choice in an attempt to prevent the incidence of side-effects and complications and to maintain treatment. The present study confirms the effectiveness of all four antiandrogens, flutamide, finasteride, ketoconazole, and cypro-

terone acetate, in the treatment of hirsutism, even if given in very low doses; however, some differences do exist.

Low as well as high doses of flutamide alone (4, 25) were effective. The hirsutism score decreased progressively (–55%), and the improvement of hirsutism was associated with a rapid decrease in hair diameter (–11% after 3 months) and a progressive decrease in the daily hair growth rate (–41% after 12 months). A net decrease in T, Tf, DHT, A, 17-P, DHA, and DHAS plasma levels during treatment was observed, in agreement with some reports (26, 27) and in disagreement with others (1, 2, 5, 28), suggesting that the

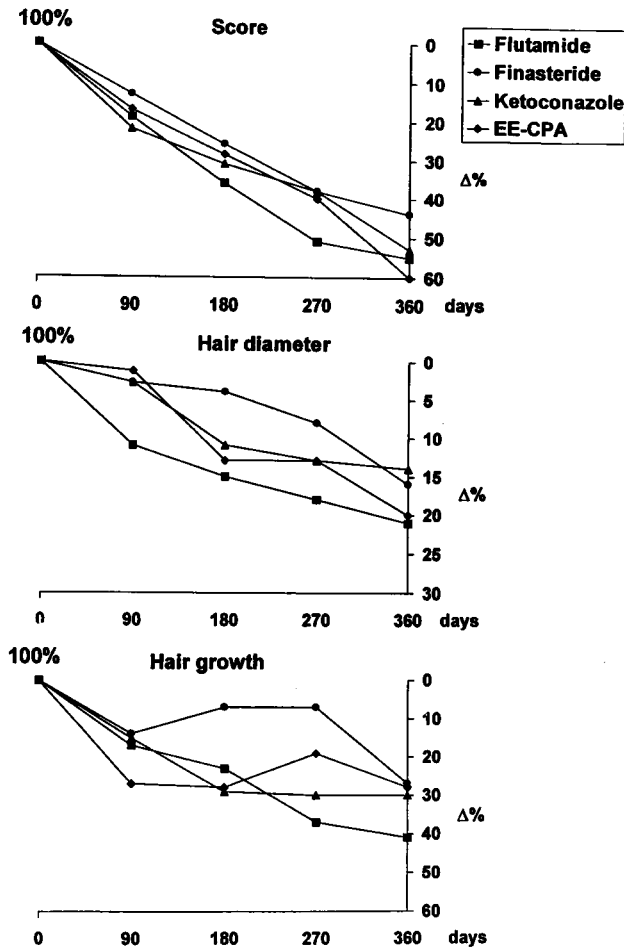


FIG. 2. Mean decreases in hirsutism score, hair diameter, and hair growth rate detected during the different treatments. Decreases are expressed as percentages with respect to basal values. For score: by ANOVA among groups during treatment, significant differences at 360 days ($F = 3.1$; $P < 0.03$); maximum change in the percent flutamide vs. finasteride after 360 days, $P < 0.05$; maximum change in the percent EE-CPA vs. finasteride after 360 days, $P < 0.01$. For hair diameter: by ANOVA among groups during treatment, significant differences at 90 ($F = 8.6$; $P < 0.001$) and 180 ($F = 3.1$; $P < 0.03$) days. For hair growth: by ANOVA among groups during treatment, significant differences at 90 ($F = 3.1$; $P < 0.03$), 180 ($F = 5.2$; $P < 0.003$), and 270 ($F = 9.9$; $P < 0.001$) days. For maximum change in percent flutamide vs. finasteride after 360 days, $P < 0.05$.

efficacy of flutamide must be ascribed to a reduction of androgen synthesis and to its action on target tissues. At a dose of 250 mg/day flutamide, neither liver failure nor the side-effects generally seen with high doses (2, 4, 27, 29, 30) were observed. Moreover, a significant decrease in the cholesterol and triglycerides values was observed, in contrast to the data reported by Dodin *et al.* (4).

Finasteride, generally used at a dose of 5 mg/day (6–10), caused a significant decrease in the hirsutism score (–44%), hair diameter (–16%), and daily hair growth rate (–27%). In our experience, the results were less satisfactory than those reported by some (7–10), but in accordance with others (31, 32). The administration of finasteride has been associated with a decrease in DHT plasma values (7, 8, 10) and an increase in T levels (7–10, 31); moreover, our data showed a

decrease in DHAS levels, suggesting a slight inhibitory effect on adrenal steroidogenesis. Clinical parameters did not change, and no side-effects were reported during the administration of finasteride, confirming its favorable clinical applicability.

Using a low dose ketoconazole treatment regimen, the hirsutism score improved markedly in the patients who completed 12 months of therapy (–53%), and both hair diameter (–14%) and daily hair growth rate (–30%) decreased significantly. However, eight patients dropped out of the study because of side-effects and complications. We believe that ketoconazole should be used with caution. Our findings confirm a decrease in T, Tf, A, DHT, and DHAS values and an increase in 17-P values, and give evidence of a strong inhibition of 17-hydroxylase, 17,20-desmolase, and 11-hydroxylase activity (12, 33, 34).

High EE-CPA doses are very effective (15–18, 20); in the present study we used very low amounts of EE and CPA, and we confirm their high efficacy. Hirsutism progressively improved (as much as 60% less), and hair shaft diameter decreased significantly (–20%), even though the initial slowing of hair growth (–30% at 90 days) did not improve any further after the first 3 months of therapy. The beneficial effect of EE-CPA seems to be related to the well known peripheral effect and to the decrease in both ovarian and adrenal androgens as well as the increase in SHBG reached despite the low EE doses given. The effects of the EE-CPA on lipid metabolism are still being debated (35–38). Despite the low EE doses employed, an increase in triglycerides, which remained within the normal range, and a slight increase in total cholesterol were observed. The few transient side-effects reported during CPA-EE treatment did not require discontinuing the therapy.

In correctly evaluating and comparing the results of different treatments of hirsutism, we added the evaluation of the hair growth rate to the hirsutism score (22) and hair shaft diameter (31). This is a parameter whose behavior is partially independent of the hirsutism score and hair diameter (39), and this may explain the differences in the time response to the different therapies.

Finasteride appears to be the drug with the slowest time of action; it induces the least decrease in hirsutism score of the four treatments. However, the drug is highly effective, as the hair diameter at the end of the treatment is similar to that found with the other therapies. It is the best tolerated, and this therapy is probably the most effective in treating normoandrogenic hirsutism.

The EE-CPA combination induces the quickest reduction of hair growth and gives the greatest hair score decrease after 12 months of treatment. It is the treatment of choice in ovarian and adrenal hirsutism in sexually active women, because of steroid suppression, contraceptive effects (40) due to gonadotropin suppression, and optimal control of the menstrual cycle.

Flutamide has a quick and progressive effect on all parameters up to 12 months, very similar to the effects of EE-CPA and ketoconazole. The strong suppression of both adrenal and ovarian androgens without interference with gonadotropin secretion, the improved glucose tolerance (41), the cholesterol and triglycerides reduction, as well as the

TABLE 3. Side-effects, complications, and clinical changes during therapy with different treatment regimens

	Flutamide	Finasteride	Ketoconazole	EE-CPA
Headache	2 ^a		3	2 ^a
Nausea	1		4	
Asthenia			4	
Wt gain ^b				5
Change of libido				1
Mastodynia ^a				2
Loss of scalp hair			4	
Menstrual irregularity			3	2
AST-ALT ^c			2	
Cholesterol (mg/dL) ^d				
A	185 ± 22		180 ± 32	180 ± 38
C	165 ± 29 ^e	NS	150 ± 15 ^f	227 ± 20 ^g
Triglycerides (mg/dL) ^d				
A	63 ± 23		71 ± 18	65 ± 24
C	49 ± 12 ^e	NS	53 ± 13 ^f	106 ± 36 ^g
Satisfied		3	4	
Highly satisfied	15	10	6	20
Dissatisfied		2	6	
Drop out			8	1

Values given are the number of subjects. A, Basal; C, 360 days. Significance is given for values within the same regimen.

^a Slight and transient.

^b Mild weight gain less than 2 kg.

^c Aspartate amino-transferase-alanine transferase.

^d Mean values ± DS of all treated subjects.

^e $P < 0.05$ vs. basal.

^f $P < 0.01$ vs. basal.

^g $P < 0.001$ vs. basal.

absence of side-effects at low doses enable this drug to be used in a flexible way, especially for hyperandrogenism in nonsexually active adolescents, in obese subjects, and in patients at cardiovascular risk.

Ketoconazole improves all parameters of hirsutism, as do the other treatments; however, in view of its important and frequent side-effects and complications, its use should be discouraged.

Finally, we emphasize that the treatment of hirsutism is aimed at the cause, and that each drug acts in its own way on anagen or telogen, hair diameter, or hair growth. However, the drugs employed in the present report together with spironolactone (42), which competes at the androgen receptor level, currently constitute very satisfactory alternative therapeutic regimens in the treatment of hirsutism.

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