

## Management of hirsutism

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Hirsutism is the presence of excess hair growth in women, and the term usually refers to excessive growth of terminal hair in an androgen dependent distribution. Although it is often thought to be a cosmetic problem, unwanted hair growth adversely affects psychological wellbeing.<sup>1</sup> It can have a similar effect on quality of life scores to that of asthma, epilepsy, and diabetes,<sup>2</sup> and effective treatments reverse these adverse scores.<sup>3</sup>

Several new treatments have emerged in recent years, including the wider availability of laser depilation, topical suppressors of hair growth (eflornithene), and a progestogen with antiandrogenic properties (drospirenone). In this review, we assess the evidence base for new treatments in the context of established treatments, although the worldwide availability of these preparations varies greatly. The overall quality of primary evidence of the relative efficacy of treatments for hirsutism is weak and is based on small studies of short duration that lack quality of life outcomes. Recently, however, systematic reviews have amalgamated this evidence and new guidelines are now available.<sup>4</sup>

### What are the possible causes of hirsutism?

Most women with hirsutism have polycystic ovary syndrome or idiopathic hirsutism (box 1). Treatment options are the same for both, so ovarian ultrasound is not essential in many cases.

Mild to late onset adrenal hyperplasia is a rare cause of hirsutism that overlaps clinically with polycystic ovary syndrome. Classic congenital adrenal hyperplasia is obvious because it presents in infancy, and it commonly causes severe hirsutism, particularly if adherence to glucocorticoids is poor. Ovarian tumours

that secrete androgens are rare and tend to cause severe hirsutism. Adrenal tumours usually co-secrete cortisol and the clinical picture is that of Cushing's syndrome.

At the time of the menopause, hair growth is promoted by a fall in the production of ovarian oestradiol but relatively well maintained testosterone production. In some instances, rising concentrations of luteinising hormone lead to stromal hyperplasia, high testosterone concentrations, and severe menopausal hirsutism.

### What aspects of the history and examination are important?

For research purposes, hair growth can be measured using a scoring system established by Ferriman and Gallwey.<sup>5</sup> In clinical practice, subjective assessment is usually adequate, although personal perception of body hair can vary greatly among individuals.<sup>6</sup> Insulin resistance may be clinically evident as acanthosis nigricans.

The most important clinical feature to be aware of is the recent onset and rapid progression of hair growth seen with the rare androgen secreting tumours. Conversely, onset of mild hirsutism around the time of the menarche implies that androgen excess has a non-tumour ovarian origin, as in polycystic ovary syndrome (box 2).

### What investigations are needed?

Measurement of serum testosterone concentrations helps identify the occasional case of severe androgen excess that needs further investigation, but it is not essential in women with a clearly benign presentation, especially as testosterone assays perform poorly in the female range.<sup>7</sup> According to current guidelines, testosterone measurement is needed only for women with moderate to severe hirsutism, when other symptoms of polycystic ovary syndrome are present, or when there is rapid progression of hirsutism or other signs of virilisation.<sup>4</sup> Obese women with polycystic ovary syndrome, particularly those with a family history of type 2 diabetes, should be assessed for metabolic syndrome with an oral glucose tolerance test and cholesterol profile.<sup>8</sup>

Biochemical screening for non-classic adrenal hyperplasia with measurement of serum 17 hydroxyprogesterone concentrations is not usually productive

#### Box 1 Main causes of hirsutism

- Polycystic ovary syndrome
- Idiopathic hirsutism
- Congenital adrenal hyperplasia
- Androgen secreting tumours (ovarian or adrenal)
- Cushing's syndrome
- Acromegaly
- Drugs

Hirsutism is the subject of a forthcoming article on Rational Testing, a new *BMJ* series starting this month

**Box 2 Important aspects of the history**

- How quickly has the hair growth progressed?
- What measures have been used to control excess hair?
- Does the woman have any other features of androgen excess (acne or alopecia)?
- What is the pattern of menstruation?
- Has her weight changed recently?
- What is the history of use of the oral contraceptive pill?
- Is there a family history of type 2 diabetes?

because glucocorticoids are rarely the optimal treatment even in confirmed cases; most women do better with ovarian suppression with or without an anti-androgen. Late onset congenital adrenal hyperplasia is, however, important to exclude in hirsute women wishing to conceive when glucocorticoids are the treatment of first choice during periconception. Screening for Cushing's syndrome by 24 hour urine collection for free cortisol or dexamethasone suppression tests is indicated if clinical features are present. Laboratory tests to investigate the causes of hirsutism will be covered in more detail in an upcoming rational testing article on hirsutism. Computed tomography imaging of the adrenal glands should be undertaken only if the index of suspicion of a tumour is high—for example, when hair growth is particularly sudden and heavy. Imaging results are often normal in mild forms of adrenal hyperplasia and there is the added complication of identifying an incidentoloma.

**What are the principles of treatment?**

Most women can be treated in primary care. Box 3 lists the indications for specialist referral. Most therapeutic trials have lasted for six to 12 months only, so we do not know how long it takes for many treatments to reach their maximal effect.

Hair grows in cycles, and it can take months for an individual hair follicle to proceed through catagen, anagen, and telogen phases. All systemic treatments reduce stimulation of the anagen growth phase by testosterone, and enough follicles have to pass through anagen before a clinically obvious effect is seen. In other words, progress can be slow and little improvement is seen within four months. Once satisfactory suppression of unwanted hair has been achieved, the goal of management is to find the lowest effective dose of any agent that maintains the benefit gained in the first phase of treatment.

**What non-systemic treatments are available?**

Many women will be familiar with routine methods of hair removal such as shaving, threading, waxing, and using depilatory creams and can be reassured that these methods do not exacerbate hair growth. Electrolysis and laser epilation or photoepilation are also widely available. A systematic review of 11 trials of laser and light assisted hair removal in 444 patients showed a 50% reduction in hair over six months but

noted that the long term efficacy of these treatments is not well established.<sup>9</sup> Laser treatment is less effective in darker skin because a contrast is needed between skin and hair pigments, but some types of photoepilation can be of benefit for darker skin.

Eflornithine, a topical agent, inhibits the enzyme ornithine decarboxylase, which in turn reduces matrix cell proliferation in the hair follicle. A large sponsored randomised trial showed a 26% reduction in facial hair after 24 weeks of treatment, with most of the benefit achieved in eight weeks.<sup>10</sup>

**What about systemic treatments?**

Systemic treatments aim to suppress ovarian androgen secretion or reduce the action of testosterone on the androgen receptor. In a systematic review of 28 randomised trials of systemic treatments for hirsutism that included 1227 women, we found that the following drugs were effective: metformin (19.1% suppression of hirsutism over baseline over six months compared with placebo), finasteride (20.3%), oral contraceptive pills (27%), thiazolidinediones (31.5%), cyproterone acetate and ethinylestradiol in combination (36%), spironolactone (38.4%), and flutamide (41.3%).<sup>11</sup> The beneficial effects of cyproterone acetate and spironolactone have also been confirmed by individual systematic reviews.<sup>12 13</sup>

The primary driver of ovarian androgen secretion is luteinising hormone, which can be suppressed using a combined oral contraceptive pill. The effectiveness of oral contraceptives in suppressing hirsutism will depend on the content of ethinylestradiol (20-35 µg) and on the nature of the progestogen. Pills containing progestogens with antiandrogenic properties (such as Dianette and Yasmin) are effective in hirsutism,<sup>14</sup> whereas those containing levonorgestrel and norethisterone are more androgenic and could potentially exacerbate hirsutism.<sup>15</sup> Third generation progestogens such as desogestrel or gestodene have relatively neutral androgenic effects,<sup>16</sup> and oral contraceptives containing these compounds can usefully be combined with an antiandrogen such as spironolactone. Only one small randomised controlled trial has compared different oral contraceptive pills, and current guidelines do not recommend one specific pill for treating hirsutism.<sup>4</sup>

Insulin, which acts as a co-gonadotrophin and amplifies luteinising hormone induced testosterone

**Box 3 When to refer to a specialist**

- If hirsutism is particularly severe
- If hair growth is of recent onset and rapid progression
- If first and second line treatments have not been effective over six to 12 months
- If the serum testosterone concentration is more than twice the upper limit of normal
- If the presence of the metabolic syndrome requires a multidisciplinary approach

**SOURCES AND SELECTION CRITERIA**

We reviewed all references to "hirsutism" in Medline and the Cochrane Collaboration and selected randomised controlled trials for inclusion in the evidence base. We also referred to the Endocrine Society's clinical practice guidelines for the management of hirsutism.<sup>4</sup> Clinical experience is based on a tertiary referral endocrine service.

production, is a secondary driver of ovarian androgen secretion. Conveniently, women for whom suppression of luteinising hormone is not possible (for example, obese women who should not take the oral contraceptive pill because of the risk of thrombosis) are often the very women for whom suppression of insulin is most effective. Lifestyle measures that promote weight loss through diet and exercise are of paramount importance because obesity has an adverse effect on the outcome of all systemic treatments. A systematic review of 16 eligible trials of insulin sensitisers concluded that this group of drugs is, at best, of limited use as sole treatment for hirsutism.<sup>17</sup>

In a proportion of women, ovarian suppression alone may not be sufficient, and antiandrogens will need to be added. A recent systematic review of 12 trials showed that antiandrogens are efficacious for treating hirsutism but highlighted the poor methodological quality of the studies involved.<sup>18</sup> Three competitive antagonists of the androgen receptor have been widely used to treat hirsutism. Firstly, cyproterone acetate (12.5-100 mg) can be added to the first 10 days of each calendar pack of the oral contraceptive<sup>12</sup>—more prolonged use tends to induce amenorrhoea because of its progestogenic properties. Common side effects of cyproterone acetate include weight gain, depression, and headache. Secondly, a Cochrane review of eight trials showed that spironolactone (25-200 mg) can effectively suppress hirsutism.<sup>13</sup> According to our clinic experience, its anti-mineralocorticoid and diuretic properties are rarely prominent in young women. The troublesome limiting side effect of spironolactone is menorrhagia or unscheduled menstrual bleeding, which is a feature of its oestrogenic

**ADDITIONAL EDUCATIONAL RESOURCES****Educational resources for healthcare professionals**

*BMJ Clinical Evidence* (<http://clinicalevidence.bmj.com/cweb/conditions/woh/1408/1408.jsp>)—The latest clinical evidence on hirsutism

Endocrine Society ([www.endo-society.org/guidelines/final/upload/Hirsutism\\_Guideline.pdf](http://www.endo-society.org/guidelines/final/upload/Hirsutism_Guideline.pdf))—The latest guideline on the medical management of hirsutism in premenopausal women from the American Endocrine Society

**Information resources for patients**

Verity (<http://verity-pcos.org.uk>)—UK charity for women whose lives are affected by polycystic ovary syndrome

properties. Flutamide (125-250 mg) is probably the most potent of the three drugs, but its use is relatively contraindicated because of its relatively high liver toxicity.<sup>19</sup>

If additional treatment is needed, then finasteride would be a sensible option because it has a different mode of action. Finasteride suppresses the enzyme 5 $\alpha$  reductase, which converts testosterone to the more potent dihydrotestosterone. Evidence exists for the use of finasteride as a single agent or combined with an oral contraceptive or a competitive anti androgen.<sup>20,21</sup>

As outlined in the *British National Formulary*, all anti-androgens, and particularly finasteride, are potentially teratogenic, so some clinicians prescribe them only to women using reliable contraception.

**Common clinical scenarios****Lean young women**

In a young woman with hirsutism and no risk factors for thrombosis, an oral contraceptive pill containing cyproterone acetate or drospirone is an appropriate first choice. When rapid suppression of hair growth is warranted because of distress from the condition then topical eflornithene could be added for 12 weeks. If after six months little progress has been made, then an antiandrogen such as cyproterone acetate or spironolactone could be added. Occasional resistant cases may need the addition of finasteride.

**Obese women with polycystic ovary syndrome**

In obese women the first line treatment must be to promote weight loss using a combination of lifestyle changes and perhaps weight loss drugs because effective suppression of hair growth is unlikely without weight loss.<sup>11</sup> The combination of metformin and spironolactone would be a common first line systemic combination, although careful counselling on the consequences of pregnancy is even more important in this situation because metformin may improve the chances of conception.

**Severe hirsutism in congenital adrenal hyperplasia**

Congenital adrenal hyperplasia is probably the most common condition that causes severe intractable hair growth, although in theory optimised adrenal suppression with glucocorticoids should be achievable. In this condition we have found that antiandrogens are not very effective—presumably because they are overwhelmed by the circulating androgens that can occur between doses of steroids. In this exceptional case, laser treatment should be made available if possible.

**Hirsute women approaching menopause**

Practically no evidence base exists for the treatment of hirsutism during the menopause, so recommendations on managing this common condition are based on clinical experience. Mild hirsutism at the menopause can benefit from oestrogen replacement, often in conjunction with an antiandrogen such as drospirone

**SUMMARY POINTS**

Hirsutism is a common and distressing condition  
 The underlying cause is usually polycystic ovary syndrome  
 Serum testosterone measurements are not needed in most cases  
 Topical and systemic treatments or combinations of the two can adequately control hirsutism in most cases  
 Allow four to six months for any treatment to be effective

(Angeliq) or spironolactone (prescribed separately). If the potential risks of hormone replacement therapy are a concern then cyproterone acetate or spironolactone alone or topical eflornithine may be preferred options. The use of gonadotrophin releasing hormone analogues is recommended for severe hirsutism of ovarian origin at the menopause, such as that caused by stromal hyperplasia,<sup>4</sup> but oophorectomy might be needed to remove the source of excess androgen production permanently.

**How should women on treatment be followed up?**

The success of treatment is usually based on subjective assessment, and clinicians should not contribute to unrealistic expectations of effectiveness. Most systemic treatments reduce the growth of hair by around 25-30% at most. Women with mild hirsutism may not notice much benefit, and some women will prove resistant to all treatments. Psychological interventions may be useful for women with unsatisfactory outcomes, but no trials have assessed the effectiveness of such interventions specifically for hirsutism. Testosterone measurements can be misleading because oral contraceptives cause a rise in sex hormone binding globulin, which results in an increase in the total blood testosterone concentration. No specific guidelines exist for monitoring long term treatments, but it seems logical to measure liver function in users of cyproterone acetate; plasma potassium, liver function, and renal function in users of spironolactone; and vitamin B12 concentrations in users of metformin (which is associated with low concentrations of this vitamin).

In conclusion, hirsutism is a common problem, the effect of which is often underestimated. Various treatment options are available, which—when used in logical combinations and tailored to the individual’s clinical profile—can achieve good results in most cases.

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*Endpiece*  
**Forty winks**

On a junior doctor’s attempts to get some sleep while on call overnight:

“Two hours is bliss, a revelation of humanity, a soft dawning of morning. An hour is enough—enough that the night has been broken and I can stand on it, casually shuffle my feet over its back. Forty-five minutes is like a deep breath, like a good sigh, a fresh drink, but it is just a moment’s reprieve and sad in its ending. Half an hour is laying down and being smacked awake...”

Vincent Lam. *Bloodletting and Miraculous Cures*. London: Fourth Estate, 2008.

Submitted by Usman Shaikh, specialist registrar in radiology, Alder Hey Children’s NHS Foundation