



Androgen Excess- Hirsutism & Alopecia in PCOS



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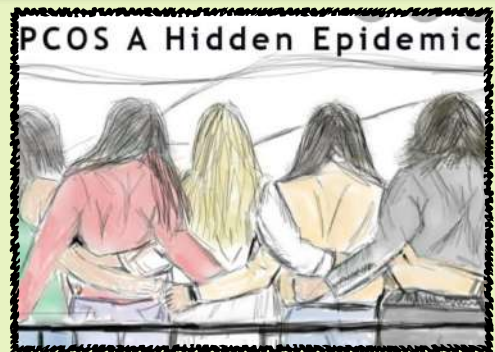


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Introduction

Hirsutism is the medical term that refers to the presence of excessive terminal (coarse) hair in androgen-sensitive areas of the female body (upper lip, chin, chest, back, abdomen, arms, and thighs). It is a common medical complaint among women of reproductive age.

The most common cause of hirsutism is represented by the polycystic ovary syndrome (PCOS). A recent study reported that 74.7% of women with PCO presented with hirsutism (1). In these women, hirsutism often tends to be more severe in the presence of obesity, particularly the abdominal phenotype. Androgenic alopecia is one of the most common causes of hair loss in women



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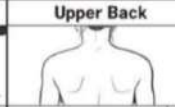
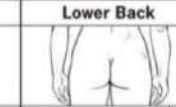
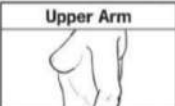

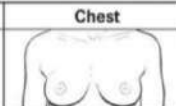
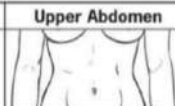
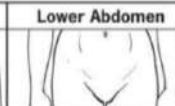
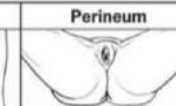


DIAGNOSIS

The quantification of hirsutism by objective methods, such as photographic evaluations, weighing of shaved or plucked hairs and microscopic measurements, is reliable. However, the complexity of these methods limits their use in clinical practice (21). Subjective methods have the advantage of being easy, convenient cheap, and fast, although they are subject to some large inter-observer variation that can be reduced by trained physicians. The modified Ferriman-Gallwey score (mFG) is the most commonly used method (2), but at least three open questions related to the interpretation of the mFG score still remain.

1. Which cut-off value should be used to diagnose the presence of hirsutism?
2. How to interpret hirsutism predominantly localized on the face with respect to that localized on the trunk or arms?
3. The interpretation that should be given to the presence of terminal hairs selectively on the face?

The Androgen Excess and Polycystic Ovary Syndrome Society recently issued recommendations regarding the cut-off value of the mFG score to be applied. They recommended adapting the cut-off to the race and ethnicity of the population to which it is applied and, if this value is unavailable, using a cut-off value of eight or above for White, Black and South-East Asian women, and a cut-off of three or above for Far-East Asian women (3)

Age _____		Height _____		Weight _____		Body Mass Index _____		Blood Pressure _____	
Caucasian <input type="checkbox"/>		African American <input type="checkbox"/>		Asian <input type="checkbox"/>		N. American Indian <input type="checkbox"/>		Mediterranean <input type="checkbox"/>	
Upper Lip	Sideburn Area	Chin	Lower Jaw & Neck	Upper Back	Lower Back	Subtotal			
						Subtotal			
Small number of terminal hairs over upper lip & outer lip border 1	Sparse terminal hairs 1	Sparse terminal hairs on chin 1	Sparse terminal hairs over lower jaw & upper neck 1	Sparse terminal hairs over upper back 1	Sacral area with hair coverage less than 4 cm wide 1	Subtotal			
Thin moustache covering less than 50% of upper lip or at the outer border 2	Sparse terminal hairs with small thickened areas 2	Sparse terminal hairs with small thickened areas 2	Sparse terminal hairs with small thickened areas 2	Increased number of spread terminal hairs 2	Increased sides coverage 2	Subtotal			
Moustache covering 50% from outer margin of the lip or 50% the lip height 3	Light hair growth over sideburn area 3	Entire chin covered with light growth 3	Entire area covered with light growth 3	Entire area covered with light growth 3	75% of lower back covered with terminal hairs 3	Subtotal			
Moustache covering most of upper lip & crossing the midline lip 4	Thick growth over sideburn area 4	Entire chin covered with heavy growth 4	Entire area covered with heavy growth 4	Entire area covered with heavy growth 4	Entire area covered with heavy growth 4	Subtotal			
Upper Arm	Thigh	Chest	Upper Abdomen	Lower Abdomen	Perineum	Subtotal			
						Subtotal			
Scattered terminal hairs over less than 25% of upper arm 1	Scattered terminal hairs over less than 25% of the thigh 1	Circumareolar or midline terminal hairs 1	Scattered midline terminal hairs 1	Small number of scattered midline terminal hairs the length of linea alba 1	Scattered perianal terminal hairs 1	Subtotal			
Increased but incomplete coverage 2	Increased but incomplete coverage 2	Circumareolar and midline terminal hairs 2	More terminal hairs, sbl midline 2	Midline concentration of terminal hair the length of the linea alba 2	Spread of terminal hair to the gluteal cleft 2	Subtotal			
Entire area covered with light growth 3	Entire area covered with light growth 3	75% of chest covered with terminal hairs 3	50% of upper abdomen covered 3	A midline thickened band of terminal hair less than 1/2 width of pubic hair at base 3	75% of perineum covered with terminal hairs 3	Subtotal			
Entire area covered with heavy growth 4	Entire area covered with heavy growth 4	Entire area covered with terminal hair growth 4	Entire area covered with terminal hair growth 4	An inverted V-Shaped coverage 1/2 width of pubic hair at base 4	Entire area covered with terminal hair growth 4	Subtotal			
						Total Score =			

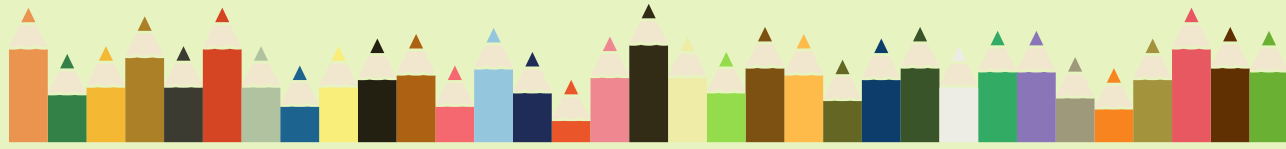


Table 1. Androgen sensitive sites of hair growth

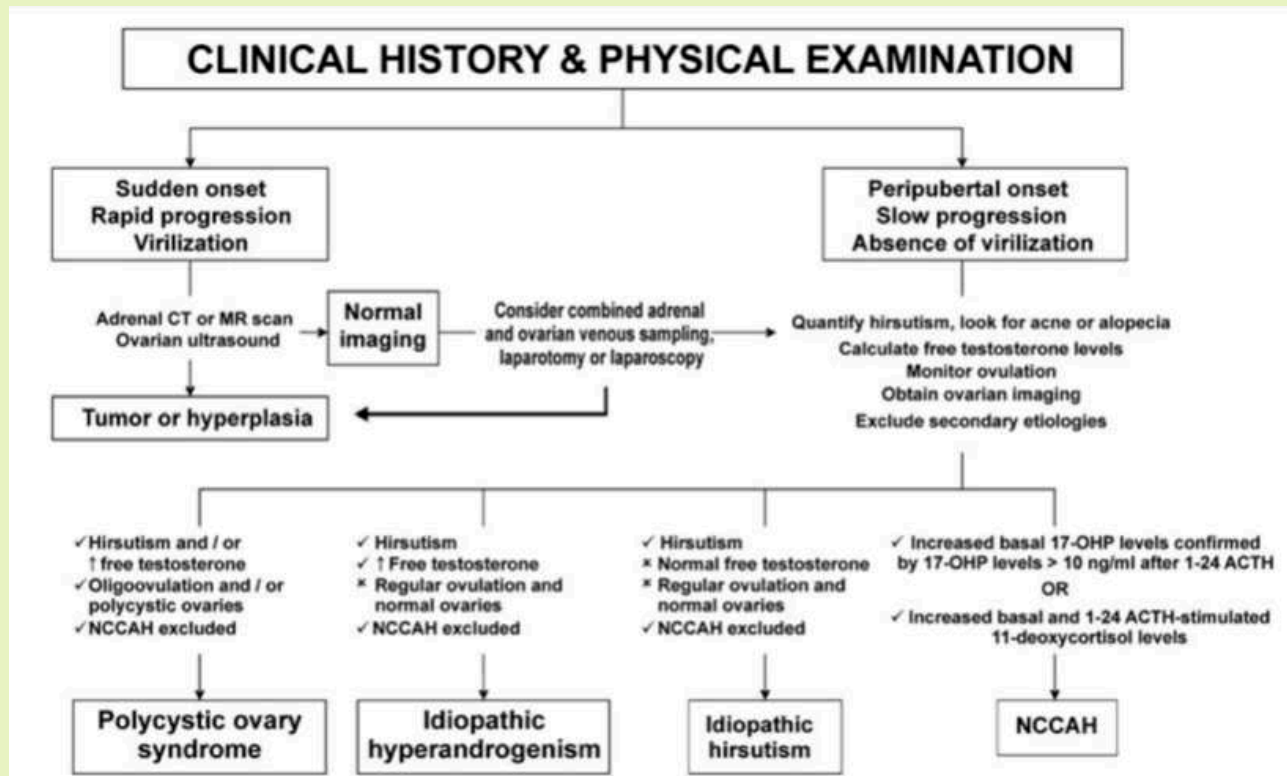
<p>More common</p> <ul style="list-style-type: none">• Upper Lip• Beard area• Breasts• Lower abdomen• Inner thighs• Lower back	<p>Less common</p> <ul style="list-style-type: none">• Chest and sternum• Upper abdomen• Upper back
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Table 2. Causes of Hirsutism

<ul style="list-style-type: none">• Excess production by androgens by the ovaries (Polycystic ovary syndrome tumor)• Excessive sensitivity of hair follicles to androgens(genetic)• Excessive production of androgens by the adrenal glands (NCAH)• Insulin resistance• Hyperandrogenism, Insulin resistance, acanthuses nigricans (HAIR-AN syndrome)• Excessive production of cortisol by the adrenal glands (Cushing syndrome)• Menopause• Medications



Algorithm 1: Diagnosis of the cause of Hirsutism. (3)



MANAGEMENT OF HIRSUTISM

- Hirsutism is not a disease in itself but a clinical sign.
- Its presence may not always warrant a treatment, particularly if the woman is suffering from mild or moderate hirsutism and is not worried about it.
- Physicians should therefore decide whether hirsutism is to be treated or not by evaluating not only the severity of the hair growth but also the perception of the woman and the age group that she is in (childhood, adolescence, youth and adult age of postmenopause) , which may not necessarily correspond to the true extent of hair growth.
- Management of hirsutism should only be done on the basis of a diagnosis of the underlying cause and after clearly explaining to the patient the efficacy of the treatment options offered.



Table 3. Treatment of hirsutism

Medications	Cosmetic treatments
Birth control pills	Shaving
Androgen receptor blockers	Eflornithine cream
Spiroglactone	Waxing
Flutamide	Bleaching
Glucocorticosteroids	Plucking
Dexamethasone	Depilatory agents
Prednisone	Electrolysis
Methylprednisolone	Laser
Enzyme inhibitors	
Finasteride	
GnRH analogs	

Cosmetic procedures (4)

- Cosmetic measures may be particularly effective in controlling mild and localized hirsutism.
- They may also be recommended as adjuvant to pharmacological therapy in moderate to severe cases. Techniques of actually removing the hair may be categorized into depilatory methods or epilatory methods.
 - Using bleaching and temporary methods of hair removal, such as shaving, plucking, waxing or the use of chemical depilatory agents, in the first months of treatment while waiting for drug treatment to be noticed, or even as single treatment in milder cases. The patient must be assured that shaving does not increase the growth and thickness of hair, which is a common misbelief among patients because the blunt tip of shaved hair is more visible than the tapered tip of uncut hair.
 - Using galvanic or blended electrolysis for localized areas, such as the face, as single procedure or as an adjuvant to pharmacological intervention but only in the hands of an experienced operator.
 - Using alexandrite or diode laser photoepilation for generalized hirsutism, as the single procedure in mild cases, or as an adjuvant to pharmacological intervention in patients presenting with moderate or severe hirsutism, or in those requiring such treatment for associated conditions.



Pharmacological(3)

Drug treatment of hirsutism is limited to patients with hirsutism who are not seeking immediate fertility.

1. Topical eflornithine

Continuous topical administration of eflornithine 13.9% cream reversibly slows facial hair growth in up to 70% of patients. However, eflornithine is not approved for the treatment of unwanted terminal hair in areas other than the face, and its cost is relatively high. The problem that limits the possibility of using eflornithine cream in larger skin areas is linked to the possibility of undesirable effects in the case of significant systemic absorption

2. Oral contraceptive pills

Oral contraceptive pills (OCPs) contain estrogen plus progestin have been the mainstay for hirsutism therapy for decades. It decrease in circulating free androgens results in an improvement in the hirsutism, provided that OCPs are administered chronically

Table 4 : Mechanism of Oral Contraceptive pills in treatment of Hirsutism

- Suppression of LH secretion from the pituitary
- Anti- androgen level of hair follicle
- Elevation of SHBG(Estrogen effect)
- Progestinsin OC pills inhibits 5α -reductase activity in skin
- Inhibits adrenal androgen secretion.

Hence it is recommended to prescribe low-dose neutral or antiandrogenic OCP as first-line therapy for hirsutism:

- (i) As a single drug in women with mild hirsutism.
- (ii) As an adjuvant to antiandrogen administration in women with. moderate or severe hirsutism and to provide adequate contraception to these patients.
- (iii) To guarantee regular menstrual bleeding in hirsute patients with PCOS presenting with oligo- or amenorrhea.



3. Antiandrogens

Antiandrogens (androgen receptor blockers and 5 α -reductase inhibitors) are possibly the most effective drugs for hirsutism, although the evidence supporting this statement is relatively weak

Recommendations are as follows

- (i) Combined with OCPs in women presenting with moderate or severe hirsutism, or in those with a milder hirsutism who do not reach a satisfactory control of hair growth using OCPs alone after 1 year of treatment.
- (ii) As single drugs in women in whom OCPs are contraindicated, warranted that a reliable contraceptive method is used.

4. Insulin sensitizers

Insulin sensitizers are widely used for PCOS because insulin resistance contributes to the pathogenesis of this disorder (Azziz et al., 2009). Insulin sensitizers improve insulin resistance and menstrual dysfunction and may decrease serum androgen concentrations (Lord et al., 2003); their effects on hirsutism are much less clear.

Algorithm 2: Management of Hirsutism with OCP (3)

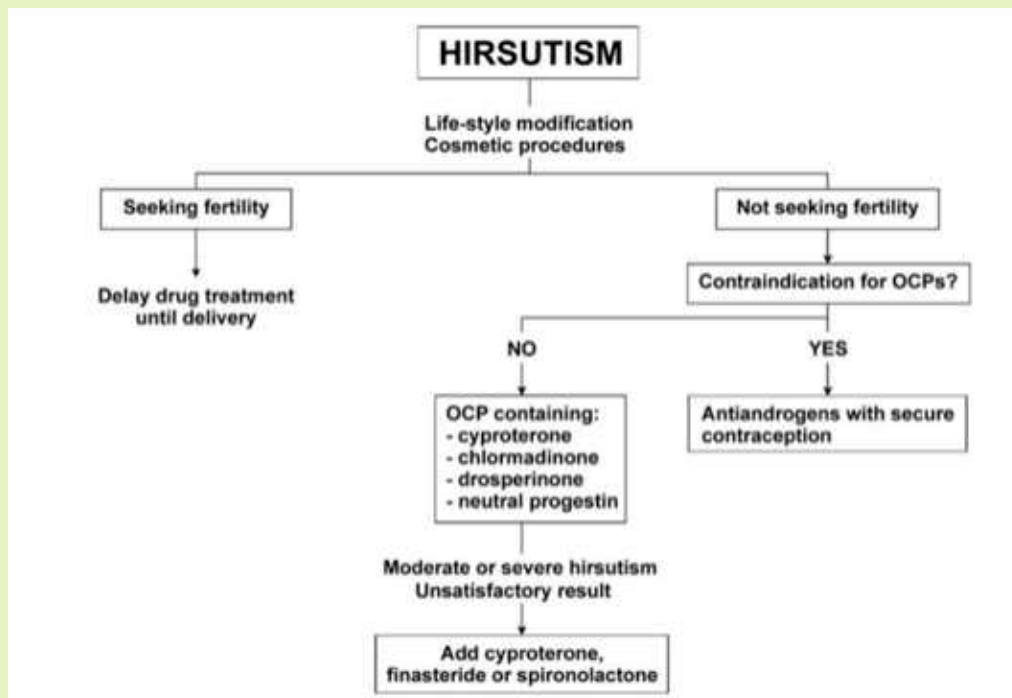
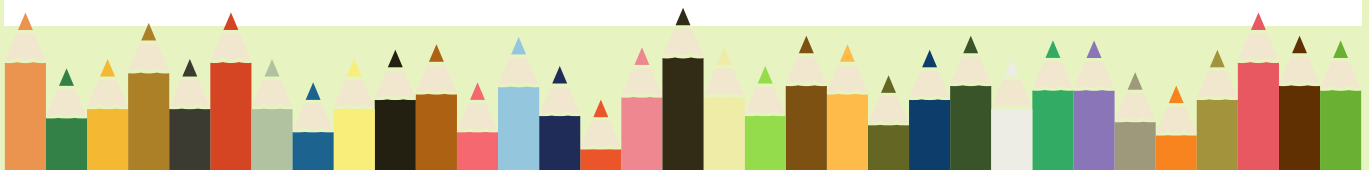


Table 5: Different Pharmacological agents which can be used for the management of Hirsutism (5)

Medications Commonly Used in the Treatment of Hirsutism

Class of drug	Drug	Dosage	Side effects and warnings*	Comments
Oral contraceptives	Ethinyl estradiol with norgestimate, desogestrel, norethindrone, ethynodiol diacetate	One tablet per day for 21 days, followed by seven-day pill-free interval	GI distress, breast tenderness, headache, intolerance to contact lenses	Pregnancy category X No FDA labeling for treatment of hirsutism Least androgenic progestin component preferred
	Ethinyl estradiol with drospirenone		Hyperkalemia may occur. Contraindicated with hepatic dysfunction, renal insufficiency, adrenal disease	Monitor serum potassium during first cycle with concurrent use of NSAIDs, ACE inhibitors, angiotensin-II receptor blockers, heparin, potassium supplements, potassium sparing diuretics.
Antiandrogens (no FDA labeling for treatment of hirsutism)	Spiroclactone (Aldactone)	50 to 200 mg per day	Hyperkalemia (rare), theortic feminization of male fetus, gynecomastia	Pregnancy category D Irregular bleeding may occur, monitor electrolytes.
	Flutamide (Eulexin)	250 mg two to three times daily	Monitor liver function.	Combine with other method of contraception. Pregnancy category D.
	Finasteride (Proscar)	5 mg daily	Monitor liver function.	Pregnancy category X
Glucocorticoids (no FDA labeling for treatment of hirsutism)	Dexamethasone	0.5 mg nightly	Weight gain, hypokalemia, decreased bone density, immune suppression	Pregnancy category C. May be combined with oral contraceptives or Gn-RH agonists for severe hirsutism.
	Prednisone	5 to 10 mg daily		Pregnancy category C
Gn-RH agonists (no FDA labeling for treatment of hirsutism)	Leuprolide (Lupron)	3.75 mg IM per month for up to six months	Hot flashes, decreased bone mineral density, atrophic vaginitis	Pregnancy category X. Use with caution for short periods because of hypoestrogenic effect.
		11.25 mg IM every three months (depot form)	May need add-back HT.	Use nonhormonal contraception during treatment.
Antifungal agents (no FDA labeling for treatment of hirsutism)	Ketoconazole (Nizoral)	400 mg daily	Scalp hair loss, dry skin, abdominal pain, fatigue, headache, vaginal spotting, hepatotoxicity Monitoring of hepatic function necessary	Pregnancy category C. Use as last resort.
Topical hair growth retardant	Eflornithine HCl (Vaniqa)	Apply to face twice daily at least eight hours apart.	Skin adverse effects include acne, erythema, stinging/burning, dry skin. FDA approval for reduction of unwanted facial hair	Pregnancy category C May cause mild elevations in transaminase levels. No significant drug interaction known
Insulin-sensitizing agents (not FDA approved for treatment of hirsutism)	Metformin (Glucophage)	500 mg twice daily 1,000 mg twice daily (maximal dosage 2.0 to 2.5 g per day) 850 mg three times daily	GI distress, lactic acidosis (rare with mortality nearly 50 percent), numerous drug interactions Monitor liver function, confirm normal renal function before starting, and monitor.	Pregnancy category B Resumption of ovulation may occur. No FDA labeling for treatment of PCOS



CONCLUSION

Hirsutism is one of the most common disorders affecting women during the reproductive years. Although often caused by relatively benign functional conditions, hirsutism may be the presenting symptom of a life-threatening tumor requiring immediate intervention. In most cases, hirsutism is a chronic disorder benefiting from long-term follow-up. The use of evidence-based strategies to improve the hirsutism and to treat the underlying disorder is essential for the proper management of women with hirsutism.

ANDROGENIC ALOPECIA ASSOCIATED WITH PCO

Androgenic alopecia is one of the most common causes of hair loss in women (6). Polycystic ovary syndrome (PCOS) is the most common endocrine disorder to affect women of reproductive age and is, conventionally, defined as the association of hyperandrogenaemia and chronic anovulation in women with polycystic ovaries (PCO) (7,8).

- Clinical hyperandrogenaemia is represented by hirsutism, acne or alopecia. Alopecia is a recognised feature of PCOS (9). but the prevalence of PCO in women who present with alopecia is not known.
- Female androgenetic alopecia (FAGA) is a common cause of non-scarring alopecia in women.
- FAGA is a slowly progressive disease.
- The onset may be at any age following puberty and the frequency increases with age. Clinically, it shows a diffuse hair thinning over the central scalp, while the frontal hairline is usually retained.
- FAGA can have a significant psychological impact, leading to anxiety and depression. For this reason, early diagnosis is very important to stop the progression of the disease.

A complete clinical examination and a blood examination can reveal other signs of hyperandrogenism. Trichoscopy shows the typical hair miniaturization. A scalp biopsy can be useful when the clinical evaluation does not provide a definitive diagnosis or when cicatricial alopecia with hair loss in the distribution of FAGA or alopecia areata are suspected. The goal of therapy is to stop the progression and to induce a cosmetically acceptable hair regrowth. The most important drugs are topical minoxidil and oral anti-androgens.



ALGORITHM 3: Management of Alopecia in Reproductive age group

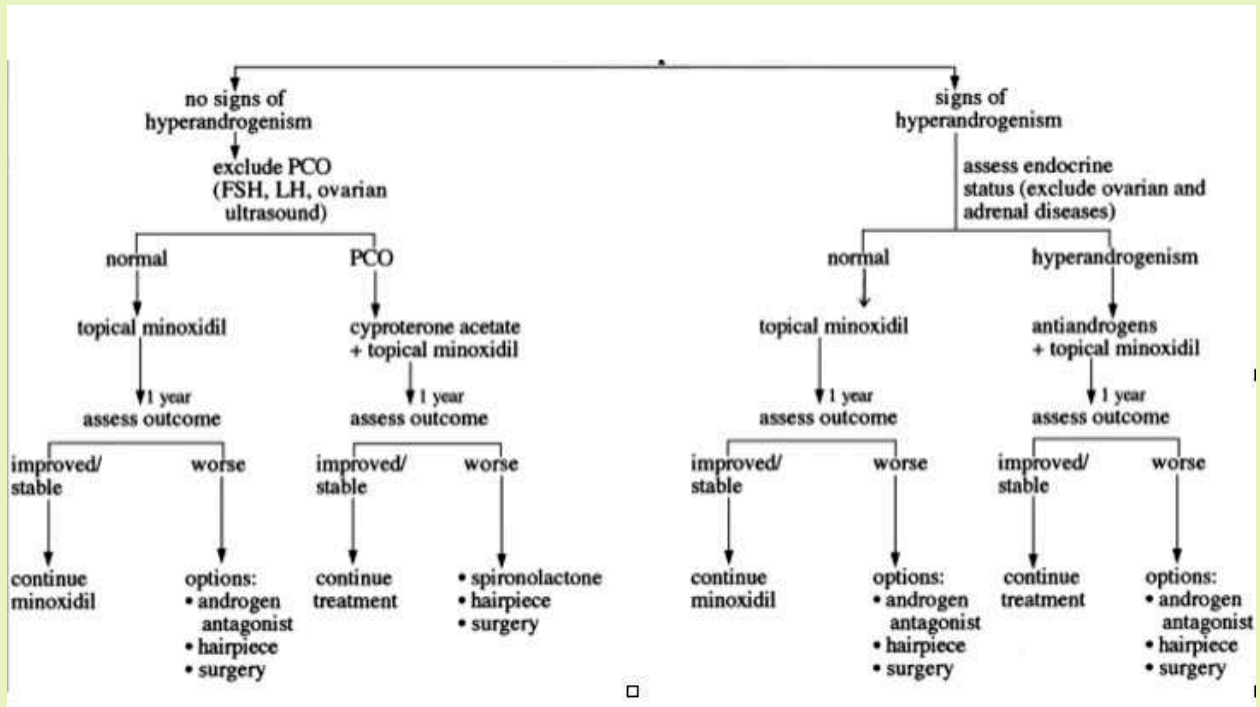


Table 6: Dosing and Adverse effects and counselling points of main drugs use in management of androgenic alopecia. (10)

Drug	Dosage	Side Effects	Counseling Points
Finasteride oral tablets (Rx only)	1 mg daily	Orthostatic hypotension (9%), dizziness (7%), erectile dysfunction (5%-19%), ejaculatory dysfunction (1%-7%), decreased libido (2%-10%)	May take 3 months or longer to see benefit. Must continue product to maintain results. Side effects may decrease over time. Pregnant females or those of childbearing age should avoid direct contact with crushed or broken tablets
Dutasteride oral tablets (Rx only)	0.5 mg daily	Decreased libido ($\leq 3\%$), gynecomastia ($\leq 1\%$), impotence ($\leq 5\%$)	May take 3 months or longer to see benefit. Must continue product to maintain results. Side effects may decrease over time. Pregnant females or those of childbearing age should avoid direct contact with crushed or broken tablets
Minoxidil topical foam/aerosol 5% (OTC)	One-half capful twice daily	Local erythema (6%), pruritus (6%), hair color or texture may change	Hair color or texture may change. Must continue the product to maintain results. Foam may melt on warm fingers, so run cold water over fingers and dry hands before use
Minoxidil topical 2% or 5% solution (OTC)	1 mL twice daily	Local erythema (6%), pruritus (6%), hair color or texture may change	Hair color or texture may change. Must continue the product to maintain results



Table 7: Main adjuvant emerging in the management of androgenic alopecia

Treatment options	Treatment approval: US FDA	Mechanism of action	Suggested protocols ^a	Major adverse effects
Low-level laser therapy (655 nm)	Approved	Possibly activation of dormant hair follicles, increased blood flow, upregulated growth factors and adenosine triphosphate, and stimulation of anagen hair	20 min/day, 3 times a week	
Fractional erbium-glass laser (1550 nm)	Not approved/ off-label	Possibly activation of dormant hair follicles, increased blood flow, upregulated growth factors and adenosine triphosphate, and stimulation of anagen hair	5–10 sessions at 2-week intervals	Thermal hair follicle injury and scarring?
Platelet-rich plasma	Not approved/ off-label	Possibly induces differentiation of bulge stem cells into hair follicles, prolongs anagen phase, and protects cells from apoptosis	Various: 4 sessions at 2-week intervals; 3 sessions at 3-week intervals + 1 session after 6 months; 2 sessions at 3-month intervals; or 3 sessions at 1-month interval	Minimal pain, redness at the time of injection, pinpoint bleeding
Scalp microneedling	Not approved/ off-label	Possibly induces release of platelet-derived growth factor, activation of follicle stem cells, and overexpression of hair growth-related genes	1 session per week for 12 weeks; or 1 session per week for 4 weeks + 1 session every other week for 24 weeks total	Minimal pain, pinpoint bleeding

FDA Food and Drug Administration

^a According to the protocols for each treatment option given in the published articles

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