Introduction and background

Hirsutism may have a detrimental impact on a woman’s body image and quality of life, as it contradicts cultural and social perceptions of what is physically attractive or acceptable. Facial hirsutism especially is a source of considerable emotional distress and social embarrassment to women.1–5 The purpose of this document is to propose evidence-based guidelines for the diagnosis and management of female facial hirsutism. Female hirsutism is defined in this context as the presence of terminal coarse hair growth in male patterns in women with normal or elevated circulating androgen levels, where the impact of the hair growth on the woman’s quality of life has prompted her to seek medical advice. In this regard, it should be differentiated from hypertrichosis, which refers to excessive hair growth in general in both sexes. It can be a manifestation of a number of hyperandrogenic conditions, including polycystic ovary syndrome (PCOS), virilising tumours and congenital adrenal hyperplasia.6 Clinically and therapeutically, hirsutism has so far been a relatively ill-defined condition with little consensus regarding diagnosis and treatment. It has been suggested that, ultimately, the woman herself could be the judge of her condition.7

The management of hirsutism in clinical practice will be discussed in the context of the most common associated conditions, namely PCOS, menopause-related hirsutism, and idiopathic hirsutism in women with normal serum androgen levels.

Hirsutism in PCOS

Presentation

PCOS is defined as a syndrome featuring disturbed menstrual cycle, hyperandrogenaemia, and characteristic polycystic ovaries, although symptoms can be highly variable between individuals.8 Common presenting symptoms of PCOS such as acne and/or hirsutism, obesity and insulin resistance are related to hyperandrogenism.8 The Rotterdam Consensus defines PCOS as occurring when two of the following three are present:

- Oligo- or anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovaries

Potential underlying causes of excess hair growth⁶

- PCOS
- Menopause
- Idiopathic hirsutism
- Congenital adrenal hyperplasia
- Androgen-secreting adrenal tumours
- Androgen-secreting ovarian tumours
- Cushing’s syndrome
- Severe insulin resistance
- Anabolic steroid use
- Postmenopausal androgen therapy

Guidelines working party

Mr Stuart Lavery (Chair) – Consultant Gynaecologist, Hammersmith Hospital, London
Margaret Mackie – Development Pharmacist, NHS Grampian Medicines Unit, Aberdeen
Dr Stephen Kownacki – GP, Albany House Medical Centre, Wellingborough, Northamptonshire
Dr Rod Smith – GP, Balmore Park Surgery, Reading
Professor Maurice Scanlon – Professor of Endocrinology, Cardiff University
Dr Gerard Conway – Consultant Endocrinologist, The Middlesex Hospital, London
Dr Andrew Messenger – Consultant Dermatologist, Royal Hallamshire Hospital, Sheffield

These guidelines can be viewed at www.evidence-based-medicine.co.uk
and exclusion of other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing’s syndrome). PCOS is one of the most common endocrinological disorders affecting women, with reported prevalence values in the order of 3–7%. Although other concerns were also raised, such as menstrual problems and infertility, hirsutism and weight, in particular, have been shown to cause the greatest concern for women with PCOS.

**Diagnosis**

Diagnosing hirsutism as a manifestation of hyperandrogenism in PCOS is to a large extent a question of excluding other, potentially serious underlying causes of excess hair growth such as androgen-secreting tumours of adrenal or ovarian origin, Cushing’s syndrome, severe insulin resistance and anabolic steroid use. The most important diagnostic tool for exclusion is the clinical history. Rapid onset of hirsutism and/or severe hirsutism is strongly indicative of a more sinister underlying cause and should warrant further investigation and prompt referral for specialist assessment.

Another important component in diagnosing PCOS-related hirsutism is a pelvic ultrasound scan. This is a routine part of diagnosing PCOS – the most common cause of hirsutism. However, the outcome of a pelvic ultrasound may not alter the treatment pathway of PCOS-related hirsutism.

A clinical history and the hormonal profile of a female patient with hirsutism will provide valuable information on any link to PCOS, and is required to exclude other underlying causes (see Table 1).

Once the diagnosis of PCOS-related hirsutism has been established and more serious underlying causes excluded, it is useful to assess the severity of the condition to select the optimal course of treatment. Hirsutism can be evaluated using the Ferriman–Gallwey scoring system. Although valuable as a clinical research tool, this scoring system is impractical for routine use in clinical practice. A potentially more convenient and relevant approach to evaluating the degree of hirsutism might be to base the decision on the patient’s own perception of the condition and extent it impacts on her quality of life.

**Management**

Although the symptomatic treatment of hirsutism will be based on largely the same principles regardless of the underlying cause, each individual condition will of course pose specific therapeutic challenges (see Figure 1).

The primary principle of the management of hirsutism is that any pharmacological treatment should be prescribed in conjunction with appropriate self-help and/or lifestyle measures. It is outside the scope of these guidelines to discuss methods of hair removal such as laser therapy and/or electrolytic depilation, but methods of hair removal should be discussed with the patient as they will remain an important part of managing the condition. It may be necessary to direct patients to a local practitioner specialising in hair removal. These measures have been discussed in detail elsewhere.

For overweight or obese women presenting with hirsutism in association with PCOS, the most important recommendation is weight loss, since this is likely to improve metabolic and endocrine parameters, and also have a beneficial effect on the patient’s self-esteem and overall quality of life. There are only two treatments currently licensed in the UK specifically for the treatment of facial hirsutism – combined cyproterone acetate/ethinylestradiol (Dianette®, Schering Health Care), and eflornithine 11.5% cream (Vaniqa®, Shire Pharmaceuticals) – most treatments are used on the basis of anecdotal evidence and clinical experience.

**Combined cyproterone acetate/ethinylestradiol**

Cyproterone acetate is a synthetic progestogen with antigonadotrophic and anti-androgenic peripheral activity. Combined treatment with the oestrogen ethinylestradiol has been shown in placebo-controlled and comparative trials to be effective against hirsutism in women with PCOS at a dose of 2 mg of cyproterone acetate and 35 µg ethinylestradiol. A long-term study in which 140 women with PCOS received combined cyproterone acetate/ethinylestradiol for 60 cycles showed 69.4% of patients experienced resolution of hirsutism. Combined cyproterone acetate/ethinylestradiol provides contraceptive protection, however, it is important to bear in

---

**Table 1. Investigations in the diagnosis of hirsutism in PCOS**

<table>
<thead>
<tr>
<th>Investigations in primary care</th>
<th>Investigations in secondary care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic ultrasound</td>
<td>Dehydroepiandrosterone (DHEAS)</td>
</tr>
<tr>
<td>Total testosterone</td>
<td>Androstenedione</td>
</tr>
<tr>
<td>Thyroid function</td>
<td>17-α hydroxy progesterone</td>
</tr>
<tr>
<td>Follicle stimulating hormone (FSH)</td>
<td>Cortisol</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Ovarian ultrasound</td>
</tr>
<tr>
<td>Luteinising hormone (LH)</td>
<td></td>
</tr>
</tbody>
</table>
mind that the product is not licensed for use solely as a contraceptive and should be withdrawn three to four cycles after the condition has resolved. Combined cyproterone acetate/ethinylestradiol has been shown to be associated with an increased risk of venous thromboembolism (VTE) compared with other combined oral contraceptives, and is therefore contraindicated in women with a personal or familial history of VTE or related disorders.

Certain factors may also increase the risk of VTE, for example severe obesity (body mass index >30 kg/m²), increasing age, prolonged immobilisation, major surgery, surgery to the legs, or major trauma.

**Eflornithine 11.5% cream**

Eflornithine is an irreversible inhibitor of L-ornithine decarboxylase, a rate-controlling enzyme involved in the growth and proliferation of hair. When applied topically in the form of 11.5% cream, eflornithine has been shown to reduce both the size and growth rate of terminal hairs. The product is licensed for use in the treatment of hirsutism specifically in the face, administered twice daily. Effects were seen within eight weeks. Two randomised, placebo-controlled, clinical trials involving a total of 596 women with facial hirsutism showed that, at Week 24, 70% of patients experienced some improvement in their condition, as shown by Physician’s Global Assessment (PGA), compared with only 40% in the placebo group, although the difference was not statistically significant. Similar differences in favour of eflornithine were observed for the secondary variables, including the Subject’s Self-Assessment Questionnaire (SSAQ) and Video Imaging Analysis (VIA).

The long-term safety and efficacy of eflornithine 11.5% cream has been demonstrated in open-label trials over six and 12 months. The treatment was well tolerated in these studies: the most commonly reported adverse events being skin reactions and acne exacerbations. The Scottish Medicines Consortium (SMC) has completed its assessment on Vaniqa, and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) that eflornithine 11.5% cream is accepted for restricted use within NHS Scotland for the treatment of facial hirsutism in women. It is restricted to use in women for whom alternative drug therapy is ineffective, not recommended or considered inappropriate.

**Unlicensed therapies**

Some clinicians use cyproterone acetate alone in high doses (25–100 mg) in the early treatment of facial hirsutism, but this...
is unlicensed and little evidence exists for its efficacy. Suppression of androgen secretion from the ovaries can be achieved by treatment with gonadotropin-releasing hormone (GnRH) analogues, via suppression of luteinising hormone (LH) and follicle stimulating hormone (FSH). While effective for the treatment of hirsutism associated with severe hyperandrogenism in PCOS patients, these drugs require parenteral administration, should be used together with oestrogen–progestagen supplementation to avoid oestrogen deficiency, and result in overall high treatment costs. The evidence for the use of insulin-sensitising agents for the treatment of PCOS-related hirsutism has been contradictory although it is ever expanding and, on balance, it appears as if insulin-sensitising agents may be of moderate efficacy on hirsutism in PCOS. However, these agents tend to take a longer time to take effect and treatment must often be continued for some time before any clinical benefit is seen.

Peripheral androgen blockade can be achieved by blocking androgen action either directly via androgen receptor blockade, or by blocking the peripheral 5α-reductase-mediated conversion of testosterone to dihydrotestosterone. Spironolactone is an aldosterone antagonist which, in addition to being widely used as a diuretic, has been shown to be effective against hirsutism regardless of the degree of hyperandrogenaemia at a dose ranging from 100 mg daily to up to 200 mg daily in severe cases. The dose should be started low and gradually increased to minimise side-effects. Common side-effects include menstrual disturbances, nausea, skin reactions, breast tenderness, headache and fatigue. In addition, patients already receiving a potassium-sparing diuretic, angiotensin-converting enzyme inhibitor, angiotensin II antagonist, aldosterone blocker, potassium supplement, diet rich in potassium or salt substitute containing potassium for the treatment of hypertension may be at risk of developing hyperkalaemia.

The androgen blocker flutamide and the 5α-reductase inhibitor finasteride are licensed for the treatment of prostate cancer and benign prostate hyperplasia, respectively, and have both been found to be effective against hirsutism in women. However, the use of flutamide may be limited by its potential hepatotoxicity, and finasteride is contraindicated in women who are or may potentially become pregnant because of its teratogenic effect and its potential to feminise a male foetus.

Ketoconazole is an antifungal agent, which is also a potent inducer of cytochrome P450 metabolic pathways. The rationale for using ketoconazole in hirsutism is to induce hepatic elimination of, and thus reduce circulating levels of, androgens. However, ketoconazole is associated with a number of adverse effects and should only be used as a ‘last resort’ option.

**Recommendations**

- Women presenting with hirsutism in association with PCOS should be evaluated thoroughly to exclude any other, potentially serious underlying causes such as an androgen-secreting tumour or Cushing’s syndrome.
- The diagnostic work-up of hirsutism in PCOS should include a full clinical history and a hormonal profile comprising primarily serum testosterone levels. A pelvic ultrasound scan may also be valuable when there is diagnostic doubt.
- Women with rapid-onset and/or severe hirsutism, or any other signs of a severe underlying cause of hirsutism, should be referred to specialist for assessment.
- Pharmacological treatment should be prescribed in conjunction with lifestyle changes (primarily weight loss) and any methods of hair removal that are acceptable to the patient.
- The firstline pharmacological treatment of hirsutism is combined cyproterone acetate/ethinylestradiol, 2 mg/35 µg daily for women in whom treatment with a combined oral contraceptive is deemed appropriate.
- Eflornithine 11.5% cream is the firstline treatment option for facial hirsutism in women in whom treatment with combined cyproterone acetate/ethinylestradiol is contraindicated due to the risk of VTE or other risk factors, or has not shown efficacy.
- If no beneficial effects are seen with eflornithine 11.5% cream after four months, discontinue treatment.
- Any therapies not licensed for use specifically in hirsutism should be prescribed only by specialists.
- In addition to the patient’s subjective perception of improvement of the condition, treatment success can be monitored objectively by the time spent by the patient on cosmetic hair removal.

**Hirsutism during the menopause**

**Presentation**

Women who develop hirsutism during and following the menopause can in many respects be said to represent a ‘forgotten’ group of hirsute patients. Up to 17% of women referred to a hirsutism clinic were postmenopausal, and in contrast to younger women, this group presented almost exclusively with facial hirsutism. Overweight women may be at greater risk due to their larger proportion of body fat.

**Treatment**

Combined cyproterone acetate/ethinylestradiol is not usually considered suitable for use on its own during the menopause; however, cyproterone acetate alone can be used in combination with hormone replacement therapy (HRT). Combined estradiol/drospirenone (Angeliq®, Schering Health, Germany) is a new HRT recently launched in the UK, which
has anti-androgenic properties.\textsuperscript{38}

Spironolactone, although not licensed for use in postmenopausal hirsutism or any other presentation of hirsutism, is widely prescribed in this setting and may be regarded by general practitioners as a ‘safer’ alternative than a combined HRT.

Eflornithine 11.5\% cream is licensed for use in facial hirsutism and therefore may be preferred over spironolactone in women who cannot take HRT.

**Recommendations**

- Hirsutism in peri- and postmenopausal women should be evaluated in the same way as in younger women, to exclude any serious underlying causes such as a tumour.
- Weight loss should be recommended for women who are overweight.
- Pharmacological treatment should be prescribed in conjunction with any methods of hair removal that are acceptable to the patient.
- Eflornithine 11.5\% cream is licensed for facial hirsutism in postmenopausal women.
- If no beneficial effects are seen with eflornithine 11.5\% cream after four months, discontinue treatment.
- Spironolactone, although not licensed for the treatment of postmenopausal hirsutism, has been found to be effective and safe and is widely used in this setting. However, in the absence of a licence, treatment should be initiated by a specialist.
- Combined cyproterone acetate/ethinylestradiol is not suitable for use in postmenopausal women. However, a combination HRT comprising estradiol/drospirenone, recently launched in the UK, is likely to provide a suitable alternative.
- In addition to the patient’s subjective perception of improvement of the condition, treatment success can be monitored objectively by the time spent by the patient on cosmetic hair removal.

**Other causes of hirsutism**

**Idiopathic hirsutism**

Idiopathic hirsutism is defined as hirsutism in the absence of detectable androgen excess and with normal ovulatory function.\textsuperscript{39} Defined thus, this diagnosis applies to approximately 5–15\% of all women presenting with hirsutism.\textsuperscript{39} While the overall prevalence of hirsutism is not significantly different in different races,\textsuperscript{10} it should be remembered that excess body hair may carry different degrees of social and cultural stigma in different ethnic groups, which may in turn affect the woman’s own perception of the severity of her condition.

Although the causes of idiopathic hirsutism are not fully known, suggested mechanisms include increased peripheral 5\alpha-reductase activity, and abnormalities in androgen receptor morphology or androgen metabolism, leading to increased sensitivity to androgenic stimulation of terminal hair growth.\textsuperscript{39}

The pharmacological treatment of idiopathic hirsutism is essentially the same as for hirsutism in relation to PCOS or the menopause. Most clinical studies have included patients with idiopathic hirsutism without making any distinction from other forms. Combined cyproterone acetate/ethinylestradiol is the firstline treatment option, with eflornithine 11.5\% as an alternative for women in whom combined cyproterone acetate/ethinylestradiol is contraindicated or is not effective. Off-label use of agents such as spironolactone or flutamide, alone or as adjuvant therapy, may be effective but should be initiated by a specialist.

**Drug-induced hirsutism**

A number of drugs are known to induce hirsutism. These include cyclosporin, diazoxide glucocorticoids and minoxidil, while anti-epileptics such as phenytoin and phenobarbitone may cause excess hair growth.\textsuperscript{6} The primary aim of any medical therapy should be to eliminate the underlying cause as far as possible, by means of reducing the dose or switching to a treatment with a more favourable tolerability profile. Symptomatic treatment will be similar to other forms of hirsutism as described above.

**Implications and summary**

It has been estimated that 900,000 women in England suffer from excess or unwanted facial hair, with only a small
percentage of these consulting their GP. Although there are no specific data for facial hirsutism available, clinical experience has shown that most women with hirsutism will probably not present for treatment if the face is not affected (see Figure 2).

The direct costs associated with the treatment of hirsutism will consist of the cost of the medication, consultations within primary and secondary care, and the costs associated with any treatment of adverse events. The overall impact of these factors on primary care trust budgets can be estimated to be relatively small, especially in light of potential long-term cost savings in relation to improving the health-related quality of life of hirsute women.

In summary, effective treatments are now available for hirsutism, and the rationale for investigating and treating the condition is provided by the often detrimental impact on the patient’s quality of life. The diagnostic evaluation should be carried out with the primary aim of eliminating any serious underlying causes of excess hair growth, such as androgen-secreting neoplasia. Treatment should aim at correcting the underlying cause of hirsutism, such as the dose adjustment of prescription drugs. Symptomatic treatment involves androgen suppression and peripheral androgen receptor blockade with therapies such as combined cyproterone acetate/ethinylestradiol, as well as topical treatment with eflornithine 11.5% cream. Women with hirsutism should also be encouraged to explore mechanical and/or cosmetic means of hair removal to achieve optimal effect and, in the case of eflornithine 11.5% cream, they may need to continue using mechanical means of removal to achieve efficacy.

References