Hirsutism

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Abstract

Hirsutism is excess terminal hair growth with a male pattern distribution. It can be one of the most distressing conditions for women. Occasionally it is underlined by serious pathology, hence the importance of thorough history, examination and investigation. This article first examines the underlying physiology associated with human hair growth and relevant to the understanding of the causes and treatment of hirsutism. Causes of hirsutism are discussed, the most common being polycystic ovarian syndrome. Other causes of disordered androgen metabolism are also discussed. Treatment of hirsutism includes treatment of the underlying cause and often lifestyle modifications such as weight loss are needed. Cosmetic measures are helpful for existing hair while prevention of new hair growth often requires pharmacological intervention. This is most commonly achieved using the combined oral contraceptive pill, while anti-androgens are reserved for more severe and resistant cases.

Keywords androgens; hirsutism; hyperandrogenism; PCOS

Introduction

Hirsutism is a condition where a female develops a male pattern growth of thick, pigmented androgen dependant terminal hair. Although hirsutism is generally thought to affect 5—10% of women of reproductive age, it is important to bear in mind that the incidence is highly affected by location and ethnicity being higher in those of African or Mediterranean descent.

Types of hair and the hair cycle

The only areas free of hair follicles are the soles of the feet, palms of the hands, and the lips. There are very few new hair follicles formed after birth, and the number of hair follicles begins to decrease after the age of 40.

There are 3 types of hair. Lanugo is soft hair covering the skin of the fetus. Vellus hair is fine, non-pigmented and short and is found in apparently hairless areas of the body. Terminal hair is long and pigmented and is found in eyebrows, eyelashes, scalp, pubic and axillary hair.

There are three phases to the hair cycle: Anagen, Catagen and Telogen.

Anagen is the active growing phase. This stage is the target of pharmacological agents used for treatment of hirsutism.

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Catagen is the phase when hair stops growing and lasts for 2—3 weeks. Finally during the Telogen phase the hair is resting for 3—4 months before it gets shed as new hair displaces it.

Androgen metabolism in the female

In the female androgens originate from the ovaries and the adrenal glands. The different types of androgens produced include:

- Testosterone: produced mainly by the ovarian theca cells under the control of LH and insulin acting through insulin like growth factor 1 (IGF-1). Testosterone is then converted by aromatase enzyme in the granulosa cells to oestradiol. Disturbance of this process in women with polycystic ovarian syndrome (PCOS) leads to failure of transition from an androgen to oestrogen dominant microenvironment and therefore relative increase in ovarian androgen production. Furthermore testosterone is also produced from peripheral conversion of adrenal androgens.
- Androstenedione: produced by both the ovary and the adrenals.
- Dehydroepiandrosterone (DHEA) and Dehydroepiandrosterone sulphate (DHEAS): produced by the adrenals.

The majority of circulating androgens are bound in an inactive form to sex hormone-binding globulin (SHBG) and a smaller free unbound fraction is metabolically active and able to stimulate hair growth but only after further metabolism by hair follicle 5α-reductase into dihydrotestosterone (DHT).

Aetiology of hirsutism

Androgenic causes are by far the most common cause of hirsutism, accounting for approximately 75—85% of such patients. Androgen disorders include (Box 1):

- PCOS, which affects about 70—80% of hirsute women
- hyperandrogenic insulin-resistant acanthosis nigricans syndrome, affecting about 3%;

Causes of hirsutism

Increased androgen production

- PCOS
- Adrenal disorders: Cushing's syndrome and CAH
- Androgen-producing ovarian and adrenal tumours
- XY-females

Increased free androgens

- Insulin resistance
- Obesity
- PCOS

Iatrogenic hirsutism

- Androgen therapy
- Danazol
- Sodium valproate
- Anabolic steroids

Box 1

- idiopathic hyperandrogenism, when women present with clinical and biochemical hyperandrogenism with regular ovulatory cycles and normal ovarian morphology,
- idiopathic hirsutism, when women have normal androgen concentrations, ovulatory cycles and ovarian morphology,
- adrenal disorder, including Cushing syndrome and 21-hydroxy–deficient non-classic adrenal hyperplasia (NCCAH),
- XY females with functioning testicles: they present mainly with primary amenorrhoea and the diagnosis can be confirmed with karyotyping and
- rarely, ovarian or adrenal androgen-secreting neoplasms

The most common disorder, PCOS, is a diagnosis of exclusion such that this disorder is attributed to patients with evidence of ovulatory dysfunction in the face of either biochemical or clinical evidence of hyperandrogenism, after the exclusion of related disorders (*i.e.* non-classic adrenal hyperplasia, hyperandrogenic insulin-resistant acanthosis nigricans syndrome, androgen secreting neoplasms, and thyroid and prolactin dysfunction).

The hyperandrogenic insulin-resistant Acanthosis Nigricans syndrome (HAIR-AN) is an inherited disorder of severe insulin resistance. Approximately 3% of hyperandrogenic women suffer from these disorders, which are characterised by extremely high circulating levels of insulin.

Between 1 and 8% of hyperandrogenic women suffer from 21-hydroxylase–deficient non-classic adrenal hyperplasia, a homozygous recessive disorder resulting in excessive accumulation of 17 hydroxyprogesterone (17-OHP) and androstenedione. Steroidogenesis is consequently diverted to the androgen pathway.

Cushing's syndrome may result from a primary adrenal disorder leading to an increased release of cortisol or secondary oversecretion of ACTH from the pituitary gland (Cushing's disease).

Androgen-secreting neoplasms are rare. They should be suspected clinically when the onset of androgenic symptoms is rapid or when they lead to virilisation and masculinisation or are associated with cushingoid features.

Iatrogenic hirsutism is caused by androgen therapy or medications such as danazol, sodium valproate or anabolic steroids.

Diagnosis

A diagnosis should be made after detailed consideration of the patients' history, examination and arranging appropriate investigations:

History

The history should include the presence of associated menstrual disturbances and infertility which could relate to PCOS. Furthermore, the duration and severity of symptoms are important as rapidly progressive and severe hirsutism maybe caused by androgenic tumours. Any history of associated endocrine disorders or relevant medications should be obtained as well as a family history of hair patterns as idiopathic hirsutism is often familial.

Examination

A thorough general examination should be conducted and may reveal other manifestations of hyperandrogenism such as acne or signs of virilism such as clitoromegaly. Velvety, pigmented skin patches (Acanthosis Nigricans) may be observed in the groin, neck or axilla in women with insulin resistance.

The modified Ferriman–Gallwey (mFG) score is the gold standard for the evaluation of hirsutism and includes 9 of the 11 body areas (upper lip, chin, chest, upper and lower back, upper and lower abdomen, arm and thigh) originally suggested by Ferriman and Gallwey in 1961. The lower legs and forearms are excluded in the modified scoring system as they were found to have poor correlation with androgen excess. A score of 0–4 is given to each site depending on the presence/absence of abnormal hair growth and its severity. A score of $\geq$8 is necessary for diagnosis. This scoring system does not account for some other relevant areas such as the buttocks and side burns. A more recent simplified scoring system has been suggested that evaluates hair growth at only three sites, upper abdomen, lower abdomen and chin. This system was found to be as effective as a full body evaluation of the traditional nine sites and a score of $\geq$3, is used to establish a diagnosis. Furthermore, terminal hair growth is also dependant on race and ethnicity. A pelvic examination should be undertaken to exclude a pelvic mass from androgen-producing ovarian tumours.

Investigations

Testosterone concentrations are measured in the form of the free androgen index as it reflects the active form of circulating testosterone. It is important to remember that testosterone concentrations correlate poorly with the severity of hirsutism due to individual variations in hair follicle response. Exceedingly high testosterone concentrations (>5 mmol/l) however should prompt further investigations such as pelvic imaging (CT and MRI) to exclude the possibility of ovarian or adrenal androgen-producing tumour.

Baseline 17-OH progesterone measurements should be performed as a screening test for late onset congenital adrenal hyperplasia. Equivocal results need to be confirmed using a short Synacthen test, where 17-OH progesterone concentrations are measured at baseline and 1 h after intramuscular injection of 250 mg of Synacthen. A significant rise in 17-OH progesterone concentrations is diagnostic of CAH.

Adrenal androgens such as DHEA may be measured in women where an adrenal cause is suspected.

Dexamethasone suppression test or 24 h urinary free cortisol for suspected cases of Cushing's syndrome.

In cases where androgen-secreting tumours are suspected but pelvic imaging is negative selective venous sampling from the ovarian and adrenal veins may be performed.

Treatment

Treatment should improve hirsutism and/or treat possible associated metabolic derangements and if possible the underlying cause.

Life style modification: Life style management in the form of exercise and diet in obese women can lead to a decrease in insulin resistance and increase in SHBG, ultimately leading to a decrease in androgen production.