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A Risk-Benefit Assessment of Pharmacological Therapies for Hirsutism

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Abstract

In recent years, many new therapeutic regimens for hirsutism have been introduced. This has considerably enlarged the different choices of the physician but at the same time has produced considerable confusion and uncertainty as to what is the best possible therapy for the single patient or for the different pathologies of this condition.

This review presents data on the characteristics, adverse effects and effective dosage for the more commonly used drugs for hirsutism.

In most patients, low doses of antiandrogens (cyproterone acetate, flutamide or spironolactone) are used with few adverse effects and good results in terms of improvement of the hirsutism. Patients with severe hyperandrogenic hirsutism may require larger doses of antiandrogens. In only a few patients, therapy with agents that primarily reduce androgen secretion (mostly a gonadotropin releasing hormone agonist) is needed. In responsive patients, dexamethasone may be used at low doses (associated with an antiandrogen) to prolong the length of the remission. Finally, agents that inhibit 5α-reductase activity (finasteride) may be

used as alternative to low dose antiandrogen therapy but the results are often less satisfactory.

In recent years, many new therapeutic regimens for hirsutism have been introduced. This has considerably enlarged the different choices of the physician but at the same time has produced considerable confusion and uncertainty as to what is the best possible therapy for the single patient or for the different pathologies of this condition.

In approaching this question we will first review the characteristics of the drugs that are more commonly used, then we will discuss the possible differences and advantages in using the various therapies.

This review will not discuss the use of mechanical measures to control hirsutism. However, the role of electrolysis and/or of laser epilation therapy should not be overlooked. Patients with mild or localised hirsutism may need only mechanical measures and also in patients with moderate or severe hyperandrogenism, careful use of electrolysis or laser epilation may be associated to pharmacological treatment so permitting better cosmetic results.

1. Androgen Receptor Blockers

Antiandrogens are frequently used in the treatment of hirsutism. These products are generally effective when given for sufficient time (for at least 6 months, but generally for 1 year or more). All are teratogenic and may induce feminisation of the fetus. Therefore, women of reproductive age using these drugs must use effective contraception. Antiandrogens (mostly spironolactone and cyproterone acetate) have been also used topically in localised forms of hirsutism[1] but, in our experience, mechanical measures (electrolysis or laser epilation) give better results and should be preferred in these situations.

Although the list of antiandrogens includes many drugs, we will review only the most used.

1.1 Spironolactone

In the US, the most common androgen blocker used in treatment of hirsutism is spironolactone, an aldosterone-related steroid, that was initially approved and marketed as an aldosterone-blocking diuretic but is now mostly used in treatment of all forms of hirsutism.[2-4] In fact, with long term use, patients rapidly develop a tolerance to its diuretic effect and it is uncommon to observe changes in serum electrolyte levels or blood pressure.[5,6] The utility of spironolactone in hirsutism depends on its capacity to compete with dihydrotestosterone (DHT) in binding to the androgen receptor, but the product has also a minor effect on 5α-reductase and may compete with androgens for binding to sex hormone binding globulin (SHBG).[7,8] Finally, spironolactone inhibits cytochrome P450 enzymes involved in ovarian and adrenal steroidogenesis, resulting in decreased levels of testosterone and androstenedione.[8-10]

Spironolactone is generally used at dosages of 100 mg/day and at these dosages no changes in serum androgens are observed.[11] Larger dosages are rarely necessary although doses of 200 mg/day may be needed in severe hirsutism and are also able to reduce serum androgen levels.[10]

Because spironolactone has some anti-aldosterone activity, serum electrolyte levels and blood pressure should be controlled 2 weeks after treatment is started and use of other diuretics (mostly potassium-sparing diuretics) should be avoided. However, in long term treatment of hirsutism, the most common adverse effect by far is the appearance of metrorrhagia/polymenorrhoea in women who previously had normal menses. This disturbance is generally well tolerated, but an important component of any prolonged therapy with spironolactone is to advise the women about this possibility as in some patients it may lead to discontinuation of therapy. Combining the medication with an oral contraceptive pill[12,13] may minimise the incidence of this adverse effect. In our experience, other systems (such as giving the drug cyclically)[5] are less effective.

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Other adverse effects include gastritis, fatigue, headaches and dry skin. However, these effects are uncommon and are generally only seen at high dosages.

Spironolactone treatment is often combined with other treatments that reduce the serum androgen production, such as estroprogestins[12,13] or glucocorticoids.[14] Although it may increase its activity, our experience did not show any difference in improvement of hirsutism between patients treated with spironolactone alone or with a combined therapy of spironolactone and dexamethasone.[11]

1.2 Cyproterone Acetate

Cyproterone acetate is a progestin derivative that acts as a competitive inhibitor of DHT binding to its receptors and is used worldwide (but not in the US) for the treatment of hyperandrogenism and hirsutism.[15-17] Because of its progestin activity, cyproterone acetate also has a powerful antigonadotropic action and inhibits ovarian androgen secretion. Therefore, cyproterone acetate is effective in the treatment of hirsutism by both reducing androgen secretion and blocking androgen peripheral activity. Because of its antigonadotropic action, in order to avoid menstrual disturbances, cyproterone acetate is usually administered together with estrogens and because it is stored in the adipose tissue from where is slowly released when high doses are needed, the drug should be given only during the first half of the cycle.

Cyproterone acetate is generally administered at low dosages (2 mg/day) in the form of an oral contraceptive while at higher dosages (usually 50 mg/day) it is given with estrogens in a reverse sequential regimen. The classic Hammerstein regimen consists of cyproterone acetate 50 mg/day from days 5 to 15 and ethynilestradiol 50 μg/day administered from days 5 to 25.[15] However, this regimen was devised in the mid-1970s when high dosages of estrogens were commonly used for oral contraceptive therapy. In order to reduce the adverse effects and risks associated with high dosage estrogen, notably thrombosis, the dosages of estrogens have been reduced and several new regimens have been proposed. Several years ago, Knuttenn et al.[18] proposed the use of transdermal estrogens with cyproterone acetate. However, this regimen has not been widely used because it is now known that oral estrogens may be more useful in treating women who are hyperandrogenic because of the rise in SHBG, thus increasing the beneficial androgen inhibitory effects of therapy. Recently, we have shown that low dosages of ethynilestradiol (20 μg/day from days 5 to 25) may be given with high dosages of cyproterone acetate (50 mg/day from days 5 to 15) without producing menstrual disturbances and giving the same improvement in hirsutism observed with ethynilestradiol 50 μg/day.[19] Others have proposed regimens with intermediate dosages of cyproterone acetate (12.5 mg/day of cyproterone acetate from day 5 to 15) associated with low dosages of ethynilestradiol (from 10 to 20 μg/day).[20]

While in many countries cyproterone acetate is widely used and considered a quite safe drug, in the US it has never been approved because of the finding of increased liver tumour incidence in rats treated with the drug. However, an analysis by the European Union's Committee for Proprietary Medicinal Products of the oncological register found no association between cyproterone acetate and liver cancer.[20]

A part this potential concern, the main problem with cyproterone acetate relates to its effect on serum lipid levels. In fact, at high dosages (12.5 to 50 mg/day) cyproterone acetate may worsen the lipid profile[19-21] (fig. 1). The main metabolic derangement observed is a reduction of high density lipoprotein (HDL)-cholesterol levels[19,21] although an increase of total cholesterol and triglyceride levels may be also observed.[20] These metabolic effects of cyproterone acetate are particularly relevant in women who are hyperandrogenic who often present with an altered lipid profile because insulin resistance.[22] Interestingly, similar lipid changes were observed when cyproterone acetate was given with ethynilestradiol 20 and 50 μg/day,[19] suggesting that even high dosages of estrogens are not able to overcome the negative effect of high dosage cy-

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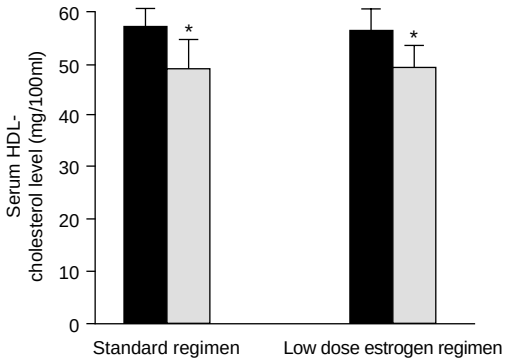

Fig. 1. Serum high density lipoprotein (HDL)-cholesterol changes after 1-year of treatment with cyproterone acetate (CPA) [50 mg/day from day 5 to 15 of the cycle] compared with the changes seen with ethynilestradiol 50 μg/day (standard regimen) or 20 μg/day (low dose estrogen regimen) [reproduced from Carmina and Lobo,[19] with permission]. * = $p < 0.05$.

proterone acetate that predominates in its effect on lipid profile. Therefore, when using high dosages of cyproterone acetate it is important to carefully monitor lipid profile, reducing the dosage or moving to another therapy if lipid levels, notably HDL-cholesterol, become altered.

Because of the potential adverse effects of high dosages of cyproterone acetate, there has been much debate on the need to use such high dosages. In fact, it has been shown that cyproterone acetate 2 mg/day appears to be as effective as higher dosages for the treatment of hirsutism suggesting that high dosages of cyproterone acetate only accelerate the therapeutic effect.[23] While it may be the case in most patients with hirsutism, in patients with severe hirsutism high dosages (50 mg/day) of cyproterone acetate produce a significantly larger improvement of the hirsutism.[24]

Other adverse effects of cyproterone acetate are less common and include bodyweight gain, depression and reduced libido.[15-17] Recently, there has been much interest in the possibility that subnormal levels of serum androgens (as observed after surgical menopause or with high dosages of some drugs like cyproterone acetate) may determine the reduction of libido.[25] However, no specific studies on the relationships between libido and serum androgen levels have been performed in women with hirsutism treated by androgen blocking agents.

In summary, cyproterone acetate is an effective therapy for hirsutism. At low dosages this therapy appears to be quite safe and may be used in most patients with hirsutism who have normal or slightly increased androgen levels. Patients with severe hirsutism and/or severe hyperandrogenism should use higher dosages but they require a careful assessment of their lipid profile.

1.3 Flutamide

Flutamide (4′-nitro-3′-trifluoromethylisobutyranilide) is a nonsteroidal inhibitor of androgen receptors[26] that was introduced for the treatment of prostatic cancer but is also used in the therapy of hirsutism.[27-29] Although it was considered a pure antiandrogen blocker, it may reduce the synthesis of the androgens[30] or increase their metabolism.[31] In fact, a net decrease of all androgens may be observed during treatment and although this effect is more evident at high doses, it may be observed also at low doses.[20,32]

In the treatment of hirsutism, flutamide was initially administered at dosages of 500 to 750 mg/day but the dosage has been progressively reduced and most authors actually use dosages of 250 to 375 mg/day.[20,32,33] Use of a lower dosage significantly reduces the toxicity of the drug. In fact, the main problem with flutamide has been the possible appearance of liver toxicity. Using higher dosages of flutamide (between 750 and 1500 mg/day), elevations in serum transaminase levels during the first months of therapy are quite common while serious hepatic disease may appear in some patients (0.36%)[34,35] and there are rare instances of patients dying of progressive liver disease.[35,36] Using low dosages of flutamide (250 to 375 mg/day), alterations of hepatic enzyme levels are quite uncommon and no cases of severe liver diseases have been reported.[20,32,33] However, some cases of reversible liver toxicity have been observed with a dosage of 250 mg/day (unpublished observation). We recommend that hepatic enzyme levels are monitored in all patients treated with flutamide, re-

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gardless of dosage, every month, for the length of the treatment.

Other less important adverse effects of flutamide include dry skin and a greenish tint to urine.

2. 5α-Reductase Inhibitors

An increase in peripheral 5α-reductase level is essential for the development of hirsutism.[37] In fact, several years ago it was shown that peripheral conversion of testosterone to DHT is a necessary step for androgen activity in the skin and that patients with low peripheral levels of 5α-reductase do not develop hirsutism even in presence of hyperandrogenism.[38,39] More recently, it has been found that 2 isoenzymes of 5α-reductase exist (type 1 and 2)[40] and that patients with hyperandrogenic or idiopathic hirsutism have an increase of the isoenzyme type 1 in the skin.[41,42] Therefore, agents able to inhibit peripheral activity of 5α-reductase may be useful in the treatment of hirsutism. One such agent, finasteride, is currently available and has been used to treat hirsutism in women. Others, such as dutasteride, are being investigated in clinical trials.

2.1 Finasteride

Finasteride is a 4-aza steroid compound that is a specific competitive inhibitor of 5α-reductase, mostly of the type 2 isoenzyme.[43,44] It has no affinity for the androgen receptor and has no known hormonal effect.[43] It is used for the treatment of prostatic hyperplasia and is also used in therapy of alopecia and premature balding.[44]

At a dosage of 5 mg/day, finasteride has been shown to be an effective therapy of hirsutism.[20,45,46] Probably, at this dosage, inhibition of the type 1 isoenzyme of 5α-reductase is also obtained. During treatment, plasma levels of DHT and androgen metabolites are reduced while serum testosterone levels are increased.[46]

In many studies, finasteride has demonstrated similar efficacy to low dosage antiandrogen therapy in the treatment of hirsutism.[20,45,46] However, in our experience, some patients with moderate or severe hirsutism do not respond to finasteride or only experience an initial improvement. Therefore, we use finasteride as a second-line therapy and only in patients with idiopathic hirsutism or with mild hyperandrogenic hirsutism.

The main advantage of finasteride is that no adverse effects or complications have been reported following its use as a therapy for hirsutism in women. As for antiandrogen products, effective contraception is mandatory because the teratogenic effect of the drug.

3. Inhibitors of Androgen Secretion

A third group of products that may be used in the therapy of hirsutism includes agents that, by different mechanisms, are able to reduce androgen secretion. These products also include agents that we have considered in the group of antiandrogens. In fact, when given at high dosages, antiandrogens (cyproterone acetate, spironolactone and flutamide) also reduce circulating androgen levels.

In spite of the fact that most women with hirsutism have increased levels of circulating androgens,[47] the use of agents that reduce androgen secretion is generally limited and restricted to patients with particular hyperandrogenic syndromes.

3.1 Gonadotropin Releasing Hormone Agonists

For several years it has been known that gonadotropin releasing hormone (GnRH) agonists are able to reduce androgen secretion in women with ovarian hyperandrogenism.[48] However, their use in the treatment of hyperandrogenic hirsutism was limited by the finding that prolonged administration of GnRH agonists also induce hypoestrogenism with consequent adverse effects that include amenorrhoea, bone loss, vasomotor symptoms, urethral and vaginal atrophy.[49,50] More recently, we and other investigators have shown that supplementation with low dosage estrogen or with estroprogestins can enhance the effect of GnRH agonist treatment in patients with severe hyperandrogenism while preventing most adverse effects.[51-53] Several regimens for steroid supplementation of GnRH agonists have been proposed, from low dos-

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age conjugated estrogens (0.625 mg/day) + progestins given in cyclic manner[51] to estroprogestins using 20 to 25 μg/day of ethynilestradiol.[52,53] However, some concern has been expressed about the use of low dosages of estrogens in premenopausal women using GnRH agonists because these dosages may not be sufficient to prevent bone loss.[54] Therefore, we generally use 1.25 mg/day of conjugated estrogens + progestins in cyclic manner to supplement GnRH agonist therapy.[55] With these modalities, this therapy is well tolerated and is also effective in reducing hirsutism in patients with severe hyperandrogenism. The main problem of this kind of therapy is the high cost of GnRH agonist therapy and the lack of significant advantages in terms of efficacy and safety compared with the less expensive antiandrogens.[24] In fact, although GnRH agonists give a slightly longer remission of hirsutism than antiandrogens, their effect is similar to that of high dosage cyproterone acetate.[24] Therefore, the use of GnRH agonists plus add back therapy remains limited to patients with severe hyperandrogenic hirsutism who do not respond to more conventional therapies.

3.2 Oral Contraceptives

In countries where cyproterone acetate is not available, women with hirsutism who also have mild or moderate ovarian hyperandrogenism are often treated by the administration of oral contraceptives.[56,57] While the older formulations containing 50μg of ethynilestradiol had a marked capacity to decrease luteinising hormone (LH) and testosterone secretion,[58] the new products containing lower doses of estrogens induce small if any decrease of serum androgens levels but very efficiently increase SHBG levels therefore reducing levels of unbound testosterone.[59] Minor effects of estroprogestins include a 20 to 30% reduction in adrenal androgen levels[60] and a mild inhibitory effect on 5α-reductase and androgen receptors.[59]

When choosing an oral contraceptive, it is important to avoid compounds that contain a progestin with intrinsic androgen activity, such as the derivatives of 19-nortestosterone (i.e. norgestrel and norethindrone). Oral contraceptives that contain progestins with less intrinsic androgen activity or the new generation of 19-testosterone derivatives (i.e. gestodene, desogestrel and norgestimate) should be preferred. In fact, the new 19-testosterone derivatives have a higher progestational activity but unchanged androgen activity and can be used at lower dosages that provide similar progestative activity but lower androgen activity. It has been reported that oral contraceptives that contain desogestrel have the same effect on hirsutism as products containing low doses of cyproterone acetate, but do not affect lipid metabolism.[57]

3.3 Corticosteroids

Adrenal androgens are extremely sensitive to corticosteroid suppression[61] and in the past products such as dexamethasone and prednisone have been largely used in hyperandrogenic hirsutism.[62,63] However, the results have been often disappointing[11,64] and several adverse effects have been reported.[64] In fact, glucocorticoid therapy may be associated with bodyweight gain, skin striae, cushingoid features, long term suppression of cortisol secretion, osteoporosis, glucose intolerance, insulin resistance and effects on the fetus. These adverse effects are strictly related to the dosage used and may be present at dosages as low as dexamethasone 0.5 mg/day.[64] However, lower dosages (0.3 to 0.375 mg/day) are not generally associated with adverse effects[65] and in our experience therapy with such low dosages of glucocorticoids is well tolerated.[11,65] Therefore, corticosteroid therapy should be reserved only for patients in whom very low dosages of corticosteroids are sufficient to suppress circulating androgens. However, the results in terms of improvement of hirsutism in such patients are generally disappointing and the addition of an antiandrogen is needed to produce a significant reduction in hair growth.[11]

The main advantage of a corticosteroid therapy is the finding that in sensitive patients prolonged remission of the hyperandrogenism (probably as consequence of the long term suppression of adrenal androgen secretion) may be obtained.[65] It sug-

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gests that corticosteroid therapy still has a place in the therapy of hirsutism, at least in some patients.

4. Topical Agents

As we previously discussed (see section 1), some antiandrogens have also been used topically in localised forms of hirsutism.[1] Recently, a new agent, eflornithine, has been approved in the US for topical use in facial hirsutism. It was developed for the treatment of trypanosomal sleeping sickness, but is also useful in the treatment of hirsutism because it inhibits the enzyme ornithine decarboxylase that is localised inside the hair follicle and has an important role in hair growth.[66] Two multicentre, randomised, placebo-controlled studies have shown that prolonged topical administration of eflornithine significantly reduces facial hirsutism (although it recurred after drug withdrawal).[66,67] While more studies are needed to establish the real role of topical eflornithine in the treatment of hirsutism, it can be anticipated that this drug may have an important role not only in localised forms but also in many patients with idiopathic hirsutism or with hyperandrogenic hirsutism. In fact, the excess of facial hair is often the cause of major distress for these patients.

5. Choosing the Most Appropriate Therapy

5.1 Agents that Act Peripherally Versus Agents that Block Androgen Secretion

Generally, agents that block androgen secretion do not offer any advantage over agents that act peripherally. Because of this, many authors believe that it is sufficient to exclude some uncommon conditions like tumours, Cushing's syndrome and enzymatic deficiencies, and then all women with hirsutism should be treated with peripherally acting agents irrespective of their androgen levels.[68] While it is generally true, patients with severe hyperandrogenic hirsutism may need treatment with GnRH agonists or with a dosage of antiandrogen that blocks ovarian androgen secretion.[24,69] Moreover, we have observed that low dosage glucocorticoid therapy may provide an important advantage in patients who are sensitive to dexamethasone. In fact, in these patients, long term dexamethasone therapy (generally associated to spironolactone to potentiate the effects on hair growth) may induce prolonged remission of the hyperandrogenism and hirsutism, probably because by inducing long term inhibition of adrenal androgen secretion without inhibiting cortisol secretion.[65] On the contrary, therapy with antiandrogens is followed by almost immediate return of hyperandrogenism and exaggerated hair growth.[24,70] The personal approach of the author is shown in figure 2. All women with hirsutism who are hyperandrogenic with normal menses are tested for dexamethasone sensitivity. Dexamethasone 2 mg/day for 3 days is given and serum androgens (total) testosterone and unbound testosterone) are evaluated. If androgen levels are suppressed to low-normal levels, patients are treated with a combination of low dosage dexamethasone (0.375 mg/day) plus spironolactone (100 mg/day) for 1 to 2 years. In women with hirsutism who are hyperandrogenic and who have normal menses but are not sensitive to dexamethasone, women with hirsutism who are hyperandrogenic and who have irregular menses and women with hirsutism with normal androgen levels (idiopathic hirsutism) are treated by products that block androgen activity peripherally.

Patients who are hyperandrogenic who do not respond to prolonged treatment with high dosage antiandrogens may be treated with GnRH agonists but this is an uncommon occurrence. In clinical practice, with the exception of some patients who present with high sensitivity to dexamethasone, most women with hirsutism are treated with antiandrogens.

5.2 Agents that Block Peripheral Androgen Activity

Many studies have compared the different products that peripherally block androgen activity (antiandrogens and 5α-reductase inhibitors). In most cases, using comparable dosages, no differences were found.[20,45,71-73] However, we and others[74]

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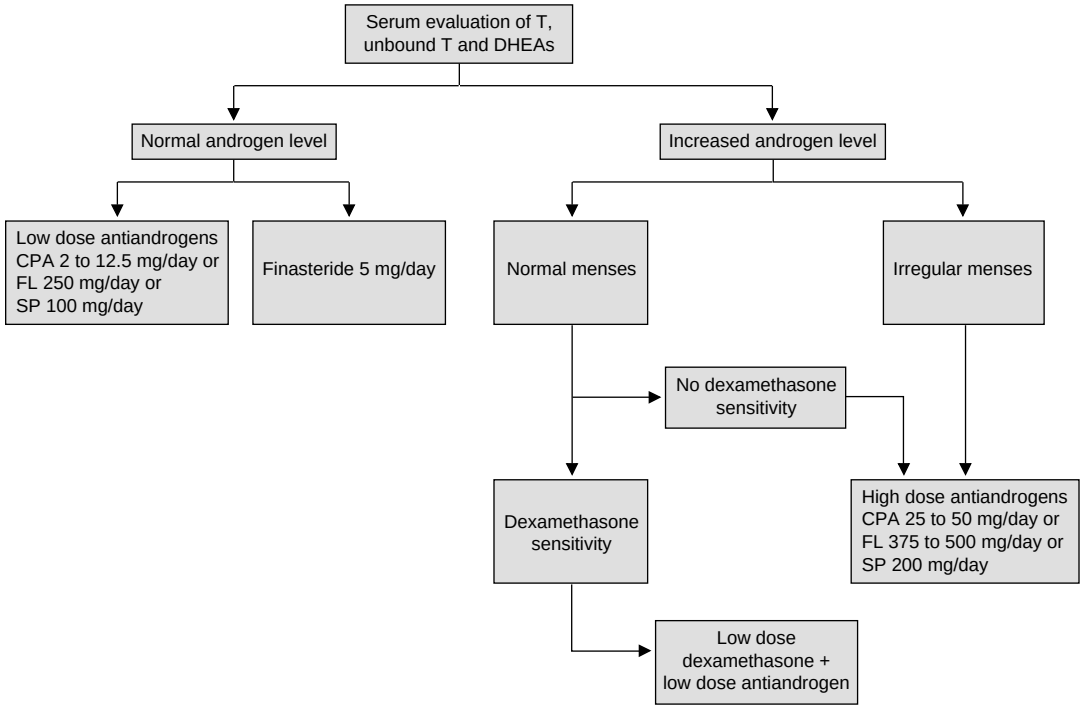

Fig. 2. Schematic approach to the treatment of patients with hirsutism. **CPA** = cyproterone acetate; **DHEA** = dehydroepiandrosterone sulfate; **FL** = flutamide; **SP** = spironolactone; **T** = testosterone.

have observed that finasteride is generally less active (mostly following prolonged treatment) than antiandrogens and we actually only use this product for mild hirsutism if low dose antiandrogen treatment induces adverse effects.

Therefore, the main question is generally how to choose the appropriate antiandrogen dose and how to monitor for possible adverse effects. In idiopathic hirsutism and in mild or moderate hyperandrogenic hirsutism, low dosages of spironolactone (100 mg/day), or estroprogestins or, where available, low dosages of cyproterone acetate (from 2 to 12.5 mg/day given with estrogens) are generally preferred and represent effective and well tolerated therapies. Low dosages of flutamide (250 mg/day) represent a valuable alternative but may induce a reversible increase in liver enzyme levels. Patients who do not show any significant improvement in hirsutism or who present with severe hyperandrogenic hirsutism should be treated with higher dosages of cyproterone acetate (25 to 50 mg/day given with low doses of estrogens in a sequential reverse regimen) or with flutamide (375 mg/day) or spironolactone (200 mg/day). The appearance of adverse effects and experience in the utilisation of a specific antiandrogen are the main factors in this choice. Therefore, a worsening of the lipid profile with levels of HDL-cholesterol lower than normal suggest the need to withdraw cyproterone acetate and change to flutamide (with careful monitoring of liver enzyme levels) or to spironolactone (with careful monitoring of serum electrolyte levels and assessment of the patient's compliance with the polymenorrhoea that may possibly occur). Finally, it has to be remembered that prolonged treatment (for at least 6 months) is needed to determine a clinically evident improvement in hirsutism and that shorter treatment periods are gen-

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erally not useful and may erroneously suggest the lack of response to a particular therapy.

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