Comparison of Spironolactone, Flutamide, and Finasteride Efficacy in the Treatment of Hirsutism: A Randomized, Double Blind, Placebo-Controlled Trial*

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ABSTRACT

To compare objectively the efficacies of spironolactone (100 mg/day), flutamide (250 mg/day), and finasteride (5 mg/day) in the treatment of hirsutism, 40 hirsute women were randomly assigned to double blind treatments with 1 of these 3 drugs or placebo for 6 months. Before and at the end of treatment, hirsutism was quantitatively measured in each subject by determination, by computer-assisted light microscopy, of the largest diameter of 5 hairs plucked from the linea alba. These measurements were averaged to produce a mean hair shaft diameter. For each subject, baseline and posttreatment assessments were carried out at the same time by an investigator blinded to both time and type of therapy. In addition, a semiquantitative clinical evaluation was carried out by a modification of the Ferriman-Gallwey (F-G) scoring method, performed by a single investigator. At baseline the 4 groups of women had similar hair diameters and F-G scores. After 6 months of therapy all groups of subjects given active drugs showed reductions of their hair diameters, without statistically significant differences among groups (mean change ± SEM, −11.7 ± 5.6%, −18.0 ± 6.1%, and −12.6 ± 6.7%, respectively, in the spironolactone, flutamide, and finasteride groups). F-G scores were also significantly reduced in women receiving antiandrogen drugs, again without differences among groups (mean change, −41.0 ± 5.5%, −38.9 ± 7.2%, and −31.6 ± 3.7%, respectively). No significant changes from baseline values were recorded by either hair diameter (−1.4 ± 5.2%) or F-G score (−5.4 ± 3.7%) assessment in the placebo group. In conclusion, spironolactone, flutamide, and finasteride are all effective in the treatment of hirsutism. After a 6-month course of therapy, the clinical efficacies of these drugs, at least at the doses used, are similar. (J Clin Endocrinol Metab 85: 89–94, 2000)

HIRSUTISM is a very common clinical problem in endocrinological practice, with potentially serious psychosocial consequences (1). Mechanical hair removal is effective in many hirsute women. Nevertheless, a pharmacological approach is often required in subjects with moderate to severe hirsutism to suppress androgen production and/or action. Contraceptives are widely used for this purpose, but their efficacy is limited in established hirsutism (2). Although GnRH analogs may be indicated in selected patients (3), the most reliable therapeutic tool in these women is the use of antiandrogen drugs, usually in association with nonandrogenic oral contraceptive therapy (2).

Spironolactone and cyproterone acetate are the antiandrogens most commonly used in the treatment of hirsutism. Both of these steroidal compounds possess intrinsic hormonal activity and interfere with steroidogenesis (4, 5). In addition, cyproterone acetate shows significant antigonadotropic effects. Side-effects of these drugs include frequent menstrual irregularity. The progestinic activity of cyproterone acetate requires this drug to be associated with estrogens.

Other antiandrogen drugs, such as flutamide and finasteride, have been proposed in the treatment of hirsutism. Flutamide is a nonsteroidal compound that seems to act only at the androgen receptor site and is therefore considered a pure antiandrogen (6). However, some data suggest that flutamide might also reduce the synthesis of androgens (7) and/or increase their metabolism to inactive molecules (8). This drug is efficaciously used in the treatment of advanced prostatic carcinoma and was successfully evaluated in hirsute women (9–11). Liver toxicity is a rare but potentially severe side-effect of flutamide (12).

Finasteride is a very potent competitive inhibitor of the type 2 isoenzyme of 5α-reductase, the enzyme responsible for conversion of testosterone to the active metabolite dihydrotestosterone (13). The drug has recently been approved for the treatment of benign prostatic hyperplasia (14). As increased 5α-reductase activity is considered a pathogenetic mechanism of hirsutism (15), selective enzyme inhibition has been proposed as a rational medical approach to this condition as well. Consistently, studies in hirsute women gave promising results, without appreciable side-effects (16–18).

Rigorous clinical trial methodology is very rarely encountered in reports evaluating antiandrogenic therapies in hirsute women (1, 19, 20). Furthermore, the majority of researchers who previously assessed the effects of these drugs...
used subjective parameters, namely the Ferriman-Gallwey (F-G) (21) or other similar scoring systems, as the only methods to measure hirsutism, making comparison of data among different studies unreliable (19). In addition, in several studies antiandrogens were given in combination with oral contraceptives, making it difficult to quantify the therapeutic efficacies of the antiandrogen compound and the estrogens separately. Until now only a few studies directly compared the clinical efficacies of different antiandrogen drugs in hirsute women. Although some of these studies used objective methods to measure hair growth (17, 22, 23), none of them was double blind or placebo controlled. Thus, the scale of relative potency of these drugs remains undetermined.

To address this issue, the present study compared the clinical efficacy, in 40 hirsute women, of a 6-month course of double blind, placebo-controlled treatments with spironolactone, flutamide, or finasteride. Hair growth was estimated by both a modification of the F-G score and the objective measurement of shaft diameters of hairs plucked from the linea alba.

**Materials and Methods**

**Subjects**

Forty young women (age, 20.4 ± 0.5 yr; body mass index, 24.5 ± 0.7 kg/m²; mean ± SEM), consecutively referred to our division for moderate to severe hirsutism, were included in the study. The mean modified F-G score (24) was 17.5 ± 0.7 (range, 11–27.5). Two subjects also suffered from mild acne.

Twenty-one women had polycystic ovary syndrome, diagnosed according to the presence of hyperandrogenism and chronic anovulation (25). All of them showed a 17-hydroxyprogesterone hyperresponse to GnRH agonist testing (26). Eighteen of these subjects had oligoamenorrhea.

Cushing’s syndrome, adrenal enzyme defects, adrenal and ovarian tumors, hyperprolactinemia, and thyroid dysfunction were excluded in each subject. No patient suffered from any other disease or had been treated with oral contraceptives or antiandrogen drugs in the previous 12 months.

Patients were clearly informed of potential risks of the treatments, with a particular caution to avoid pregnancy because of possible male fetus feminization. Sexually active women were advised to use barrier contraceptive methods or intrauterine devices during the study. The study was conducted in accordance with the Declaration of Helsinki on human experimentation. Each patient gave her written informed consent to the study protocol, which was approved by the local ethical committee.

**Protocol**

Patients were randomly assigned to double blind treatments, once daily orally as a wafer capsule, for 6 months with one of the following: 1) spironolactone (100 mg), 2) flutamide (250 mg), 3) finasteride (5 mg), or 4) placebo. Basally and at the end of treatment, hirsutism and hormonal parameters were evaluated in each subject, as described below.

Patients were instructed to report any untoward effect during the treatment period. In addition, safety parameters were assessed before treatment and at 2-month intervals during the study. The safety evaluation comprised hematology tests (hemoglobin, red blood cells, white blood cells, platelets, and leukocyte differential count) and biochemistry tests (plasma glucose, uric acid, liver and renal function, and serum electrolytes). To be considered clinically significant, changes in safety parameters had to either exceed the normal limits or double the baseline values.

**Hirsutism assessment**

Hair growth assessment included both an objective method and a hirsutism score, graded by a modified F-G method. An objective evaluation of hirsutism in each patient was obtained by averaging the largest diameters of five hairs plucked, using regular facial tweezers, from a 2 × 2-cm area in the linea alba. To avoid any hair damage, hairs were not cut, shaved, or submitted to any cosmetic procedures in this specific area for 3 months beforehand. Plucking was immediately followed by shaving, and no additional cosmetic measure was allowed in this body region throughout the study. Hairs were gently embedded in Eukitt (mounting medium O, Kindler GmbH & Co., Freiburg, Germany) on a glass microscope slide, using a small anatomical forceps; they were mounted longitudinally on the slide and protected by a cover glass previously bathed with xilol.

The slides were examined using a fully integrated, optical microscope (Leitz DMRB, Wetzlar, Germany), with a 12-V, 100-watt halogen illuminator for transmitted light and a computer workstation system, the CAS 200/486 imaging analysis system (Cell Analysis Systems, Inc., Elmhurst, IL). This device included an IBM enhanced AT computer, two full-color display monitors, a graphics and system control/menu selection monitor, and a digital image display for displaying real-time digital images. Internally, images are stored at 256 × 256 pixel resolution, with the corresponding image resolution determined by the objective lens chosen (27). The image analysis program used was Micrometer version 0.7, application 1992 (Cell Analysis Systems, Inc., version 1.0). Hair shaft diameter was measured at ×10 magnification, and the Video Trace mode was used for drawing a line from one point to another. Vertical resolution was 0.0766053/μm, and horizontal resolution was 0.0446314/μm. The hair shaft diameter was measured just above the keratogenous zone. This zone appears as a dark area of the hair shaft located above the hair bulb. In this area, hair matrix cells undergo complete keratinization, and the hair fiber decreases in diameter by about 25%, mainly because of water loss. A mean hair shaft diameter was obtained for each patient by averaging the measurements obtained from the anagen hairs present in the sample.

All measurements relative to each patient were made at the same time by a single investigator blinded to both time and type of therapy. With this method, both intra- and intersubject mean coefficients of variation were less than 2%.

A semiquantitative, clinical evaluation of hirsutism was also performed in these subjects by a modification of the F-G method (24). The hirsutism scores were determined twice in the pretreatment period, with a 3-month interval between measurements, and subsequently at the end of the 6-month treatment period. Patients using cosmetic measures were requested not to depilate for at least 1 month before each evaluation. All evaluations were carried out by a single investigator, blinded to the ongoing therapy. The mean difference in hirsutism scores for each subject between the two baseline evaluations was 0.4 (range, 0–3.5).

The patients’ subjective opinion of the clinical outcome of therapy (excellent, good, fair, or poor) was also obtained. In addition, before and at the end of treatment each woman completed a questionnaire specifying any cosmetic measures for hair removal, with details of type (plucking, waxing, shaving, bleaching, or depilatory cream), site, and frequency.

**Endocrine assessments**

A standard hormonal profile, including serum gonadotropins and androgens (total and free testosterone, dehydroepiandrosterone sulfate, androstenedione, and 3α-androstenediol glucuronide), was determined at baseline and at the end of treatment from a blood sample obtained at 0800 h. Twenty-four-hour urine was collected at the same time points for C19 and C21 steroid metabolite determinations. In the eumenorrheic patients blood samples were collected in the early follicular phase of the menstrual cycle, whereas in the oligoamenorrheic subjects luteal phase was excluded by serum progesterone assay.

**Assays**

Serum hormones were measured by commercial kits, as previously described (16). All samples from each patient were run in the same assay, in duplicate. Urinary steroid metabolites were assayed by gas chromatography, as previously described (16).
Statistics and calculations

Results were analyzed by Student’s t test for paired and unpaired data, Wilcoxon’s rank sum test, and ANOVA. All tests of significance were two tailed, and \( P \leq 0.05 \) was considered significant. Etiocholanolone/androsterone and tetrahydrcortisol/alotetrahydrocortisol urinary metabolite ratios were calculated as indexes of 5α-reductase activity. Data were expressed as the mean ± SEM.

Results

Tolerability

Metrorrhagias were reported by five women, all given spironolactone. This side-effect was transient in four subjects and sustained in one, but not so severe as to require interruption of treatment. On the other hand, previous menstrual abnormalities improved after treatment in five patients (three in the flutamide group and one in each of the other groups receiving active drugs).

One patient receiving flutamide complained of sleepiness and hyporexia, which spontaneously disappeared after the first month of therapy. One woman in the finasteride group complained of a transient sensation of being “swollen.” Finally, one patient in the placebo group reported mild, transient headache and nausea.

Safety parameters did not show significant changes in any subject during the study period.

Hirsutism

At baseline, mean shaft diameters of hairs plucked from the linea alba and modified F-G scores were comparable in the four groups of hirsute women (Table 1). After 6 months of therapy, all groups of subjects given active drugs showed significant decreases in hair diameter (Fig. 1), without differences among groups (144 ± 12 vs. 164 ± 8, 139 ± 10 vs. 172 ± 13, and 146 ± 8 vs. 172 ± 9 μm, respectively, in the spironolactone, flutamide, and finasteride groups; all \( P < 0.01 \) vs. changes in the placebo group). Hirsutism scores also showed significant improvements in women receiving antiandrogen drugs (Fig. 1), without statistically significant differences among groups (10.0 ± 1.1 vs. 16.9 ± 0.9, 11.1 ± 1.8 vs. 17.5 ± 1.5, and 13.0 ± 1.3 vs. 18.4 ± 1.3 in the three groups; all \( P < 0.001 \) vs. placebo). Similar improvements were found in women with polycystic ovary syndrome and in those with nonovarian hyperandrogenism considered as a whole, regardless of treatment group (changes in hair diameter, −11.9 ± 4.8% vs. −15.7 ± 5.2%; changes in hirsutism

**TABLE 1.** Baseline clinical characteristics of hirsute women divided according to treatment

<table>
<thead>
<tr>
<th></th>
<th>Spironolactone</th>
<th>Flutamide</th>
<th>Finasteride</th>
<th>Placebo</th>
<th>( P^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>19.7 ± 0.7</td>
<td>20.2 ± 1.1</td>
<td>19.8 ± 0.8</td>
<td>21.8 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.3 ± 1.4</td>
<td>23.6 ± 1.0</td>
<td>23.3 ± 0.7</td>
<td>25.8 ± 2.0</td>
<td>NS</td>
</tr>
<tr>
<td>Modified Ferriman-Gallwey score</td>
<td>16.9 ± 0.9</td>
<td>17.5 ± 1.5</td>
<td>18.4 ± 1.3</td>
<td>17.2 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Hair diameter (μm)</td>
<td>164 ± 8</td>
<td>172 ± 13</td>
<td>172 ± 9</td>
<td>153 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>Menses (irregular/regular)</td>
<td>2/8</td>
<td>8/2</td>
<td>4/6</td>
<td>4/6</td>
<td>NS</td>
</tr>
<tr>
<td>PCOS/other</td>
<td>4/6</td>
<td>8/2</td>
<td>4/6</td>
<td>5/5</td>
<td>NS</td>
</tr>
<tr>
<td>Cosmetic measures (yes/no)</td>
<td>5/5</td>
<td>4/6</td>
<td>8/2</td>
<td>7/3</td>
<td>NS</td>
</tr>
</tbody>
</table>

* By ANOVA or \( k^2 \), as appropriate.

**Fig. 1.** Changes after therapy (Δ%) in modified F-G score and mean hair shaft diameter in the four treatment groups.
score, $-41.6 \pm 4.3\%$ vs. $-31.0 \pm 4.8\%$). No significant changes from baseline values were found by either hair diameter ($156 \pm 11$ vs. $153 \pm 7 \mu m$) or hirsutism score ($18.0 \pm 1.7$ vs. $17.2 \pm 1.6$) in the placebo group.

Before treatment 24 women were using cosmetic measures. These consisted of waxing ($n = 20$), waxing and plucking ($n = 2$), waxing and shaving ($n = 1$), or depilatory cream ($n = 1$), with variable frequency (2-30 days). Changes in these procedures were reported only by patients given active drugs. Four of these subjects (2 in the spironolactone and 2 in the flutamide groups) stopped waxing. All of the other 13 women given antiandrogens reported a reduction in frequencies of hair removal procedures, without substantial differences among groups (data not shown). On the other hand, no change was reported by women receiving placebo.

Patients' self-evaluations of clinical outcome at the end of the study were also consistent with changes in hair diameter and hirsutism score (Table 2).

### Clinical and endocrine features

Tables 1 and 3 show the main clinical and endocrine features of women in the four groups, before and during the trial. At baseline all groups showed similar characteristics. The frequency of menstrual irregularities was higher in the flutamide group, but this difference was not statistically significant.

After treatment a significant reduction of serum dehydroepiandrosterone sulfate was found in the flutamide group, whereas 3α-androstanediol glucuronide levels, an index of 5α-reductase activity, were significantly reduced in the finasteride group. Consistently, women given finasteride also showed significant increases in C19 and C21 urinary 5α-reductase metabolite ratios (data not shown). Free testosterone showed a tendency to decrease in the flutamide group and to increase in the finasteride group, but these differences did not reach statistical significance. Women given spironolactone as well as those given placebo did not show any changes in endocrine parameters.

### Discussion

The vast majority of the published work concerning hirsutism treatment shows considerable shortcomings, such as lack of a control group, assessment of results only by subjective methods, or too short a duration in relation to the physiology of hair growth (1, 19, 20). These limitations make it at present impossible to establish a scale of relative potency among antiandrogen drugs. Indeed, some of the few controlled studies were even unable to demonstrate differences in hair growth during antiandrogen therapy vs. placebo administration (4). Furthermore, until now only a limited number of studies directly compared the clinical efficacies of different antiandrogen drugs in the treatment of hirsute women (17, 22, 23, 28–34). Although some of these studies were randomized (17, 22, 28, 31), only a few used objective measures of hair growth (17, 22, 23), and none of them was double blind or placebo controlled.

The present study is the first to evaluate the efficacy on hirsutism of three different drugs, spironolactone, flutamide, and finasteride, by a rigorous clinical trial methodology of a double blind, placebo-controlled, randomized study. Furthermore, hair growth changes were measured not only by the subjective F-G scoring, commonly used in clinical practice as a semiquantitative measure of degree of hirsutism, but also by an objective method, measurement of hair shaft diameters.

This method was previously validated and used in clinical trials (19), although its sensitivity, at least using simple optical microscopy, is not high (3, 19). To increase both the sensitivity and reproducibility of this procedure, in the present study a computer-assisted measurement was performed. On the other hand, although other procedures have been proposed for the objective measurement of hair growth, at present none of them may be considered a gold standard (19). Our data were further supported by consistent results of patients' self-evaluation of clinical outcome and by changes in frequency of recourse to mechanical hair removal.

In this study the changes in F-G score were 2–3 times greater than those in hair diameter. This observation is not surprising, as subjective perception of hair growth excess

### TABLE 2. Patients' self-evaluation of clinical outcome of the therapy

<table>
<thead>
<tr>
<th></th>
<th>Spironolactone</th>
<th>Flutamide</th>
<th>Finasteride</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Good</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Fair</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Poor</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>

### TABLE 3. Standard hormonal profiles, before and after treatment, in the four treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Spironolactone</th>
<th>Flutamide</th>
<th>Finasteride</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>After treatment</td>
<td>Basal</td>
<td>After treatment</td>
</tr>
<tr>
<td>Free testosterone (pg/mL)</td>
<td>3.47 ± 0.31</td>
<td>3.43 ± 0.24</td>
<td>3.36 ± 0.45</td>
<td>2.78 ± 0.27</td>
</tr>
<tr>
<td>DHEA-S (μg/L)</td>
<td>2177 ± 319</td>
<td>2336 ± 270</td>
<td>1962 ± 231</td>
<td>1349 ± 188*</td>
</tr>
<tr>
<td>3α-Androstanediol glucuronide (ng/mL)</td>
<td>4.24 ± 0.56</td>
<td>5.64 ± 0.66</td>
<td>4.05 ± 0.71</td>
<td>3.54 ± 0.40</td>
</tr>
<tr>
<td>LH (IU/L)</td>
<td>7.7 ± 1.4</td>
<td>8.3 ± 1.4</td>
<td>5.5 ± 0.9</td>
<td>8.3 ± 1.7</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>4.9 ± 0.2</td>
<td>5.3 ± 0.2</td>
<td>5.1 ± 0.3</td>
<td>4.8 ± 0.4</td>
</tr>
</tbody>
</table>

Values are the mean ± SEM.

* $P < 0.01$ vs. basal.
depends not only on hair diameter, but also on the length and density of terminal hairs.

The present controlled trial demonstrates that spironolactone, flutamide, and finasteride are effective in the treatment of hirsutism, supporting conclusions of previous, almost all uncontrolled, studies (17, 22, 23, 28–30, 32). However, the most interesting finding of the present study is that, in a population of unselected women with moderate to severe hirsutism, the clinical efficacies of these drugs were similar despite their differing mechanisms of action.

Spironolactone has been given to hirsute women in previous studies in doses ranging from 50–400 mg/day (4). The large majority of researchers used daily doses of 100 mg, as in the present trial, because an increased frequency of side-effects is associated with higher doses (35). Flutamide, too, was previously given to hirsute women in a large range of doses, from 250–750 mg/day (10, 11, 36, 37). We chose the lowest of these amounts to minimize any potential risk of liver toxicity. Furthermore, a dose-range study reported similar improvements in hirsutism with 250 vs. 500 mg flutamide (37). On the other hand, 5 mg finasteride is the dose used in all published trials with this drug, although similar effects on skin androgens were found with 1 mg (38).

We cannot exclude that by using different doses of drugs or by extending the duration of treatments it might be possible to identify some differences in clinical efficacy among these drugs. Nevertheless, differences of clinical relevance are unlikely. This opinion is supported by the observation that the extent of improvements in F-G score in this study was roughly comparable with previously reported results at higher doses of these antiandrogens (4, 36, 37), although in a short term (3-month) trial Lobo et al. (39) showed greater reduction of hair shaft diameters with 200 than 100 mg/day spironolactone. Another potential bias is the different percentage of ovarian vs. nonovarian hyperandrogenism in our treatment groups, although this difference did not reach statistical significance. However, considering the whole population of women receiving active drugs, we did not find any difference in improvement of hirsutism between subjects with polycystic ovary syndrome and those with other forms of androgen excess.

The tolerability of antiandrogen drugs examined in the study was good, with the noticeable exception of polymenorrhea in 50% of subjects given spironolactone. This is a well known adverse effect of the drug. However, in most of these women the side-effect was transient, resolving within 3 months. No patient receiving flutamide showed liver toxicity. This side-effect of flutamide showed a low incidence (<0.5%), but was occasionally fatal in large populations of men with advanced prostate carcinoma treated with 750-1500 mg/day (12). We and others previously also observed occasional mild, transient hepatotoxicity in women given low doses of the drug (375–500 mg/day) (11, 40). As a whole, these observations suggest that the use of this compound for the treatment of hirsutism should be carefully challenged in each subject. On the other hand, Diamanti-Karatmandis et al. recently reported that flutamide has favorable effects on lipid profile in women with polycystic ovarian syndrome (41); this effect is of clinical interest in subjects who frequently show several metabolic abnormalities (42). From the point of view of tolerability, finasteride, devoid of appreciable side-effects, seems to be the current best choice. It should be borne in mind that all antiandrogens imply the need to avoid a pregnancy, given the potential risk of feminization of male fetuses.

Finally, at the doses used in this study the retail costs of a 1-month course of therapy are $21.3, $95.4, and $56.1, respectively for spironolactone, flutamide, and finasteride (source of data: drugstore.com web site, July 26, 1999). This aspect should also be considered in the choice of an antiandrogen therapy, particularly as the efficacies of these drugs are similar.

In conclusion, this double blind, placebo-controlled study demonstrates that spironolactone, flutamide, and finasteride are all effective in the treatment of hirsutism. Moreover, after a 6-month course of therapy the clinical efficacies of these drugs are similar. Further research should investigate the potential for synergic effects of combined therapies with drugs acting at different levels in androgen secretion and/or action.

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References


