Hirsutism and virilism

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Objectives:

1. Definition of hirsutism & virilism and how to differentiate between the two conditions.
2. Knowing the causes of both conditions and their associated signs and symptoms.
3. Learning how to manage these cases.
Hirsutism is defined as the excessive growth of thick dark hair in an androgen-dependent pattern where hair growth in women is usually minimal or absent - e.g., the face, chest, and areolae. It occurs as a result of increased androgen production, increased skin sensitivity to androgens, or both.
• Idiopathic hirsutism and **polycystic ovary syndrome (PCOS)** are the most common causes. When hirsutism in women is accompanied by other signs of virilism, it may be a manifestation of a more serious underlying disorder causing hyperandrogenism, such as an ovarian tumour or adrenal neoplasm.
Normal hair growth: human hair grows in three phases:

1. Anagen: growing phase, lasts for several months to 2-5 years on the scalp.

2. Catagen: follows anagen and lasts for about 2 weeks; during this period the hair stops growing and the lower portion of the hair follicles involutes.

3. Telogen: resting phase that lasts about 3 months.
Epidemiology

- Hirsutism is a common disorder affecting between 5% and 15% of women of reproductive age.
- It is less common in Asian people.
- There is racial variation in amount of terminal body hair.
- The Ferriman-Gallwney score is used in evaluation of hirsutism, and reflects the amount of hair over different body areas. This may require adjustment for racial variation.
- **Obesity** is associated with increased hirsutism
**Pathogenesis**: The dermal papillae androgen receptors interact with dihydrotestosterone, the active metabolite of testosterone, this interaction results in an increase in the size of the hair follicle and the type of hair produced by the follicle.
Causes of hirsutism

• Idiopathic hirsutism:
  – Common and often familial.
  – Is a diagnosis of exclusion and thought to be related to disorders in peripheral androgen activity.
  – Onset occurs shortly after puberty with slow progression.
  – There are no other signs of virilism, and menstrual function and investigations are normal.
Drug-induced hirsutism - eg, anabolic steroids, danazol, minoxidil, metoclopramide, methyldopa, phenothiazines and progestogens.

Ovarian causes:
- PCOS: virilisation is minimal, and hirsutism is often prominent. This is the most common cause and is present in approximately 70% of cases.
- Menopause.
- Androgen-producing ovarian tumours - eg, luteoma of pregnancy, arrhenoblastomas, Leydig cell tumours, hilar cell tumours, thecal cell tumours.
• Adrenal causes:
  – Androgen-producing adrenal tumour.
  – *Congenital adrenal hyperplasia (CAH)*.
  – *Cushing's syndrome*.

• Other causes include severe insulin resistance, anorexia nervosa, prolactinoma, acromegaly, hypothyroidism and porphyria.
• Presentation
• Excess terminal hair in a masculine pattern: face (particularly the moustache, beard and temple areas), chest, areolae, linea alba, upper and lower back, buttocks, inner thighs, external genitalia.
Virilism

- Signs of associated virilism (hyperandrogenism) may be present, and include:
  - Acne
  - Alopecia, temporal hair recession
  - Male-pattern (truncal) obesity
  - Clitororomegaly
  - Deepening of voice
  - Increased libido
  - Increased muscle mass (primarily shoulder girdle)
  - Loss of breast tissue or normal female body contour
  - Malodorous perspiration
  - Infertility
  - Menstrual dysfunction
Differential diagnosis

• Hypertrichosis: this is androgen-independent and causes uniform growth of vellus hair over the body, especially in non-sexual areas. The aetiology of hypertrichosis includes:

  1-Familial.

  2-Related to drugs - eg, phenytoin, ciclosporin or topical steroids.

  3-Non-endocrine causes such as anorexia nervosa.
Management

- It is important to investigate to establish the cause of hirsutism, even when mild, as the degree of hirsutism does not correlate well with the magnitude of androgen excess. However, the first stage is careful history and examination, and if there is no suggestion of hyperandrogenism, full endocrine evaluation may not be required.
• History
• Age of onset, rate of progression.
• Menstrual history, age of menarche.
• Medication including over-the-counter preparations and anabolic steroids.
• Family history of hirsutism.
• Level of distress caused by hirsutism
• Examination
• For signs of hyperandrogenism.
• For signs of Cushing's syndrome (moon face, stretch marks, easy bruising, proximal muscle weakness).
• To exclude pelvic masses.
• Blood pressure.
• BMI.
• **Initial investigations**

  These include:[2]

• **Testosterone:**
  
  – A high total testosterone concentration indicates that hyperandrogenaemia may be caused by an ovarian or adrenal tumour.
  
  – If the total testosterone is normal or only slightly raised, an androgen-secreting tumour can be excluded.
– Free testosterone is more sensitive and may be raised in PCOS.
– Testosterone concentrations more than 1.5-2 times the upper limit of normal or a history of rapid virilisation are likely to be associated with tumour-associated hyperandrogenism.
– Dehydroepiandrosterone sulfate and androstenedione should then be measured to identify an adrenal or ovarian source of the hyperandrogenaemia.
• Free androgen index:
  – Total testosterone is often normal in PCOS but the free androgen index is raised because sex hormone-binding globulin is suppressed.
  – The free androgen index is calculated by also measuring sex hormone-binding globulin (free androgen index is total testosterone concentration divided by sex hormone-binding globulin concentration multiplied by 100).
• Follicle stimulating hormone (FSH), luteinising hormone (LH): Women with PCOS may have an increased LH/FSH ratio (>2 is common).
• 17-hydroxyprogesterone:
  – Blood should be taken at about 9 am in the first half of the menstrual cycle.
  – A 17-hydroxyprogesterone value of 5 nmol/L has a sensitivity of 100% and specificity of 88.6% for diagnosing non-classical CAH.
• 24-hour urine cortisol (to rule out Cushing's syndrome if suspected):
  – Cushing's syndrome is a rare cause of hirsutism and exclusion is not necessary unless the patient has Cushingoid features.
• Pregnancy should be ruled out in women with irregular or absent menstrual cycles.

• Prolactin:

• Prolactin affects the menstrual cycle and hyperprolactinaemia can be associated with hirsutism.
• TFTs: thyroid dysfunction can affect menstruation and hypothyroidism is associated with changes in hair.
• Ultrasound: patients with either menstrual disturbances or clinical or biochemical evidence of hyperandrogenism alone should have transvaginal ultrasound imaging of the ovaries.
• Further investigations as indicated:
  – Glucose tolerance test with serial growth hormone measurements if acromegaly is suspected.
  – Lipid profile.
  – HbA1c.
  – Ultrasound, CT, MRI: if an adrenal or ovarian tumour is suspected. MRI brain scan: if a pituitary tumour is suspected.
TREATMENT

• Treatment for hirsutism is unnecessary if no abnormal aetiology can be diagnosed and if the patient is not concerned about the cosmetic appearance. Management is mainly directed at any underlying cause if present.

• nising
• Lifestyle modification:
  – Encourage weight loss if overweight:
  • Weight loss increases steroid hormone-binding globulin levels and decreases insulin resistance and the levels of serum androgens and luteinising hormones.
  • Obesity has an adverse effect on the outcome of all systemic treatments.
- Women who are overweight, hyperandrogenic or hyperinsulinaemic are at increased risk of diabetes mellitus and cardiovascular disease.
- Smoking cessation advice.

• Because of the cyclical nature of hair growth, any systemic treatment may take up to six months to be effective.

• Treatment of hirsutism is not usually curative, unless a treatable underlying cause has been found.
• Topical cosmetic therapies
• Shaving, threading, waxing, using depilatory creams, electrolysis and laser epilation or photo-epilation do not exacerbate hair growth and are effective, at least in the short-term
• Bleaching.
• Shaving: Removes all hairs superficially but regrowth produces a rough stubble. Most women prefer not to shave facial hair.
• Chemical depilation may be suited to treatment of large hairy areas in patients unable to afford more expensive treatments such as electrolysis and laser epilation.
• Temporary epilation:
  – Plucking: this may result in irritation, damage to the hair follicle, folliculitis, hyperpigmentation, and scarring.
  – Waxing: this can be painful and sometimes results in folliculitis. With repeated treatments it may reduce the number of hairs permanently.
  – Home epilating devices that remove hair by rotation or friction: these may produce traumatic folliculitis.
• Permanent epilation:
  – Electrolysis and thermolysis:
    • Thermolysis (diathermy) is much faster than the traditional electrolysis method.
    • Electrolysis and thermolysis can be used on all skin and hair colours, but they require multiple treatments.
    • Results depend on the skill of the operator.
• Electrolysis and thermolysis can be uncomfortable and may produce folliculitis and post-inflammatory pigmentary changes in the skin
– Laser epilation:
  • Can treat larger areas faster than electrolysis and thermolysis.
  • Is most effective on dark hairs in fair-skinned people.
  • Multiple treatments may be necessary for long-term hair destruction.

• Folliculitis, discomfort and pigmentary changes may occur
Drug therapy

The following drugs are effective: finasteride, oral contraceptive pills, thiazolidinediones, cyproterone acetate and ethinylestradiol in combination, spironolactone, and flutamide. However, a systematic review of trials of insulin sensitisers concluded that this group of drugs is of limited use as sole treatment for hirsutism.
• Combined oral contraceptives:
  – Recommended as first-line treatment.
  – Pills containing progestogens with anti-androgenic properties (e.g., Co-cyprindiol (Dianette®) or Yasmin®) are effective but those containing levonorgestrel and norethisterone are more androgenic and could potentially exacerbate hirsutism.
• Third-generation progestogens (e.g., desogestrel or gestodene) have relatively neutral androgenic effects and oral contraceptives containing these progestogens can be combined with an anti-androgen such as spironolactone.
• Anti-androgens:
  – Flutamide, finasteride and spironolactone have all been found to be effective in the management of hirsutism.
  – May be combined with oral contraceptives for the treatment of hirsutism.
  – Cannot be used in pregnancy, and should be prescribed with secure contraception.
  – May be associated with side-effects.
• Gonadotrophin-releasing hormone (Gn-RH) agonists:
  – For severe cases, these are occasionally used in secondary care.
  – Gn-RH agonists such as leuprorelin should be reserved for use in women who do not respond to combination hormonal therapy or those who cannot tolerate oral contraceptives.
  – Long-term adverse effects include hot flushes, bone demineralisation, atrophic vaginitis.
• Metformin has been shown to improve insulin sensitivity and decrease testosterone levels in patients with PCOS but the evidence is currently against it being effective for hirsutism alone.
• Eflornithine, a topical hair growth retardant, inhibits the enzyme ornithine decarboxylase. It may reversibly slow facial hair growth in up to 70% of patients:
  – It must be used indefinitely to prevent regrowth.
  – It is only licensed for facial hair.
  – Continuous use for eight weeks is required before benefit is seen.
  – It should be discontinued in the absence of improvement after treatment for four months.
THANK YOU!