

Hirsutism

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She was 17, recently moved to the UK from Turkey, dragged down to see me by her mother. She sat in the corner looking sheepish, “Well go on then...” said mum. She remained quiet. “She thinks she’s got too much hair, you know, on her body.” She squirmed.

Hirsutism can have a significant impact on psychological well being and quality of life. It may be seen as a cosmetic problem but patients often want to discuss this issue. So when should we be concerned about an underlying problem? When should we investigate and how? What treatments are available? These issues were considered in two clinical reviews in the BMJ.

What are the common causes?

Hirsutism is excess hair growth in women in an androgen dependent distribution. It occurs as a result of increased androgen production or increased skin sensitivity to androgens.

Common causes:

Polycystic ovary syndrome (PCOS) (72%)
Idiopathic hyperandrogenism (23%)

Rarer causes include:

Congenital adrenal hyperplasia (CAH) (4.3%)
Androgen secreting tumours (<1%)
Cushing’s syndrome
Acromegaly
Drugs

Concerning features:

- **Recent onset and rapid progression of hirsutism.**
- **Other signs of virilisation e.g. deepening of voice, clitoromegaly.**

How should we investigate?

As PCOS is the most common cause, first ask whether the patient fulfils the 2003 consensus criteria for diagnosis:

Revised 2003 Rotterdam criteria for diagnosing polycystic ovarian syndrome:

Two out of three must be present:

- *Clinical oligomenorrhoea or amenorrhoea – cycle > 35 days or <10 periods/year.*
- *Clinical or biochemical evidence of hyperandrogenism (hirsutism, acne, alopecia or raised free androgen index).*
- *Polycystic ovaries on ultrasound examination.*

If not, then consider the investigations listed overleaf.

For those whose history is not suggestive of PCOS:

- Thyroid function (TSH)
- Prolactin
- Total testosterone and sex hormone binding globulin (SHBG) – you can then calculate the free androgen index (see over).

If clinically indicated:

- 17-hydroxyprogesterone (?congenital adrenal hyperplasia)
- 24 hour urinary cortisol (if clinical signs of Cushing's)
- **Ovarian ultrasound scan should be offered to all women with isolated hyperandrogenaemia in the absence of other clinical features** – transvaginal is more sensitive than transabdominal.

- **If PCOS is diagnosed, remember to screen for metabolic syndrome (glucose, lipids and BP).**

When is a testosterone level too high?

Total testosterone is reported when you request a test from most UK laboratories.

| | | |
|--------------------|-------------|---|
| Total Testosterone | <4.1 nmol/l | Normal |
| | <5 nmol/l | Probable PCOS: androgen secreting tumour excluded |
| | >6.2 nmol/l | Androgen secreting tumour more likely |

The cases with a significantly raised testosterone warrant referral to secondary care for further biochemical and imaging assessment.

- **Total testosterone is affected by the concentration of circulating sex hormone binding globulin (SHBG).** SHBG concentration is increased by the COCP and reduced by insulin resistance and obesity. Free androgen index (FAI) may be a better measure in these situations as it indicates the testosterone which can exert its effect on tissues:

$$\text{FAI} = (\text{total testosterone}/\text{SHBG}) \times 100\%$$

In normal woman FAI should be less than 3%.

When should I suspect non-classic congenital adrenal hyperplasia?

Non-classic CAH is caused by a partial 21-hydroxylase deficiency and presents later in life. Clinically this condition can be indistinguishable from PCOS. It is more common in Hispanics, Yugoslavs, Eastern European Jews and people from the southern Mediterranean.

- 17-hydroxyprogesterone should be measured on days 1-14 of the menstrual cycle at 9am to avoid diurnal variation.
- If >5nmol/L refer for further endocrinology assessment with a short synacthen test. At this cut off 17-HP has a 100% sensitivity and 86% specificity for diagnosing non-classic CAH.

In practice, making this diagnosis is most important if the woman is planning to conceive when glucocorticoids are the treatment of choice in the peri-conception period. Otherwise, the authors tell us that women with this condition respond best to ovarian suppression.

How can we treat hirsutism?

The authors conclude that the overall quality of primary evidence is low and that most studies only run for between 6-12 months which may not allow sufficient time for treatments to reach their maximal effect.

Non-systemic treatments:

- Shaving, waxing & depilatory creams are widely used & **do not** exacerbate hair growth.
- Laser and light assisted hair removal: A systematic review of 11 trials including 444 patients showed a 50% reduction in hair growth over a 6 month period. They concluded that long term efficacy was not known (Cochrane 2006;(4):CD004684). Those with darker skin may benefit less because of less contrast between skin and hair pigment.

Eflornithine (Vaniqa) a single drug company sponsored trial showed a 26% reduction in facial hair after 24 weeks of treatment. This reduction in hair growth was determined by investigators and the women's views on the success of treatment were not reported(!). Hair growth returns to pre-treatment levels 8 weeks after stopping treatment. There have been no head to head trials with systemic treatments.

The cost to the NHS is £156-£312 per year.

- **The DTB concluded that eflornithine only had a place where local hair removal treatments are unsuccessful and systemic treatments unsuitable** (DTB 45(8):62 2007).
- This cream remains black listed by many PCT's.

Systemic Treatments

These aim to suppress ovarian androgen production or reduce the effect of testosterone on its receptor.

A systematic review of treatments for hirsutism compared the following agents:

| Drug | Suppression of hair growth over 6m compared with placebo |
|---|---|
| Flutamide | 41% |
| Spirolactone (25-200mg) | 38% |
| Cyproterone and ethinylestradiol (Dianette) | 36% |
| Thiazolidinediones (glitazones) | 31% |
| COCP | 27% |
| Finasteride | 20% |
| Metformin | 19% |

- **All anti-androgens are potentially teratogenic and should be prescribed with a reliable contraceptive** (cyproterone, finasteride, spironolactone and flutamide).
- **The use of flutamide is limited by its potential for liver toxicity.**
- COCP's containing levonorgestrel and norethisterone are more androgenic and *may* potentiate hirsutism. There have been no head to head trials comparing the efficacy of different COCP's in treating hirsutism.
- There is no standard advice regarding follow up or judging success of these treatments **though the authors urge us to encourage women to have realistic expectations of what treatment can offer.**

In choosing treatment the authors make the following recommendations:

| Scenario | Drug Regimen |
|--|--|
| Lean young women (low thrombosis risk) | COCP containing cyproterone/drospirinone If no progress in 6m: Add in cyproterone acetate or spironolactone Resistant cases: Add in finasteride |
| Obese women with PCOS | First line: weight loss Second line: metformin +/- spironolactone |
| Severe Hirsutism in CAH | Adrenal suppression with glucocorticoids Laser treatment |
| Hirsutism approaching menopause | Very little evidence base! ?Oestrogen replacement +/- drospirinone or spironolactone |

Take Home Messages: Hirsutism

- PCOS and idiopathic androgen excess are the most common causes.
- Baseline investigations should include plasma testosterone, free androgen index, TSH and prolactin and if clinical suspicion 17-hydroxyprogesterone and 24 hour urinary cortisol.
- Androgen secreting tumours are rare and are more likely with rapid onset hirsutism and a testosterone >1.5 times the upper limit of normal.
- Treatment should be tailored to the individual and we should be realistic about the likely extent of improvement a 20-40% reduction in hair growth.
- Effective hair removal treatments remain important though are not widely available through the NHS.

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