Hirsutism - Management

Scenario: Diagnosis of hirsutism

CKS safe practical clinical answers - *fast*

How do I know my patient has it?

- **Look for excessive terminal hair in androgen-dependent areas** including the face, chest, linea alba, lower back, buttocks, and anterior thighs.
  - Some hair growth in androgen dependent areas is normal, and there is no clear cut-off for defining excessive hair growth.
- It is important to differentiate between terminal hair (which is dark, thick, and coarse) and vellus hair (which is soft, fine, and unpigmented). Vellus hair does not indicate hirsutism.

What else might it be?

- **Hypertrichosis** is excessive hair growth distributed in a generalized, nonsexual pattern.
  - It may be hereditary or drug-induced.
  - It is not caused by excess androgen.

[Martin et al, 2008]

How should I assess for an underlying cause of hirsutism?

- **Ask about, and look for, features of polycystic ovary syndrome (PCOS)** — oligomenorrhoea or amenorrhoea, infertility, acne, hair loss from the scalp, central obesity, acanthosis nigricans.
  - For information on the diagnosis of PCOS, see the section on Diagnosis in the CKS topic on Polycystic ovary syndrome.
- **Ask about, and look for, features of an androgen secreting tumour** — sudden onset or rapid progression of hair growth, severe hirsutism, signs of virilization (hair loss from the scalp, voice deepening, increased muscle bulk, clitoromegaly), a pelvic or abdominal mass.
  - Urgently refer the woman if an androgen-secreting tumour is clinically suspected.
- **Ask about, and look for, features of Cushing's syndrome** — for example: weight gain in the face (moon face), neck region, upper back, and torso; stretch marks; easy bruising; and proximal muscle weakness.
  - Refer the woman if Cushing's syndrome is suspected.
  - Consider checking free cortisol levels (using a 24-hour urine collection) or performing a dexamethasone suppression test before the outpatient appointment.
- **Ask about current medication,** including any use of anabolic steroids.

- **In women with mild hirsutism and no other signs of PCOS or other underlying condition:**

  - Investigations are not usually necessary.

- **In women with moderate-to-severe hirsutism and no other signs of PCOS or other underlying condition:**

  - Measure plasma testosterone.

  - If the testosterone level is greater than 5 nanomol/L, seek specialist advice.

- **Consider screening for late-onset congenital adrenal hyperplasia in women who are at high risk** (for example those with a positive family history, or from a high-risk ethnic group [such as Ashkenazi Jewish, Hispanic, and Slavic people]), especially if they wish to conceive.

  - Measurement of early morning 17-hydroxyprogesterone is recommended — check with the local laboratory for details of when and how this test should be performed.

  - Refer the woman to an endocrinologist if 17-hydroxyprogesterone levels are elevated.

Basis for recommendation

Underlying conditions

- The recommendations to ask about, and look for, features of polycystic ovary syndrome (PCOS), androgen-secreting tumours, and Cushing's syndrome are based on the fact that these are known underlying causes of hirsutism.

Medication

- Certain drugs, including danazol, sodium valproate, and anabolic steroids can cause hirsutism [Martin et al, 2008].

Investigations for mild hirsutism with no other signs of PCOS or other underlying condition

- The recommendation that investigations are not necessary in women with mild hirsutism and no other signs of PCOS or other underlying condition is in line with recommendations from an Endocrine Society clinical practice guideline, based on very low quality evidence [Martin et al, 2008]. This is supported by the opinion of CKS expert reviewers.

Checking testosterone levels in women with moderate-to-severe hirsutism and no other signs of PCOS or other underlying condition

- The recommendation to check testosterone levels in women with moderate-to-severe hirsutism and no other signs of PCOS or other underlying condition is in line with recommendations from

an Endocrine Society clinical practice guideline, based on very low quality evidence [Martin et al, 2008].

Screening for late-onset congenital adrenal hyperplasia

- The recommendation to consider screening for late-onset congenital adrenal hyperplasia in women at high risk is based on a narrative text on rational testing [Sathyapalan and Atkin, 2009].
  - Around 1–10% of women with hyperandrogenaemia have late-onset congenital hyperplasia, which is clinically indistinguishable from PCOS.
  - The prevalence is higher in Hispanic, Ashkenazi Jewish, and Slavic people. Therefore, screening in this group seems sensible.
  - Identification of late-onset congenital adrenal hyperplasia in women who are trying to conceive is important so that glucocorticoid treatment can be initiated in the peri-conceptual period [Koulouri and Conway, 2009].

Hirsutism - Management

Scenario: Hirsutism

CKS safe practical clinical answers - *fast*

How should I assess the severity of hirsutism?

- **Assess the severity of hair growth and the impact on the woman's quality of life,** as this may guide treatment.
- Some hair growth in the androgen-dependent areas is normal, and there is no clear cut-off for defining excessive hair growth.
  - **A subjective approach is generally appropriate in primary care,** using the woman's own perception of her condition and the extent it impacts on her quality of life.
  - Hirsutism can be more formally evaluated using the Ferriman–Gallwey scoring system; however, this scoring system has several limitations, and is impractical for routine use in clinical practice.

Ferriman-Gallwey scoring system

- The Ferriman–Gallwey scoring system has been designed to assess the severity of hirsutism.
- Each of the nine body areas most sensitive to androgen production is assigned a score from 0 (no hair) to 4 (heavy hair growth).
  - The nine areas are: upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, the upper arms, and the thighs.
- The separate scores are added to provide a total score (0–36).
  - A score of more than 15 is considered to indicate moderate or severe hirsutism.

[Martin et al, 2008]

Basis for recommendation

Assessment of severity

- The recommendation to assess severity is based on expert opinion in guidelines and narrative reviews [Lavery et al, 2005; Martin et al, 2008; Kumar et al, 2009].

Definition of excessive hair growth

- There is no clear cut-off for defining excessive hair growth. Although many clinical trials use a Ferriman–Gallwey score of eight or more to indicate hirsutism, many women with a lower score consider themselves hirsute.
  - In a prospective observational study in 633 women, a Ferriman–Gallwey score of two or less was observed in approximately 75% of women; 16% of these women considered themselves to be hirsute [DeUgarte et al, 2006].
  - Of the 25% of women with a Ferriman–Gallwey score of three or more, 70% considered themselves to be hirsute.
  - Similarly, 70% of women with a Ferriman–Gallwey score of eight or more considered themselves to be hirsute.
  - Overall there were no differences between black and white women.
- The Ferriman–Gallwey scoring system is a validated tool. However, it has a number of limitations, and although it is valuable as a clinical research tool, it is generally not considered to be practical for use in primary care [Lavery et al, 2005; Martin et al, 2008; Koulouri and Conway, 2009; Kumar et al, 2009].

How should I manage hirsutism in premenopausal women?

For premenopausal women (with or without polycystic ovary syndrome):

- **Encourage weight loss** in women who are overweight or obese (see the CKS topic on Obesity for more information).
- **Discuss cosmetic methods of hair reduction and removal,** as these will remain an important part of management.
- **If hirsutism is mild and does not significantly impact on the woman's quality of life,** consider no additional treatment.
- **If additional treatment is required,** offer co-cyprindiol (Dianette®) or a combined oral contraceptive (COC) containing drospirenone (for example Yasmin®).
  - Co-cyprindiol (Dianette®; a combination of ethinylestradiol and the anti-androgen cyproterone acetate) is licensed for the treatment of moderately-severe hirsutism but should be stopped three or four menstrual cycles after the woman's hirsutism has completely resolved because of an increased risk of venous thromboembolism.

- Yasmin® (a combination of ethinylestradiol and drospirenone) is not licensed specifically for hirsutism but is an alternative to co-cyprindiol for women who require long-term treatment. Yasmin® is more expensive than co-cyprindiol.

- See the CKS topic on Contraception for a full discussion of the risks of COCs.

- **Advise the woman that treatment may take at least 6 months to work.**

- **If relapse occurs when co-cyprindiol is stopped,** consider:

- Intermittent use of co-cyprindiol — stopping treatment after resolution occurs, and starting again if symptoms reappear (licensed use).

- Switching to a COC containing drospirenone (Yasmin®).

- Some experts recommend continuing treatment with co-cyprindiol if the above measures fail.

- **If COCs are contraindicated or have not worked, offer women with facial hirsutism topical eflornithine.**

- Benefit should be noticed in 6–8 weeks, and eflornithine should be discontinued if no benefit is seen within 4 months of starting treatment.

- If improvement is seen, continued treatment is necessary to maintain the benefits. Once the cream is discontinued, hair growth returns to pretreatment levels within about 8 weeks.

- Eflornithine is contraindicated during pregnancy and breastfeeding.

Methods of hair removal

- Cosmetic treatment is not usually available on the NHS.

- Cosmetic procedures can be applied in a domestic setting.

- Shaving does not increase the rate of hair growth or thicken hair, contrary to popular belief. It is a useful technique and yields instant results. However, it does leave stubble that is unpleasant, unsightly, and sharp, and may irritate the skin.

- Waxing and plucking are effective, but can be painful and may cause scarring, folliculitis, and hyperpigmentation. These techniques can also lead to resistance to electrolysis.

- Bleaching can improve the appearance of dark hair in the short term, but may also lead to skin irritation.

- Skin irritation is problematic as it is itchy, unsightly, and paradoxically can lead to increased hair growth.

- Cosmetic procedures carried out in specialist clinics tend to have a longer effect, although they are not usually permanent.

- Electrolysis uses a localized electric charge to destroy hair cells at the bulb. It is effective, but is time-consuming, painful, and may leave scars or pigmentation changes.

- Lasers are used selectively in the process of photothermolysis, a more recent technique that generally yields better results than electrolysis. It only affects hair in the growing phase, so must be repeated over several months. Laser hair removal is most effective in women with pale skin and dark hair.

Basis for recommendation

Weight loss

- The recommendation on weight loss for women who are overweight or obese is based on expert opinion [Lavery et al, 2005].
- Weight loss is likely to improve metabolic and endocrine parameters; however, in one study of overweight women with polycystic ovary syndrome, there was no direct effect of weight loss on hirsutism [Moran et al, 2003].

Permanent hair reduction techniques

- There are very few published studies on electrolysis; however, electrolysis has been widely used for a number of years.
- Limited evidence from a Cochrane systematic review (11 randomized controlled trials [RCTs]) suggests that some laser and photoepilation treatments may lead to short-term hair reduction. There is less evidence of long-term benefit.
  - One small crossover trial suggests that laser treatment is more effective that electrolysis.

Combined oral contraceptives (COCs)

- COCs are recommended as first-line treatment for premenopausal women with hirsutism in guidelines and narrative reviews [Claman et al, 2002; Lavery et al, 2005; Martin et al, 2008; Koulouri and Conway, 2009].
- COCs decrease plasma testosterone by suppression of luteinizing hormone secretion (thereby reducing ovarian androgen secretion) and by increasing the production of sex hormone-binding globulin (thereby increasing androgen binding and reducing free androgen levels) [Martin et al, 2008].
- CKS expert reviewers recommend co-cyprindiol (Dianette®) or a COC containing drospirenone as the preferred COCs for women with hirsutism.
  - Co-cyprindiol contains the anti-androgen cyproterone acetate, which has been shown to be effective in managing hirsutism. It is licensed for the treatment of moderately-severe hirsutism [ABPI Medicines Compendium, 2008].
  - Drospirenone also has anti-androgenic properties [Martin et al, 2008]. COCs containing drospirenone (such as Yasmin®) may be an alternative to co-cyprindiol in women with hirsutism, especially as long-term treatment is often necessary.

- CKS expert reviewers did not recommend second generation COCs (containing levonorgestrel and norethisterone) and third generation COCs (containing desogestrel, norgestimate, and gestodene) for the management of hirsutism.

  - COCs containing levonorgestrel and norethisterone are more androgenic and could potentially exacerbate hirsutism [Koulouri and Conway, 2009].

  - There is some concern that COCs containing desogestrel, norgestimate, and gestodene may have a greater risk of venous thromboembolism than those containing drospirenone, levonorgestrel, or norethisterone, although the absolute risk is is still low (about 25 per 100,000 women per year of use) [BNF 57, 2009].

- There is limited evidence on the efficacy of COCs in the management of hirsutism.

  - Evidence from a Cochrane systematic review (one RCT) suggests that co-cyprindiol is more effective than placebo at reducing hair growth in women with hirsutism.

  - Evidence from one RCT suggests that COCs containing drospirenone are at least as effective at reducing hair growth as those containing cyproterone acetate.

  - Evidence from one small RCT with a high drop-out rate suggests there is no difference in clinical outcomes between second and third generation COCs; further studies are needed to confirm this.

Duration of treatment

- An Endocrine Society clinical practice guideline suggests a trial of at least 6 months of treatment, based on very low quality evidence [Martin et al, 2008].

- The Committee on the Safety of Medicines recommends that co-cyprindiol should be discontinued three or four menstrual cycles after the woman's hirsutism has resolved, due to the risk of serious adverse effects such as thromboembolism [CSM, 2002].

  - There is a two- to four-fold increase in the risk of venous thromboembolism with co-cyprindiol compared with conventional second-generation COCs, although the absolute risk remains low [Vasilakis-Scaramozza and Jick, 2001; Seaman et al, 2003].

Treatment of relapse when co-cyprindiol is stopped

- The advice on whether to continue to use co-cyprindiol continuously or intermittently, or to switch to an alternative COC, is advice based on the opinions of CKS expert reviewers.

Eflornithine

- Evidence from small RCTs suggests that eflornithine may improve the appearance of facial hair in the short term (up to 6 months), but its efficacy in the longer term remains unclear.

- There is weak evidence that it may be more effective than placebo when combined with laser treatment, in the short term.

How should I manage hirsutism in postmenopausal women?

For postmenopausal women:

- **Discuss cosmetic methods of hair reduction and removal,** as these will remain an important part of management.
- **If hirsutism is mild and does not significantly impact on the woman's quality of life** — consider no additional treatment.
- **If additional treatment is required,** consider:
  - **Topical eflornithine,** for women with facial hirsutism.
  - Benefit should be noted in 6–8 weeks, and eflornithine should be discontinued if no benefit is seen within 4 months of starting treatment.
  - If improvement is seen, continued treatment is necessary to maintain the benefits. Once the cream is discontinued, hair growth returns to pretreatment levels within about 8 weeks.
  - **Referral** for initiation of specialist treatment.

Basis for recommendation

Treatment of postmenopausal women

- CKS found no evidence specifically on the management of hirsutism in postmenopausal women. Recommendations are based on the opinion of CKS expert reviewers.

When should I refer a woman with hirsutism?

- **Refer the woman,** if:
  - Hair growth is of recent onset and rapid progression, there are signs of virilization, hirsutism is particularly severe, or an abdominal or pelvic mass is detected.
  - There are clinical features suggestive of Cushing's syndrome (such as weight gain in the face [moon face], neck region, upper back, and torso; stretch marks; easy bruising; proximal muscle weakness).
  - Serum total testosterone concentration is more than 5 nanomol/L.
  - Hair growth worsens despite treatment.
  - Treatment has not been effective after 6–12 months.

Basis for recommendation

Androgen secreting tumour

- Hair growth of recent onset and rapid progression, signs of virilization, particularly severe hirsutism, and a pelvic or abdominal mass are indications of a more serious underlying cause, such as an androgen-secreting (ovarian or adrenal) tumour.

- A high total testosterone concentration may indicate an androgen-secreting tumour [Sathyapalan and Atkin, 2009].

  - If the total testosterone is normal (< 4.1 nanomol/L) or only slightly increased (< 5 nanomol/L), an androgen secreting tumour can be excluded.

When treatment in primary care has been ineffective

- Hirsutism that has failed to respond to treatment in primary care may respond to systemic treatments such as anti-androgens, insulin-sensitizing drugs, and gonadotrophin-releasing hormone agonists [Lavery et al, 2005; Martin et al, 2008; Koulouri and Conway, 2009].

- Because these drugs are not licensed for the treatment of hirsutism and have potentially serious adverse effects, CKS recommends that they should only be used under specialist supervision.

What treatments may be used in secondary care?

- Systemic treatments that may be used in secondary care include:
  - Anti-androgens (such as high-dose cyproterone acetate, spironolactone, and flutamide).
  - 5-alpha-reductase inhibitors (such as finasteride).
  - Insulin-sensitizing drugs (such as metformin and the glitazones [pioglitazone and rosiglitazone]).
  - Gonadotrophin-releasing hormone analogues (such as goserelin and leuprorelin).

Basis for recommendation

Hirsutism that has failed to respond to treatment in primary care may respond to systemic treatments such as anti-androgens, insulin-sensitizing drugs, and gonadotrophin-releasing hormone agonists [Lavery et al, 2005; Martin et al, 2008; Koulouri and Conway, 2009].

- Because these drugs are not licensed for the treatment of hirsutism and have potentially serious adverse effects, CKS recommends that they should only be used under specialist supervision.

- Weak evidence from a systematic review and meta-analysis (12 randomized controlled trials [RCTs]) suggests that anti-androgens are effective for the treatment of hirsutism [Swiglo et al, 2008].

  - Compared with placebo, anti-androgens reduced Ferriman–Gallwey scores by 3.9 points (95% CI 2.3 to 5.4).

- Weak evidence from a systematic review and meta-analysis (16 RCTs) suggests that insulin-sensitizing drugs have limited efficacy in the treatment of hirsutism [Cosma et al, 2008].
  - Compared with placebo, insulin sensitizers reduced Ferriman–Gallwey scores by 1.5 points (95% CI 0.3 to 2.8).
  - There was no evidence of a significant difference between insulin sensitizers and oral contraceptives (weighted mean difference [WMD] 0.5 points; 95% CI 3.9 to 5.0).
  - Metformin was less effective than both spironolactone (WMD 1.3; 95% CI 0.03 to 2.6) and flutamide (WMD 5.0; 95% CI 3.0 to 7.0).

Prescriptions

For information on contraindications, cautions, drug interactions, and adverse effects, see the electronic Medicines Compendium (eMC) (http://emc.medicines.org.uk), or the British National Formulary (BNF) (www.bnf.org).

Anti-androgen plus oestrogen (co-cyprindiol)

Age from 13 to 50 years

Cyproterone acetate 2mg + ethinylestradiol 35mcg (Dianette®)

Co-cyprindiol 2000microgram/35microgram tablets
Take one tablet once a day for 21 days. Start the next packet after a 7-day break. See package insert for full instructions.
Supply 63 tablets.

Age: from 13 years to 50 years
NHS cost: £6.51
Licensed use: yes

Patient information: Take the pill at the same time each day. If you forget one or more pills or experience diarrhoea or vomiting and are unsure what to do, seek the advice of a health professional.

Drospirenone plus oestrogen

Age from 13 to 50 years

Yasmin: drospirenone 3mg + ethinylestradiol 30mcg

Yasmin tablets
Take one tablet once a day for 21 days. Start the next packet after a 7-day break. See package insert for full instructions.
Supply 63 tablets.

Age: from 13 years to 50 years
NHS cost: £14.70
Licensed use: yes

Patient information: Take the pill at the same time each day. If you forget one or more pills or experience diarrhoea or vomiting and are unsure what to do, seek the advice of a healthcare professional.

Eflornithine cream

Age from 12 years onwards

Eflornithine 11.5% cream: apply twice a day

Eflornithine 11.5% cream
Apply thinly to the affected area(s) twice a day.
Supply 60 grams.

Age: from 12 years onwards
NHS cost: £52.08
Licensed use: yes

Patient information: This cream must be rubbed in thoroughly. Wait 5 minutes after applying this cream before applying any makeup. Do not wash your face for 4 hours after applying this cream.