Review Article

Hyperandrogenism – approach and management

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Abstract

Hyperandrogenism accounts for a number of distressing symptoms in the patient. Evaluation of the underlying cause is the key to the correct management of this common endocrine disorder. In this review, we analyse hyperandrogenism in terms of pathophysiology, evaluation and management options for the patient. Various Pubmed studies spanning multiple decades have been studied and evaluated in order to formulate an algorithm for diagnosis of the causes of hyperandrogenism and also to devise a management protocol for the same. The myriad underlying causes of hyperandrogenism make it imperative to have a detailed understanding of its pathophysiology so as to more effectively treat it.

Keywords: Hirsutism, hyperandrogenism, PCOS

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INTRODUCTION

Hyperandrogenism is a common endocrine disorder in women, affecting around 7% of the reproductive age group and accounts for much distress in lieu of the symptoms associated.[1] Excess androgen levels in the body are responsible for a spectrum of symptoms such as hirsutism, acne, androgenic alopecia, ovulatory dysfunction, menstrual irregularity, infertility and virilisation or masculinisation being prolonged or severe.[2] The association between masculinisation and endocrine pathology was first established by Bullock and Sequera in 1905.[3] The most common cause of hyperandrogenism worldwide is polycystic ovarian syndrome (PCOS). Apart from this, in hyperandrogenic states, there can be a dysfunctional production of androgen or inadequate conversion to oestrogen or both. In this review, we aim to discuss the various causes, presentation and management options for hyperandrogenism.

Access this article online	
Quick Response Code:	Website: www.fertilityscienceresearch.org
	DOI: 10.4103/fsr.fsr_7_19

ANDROGEN PRODUCTION IN FEMALES

There are two main sources of androgen production in females – that is the adrenals and the ovaries[4] [Figure 1].

Adrenals

The adrenal glands are predominantly responsible for the synthesis and secretion of dehydroepiandosterone (DHEA) and DHEA-sulfate (DHEA-S) 90%, androstenedione 50% and testosterone 25%.

Ovaries

Ovaries produce 50% of androstenedione, 25% of circulating testosterone and about 10% to 20% of DHEA. Rest of the testosterone (50%) is produced in extra-glandular tissue by circulating DHEA and androstenedione.

How to cite this article: Saxena P, Pandey N. Hyperandrogenism – approach and management. Fertil Sci Res 2019;6:16-22.

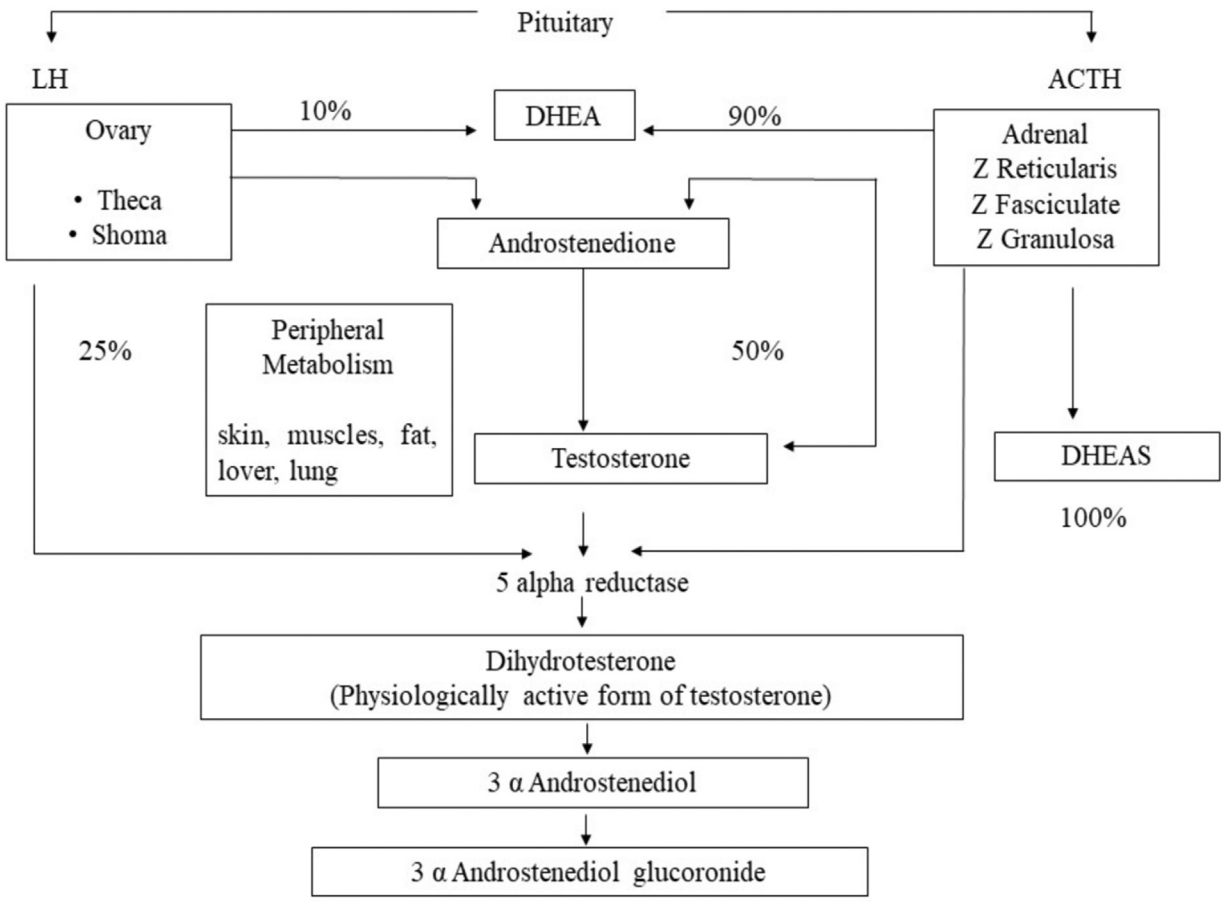

Figure 1: Principal sources of androgens in a normal female.

ANDROGEN METABOLISM

In healthy reproductive age group women, 80% of all circulating testosterone is bound to SHBG, 19% to albumin and only 1% circulates freely. Out of the circulating androgens, only active metabolite of testosterone that is dihydrotestosterone is able to act on the androgen receptors. The remaining androgens DHEA, DHEA-S and androstenedione are bound to albumin and are peripherally converted to testosterone.[5] The circulating testosterone is metabolised in the liver into androsterone and etiocholanolone, which is conjugated with glucuronic acid or sulfuric acid and excreted in the urine.

CAUSES OF HYPERANDROGENISM

Idiopathic

Idiopathic hirsutism occurs more frequently in certain ethnic population, due to skewing of X chromosome carrying the androgen receptor gene. This causes increased androgen receptor-mediated sensitivity of the hair follicle.[6]

Polycystic ovarian syndrome

PCOS is a syndrome complex that comprises of anovulation and raised androgen levels. It is manifested by hirsutism, menstrual abnormality like oligomenorrhoea, amenorrhoea, dysfunctional uterine bleeding or obesity. It affects around 10% to 20% of the reproductive age population. The basic pathology lies in dysregulation of enzyme cytochrome P450-17-α which is present in ovaries and adrenals and catalyses the activities of two enzyme systems that is 17-hydroxylase and 17,20 lyase resulting in hyperandrogenism.[7] PCOS is also associated with hyperinsulinemia and insulin resistance that leads to an increase in ovarian androgen production. In the liver, it reduces the production of insulin growth factor-binding protein-I and SHBG, which further increases free androgen levels.

Stromal hyperthecosis

Hyperthecosis is a result of the differentiation of ovarian interstitial cells into testosterone producing luteinised stromal cells.[8] These patients generally have normal LH and DHEAS levels but a higher serum insulin and testosterone level than those with PCOS. Patients with hyperthecosis present with signs of virilisation and

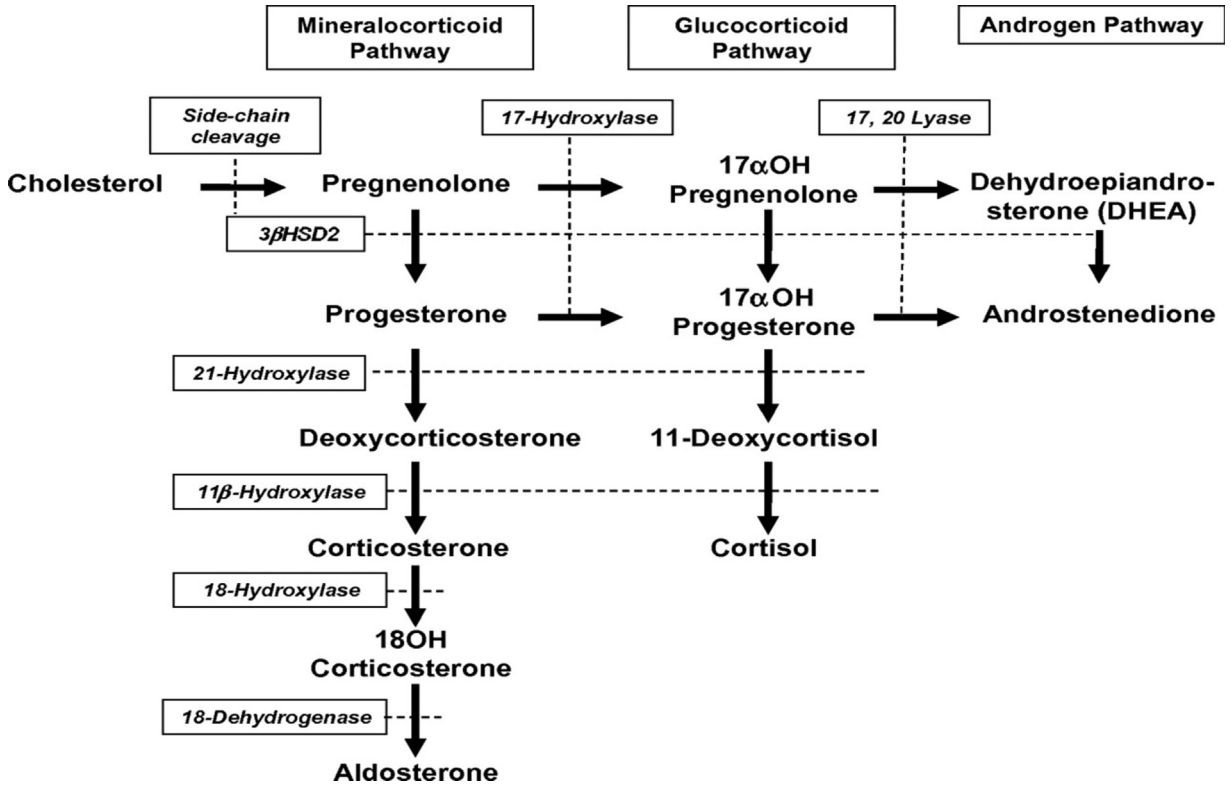

Figure 2: Androgen synthesis pathway.

decreased feminisation. The diagnosis can be confirmed only by histologic examination of the ovaries, which reveal nests of luteinised cells in ovarian stroma.

Congenital adrenal hyperplasia (CAH)

It can present in three forms[9]:

(1) *Autosomal recessive*: It is severe, presents soon after birth with evidence of adrenal insufficiency and ambiguous genitalia. There is deficiency of 21-hydroxylase leading to accumulation of 17-hydroxy progesterone which converts to excess androgens and deficiency of cortisol and aldosterone [Figure 2].
(2) *Late onset*: Slowly progressive, detected in early adulthood with short stature, irregular menstruation and positive family history. Onset of hirsutism is at puberty and occurs due to partial deficiency in the activity of 21-hydroxylase.
(3) *Cryptic form*: Generally detected by biochemistry with the patient presenting with history similar to PCOS and have hyperandrogenic chronic anovulation.

The diagnosis of late-onset 21-hydroxylase deficiency requires an elevation of early morning 17-hydroxy progesterone in the follicular phase.

Hyperinsulinemia

Insulin resistance can also lead to hyperandrogenism, although it is not a mandatory outcome. Various practical criteria have been suggested for the diagnosis of insulin resistance such as body mass index >27 kg/m^2, a waist/hip ratio >0.85, the presence of acanthosis nigricans, impaired glucose tolerance, an elevated fasting or postprandial insulin concentration and fasting glucose/insulin ratio <4.5. Hyperandrogenism associated with insulin resistance and acanthosis nigricans come under the entity of hyperandrogenism insulin resistance and acanthosis nigricans (HAIR-AN) syndrome.[10,11]

Rare causes

Rare causes of hyperandrogenism include virilising ovarian tumours and adrenal tumours. They are associated with rapid virilisation and progression of symptoms. Other rare causes include hyperprolactinoma that leads to hirsutism secondary to chronic anovulation. Cushing's syndrome and gonadal dysgenesis may also present with signs of hyperandrogenism.

CLINICAL PRESENTATION OF HYPERANDROGENISM

Acne

Persistence of acne into later teens should alert the endocrinologist to the possibility of hyperandrogenism especially if it is associated with hirsutism or menstrual

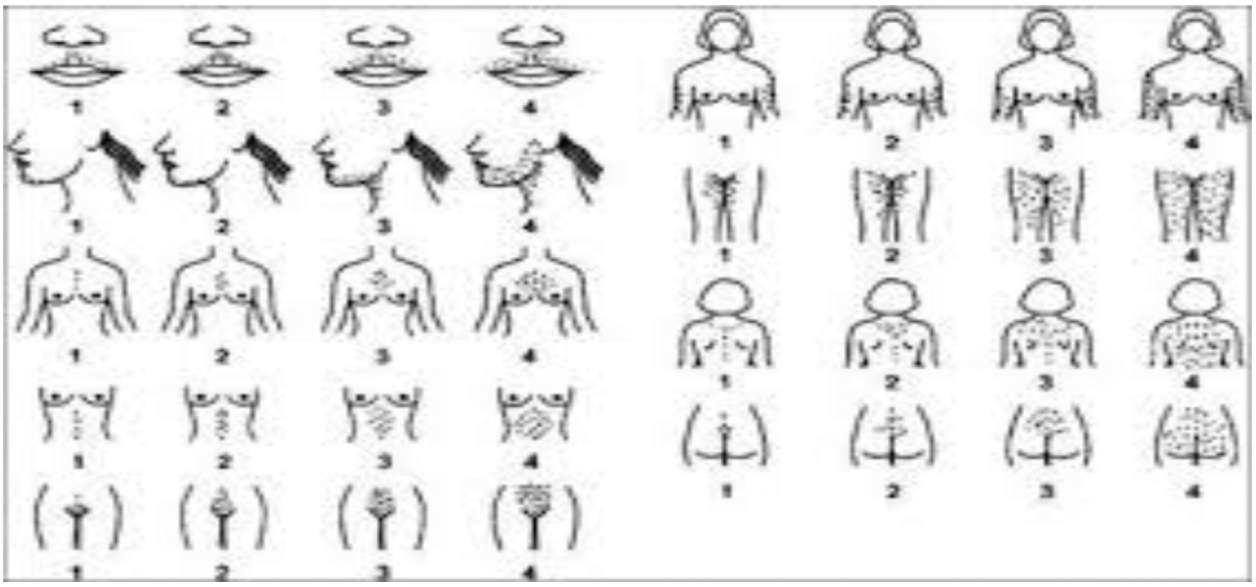

Figure 3: Ferriman Gallway scoring

irregularity.[12,13] Excess sebum production due to androgens leads to blockage of glands or pores, wherein bacteria grow and multiply leading to inflammation.

Androgenic alopecia

Androgenic alopecia, which is hair loss caused by male hormones, tends to affect the temples, the crown and the vertex. This is due to stimulation of hair growth elsewhere thereby retarding scalp growth. About 15% of women in reproductive age group presenting with alopecia and no other signs of hyperandrogenism have hyperandrogenaemia.[14]

Acanthosis nigricans

This occurs in severe hyperandrogenism and hyperinsulinemia. It presents as a velvety, mossy verrucous, hyperpigmented skin change over the nape of the neck, axillae, beneath the breast and in other body folds. Histologically, it represents hyperkeratosis, epidermal papillomatosis and hyperpigmentation.

Hirsutism

Hirsutism is defined as the presence of hair in locations where hair is not commonly found in women. These hairs are of dark colour, coarse texture and occur in androgen-dependent areas particularly over the upper lip, breast, chest, intermammary region, inner thigh and lower back.[15,16]

Depending on the effect of androgens on various types of hair, these can be divided into three groups:

(1) Hair that show no androgen dependence, for example lanugo, eyebrows and eyelashes.
(2) Hair dependent on adrenal androgens adrenocorticotropic hormone (ACTH) such as axillary or pubic hair.
(3) Hair dependent on gonadal androgens luteinizing hormone (LH) such as midline, facial and intermammary except scalp hair.

Hypertrichosis

It is a term reserved for androgen-independent growth of hair that is seen in nonsexual areas like trunk and extremities.

Virilism

It occurs because of severe hyperandrogenism and is characterized by temporal balding, deepening of voice, decreased breast size, increased muscle mass, loss of female body contour, clitoral enlargement and amenorrhoea. It is usually seen in androgenic tumours.

DIAGNOSTIC WORKUP OF A PATIENT WITH HYPERANDROGENIC DISORDER

History

A detailed history pertaining to the patient's lineage needs to be taken. Other important details are as follows:

(1) *Age of onset*: during childhood it could be due to CAH. During puberty it could be due to PCOS, CAH and Stein-Leventhal syndrome.
(2) *Mode of onset*: it is rapid in ovarian or adrenal tumours whereas it is slow, progressive in CAH and PCOS.
(3) *Personal history*: a stressful event in life such as change of place, occupation or marriage can cause disturbance in hypothalamic pituitary axis.

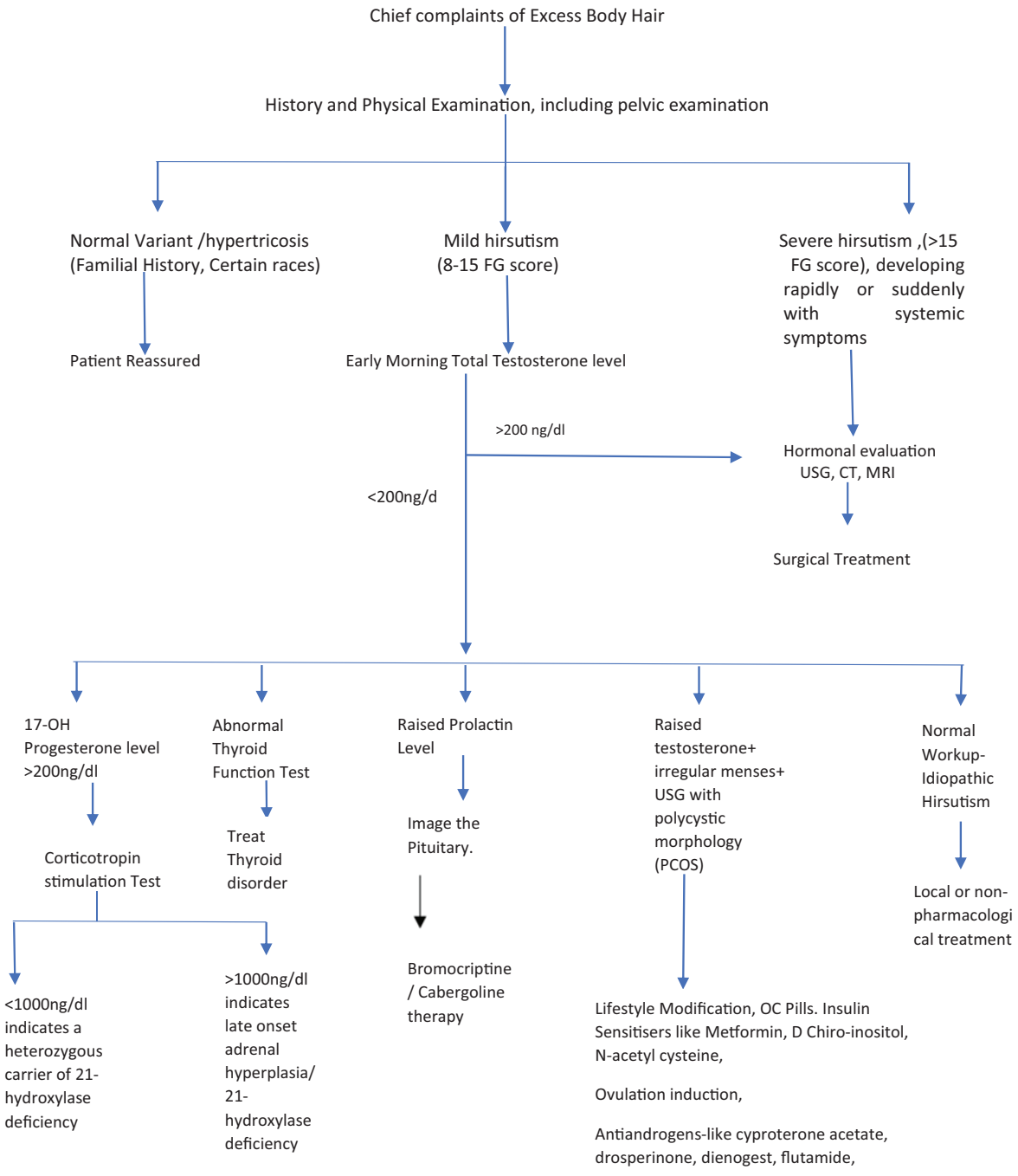

Figure 4: Algorithm of evaluation of a woman presenting with features of hyperandrogenism.

(4) *Menstrual disorders*: generally present with oligomenorrhea in PCOS, although women with gonadal dysgenesis and virilising tumours may present with amenorrhoea.
(5) *Family history*: history in other family members can point towards genetic predisposition, PCOS, metabolic syndrome and CAH.
(6) *Drugs history*: intake of androgens, danazol, 19-norprogesterone and minoxidil.

Clinical evaluation

Height, weight and body mass index should be measured since a growth spurt can be seen in CAH or virilising tumours, and women with polycystic ovarian syndrome (PCOS) and metabolic syndrome can present with increased weight.

Blood pressure may be high in patients with Cushing's syndrome, PCOS and metabolic syndrome.

Table 1: Treatment of hyperandrogenism

Class of drug	Drug	Dosage	Side effects	Comments	Mode of action
Oral contraceptives	Ethinyl estradiol plus norgestimate/desogestrel/ norethindrone/cyproterone acetate;drospirenone	One pill daily for 21 days followed by 7 day pill-free period	Gastric distress, breast tenderness, headaches	Least androgenic progestin component preferred	E – Increases SHBG in liverP – Reduces LHInhibit enzyme 5∝ reductase
Anti-androgens	Spironolactone	50–200 mg/day	Hyperkalemia	Irregular menses, combined with OC pills	Blocks androgen receptor, inhibits 5∝ reductase
	Flutamide	250 mg 2–3 times a day	Monitor liver function	Combine with other methods of contraception	Reduces secretion of adrenal androgens, blocks androgen receptor
	Finasteride	5 mg daily	Monitor liver Function	Pregnancy category X	Inhibit enzyme 5∝ reductase
Glucocorticoids	Dexamethasone	0.5 mg at 11.00 pm	Weight gain hypokalemia, decreased bone density, immune suppression	May be combined with OC pills and GnRH agonists for severe hirsutism	Pituitary–adrenal suppression
	Prednisone	5–10 mg daily			Pituitary–adrenal suppression
GnRH agonists	Leuprolide	3.75 mg IM monthly for up to 6 months	Hot flushes, decrease in bone mineral density, atrophic vaginitis	Use with caution for short periods	Reduce Gn, LH secretion
		11.25 mg depot every 3 months	May need add-back therapy	Add nonhormonal contraception	Reduce Gn, LH secretion
Antifungal agents	Ketoconazole	400 mg daily	Scalp hair loss, dry skin, hepatotoxicity, fatigue, headache, vaginal spotting, abdominal pain	Use as last resort	Reduces androgen production
Topical hair growth retardant	Eflornithine HCl	Apply to skin twice a day at least 8 h apart	Burning, stinging, dry skin, acne	May cause mild elevations in transaminase levels	Inhibits ODC enzyme
Insulin-sensitising agents	Metformin	500 mg to 1 g twice a day up to 2.5 g/day	Gastric distress, lactic acidosis	Resumption of ovulation may occur	Improves insulin sensitivity, increases SHBG, reduces LH and androgen synthesis
Anti-androgenic progestins	Cyproterone acetate	Used with ethinyl estradiol; dose of 50–100 mg/day for 21 days in a cycle	Fatigue, nausea, headache, weight gain, decreased libido	Lipid profile may get deranged	Inhibits LH, blocks androgen receptor

GnRH, gonadotropin-releasing Hormone; HCL, hydrochloride; IM, intramuscular; LH, luteinizing hormone; OC, oral contraceptive; ODC, orthinine decarboxylase; SHBG, sex hormone binding globulin.

An examination of the thyroid should also be carried out.

Abdomino-pelvic examination is not very reliable for ruling out neoplasms, as these tumours are small and patients are usually obese. Ovaries may be palpable in PCOS.

Clitoromegaly may be present in patients of CAH, virilising tumours and a few cases of PCOS.Skin evaluation can detect hyperpigmentation and acanthosis nigricans in case of HAIR-AN syndrome or Cushing's syndrome.

Clinical assessment of hirsutism should be made using the Ferriman-Gallway score. A score of 7 or less is normal, 8–15 suggests mild hirsutism and more than 15 suggests severe hirsutism.

Figure 3 gives a pictorial representation of the score.

Investigations

The algorithm of evaluation of a woman presenting with features of hyperandrogenism has been summarised in Figure 4. [17-20]

Management revolves around identification and treatment of the underlying cause. The various modalities of treatment are summarized in Table 1.

Other non-pharmacological methods for hair removal can be used such as epilation, shaving, plucking,

waxing, depilation and some permanent methods such as thermolysis, electrolysis and laser treatment.

CONCLUSION

Hyperandrogenism is a complex problem with varied manifestations. This review gives an outline of a scientific approach to a patient presenting with different clinical manifestations of hyperandrogenism. The treating physician must determine the cause of excess androgens and look for any evidence of damage to other organs. Treatment should be aimed to target the specific aetiology with the aim of prevention of long-term development of metabolic syndrome.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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