

Clinical Features, Diagnosis and Management of Hirsutism

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ABSTRACT:

Hirsutism is a common clinical condition encountered in day to day practice. It means excessive growth of terminal hair in women with male characteristics and locations and is usually related to hormonal factors, mainly to increased level of androgens. In female the main sources of androgens, which can produce hirsutism are the adrenal gland (Dehydroepiandrosterone sulfate: DHEA-S) and the ovaries (Δ 4-androstenedione). Pituitary gland (prolactin) and liver (Sex hormone binding globulin) can also cause hirsutism in few cases. Ectopic hormone production by some tumors may also be responsible for hirsutism, but in few patients all biochemical parameters are absolutely normal. Therefore, it may be sometimes very difficult to understand the pathology of hirsutism in a given case. And one may find difficult to establish the cause of hirsutism and so the treatment, because depending on the origin of the hirsutism, the treatment is based on antiandrogens, oral contraceptive pills, glucocorticoids, GnRH antagonists in association of topical or dermato-cosmetic therapy or lasers.

We conducted a literature search and analyzed the causes, types, investigations and management aspects of hirsutism that may help one to understand and manage a case of hirsutism.

KEY WORDS: Ferriman-Gallwey scoring system, HAIRAN syndrome, hirsutism, hypertrichosis, polycystic ovary syndrome (PCOS), SAHA syndrome, 17-hydroxyprogesterone.

INTRODUCTION:

Hirsutism is the presence of excess body or facial terminal hair growth in females in a male-like pattern, and is an important sign of underlying androgen excess.^[1] It is not purely an aesthetic problem, as high prevalence (80-90%) of androgen excess disorders are reported in association with it, depending on age and race.^[2,3] Among women with PCOS, hirsutism is important predictors of a low quality of life.^[4]

With the exception of the skin of lips, palms and soles, hair covers majority of the surface area. Two physiologic types of hair in adults are Vellus and Terminal hairs. Vellus hairs are non medullated, short, fine and poorly pigmented and not associated with an arrector pili muscle.^[5] Growth of vellus hairs is

primarily stimulated by growth and thyroid hormones.^[6] They grow throughout the life and also present in areas usually considered to have only terminal hairs, such as scalp. Terminal hairs are longer, rigid, pigmented and medullated. They have associated arrector pili muscle.^[5] Growth of terminal hairs is primarily stimulated by growth and thyroid hormones and, selectively, androgens also.^[7] Terminal hairs demonstrate significant regional morphologic differences (i.e. longer in some sites, more medullated or pigmented in others, etc.) due to genetically determined differences in the follicles, which is why skin grafts maintains hair characteristic of the donor site.^[8]

Both the terms 'hirsutism' and 'hypertrichosis' are used to describe abnormal hair growth. 'Hirsutism' means excessive growth of terminal hair in women with male characteristics and locations, whereas, 'hypertrichosis' generally refers to localized or generalized increase in the hair without specific pattern or location.^[9,10]

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ROLE OF ANDROGENS IN CONVERSION OF VELLUS TO TERMINAL HAIR:

Under the appropriate endocrine stimulation, terminal hairs and vellus hairs may transform into one another, known as 'miniaturization and terminalization' respectively. Androgens, particularly in excess, can terminalize vellus hairs, producing terminal hair growth in certain areas of the body or face in both genders. The process of this transformation occurs progressively over many hair growth cycles. According to androgen sensitivity, hairs on three different body areas are defined as asexual, ambo-sexual or sexual hair⁵ (Table 1). Presence of hair growth in ambo-sexual or sexual areas is considered to determine the presence of hirsutism. Ambo-sexual areas are very sensitive to androgens. Terminalization occurs even in the presence of low levels of androgens. Therefore, these areas begin to develop terminal hair even in early puberty, in both genders. Some areas respond to androgens, only to significantly higher levels of androgens. Therefore, terminal hairs in these areas develop in men, and pathologically in women.

SCORING SYSTEMS FOR EVALUATING HIRSUTISM:

The system to quantify the degree of hirsutism was developed by Ferriman and Gallwaey.^[11] In original system 11 body regions were evaluated. Today in modified Ferriman-Gallwaey scoring system, 9 regions are assessed to give score of 0 (no terminal hair) to 4 (extensive terminal hair) (table 2). The Abraham's classification stages a patient's degree of hirsutism (table 3). Functional hirsutism is defined as a score greater than 8 and organic hirsutism when score is greater than 15. Beek observed one absolute difference between male and female hair patterns, that a 'disperse upper

border of the pubic hair is only found in men and if found in women, must be considered as an absolute sign of hirsutism.^[12] Shah studied hair growth in Indian women and concluded that the presence of terminal hairs on the face, chest and upper back was absolutely unusual, and on the abdomen, upper arms and buttocks was relatively unusual in Asian Indian women. He noted that the presence of hair on the thighs was almost always present relative to hair on other parts of the body, and that hirsute women had more hair on their thighs. Lastly, not all hirsute women had hair in the same body areas and it was unusual even for hirsute women, to have excess hair in every single one of the regions.^[13]

CLASSIFICATION AND CLINICAL FEATURES:

Hirsutism can be classified into eight categories, to be used in the description of clinical types, diagnosis and treatment.^[14]

1. **Hirsutism of constitutional origin:** Usually presents with Seborrhea, Acne, Hirsutism and Alopecia (SAHA syndrome), and considered as a minor form of hyperandrogenism syndrome. When there is slight increase in adrenal androgens, this is called 'persistant adrenarche syndrome'. If androgens come from the ovaries, this is known as 'excess ovarian androgen release syndrom'. In 'SAHA syndrome due to hyperprolactinemia' slight increase in prolactin is found. In "familial hirsutism" no endocrinological abnormality is found. This is probably because of familial increase in the end organ sensitivity to normal levels of androgens. HAIRAN syndrome is considered as a fifth variant^[15] characterized by Hyperandrogenism, Insulin resistance and Acanthosis Nigricans. All 4 signs

Table 1: Localization of body areas in relation to their androgen sensitivity.

Hair type	Localization	Androgen sensitivity
Asexual hair	Eyebrows, eyelashes, lateral and occipital Scalp hair	Independent of the effects of androgens.
Ambo-sexual hair	Pubic and axillary hair, lower arm and leg.	Sensitive to low levels of androgens
Sexual hair	Chin, face, chest, abdomen, back, thighs, Upper arms.	Sensitive to high levels of androgens

Table 2: Body regions in Ferriman-Gallwaey scoring system and its modification.

Ferriman-Gallwaey scoring system	Modifiend Ferriman-Gallwaey scoring system
Upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, arm, thigh, forearm, leg (11 areas).	Upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, arm, thigh (9 areas).

of SAHA syndrome are seen only in 21.5% women.^[16] Other features are described in table 4.

2. **Hirsutism of ovarian origin:** In case of hirsutism with lateral predominance, Grade I-II alopecia, acne, seborrhea, obesity, and obvious menstrual disorders, hirsutism of ovarian origin should be presumed. Non tumoral causes are polycystic ovary syndrome (PCOS) and ovarian hyperthecosis. Arrhenoblastoma, hilus cell tumors, granulosa cell tumors, brenner's tumors, and gonadoblastomas can cause tumoral ovarian hirsutism.

PCOS is the commonest cause of ovarian hirsutism characterized by infertility, secondary amenorrhea, menstrual irregularities, obesity and large polycystic ovaries. PCOS is classically classified as type I (primary) and type II (secondary). Primary PCOS is an autosomal dominant trait with low penetrance. Secondary PCOS can be produced as a consequence of 'ovarian SAHA syndrome'. HAIRAN is the severe variant of type II PCOS. Insulin resistance in HAIRAN is categorized as type A or B. Type A syndrome is an inherited form of severe insulin

Table 3: Abraham's classification, based on Ferriman-Gallwey scoring system.

Score	Presentation
<8	Normal
8-16	Discrete hirsutism
17-25	Moderate hirsutism
>25	Significant hirsutism

Table 4: Features of hirsutism of constitutional origin (SAHA).

Feature	Adrenal SAHA	Ovarian SAHA	Hyperprolactinemic SAHA	Familial hirsutism	HAIRAN syndrome
Seborrhea	Significant	Intense	Present	-	Present
Acne	Nodulocystic with scars	Pustular	Sometimes nodulocystic	-	Present
Hirsutism	Central dominance ^a	Lateral dominance ^b	Central and lateral	facial only with long preauricular hair line.	Slowly progressive
Female AGA	Grade I-II	Grade I	Grade I	-	Temporal balding
Body weight	Thin	Obese	-	-	Obese / weight loss
Menses	Usually longer than 30 days	Usually shorter than 28 days	Oligomenorrhea	-	Irregular menstruation
Biochemical	↑DHEA-S	↑ free testosterone ↓SHBG	↑prolactin	-	↑serum insulin, ↑Testosterone, ↑4-androstenedione ↑ ESR +ve ANA in type II HAIRAN syndrome ¹⁹
Other	Continuously stressed and sometimes with severe hyperhidrosis	-	Galactorrhea may be present		Deep voice, clitoromegaly, male body habitus, increased libido, insulin resistance, skin tags, acanthosis nigricans. polydipsia, polyuria may sometimes, be present.

^a abnormal hair growth which joins the neck with the upper pubic area. ^b lateral facial and mammary hirsutism.

resistance caused by mutations of insulin receptors. Type B is acquired, resulting from autoantibodies against insulin receptors.^[17] This type of insulin resistance occurs in patients with less severe acanthosis nigricans and may accompany other immunologic abnormalities¹⁸ and with a positive antinuclear antibody screen.^[19]

Increased pulse of GnRH cause overproduction of LH and relative reduction of FSH. Increased LH stimulates the ovarian theca cells to synthesize androgens. Hyperinsulinemia and obesity is also common. Insulin enhances androgen production from theca cells and also inhibits hepatic synthesis of SHBG resulting in high serum free testosterone. Women with PCOS are at increased risk of type II diabetes.^[20] Hirsutism localized usually on the lateral surfaces, especially on the breast, lateral areas of face, neck and also on abdomen. Biochemically serum total and free testosterone, 4-androstenedione, DHEA-S, LH, LH: FSH ratio and prolactin levels are increased and SHBG levels are decreased. All cases of PCOS with severe hirsutism have increased serum PSA levels.^[21]

Ovarian hyperthecosis is similar to PCOS, but with greater production of testosterone. Signs of virilization, hirsutism, AGA of male pattern are common. Serum levels of LH and FSH are normal, but estrone levels are greatly elevated.

3. **Hirsutism of adrenal origin:** In patient with evident central hirsutism, who is thin and with patterned baldness and signs of virilization, adrenal hirsutism should be presumed. Hypercorticism due to adrenal hyperplasia causes increase of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S).

Congenital adrenal hyperplasia (CAH) is due to congenital deficiency of one of the enzymes involved in adrenal steroid synthesis. There is accumulation of intermediate products before the deficient enzyme in the pathway, which are not recognized by pituitary gland and feedback mechanism is not initiated, resulting in very high levels of ACTH. Affected patients are deficient in aldosterone, cortisol and sex steroid. There are many enzymes which can be deficient; most common is 21- Hydroxylase deficiency, which may present in three forms. The classic form or “salt losing form” is the most severe form; the non classic virilizing form is moderate; and late onset CAH is due to partial deficiency of enzyme and manifest at puberty or

thereafter when demand of steroid increases. Feature of virilization and hirsutism is found in all forms. Cushing’s syndrome and virilizing adenoma or carcinoma are other causes of severe hirsutism of adrenal origin.

4. **Hirsutism of pituitary origin:** This type of hirsutism is due to secretion of hormones from anterior pituitary, particularly Prolactin, usually due to either prolactin secreting pituitary adenomas or psychogenic drugs though there are number of etiologies. Clinical features are ‘amenorrhea-galactorrhea, syndrome’ and infertility. Hirsutism is both central and lateral though slight predominance of former may be seen. Signs of virilization may be present.

5. **Hepatic hirsutism:** High levels of free circulating testosterone and peripheral conversion to dihydrotestosterone may be greater in sex hormone binding globulin (SHBG) deficiency. Because SHBG is produced in liver, in liver diseases SHBG is reduced. This form of hirsutism is usually accompanies hirsutism secondary to ovarian or adrenal dysfunctions.^[14]

6. **Hirsutism due to ectopic Hormones:** Choriocarcinoma, metastatic lung tumors, and carcinoid tumor are capable of producing hirsutism, central or lateral depending on the hormone produced.

7. **Iatrogenic hirsutism:** Drugs are usually responsible for hypertrichosis, and not true hirsutism. Anabolic and other steroids, oral contraceptives of non steroidal progestogen type, minoxidil, ciclosporin and diphenylhydantoin have been reported to cause hirsutism when administered to women. No hormonal abnormality is found biochemically and hirsutism disappears when the drug is discontinued.

8. **Hirsutism due to failure of peripheral conversion of androgens to estrogens:** This is a hypothetical cause of hirsutism. In condition of failure of peripheral conversion of androgens to estrogen, which usually takes place in adipose tissues and liver, there may be increased free testosterone levels, causing hirsutism.

DIAGNOSIS:

First step in evaluation is to determine the source of the responsible androgen. The marker for adrenal gland androgens is DHEA-S, and the marker for ovarian androgens is 4-androstenedione. There are some general rules for the diagnosis of hirsutism (Algorithm in Figure 1). a) Hirsutism, appeared abruptly and evolve quickly, ovarian, adrenal or pituitary tumor should be suspected; b) Hirsutism mainly localized to

areola and lateral surfaces of the face and neck, androgen usually have an ovarian origin; c) Centrally located hairiness with a distribution from pubic triangle to upper abdomen, between the breasts, neck and chin, origin is usually adrenal; d) Hair localized to lateral aspect of face and back, hirsutism is usually iatrogenic. The degree of hirsutism is quantified by modified Ferriman and Gallway scoring system.

SYSTEMIC TREATMENT:

Adrenal hyperandrogenism: Two types of drugs are used in adrenal hyperandrogenism, corticosteroids for adrenal suppression and antiandrogens to avoid adrenal androgen production or their effects on the target organ. Adrenal suppression is achieved with glucocorticoids. Initially dexamethasone was used as night doses.^[22,23] Now prednisolone or Deflazacort is more preferred.^[14]

Anti androgens: androgen receptor blockers:

Spirolactone (SPA) is an aldosterone antagonist with antiandrogen activity, which competes with DHT for binding to the androgen receptor. SPA also has variable progestational activity and decreases production of ovarian androgens. Initial dose is 50 mg/day. It may be increased to 200 mg/day at least for 6 months. Low dose is usually enough for adrenal SHAH. Spirolactone may cause lethargy, gastric upsets, and menorrhagia, which is usually transient and resolve spontaneously after 2-3 months of treatment. Low dose OCP may be used simultaneously which provides adequate contraception and also decrease the incidence of menorrhagia^[24]. SPA should be taken with food as this increases its absorption and reduces its potential for gastritis.^[25] Absolute contraindications include renal insufficiency, anuria, chronic renal impairment, hyperkalemia, pregnancy, and abnormal uterine bleeding.

Cyproterone Acetate (CA) has strong progestogenic and antiandrogen properties. It also competes with DHT for binding to the receptor, and inhibits the secretion of LH and FSH through progestogen action. The recommended dose is 50-100 mg/day for 6 months. OCP is usually added to prevent menstrual alterations and feminization of male fetus. Absolutely contraindication is patients with liver diseases. **Cimetidine** is a H₂ blocker, acts as peripheral antiandrogen by blocking the binding of DHT to androgen receptor.

Flutamide is a pure non steroidal antiandrogen drug.

It is one of the most effective antiandrogen for the treatment of adrenal hyperandrogenism in women with normal ovaries.

Anti androgens: 5 alpha reductase inhibitors:

Finasteride is a potent non steroidal antiandrogen, inhibits type 2 5-alpha reductase. Finasteride is usually safe and well tolerated, but may cause feminization of male fetus. Therefore OCP must be added.

Dutasteride is a "dual" type 1 and 2, 5-alpha reductase inhibitor. The experience with this potent non steroidal antiandrogen in the treatment of hirsutism is less.

OVARIAN HYPERANDROGENISM:

Three types of treatment is used: OCP for ovarian suppression, GnRH agonists for pituitary and gonadal suppression and antiandrogens. **Ovarian suppression:** Ovarian suppression with OCP is the first line treatment for hirsutism and acne in women with ovarian SAHA syndrome and PCOS.^[26] Estrogen-progesterone combinations act by reducing GnRH secretion which reduces ovarian androgen production.^[27] They also increase the levels of SHBG resulting in lower free testosterone and also inhibit adrenal androgen production.^[24]

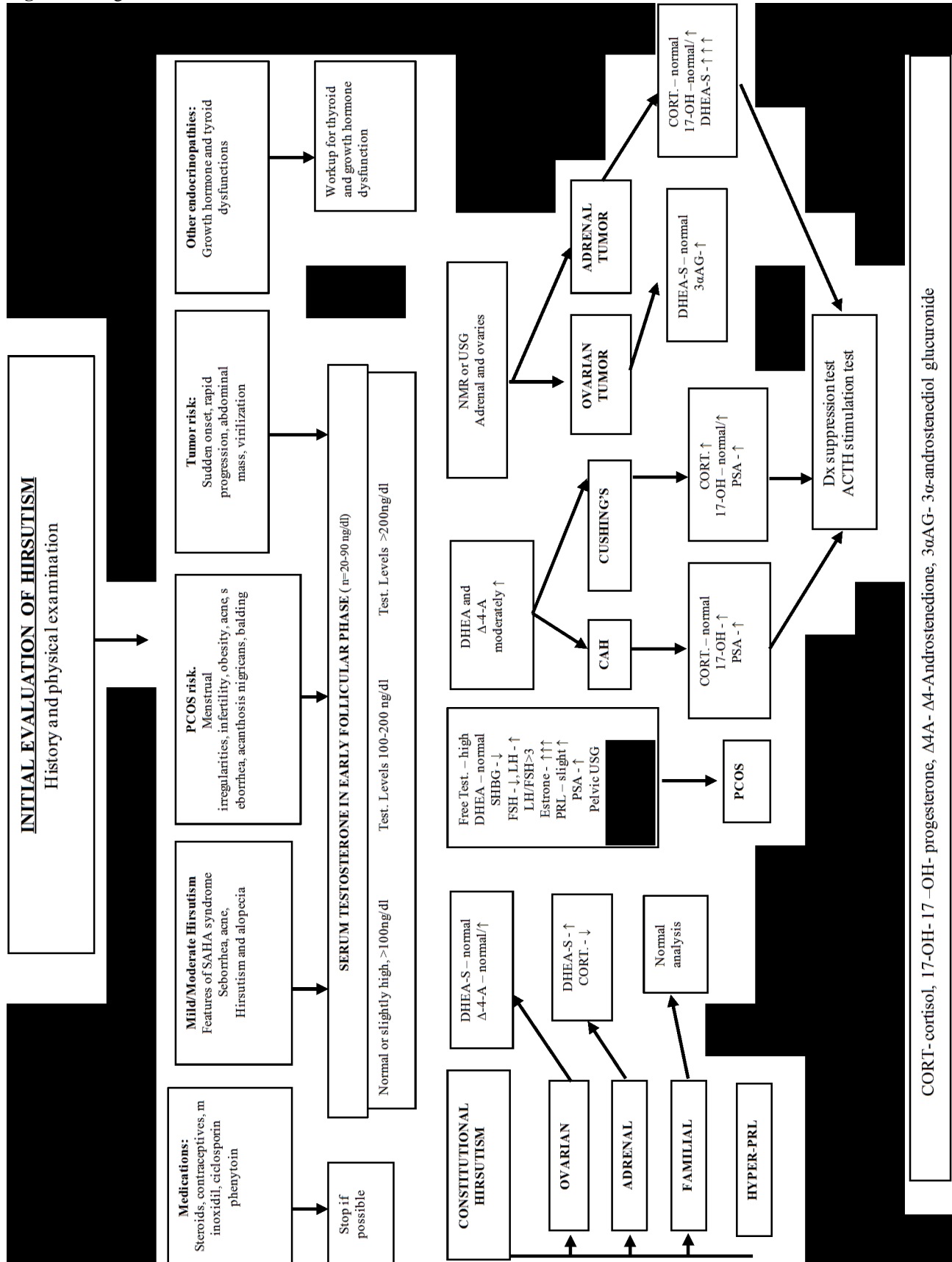
GnRh AGONISTS:

Although their use in SAHA syndrome is not usually considered, they are useful in treatment of severe forms of ovarian hyperandrogenism with severe hirsutism, nonresponsive to OCP and antiandrogens, and especially in HAIRAN syndrome. This therapy is parenteral.^[28] They stimulate pituitary gland continuously, reducing FSH and LH production. Low levels of LH leads to fall in ovarian steroid levels. They are always used in combination with OCP, to increase SHBG and to reduce the free testosterone. **Leuprolide** is the most useful GnRH agonist used in a dose of 20µg/kg/day for 6 months. **Triptorelin** is a long acting GnRH agonist. **Metformin** is very effective in treatment of HAIRAN syndrome in combination with weight loss, OCP and antiandrogens. Antiandrogens are used in ovarian SAHA and PCOS are the same as used to treat adrenal SAHA and hyperandrogenism.

TOPICAL THERAPY:

In patients with familial SHAH syndrome with minimal clinical and with normal hormonal levels, local dermato-cosmetic treatment should be used. **Topical**

Figure 1: Diagnosis of hirsutism.



spironolactone 3% and its metabolite *canrenone* 1-2%, has acceptable results in mild familial SAHA. *Eflornithine* 11-15% is an inhibitor of ornithine decarboxylase, involved in keratin synthesis, which is necessary for production of the polyamines that mediate cell migration, proliferation, and differentiation.^[29] In twice daily application schedule it is suitable alternative for facial hirsutism.

DERMTO-COSMETIC THERAPY:

Hair bleaching, shaving, depilation, waxing and electrolysis are options in this category. With repeated treatments, the efficacy ranges achieved in electrolysis is from 15 to 50% permanent hair loss.^[30]

LASERS AND INTENSE PULSED LIGHT SOURCES:

Lasers work on the principle of selective photothermolysis where the laser energy acts specifically to destroy melanin as the target.^[31,32] Alexandrite, Nd:YAG and diode laser are used for this purpose. For Indian skin types (Type IV and V), long wavelength lasers like Nd Yag laser have been found to be most effective³³. Laser hair removal is most suitable for idiopathic hirsutism with the normal androgen levels. Combination of eflornithine cream and laser hair removal results in a more rapid and complete reduction of unwanted facial hair in women when used for up to 6 months.^[34,35]

LIFESTYLE MANAGEMENT:

Diet, exercise and weight reduction should be advised to all obese women with PCOS. Weight loss of only 2-7% has been shown to improve manifestations of hirsutism^[36], decrease hyperinsulinemia, and restore ovulation and fertility in up to 75% of obese women. There is no evidence that any particular diet is more beneficial for obese women.^[37]

CONCLUSION:

Hirsutism is a common clinical condition that usually has a benign course, but requires thorough clinical examination and investigation for diagnosis and to plan a treatment. PCOS is by far the most common androgen excess disorder. For drug therapy, oral contraceptives are usually recommended for the majority of women. Antiandrogen monotherapy is not

recommended unless adequate contraception is used. For women who choose hair removal therapy, photoepilation with lasers is the preferred choice nowadays.

In rare cases, however, it may be the presenting feature of a serious underlying disease which needs proper diagnosis and appropriate treatment.

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