

HIRSUTISM: EVALUATION AND TREATMENT

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Abstract

Objectives: To review the etiology, evaluation, and treatment of hirsutism.

Evaluation: A thorough history and physical examination plus selected laboratory evaluations will confirm the diagnosis and direct treatment.

Treatment: Pharmacologic interventions can suppress ovarian or adrenal androgen production and block androgen receptors in the hair follicle. Hair removal methods and lifestyle modifications may improve or hasten the therapeutic response.

Outcomes: At least six to nine months of therapy are required to produce improvement in hirsutism.

Evidence: The quality of evidence reported in this guideline has been determined using the criteria described by the Canadian Task Force on the Periodic Health Examination.

Recommendations: Hirsutism can be slowly but dramatically improved with a three-pronged approach to treatment: mechanical hair removal, suppression of androgen production, and androgen receptor blockade. Lifestyle changes including weight loss and exercise will lower serum androgen levels and improve self-esteem. The patient should be educated regarding associated health problems or long-term medical consequences of hyperandrogenism, including obesity, irregular menses, anovulation, infertility, pregnancy-induced hypertension, diabetes, hyperlipidemia, hypertension, and heart disease.

DEFINITION

Hirsutism is defined as excessive hair growth in areas usually associated with male sexual maturity, that is, on the face, chest, linea alba, lower back, buttocks, and anterior thighs. Hirsutism results from androgenic effects on the pilosebaceous unit and is commonly associated with acne and oily skin. In addition to being a source of social embarrassment, hirsutism may also be a cutaneous sign of a systemic disease.

Virilization is an extreme degree of hirsutism that may include male pattern balding, voice deepening, increased muscle bulk, and clitoral enlargement. Virilization is a sign of high and often rapid androgen production, suggesting an androgen-secreting tumour.

ETIOLOGY

HYPERANDROGENIC HIRSUTISM

Hirsutism is usually due to increased androgen production from the ovaries or adrenal glands.¹ Elevated levels of DHEA-S are virtually always of adrenal origin,² while high testosterone levels may be of ovarian or adrenal origin. Regardless of the etiology, women with hyperandrogenism often have irregular menses, anovulation, infertility, and a risk of endometrial hyperplasia or neoplasia.

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POLYCYSTIC OVARY SYNDROME

Polycystic Ovary Syndrome is the most common cause of hirsutism.³ Although there have been many different definitions of the polycystic ovary, Polycystic Ovary Syndrome (PCOS) is best defined by hyperandrogenism in association with irregular menses in the absence of other known causes.⁴ It is often but not always associated with a high LH:FSH ratio of 2:1 or 3:1 and/or obesity.⁵ In recent years it has also been shown that this hyperandrogenic state may result from hyperinsulinemia driving ovarian androgen production.⁶⁻¹⁰ The HAIR-AN syndrome is a severe variant of PCOS characterized by hyperandrogenism, insulin resistance, and acanthosis nigricans (AN).^{7,8} The onset of acne, hirsutism, and irregular menses is frequently perimenarchal, and is often controlled by the use of oral contraceptives (OCs) in the teenage years. There may be dramatic recurrence of the clinical signs and symptoms of androgen excess when OCs are subsequently discontinued.

PCOS women are at particular risk for hypertension, hyperlipidemia, diabetes, and possibly coronary artery disease.¹¹

TUMOURS

In contrast to PCOS, the rare group of ovarian and adrenal tumours function autonomously. LH and FSH levels are often suppressed to or below the lower limit of normal, while circulating androgen levels may be twice the upper limit of normal or higher. Onset of hirsutism or virilization is often abrupt and dramatic.^{12,13}

ADULT-ONSET CONGENITAL ADRENAL HYPERPLASIA

Adult-onset congenital adrenal hyperplasia (CAH), another uncommon cause of hirsutism, is due to a partial defect of the 21-hydroxylase enzyme. CAH occurs predominantly in Ashkenazi Jews and other women of Eastern European origin.¹⁴ The clinical picture is similar to PCOS. Screening for elevated 17-hydroxy-progesterone levels is not routine¹⁵ as the disorder is uncommon and the specific diagnosis does not generally alter the treatment plan.¹⁶

MEDICATIONS

Hirsutism may develop following the use of medications such as Danazol, performance-enhancing anabolic steroids, or androgen-containing hormone replacement preparations such as Climacteron[®].¹⁷

IDIOPATHIC HIRSUTISM

Hirsutism found in association with regular menses and normal serum androgen levels is known as idiopathic hirsutism. Idiopathic hirsutism may be due to increased sensitivity to androgens in the pilosebaceous unit.¹⁸⁻²⁰ A genetic increase in 5 α -reductase activity leads to increased synthesis of the potent intracellular androgen dihydrotestosterone.¹⁸⁻²⁰ A typical example is the familial hirsutism that often affects women of Mediterranean or East Indian origin.

INVESTIGATION

The history and physical examination are vital to the assessment of women with hirsutism. In itself, cosmetically disturbing hirsutism is an indication for treatment; laboratory tests are used as an adjunct to differentiate hyperandrogenic from idiopathic hirsutism and to rule out other associated conditions.

The basic laboratory evaluation for hirsutism may include a total testosterone level (to rule out tumours) and a DHEA-S level (to document adrenal hyperandrogenism).² An LH-FSH ratio greater than 2:1 may be helpful, but has limited sensitivity and is no longer a necessary part of the diagnosis of PCOS.⁶ Women with PCOS may benefit from a fasting lipid profile as well as a fasting serum glucose and insulin. A ratio of insulin to glucose of greater than 35 suggests insulin resistance.²¹

Dexamethasone suppression tests, sophisticated imaging of the ovaries or adrenal glands, and retrograde venous catheterization of ovarian and adrenal veins have been used with variable success to investigate Cushing's disease or androgen-secreting tumours.

RECOMMENDATION:

1. Referral for subspecialist evaluation is indicated in the presence of: a) virilism; b) serum testosterone or DHEA-S levels more than twice the upper limit of normal; or c) signs or symptoms of Cushing's disease. (III-B)²²

TREATMENT

After ruling out other treatable causes, the most effective therapy for hirsutism usually involves a combination of lifestyle modifications, mechanical hair removal, and medical therapy. Medical therapy involves androgen suppression and/or androgen receptor blockade. Given the lifespan of terminal hair, at least six months of medical therapy are required before slower and finer regrowth of hair is noted.²³ Concomitant mechanical hair removal may speed up this process.²⁴⁻²⁶ Although some permanent destruction of hair follicles can be achieved with electrolysis or laser, hair growth tends to recur after cessation of medical therapy.²⁴⁻²⁶

LIFESTYLE MODIFICATIONS

Lifestyle changes that include healthy eating habits, moderate daily exercise, and weight loss are the cornerstone of treatment for obese hirsute women. Weight loss decreases serum insulin levels, ovarian androgen production, and the conversion of androstenedione to testosterone.^{5,27} Production of sex hormone binding globulin (SHBG) increases, causing a further reduction in free androgen levels.²⁸

MECHANICAL TREATMENTS

Various mechanical or topical therapies can be used safely and effectively (Table 1). The choice is dictated by cost and the patient's tolerance of the various regimens rather than by efficacy.

Bleaching, shaving, and depilatories are inexpensive and painless, but entirely cosmetic in nature, with no change in the underlying hair or follicle. Plucking, waxing, electrolysis, and laser hair removal may be more uncomfortable or costly, but may eventually reduce regrowth of hair, especially if combined with concomitant medical therapy.²⁴⁻²⁶

MEDICAL THERAPY

ANDROGEN SUPPRESSION

Suppressive therapy is designed to decrease androgen production, particularly from the ovaries. It is most useful for treatment of hyperandrogenic hirsutism, but may also play a role in idiopathic hirsutism.²⁰

Oral Contraceptives

First-line suppressive therapy involves OCs to suppress gonadotropins, decrease ovarian androgen production, and augment hepatic production of SHBG, thus decreasing free testosterone (T) levels.²⁹ Antiandrogens may be added if the clinical response is suboptimal. Alternatively, one OC (Diane®) contains an antiandrogen, cyproterone acetate, as its progestin. Diane® provides both suppression of ovarian androgen production and androgen receptor blockage.³⁰

Glucocorticoids

Although glucocorticoids can be used to suppress adrenal androgen production, androgen receptor blockers are more effective in the treatment of hirsutism, even when due to late onset congenital adrenal hyperplasia.^{16,31}

Gonadotropin-Releasing Hormone Agonists (GnRH-A)

The GnRH agonists can induce a medical oophorectomy to treat refractory hirsutism due to ovarian hyperandrogenism.³² However, hypoestrogenic side effects frequently necessitate the use of an oral contraceptive pill or estrogen/progestin add-back therapy.^{33,34} Although effective, this therapy is complex and expensive.

Insulin-Sensitizing Agents

Decreasing serum insulin levels with agents such as metformin improves a number of clinical parameters in PCOS patients, but to date there is insufficient evidence to determine the effectiveness of this approach for hirsutism.³⁵

RECOMMENDATIONS:

- In addition to mechanical treatment, all patients suffering from hirsutism should be offered oral contraceptive therapy. (III-B)**
- Antiandrogens should be added for moderate to severe hirsutism or to ensure an optimal response for milder hirsutism. (I-A)**

ANTIANDROGENS

Antiandrogens prevent androgens from expressing their activity at target tissues and are especially useful for idiopathic hirsutism or as adjuncts to androgen suppressive therapies.³⁶

TABLE I		
MECHANICAL TREATMENT OF HIRSUTISM		
	Advantages	Disadvantages
Shaving	<ul style="list-style-type: none"> Inexpensive and effective 	<ul style="list-style-type: none"> Masculine connotation unacceptable to most women Early "stubble" during initial days following shaving
Bleaching	<ul style="list-style-type: none"> Especially good for moustache, sideburns Widely available H₂O₂ cream 	<ul style="list-style-type: none"> Can cause severe skin irritation
Plucking	<ul style="list-style-type: none"> Especially good for removal of long hairs on chin, chest, and breasts 	<ul style="list-style-type: none"> Can lead to folliculitis and subsequent scarring Should not be used on periareolar areas of the breast or pigmented nevi
Waxing (mass plucking)	<ul style="list-style-type: none"> Acceptable to many women 	<ul style="list-style-type: none"> Can lead to ingrown hairs, folliculitis, and scarring
Chemical Depilatories	<ul style="list-style-type: none"> Widely available Good for general hair removal 	<ul style="list-style-type: none"> May cause skin irritation, especially on the face
Electrolysis ²⁴	<ul style="list-style-type: none"> Promotes permanent hair removal 	<ul style="list-style-type: none"> Requires qualified operator Painful Individual needles must be used to eliminate HIV and hepatitis risk Expensive and time-consuming
Laser Hair Removal ^{25,26}	<ul style="list-style-type: none"> Recently available 	<ul style="list-style-type: none"> Requires qualified operator Expensive and time-consuming May not be as permanent as electrolysis Little long-term follow-up data

Spironolactone

Spironolactone competes for the androgen receptor in skin fibroblasts and produces limited suppression of gonadal and adrenal androgen biosynthesis. The drug can be used alone in doses of 100 to 200 mg daily³⁷ or in combination with the OC.³⁸ There is a dose-related increase in irregular menses, controlled by concomitant OC administration. Side effects such as transient diuresis, fatigue, headache, gastric upset, and breast tenderness can be minimized by gradual dose increases.³⁹ There is a theoretical risk of feminizing a male fetus if pregnancy occurs while on this medication.

Cyproterone Acetate

This potent long-acting progestational agent inhibits gonadotropin release and binds competitively to androgen receptors. For mild hirsutism it is most conveniently administered as the OC Diane[®] which is effective in controlling acne and hirsutism alone, or in combination with spironolactone 100 mg daily.³⁰ For more severe hirsutism, a reverse sequential regime has been used for many years.⁴⁰ Cyproterone acetate (CPA) 100 mg daily has been given on menstrual days 5 to 14 combined with ethinylestradiol (EE) 50 µg on days 5 to 24. As well as contraception, this regime provides dramatic improvement in acne within eight weeks and hirsutism within six to nine months in most patients. An initial flare-up of acne can be seen during the first few weeks of therapy. Elevated liver function tests can be seen at 100 mg doses of CPA. CPA at low doses of 25 to 50 mg daily added to the first ten days of any low-dose OC pack is as effective as the classic reverse sequential 100 mg regimen but without side effects and only rarely associated with increased liver enzymes.²³ This protocol has few side effects and is as effective as many newer and more expensive medications being used for the treatment of hirsutism.⁴¹

RECOMMENDATION:

4. Any treatment protocol using CPA should be stopped for at least two cycles prior to attempting pregnancy in order to avoid the risk of feminizing a male fetus. (III-B)

Flutamide

Flutamide is the first nonsteroidal antiandrogen available that is devoid of any other hormonal activity. Flutamide 250 to 500 mg daily, alone or in combination with an OC, appears as or more effective than finasteride or a spironolactone-OC combination.^{42,43} Hepatotoxicity is a rare complication, but mandates periodic monitoring of liver function tests. Side effects, cost, and the risk of hepatotoxicity appear lower with the 250 mg dose.⁴⁴

Finasteride

Finasteride 5 mg blocks the 5 α -reductase enzyme responsible for converting testosterone to dihydrotestosterone and is useful in the treatment of idiopathic hirsutism.^{45,46} Although no more effective than spironolactone, flutamide,^{47,48} or the OC

Diane[®],⁴⁹ its very low side-effect profile may be beneficial.^{46,50} It should not be used in women at risk for pregnancy due to its significant teratogenic potential.

RECOMMENDATIONS:

5. Antiandrogens are best used in combination with OCs as OCs prevent pregnancy and this combination is particularly effective in managing women with moderate to severe hirsutism. (I-A)
6. Antiandrogen therapy should be stopped prior to patients discontinuing contraceptive measures to prevent feminization of the male fetus. (III-B)

OTHER HEALTH IMPLICATIONS

Women with hyperandrogenism and menstrual disturbances will benefit from regular progestin withdrawal bleeds to reduce their risk of endometrial hyperplasia and cancer.⁵¹ This is most easily accomplished with a low dose OC. These women may also require ovulation induction therapy to facilitate conception. Regular progesterone withdrawal bleeding and lifestyle modifications⁵ may reduce the long-term risk of medical complications associated with hyperandrogenism, including heavy and irregular menstrual bleeding, endometrial hyperplasia, obesity, gestational diabetes, pregnancy-induced hypertension, hyperlipidemia, maturity onset diabetes, hypertension, and cardiovascular disease.⁵²⁻⁵⁴

RECOMMENDATION:

7. All physicians counselling women with hirsutism should explore with these patients the long-term health sequelae of hyperandrogenism, including abnormal uterine bleeding/endometrial hyperplasia, infertility, pre-eclampsia, diabetes, and heart disease. Physicians caring for these patients also need to spend some time discussing lifestyle modification including exercise, healthy eating habits, and smoking cessation. (III-B)

SUMMARY

Investigating hirsutism requires a history, physical examination, and minimal laboratory investigations. Supportive counselling, lifestyle modifications, mechanical hair removal, and selected medical therapies can be used to improve self-esteem and general health in addition to reducing the hirsutism. Associated health problems or long-term medical consequences of hyperandrogenism include obesity, irregular menses, anovulation, infertility, pregnancy-induced hypertension, diabetes, hyperlipidemia, hypertension, and heart disease.

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