Investigating and managing hirsutism in a young woman

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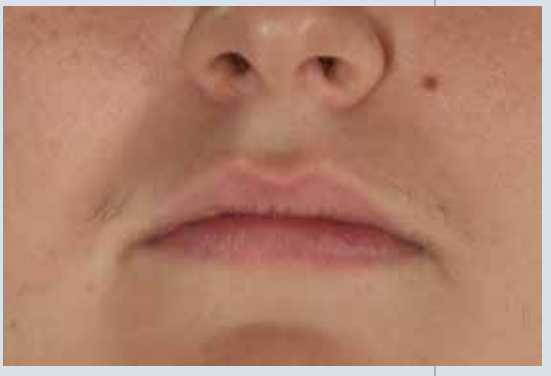
Case scenarios are used in this section to educate doctors on the best approach to the diagnosis and management of patients with different endocrine problems. The appropriate selection of tests and correct interpretation of test results are discussed.



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Case scenario

Mrs AC, a 31-year-old woman presented to her GP with concerns about her hirsutism, which had been present for many years. It had worsened since the birth of her children two and eight years ago and was distressing her. She had transient acne as a teenager, and had been diagnosed with polycystic ovary syndrome seven years ago. Menarche was at age 13 years, and she had had regular monthly menstrual periods before her first pregnancy eight years ago. Postpartum menses were irregular, with cycle length varying from six weeks to three months.

Mrs AC was obese, with a body mass index (BMI) of 36.8 kg/m^2. Over the past six months she had seen a dietitian, started exercising five times weekly and lost 10 kg in weight. Her menstrual cycle length improved to five to seven weekly, but hirsutism was unchanged and had been treated with local plucking and shaving. Her family history included type 2 diabetes mellitus and ischaemic heart disease in her father, diagnosed at age 50 years.

On examination, Mrs AC's blood pressure was 110/80 mmHg, pulse regular at 72 per minute, weight 102.5 kg and waist circumference 106 cm. She had hirsutism over her upper lip, chin, periareolar regions and midline lower abdomen with modified Ferriman-Gallwey score 14.[1] She had mild androgenic alopecia and neck skin tags but no acanthosis nigricans or signs of virilisation or Cushing's syndrome. She appeared euthyroid with no goitre.

How should women such as Mrs AC be investigated and managed?

Commentary

Hirsutism, defined as excessive terminal hair in androgen-sensitive areas of the female body, is a common problem occurring in approximately 10% of women.[2] Terminal hairs are larger diameter, more pigmented and longer than the soft, usually nonpigmented vellus hairs that occur over large parts of the body. Hirsutism is different from hypertrichosis, a generalised increase in body hair, which may be hereditary or related to medications.

The modified Ferriman-Gallwey (mFG) scoring system provides a means of assessing the degree of hirsutism (Figure).[1] A score of between 0 (no terminal hair) and 4 (normally virilised healthy adult male) is assigned for nine body areas (upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, upper arms and thighs). Hirsutism varies by ethnicity. It is defined by a cut-off score of 8 or greater (the 95th percentile) in Caucasian, African or African American women, but 3 or greater in Far East or South East Asian women.[1] Scores up to 11 can be normal for Mediterranean and Middle Eastern women. For Caucasian women, mFG scores of 8 to 15 are classified as mild hirsutism, whereas scores greater than 15 are moderate hirsutism. However, the mFG can be difficult to assess in practice as women have often treated their hirsutism before clinical assessment.

Hirsutism is one manifestation of clinical hyperandrogenism; others are acne and androgenic alopecia. Although psychological distress and desire for improved cosmesis usually prompt the initial presentation, hirsutism provides an opportunity to diagnose and manage important underlying conditions, most commonly polycystic ovary

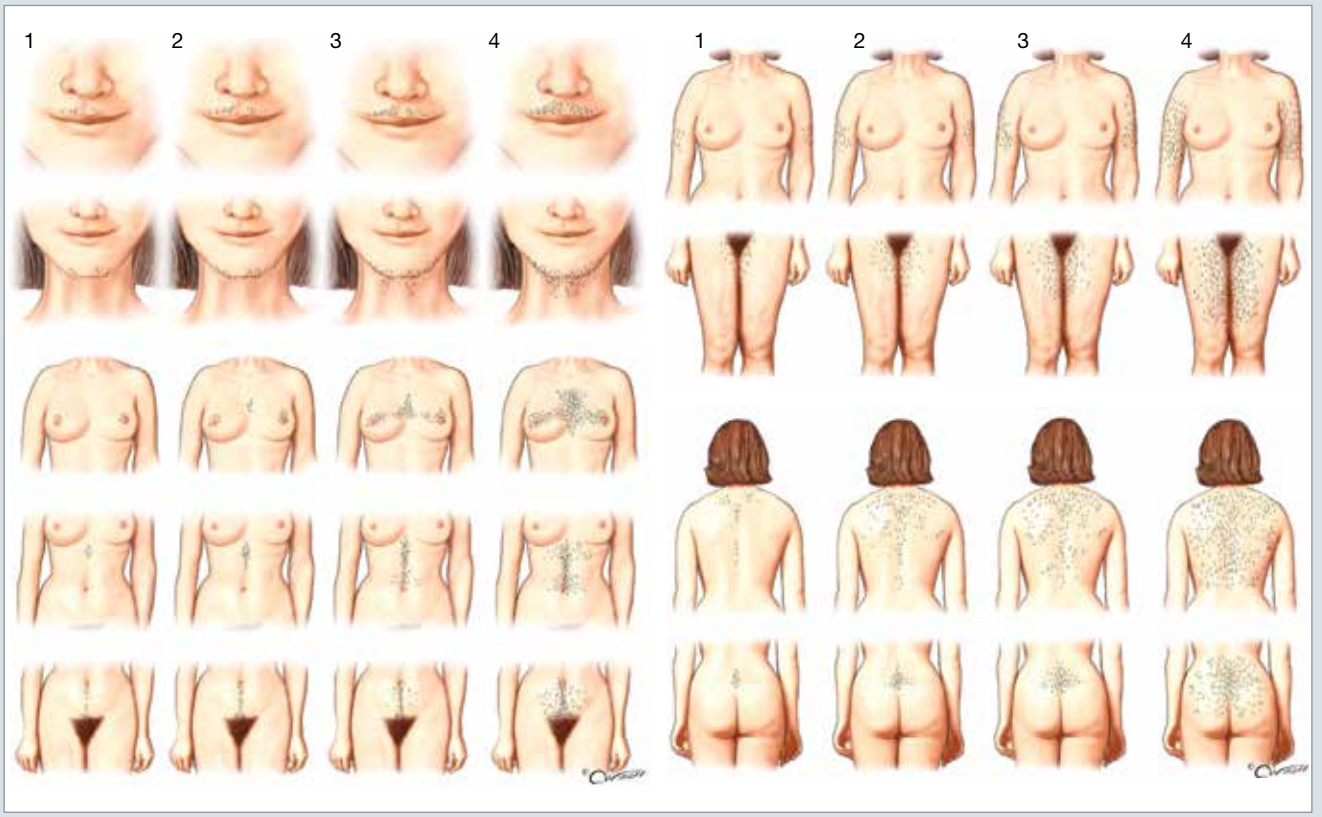


Figure. Modified Ferriman-Gallwey scoring system. Hair growth is rated from 0 (no terminal hair; not shown here) to 4 (complete and heavy cover) in nine locations, giving a maximum score of 36.

syndrome (PCOS) but rarely nonclassic congenital adrenal hyperplasia or androgen-secreting tumours. A comprehensive list of the causes of hirsutism is given in Table 1. A PCOS diagnosis prompts investigation and management of other important issues such as cardiovascular risk factors, including diabetes mellitus, potentially reduced fertility, endometrial hypertrophy and obstructive sleep apnoea.

Relevant history: what to ask

Hirsutism history

Determine the age of onset, sites and rapidity of progression of the hirsutism. Onset is often at puberty in PCOS. Rapid progression raises suspicion for a virilising tumour. Ask the patient about previous and current management strategies, their frequency and duration of use and their success. Enquire about exacerbating medications such as valproate or other anticonvulsants and anabolic steroids.

Other clinical features of hyperandrogenism

Ask patients about acne, androgenic alopecia and features suggesting virilisation – e.g. deepening of voice, clitoromegaly and increased muscle bulk.

Menstrual history

Ask about the age of menarche, oligo- or amenorrhoea and relation of menstrual irregularity and hirsutism to weight changes and exercise (because PCOS is common). Hirsutism often worsens with weight gain and increased insulin resistance in patients with PCOS.

Family history

Determine the patient's racial origin and family history of female hirsutism or alopecia, metabolic syndrome, diabetes or cardiovascular disease. Patients with PCOS often have a family history of type 2 diabetes mellitus and cardiovascular disease.

Previous investigation results

Obtain previous blood tests and pelvic ultrasound results. Blood results obtained in women taking a combined oral contraceptive pill (COCP) may show suppressed androgen levels and are often uninterpretable unless androgen levels remain high, raising suspicion of an androgen-secreting tumour. For patients currently taking the COCP, previous results of androgen level tests when they were not taking the COCP are particularly useful.

Physical examination: what to look for

Check weight, height, BMI, waist circumference and blood pressure. Look at androgen-dependent sites for hirsutism. The mFG classification system can be used, although in practice a combination of upper and lower abdominal and chin hirsutism is sufficient for diagnosis of hirsutism.

Look for other signs of hyperandrogenism, as noted above, such as androgenic alopecia

and acne and signs of virilisation – i.e. clitoromegaly, deep voice and increased muscle bulk, which suggest more severe hyperandrogenism and may be associated with androgen-secreting tumours. Androgenic alopecia in women usually presents with thinning of scalp hair, mainly over the crown, often with widening of the hair parting but usually preservation of the frontal hairline.

Look for signs of insulin resistance that point to possible PCOS: acanthosis nigricans and skin tags in the axillae and neck, which are more likely in women with higher BMI and a waist circumference greater than 80 cm.

Check for signs of hyperlipidaemia, including xanthelasma and xanthomata.

Look for signs of other endocrinopathies such as Cushing's syndrome, hypothyroidism, hyperprolactinaemia and acromegaly.

Table 1. Causes of hirsutism

Cause	Comments
Polycystic ovarian syndrome (PCOS)	70% of women with hirsutism have PCOS. Note: approximately 10% of women of reproductive age have PCOS
Pregnancy	Always consider, especially if patient has amenorrhoea
Nonclassic congenital adrenal hyperplasia	Consider in higher risk populations – i.e. Ashkenazi Jewish, Italian, Slavic or Hispanic populations
Idiopathic hirsutism	Normal androgen levels, normal ovulatory menstrual cycles and normal ovarian morphology on ultrasound
Idiopathic hyperandrogenism	High androgen levels but normal ovulatory menstrual cycles and normal ovarian morphology on ultrasound and other causes excluded
Medications	Examples include valproate, phenytoin, anabolic steroids
Androgen-secreting tumours	Usually ovarian or adrenal tumours
Other endocrine causes	Examples include hypothyroidism, hyperprolactinaemia, Cushing's syndrome, acromegaly

Investigations

There is a poor correlation between androgen levels and the presence or degree of hirsutism. Absence of hirsutism does not exclude biochemical hyperandrogenism. Although concerning hirsutism can occur in the presence of normal androgen levels, it is worthwhile checking androgen levels in all women presenting with hirsutism. Some guidelines advise against androgen testing in women with mild hirsutism (mFG 8 to 15) who have a regular menstrual cycle.[3] Certainly all women with ovulatory dysfunction should have their androgen levels checked.

Check early morning plasma total testosterone and sex hormone binding globulin (SHBG) levels. Free testosterone should not be measured directly, as it is inaccurate when performed by the usual radioimmunoassay.[4] Further investigation for an ovarian or adrenal tumour is mandated when total testosterone level is twice the upper limit of the normal range or more, or when hirsutism is of rapid onset and progression regardless of testosterone level. In such cases, order a pelvic ultrasound, preferably transvaginal to detect ovarian tumours, and adrenal imaging with fine-cut CT or MRI, looking for adrenal tumours. Pelvic ultrasound is needed in premenopausal women to check for polycystic ovaries[3,5] and associated endometrial thickening, a risk factor for endometrial carcinoma. Of note, polycystic ovaries on ultrasound are common, occurring in 22% of women of reproductive age.[6]

Checking the levels of other androgens has lower yield, so does not need to be performed routinely. Raised dehydroepiandrosterone (DHEAS) or raised androstenedione is the sole androgen abnormality in approximately 10% of women.[7] In patients from high-risk populations for congenital adrenal hyperplasia – i.e. Ashkenazi Jewish, Italian, Slavic or Hispanic – check an early morning 17-hydroxyprogesterone (17-OH progesterone) level, preferably during the follicular phase of the menstrual cycle to exclude nonclassic congenital adrenal hyperplasia (normal reference range 0.3 to 3.3 nmol/L in follicular phase). If the level is high, the patient should undergo short synacthen testing with checks of 17-OH progesterone levels at each time point.

Since PCOS is the most common cause of hirsutism, check the patient's baseline metabolic markers: fasting total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol and triglycerides; fasting plasma glucose level and liver function test results. If PCOS is confirmed, perform a 75 g oral glucose tolerance test because often only the two-hour level is elevated.[8] Measurement of concomitant insulin levels is not of value. Electrolytes, urea and creatinine levels should be checked if spironolactone therapy is contemplated to rule out hyperkalaemia and check that renal function is normal.

PCOS is a diagnosis of exclusion (Box 1),[9] so exclude other causes of ovulatory dysfunction and/or hirsutism by measuring thyroid

1. Definition of PCOS: Rotterdam Criteria 2004[9]

Presence of two or more of the following criteria, provided other causes have been excluded:

- **Clinical or biochemical evidence of hyperandrogenism**
  Hirsutism, acne, androgenic alopecia, virilisation or high androgen levels/upper end of reference range levels with low SHBG level
- **Ovulatory dysfunction**
  Oligomenorrhoea (menstrual cycles >35 days for ≥6 cycles per year) or amenorrhoea
- **Polycystic ovaries on ultrasound**
  ≥12 follicles measuring 2 to 9 mm in diameter and/or increased ovarian volume >10 mL[5]

Abbreviations: PCOS = polycystic ovary syndrome; SHBG = sex hormone binding globulin.

Table 2. Investigations for hirsutism

Investigation	Rationale for test
Blood tests	
Total testosterone, SHBG	Assess biochemical hyperandrogenism. If SHBG is higher, free testosterone is likely to be lower
LH, FSH, oestradiol	Exclude secondary hypogonadism, pregnancy. Look for high LH:FSH ratio suggestive of PCOS
+/- DHEAS, androstenedione	Not required for most women as low yield
Beta HCG	If amenorrhoea/severe oligomenorrhoea
Prolactin	Exclude hyperprolactinaemia
TSH	Exclude thyroid dysfunction
17-hydroxyprogesterone	Only in high risk racial origin groups to screen for congenital adrenal hyperplasia (reference range: follicular phase 0.3 to 3.3 nmol/L)
Fasting total cholesterol, HDL, LDL, TG	Assessment of metabolic risk in patients with PCOS
Fasting plasma glucose (if PCOS confirmed, perform 75 g OGTT)	Assessment of metabolic risk in patients with PCOS
LFTs	Initial screen for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis in patients with PCOS or obesity
Electrolytes, urea, creatinine	If considering spironolactone use and for monitoring patients on spironolactone, with particular attention paid to potassium levels
Imaging	
Pelvic ultrasound	To assess for PCO (prevalence 22% in women of reproductive age)[6] and if androgen-secreting tumour suspected
Adrenal CT (fine cuts)/MRI	Only if an androgen-secreting tumour suspected

Abbreviations: CT = computed tomography; DHEAS = dehydroepiandrosterone; HCG = human chorionic globulin; HDL = high density lipoprotein cholesterol; LDL = low density lipoprotein cholesterol; LH = luteinising hormone; FSH = follicle stimulating hormone; LFTs = liver function tests; MRI = magnetic resonance imaging; OGTT = oral glucose tolerance test; PCO = polycystic ovary; PCOS = polycystic ovary syndrome; SHBG = sex hormone binding globulin; TG = triglycerides; TSH = thyroid stimulating hormone.

stimulating hormone, prolactin, luteinising hormone, follicle stimulating hormone, oestradiol and sex-hormone binding globulin to rule out hypothyroidism, hyperprolactinaemia and secondary hypogonadism. Clinical assessment is usually adequate to exclude Cushing's syndrome and acromegaly.

Table 2 summarises the investigations for patients with hirsutism.

Management

It is important to educate patients that management provides improvement in hirsutism rather than complete cure. Measures that improve insulin resistance, such as weight loss in the overweight or obese and exercise, should be encouraged but, as for metformin treatment, despite reducing androgen levels, these measures are insufficient to improve hirsutism.[10] Management needs to be individualised. Treatment options can be local, systemic or a combination of both.

Local management options

Local management options include plucking, waxing, shaving, chemically dissolving hair, bleaching, laser, electrolysis or topical eflornithine hydrochloride. Laser treatment is most effective for dark hair on pale skin and is performed by many dermatologists. Patch testing should be performed initially as skin depigmentation can occur. Electrolysis is cheaper but uncomfortable and time consuming. Unfortunately, trials assessing efficacy of laser and electrolysis are of poor quality.

Eflornithine hydrochloride is a hair growth retardant that irreversibly inhibits the enzyme ornithine decarboxylase. It is approved for facial hirsutism and is relatively costly. Patients apply it twice daily; it takes six to eight weeks to have a visible impact on hirsutism, slowing hair growth in up to 70% of patients.[11] If stopped, hair growth will return to baseline rates after eight weeks. It can cause local skin irritation and dryness.

Systemic management options

Systemic management options available in Australia include the use of a COCP, spironolactone or cyproterone acetate. All take six months to start to become effective, so women need to use local measures meanwhile. Improvements in hirsutism may

2. Progestin types in COCPs suitable for hirsutism treatment

Neutral progestins
Gestodene
Desogestrel

Antiandrogenic progestins
Cyproterone acetate
Drospirenone
Dienogest
Nomegestrol acetate

Abbreviation: COCP = combined oral contraceptive pill.

continue to occur for up to 12 months. Systemic options other than a COCP cannot be used in any woman wishing to become pregnant in the near future due to the potential risk of teratogenicity with these other medications.

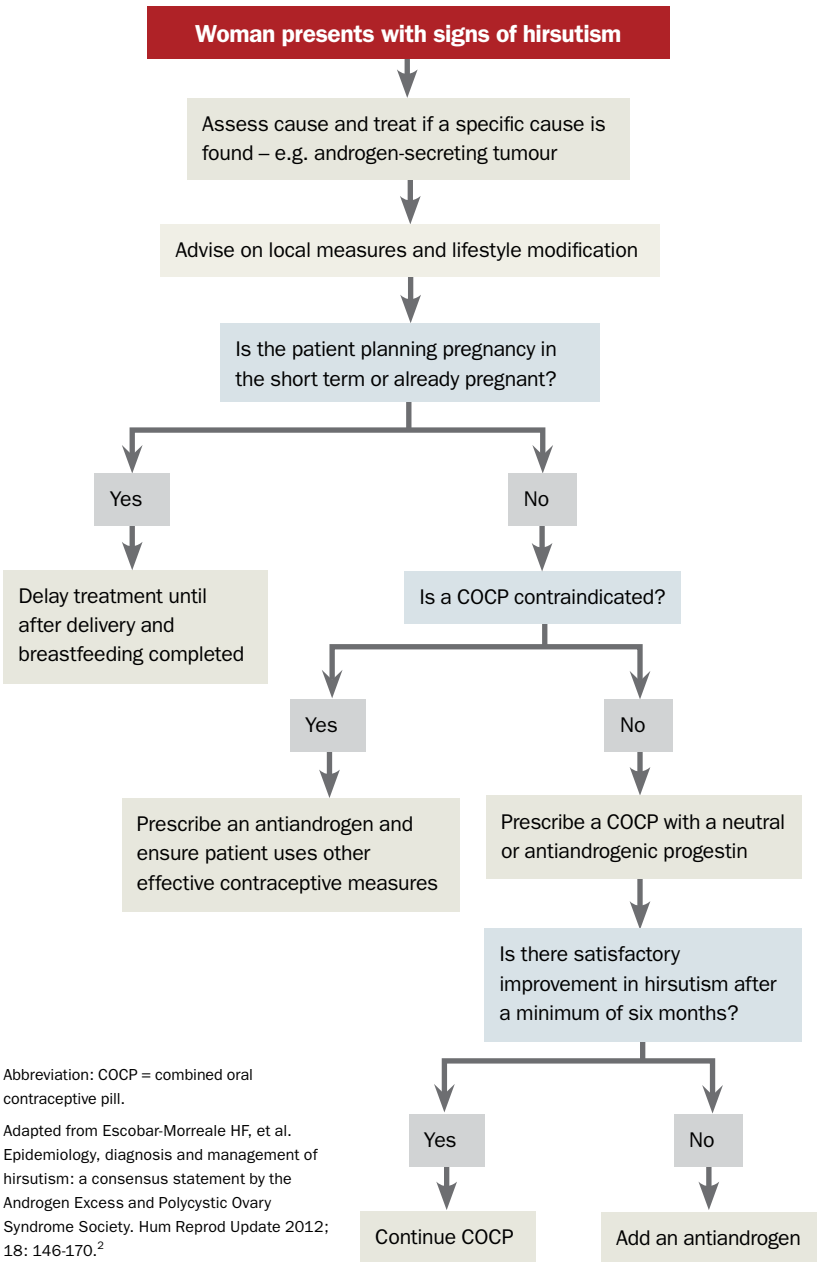
A COCP is the first line option for hirsutism, except for women who have contraindications to its use. COCPs with a neutral or nonandrogenic progestin should ideally be chosen, or an antiandrogenic progestin (Box 2). COCPs with an androgenic progestin – e.g. levonorgestrel – have a less favourable metabolic profile and can potentially exacerbate hirsutism and acne. Neutral progestins have more favourable lipid effects than older progestins such as levonorgestrel but a higher thrombotic risk. The risk of venous thrombosis for COCPs containing 30 to 35 µg of ethinyloestradiol with gestodene, desogestrel, cyproterone acetate or drospirenone is about 50 to 80% higher than with levonorgestrel with similar risk for these different progestins. There is a dose related effect of ethinyloestradiol in combination with gestodene, desogestrel, and levonorgestrel. Higher doses are associated with higher thrombotic risk.[12] Newer COCPs may also raise blood pressure. Trials have generally used COCPs with oestradiol doses of 30 to 35 µg daily, but 20 µg is sufficient to suppress ovarian androgens.[13]

If there is no significant improvement in hirsutism after at least six continuous months of COCP use, consider the addition of a more potent antiandrogen: either spironolactone or cyproterone acetate, which can be useful even in women with nonclassic congenital adrenal hyperplasia. Unfortunately, there are no good quality trials to determine relative efficacy of the antiandrogens. The antiandrogens finasteride and flutamide are not TGA approved for the management of hirsutism in Australia.

Spironolactone or cyproterone acetate must be used in combination with an effective method of contraception, as they may cause male fetus feminisation and are potentially teratogenic. A beta human chorionic gonadotropin (HCG) level should be checked before starting treatment. Women who cannot take a COCP should ensure they use other effective contraception methods.

Spironolactone is used at a dose of 100 to 200 mg daily initially in divided doses, provided renal function and serum potassium

Managing hirsutism (based on the Androgen Excess and Polycystic Ovary Syndrome Society's consensus statement)[2]



Abbreviation: COCP = combined oral contraceptive pill.

Adapted from Escobar-Morreale HF, et al. Epidemiology, diagnosis and management of hirsutism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society. Hum Reprod Update 2012; 18: 146-170.[2]

are normal. In older women, it should be started at a lower dose. Potential side effects include headache, fatigue, hyperkalaemia and rash. Electrolytes, urea and creatinine levels, to exclude hyperkalaemia, and blood pressure should be checked after a few weeks of spironolactone treatment.

Cyproterone acetate is approved for moderate to severe androgenisation. It should be started at a dose of 50 mg for days 1 to 10 of the menstrual cycle. Side effects include increased risk of thrombosis, weight gain, tiredness, headache, depressed mood, nausea and mastodynia.

Once hirsutism is well controlled, dose reduction of spironolactone or cyproterone acetate can be trialled, reducing not more frequently than six monthly until the lowest dose is reached that adequately controls hirsutism. If adequate control cannot be obtained with medication, then dermatology assessment should be sought. Some patients will choose to have concomitant laser therapy.

The flowchart summarises the management of hirsutism.

Conclusion

Hirsutism can be caused by a variety of conditions ranging from PCOS to androgen secreting tumours. It is important to investigate to determine the cause, particularly when there is sudden onset and progression of hirsutism, moderate or severe hirsutism or associated ovulatory disturbance. Management offers control rather than cure of hirsutism, but can significantly improve cosmesis and reduce patient distress. **ET**

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