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HIRSUTISM- A SYMPTOM RATHER THAN A DISEASE: A REVIEW

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ABSTRACT

Hirsutism is a relatively common condition affecting about 5%-10% of women of childbearing age. Hirsutism is defined as excessive terminal hair growth in women, which has a typical male pattern distribution. It should be differentiated from hypertrichosis, a generalized excessive hair growth that may be hereditary or result from some drugs, such as cyclosporine. Hirsutism is a relatively common disorder that affects about 5%-10% of women of reproductive age. Unwanted hair growth can be associated with significant psychosocial consequences that negatively affect patients' quality of life. Hirsutism is a symptom rather than a disease and may be a sign of a more serious medical condition, especially if it develops well after puberty. Here in, we present an overview of hirsutism with emphasis on its etiology, cause and diagnosis.

KEYWORDS

Antiandrogens, hirsutism, insulin-sensitizing agents, oral contraceptives, polycystic ovary syndrome (PCOS), virilization and dehydroepiandrosterone sulphate (DHEA-S)

INTRODUCTON

Hirsutism is defined as the abnormal growth of terminal hair in an androgen dependent pattern in women. The involved sites include face, chest, areolae, lower abdomen, and crural area. In severe cases shoulder area, lower back, upper abdomen, and upper arms are also affected. Patients may show clinical signs of virilization such as frontoparietal (male-pattern) hair loss, acne, amenorrhea, and sometimes masculinization of the muscle mass, hypertrophy of vocal cords, or clitoromegaly[1, 2]. Estimates suggest that it affects between 5% and 15% of women, varying according to characteristics. At least 5% of women of reproductive age suffer from this ailment[3]. This condition is extremely distressing and has significant negative impact on female psychological development[4]. Stress has been proposed as a contributing factor in hirsutism[2].

Hirsutism may be associated with obesity, insulin resistance, diabetes, polycystic ovary syndrome (PCOS), hypertension, infertility, and

menstrual irregularities[5]. after excluding these disorders, hirsutism is referred to as idiopathic, simple or peripheral. However this definition has evolved over years and presently idiopathic hirsutism is diagnosed in females with normal circulating androgen levels and normal ovulatory cycle, since 40% eumenorrhoic females have been demonstrated to have anovulatory cycles[6].

PREVALENCE

The prevalence of hirsutism is higher in mediterannian and South Americans than Indians and Mongoloids[1, 5].

Countries	Percentage
United States[5]	8%
India (Kashmir)[7]	10.5%

CAUSES OF HIRSUTISM[8]

There are several causes of hirsutism like:

- Excessive production of androgens by the ovaries (polycystic ovarian syndrome, tumor)
- Excessive sensitivity of hair follicles to androgens (genetic)
- Excessive production of androgens by the adrenal glands (NCAH: Non-Classic Adrenal Hyperplasia, tumor)
- Insulin Resistance (HAIR-AN Syndrome: (Hyperandrogenism, Insulin Resistance, Acanthosis Nigricans)
- Excessive production of cortisol by the adrenal glands (Cushing's syndrome)
- Menopause
- Medications

PATHOPHYSIOLOGY OF HIRSUTISM

Hair growth cycle

The hair growing cycle is comprising of 3 phases:

- Anagen (growth phase)
- Catagen (involution phase)
- Telogen (rest phase)

Depending upon the body size, hormonal regulation plays an important role in the hair growth cycle. Androgens increase hair follicle size, hair fibre diameter and the proportion of time terminal hairs spend in the anagen phase. Androgen excess in women leads to increased hair growth in most androgen sensitive sites, but will manifest with the loss of hair in the scalp region, in the part by reducing the time scalp hairs spend in anagen phase.

Hair can be categorized as either:-

- Vellus (fine, soft and not pigmented) or
- Terminal (long, coarse and pigmented)

The number of hair follicles does not change over an individual's lifetime, but follicle size and type of hair can change in response to numerous factors, particularly androgens. Androgens are necessary for terminal hair and sebaceous gland development and mediate differentiation of pilosebaceous units (PSU`s) into either a terminal hair follicle or a sebaceous gland. In the former case, androgens transform the vellus hair into a terminal hair, in the latter, the sebaceous component proliferates and the hair remains vellus[9]. When caused by increased androgen activity, hirsutism is often accompanied by virilization, which may manifest as loss of menses, increased muscle mass, voice deepening, and clitoral hypertrophy[10].

DIAGNOSIS

Clinical diagnosis is relative subjective. Physical examination and laboratory investigations can be crucial in the correct evaluation of hirsutism. The history should include the onset and progression of hirsutism, the pattern of menstruation, weight gain, and the use of androgenic drugs, such as anabolic and androgenic steroids, and valproic acid[11].

There are also several clinical findings that suggests one of the rare and more serious causes of Hirsutism:-

- Abrupt onset, short duration, or progressive worsening of hirsutism.
- Onset in the third decade of life or later, rather than near puberty.
- Symptoms or signs of virilization.
- Moderately elevated (or higher) serum androgen concentrations, e.g., in young women raise possibility of an androgen-secreting harmone[9].

According to the Endocrine Society Clinical Practice Guidelines[12], testing for androgen is recommended in women with moderate-to-severe hirsutism or hirsutism of any degree when it is associated with any of the following: sudden onset, rapid progression menstrual irregularity, infertility, central obesity, clitoromegaly, or acanthosis nigricans. The initial tests for hirsutism should include early morning plasma total testosterone and free testosterone. If testosterone levels are more than 1.5-2 times the upper normal limit, or if a history of rapid virilization is found, dehydroepiandrosterone sulphate (DHEA-S) and androstenedione should be measured to identify an adrenal or ovarian source of hyperandrogenemia.

LABORATORY TESTING[9]

- Serum androgens
  - Serum testosterone values – above 150 ng/dL
  - Serum free testosterone values – above 2 ng/dL
  - Serum dehydroepiandrosterone sulfate (DHEA – S) values- above 700 mcg/dL
- Serum prolactin above 20 g/L
- Serum luteinizing hormone
  - Follicular Phase 2.0 – 15.0 U/L
  - Ovulatory Phase 22.0 – 105.0 U/L
  - Luteal Phase 0.6 – 19.0 U/L
  - Postmenopausal 16.0 U/L – 64.0 U/L
- Pelvic Ultrasonography
- Testing for Cushing's syndrome
- Abdominal CT or MRI
- Laparoscopy or laparotomy
- Ovarian and adrenal vein sampling
- Dexamethasone suppression testing
- Clinical investigation tools
- GnRH agonist testing.

HIRSUTISM PROFILE

It is the tests performed on a female to identify the cause of increase hair growth. It includes the estimation of 3- alpha- androstanediol, androstenedione, DHEA- S, total & free testosterone.

FERRIMAN – GALLWEY SCORE (F - G)

This is the established and most prevalent system of measuring hirsutism. It was introduced in 1961 and initially it was based on the presence of hair production in 11 different areas namely the upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, arm, forearm, thigh, and lower leg. The survey was conducted at a medical clinic in UK and the cases were 430 successive females stated to be primarily of white ethnicity and aged 15 to 74 years[3].

It is a semi quantitative system for the clinical assessment of the presence and severity of hirsutism in the premenopausal woman. Each of nine body areas is graded separately from no hirsutism (grade 0) to minimal hirsutism (grade 1) to marked hirsutism (grade 4). A normal hirsutism score is less than 8[9].

HATCH AND COLLEAGUES' METHOD

This is also a variation of the Ferriman-Gallwey technique. Hatch and his fellow experts maintained the conventional score card of 0 to 4 but referred to only nine of the body locations assessed by Ferriman and Gallwey. The lower legs and lower arms were not included in their research.

LORENZO`S STUDY OF HIRSUTISM

This study was conducted on 300 random women (irrespective of racial differences) from a public health survey in Michigan. It score pattern was based on only five body regions namely chin, upper lip, chest, abdomen, and thighs and the count was the conventional 0 to 4. This survey did not record a hirsutism tally over 5 among any of the cases studied. Hence, from this analysis some experts concluded that the general score varies with the area of survey.

Apart from these three hirsutism measuring methods, there have also been studies that quantify the causes behind the syndrome. They are also indispensable for a proper prevalence study of hirsutism. Below is a common approximation (though there are many variations as well) of the prevalence of various factors that lead to hirsutism[3]:

- Polycystic Ovarian Syndrome (PCOS) - 70–80%
- Hyperandrogenism - 6.8%
- Hypothyroidism - 0.7%
- The hyperandrogenic insulin-resistant acanthosis nigricans syndrome (HAIR-AN) - 3 %
- 21-hydroxylase non-classic I adrenal hyperplasia (late-onset CAH) - 1.6%
- 21 -hydroxylase-deficient congenital adrenal hyperplasia - 0.7%
- Hyperprolactinemia - 0.3%
- Androgenic tumors - 0.2%
- Cushing's syndrome - 0-1%
- Idiopathic hirsutism - 4.7%

MANAGEMENT

There are a variety of specific medical and surgical treatments that your physician may recommend based on your diagnosis and severity of hirsutism[8]. The therapeutic options of hirsutism can be divided into systemic, topical, and dermato-cosmetic therapies. Patients should be informed that the response to systemic agents is slow; occurring over 3-6 months after therapy will begin[11].

COSMETIC HAIR REMOVAL FOR HIRSUTISM

Cosmetic hair removal does not provide long term relief from excess hair. The results are only short lived and have to be repeated regularly to maintain a lack of hair. However, the main advantage is that they can be applied at home quickly and easily[3]. In addition, cosmetic hair removal methods are cheap and widely available. A facial cream containing eflornithine hydrochloride (Vaniqa™) may be used in combination with the previously mentioned cosmetic therapies to slow the growth of excessive facial hair. Its safety in pregnancy or effectiveness on other body parts has not been established[8]. Cosmetic therapy includes two types:

- Temporary hair Removal
- Permanent hair Removal

TEMPORARY HAIR REMOVAL

SHAVING

Most women are rather reluctant to shave excess hair – particularly on the face. However, shaving is one of the quickest, cheapest and most effective ways of removing facial hair. Where the hair growth in the beard and moustache are modest the results from shaving can be very good.

The main disadvantage:-

1. Hair quickly regrows so shaving has to be done on a regular basis.
2. Shaving can cause a rash on sensitive skin.

BLEACHING

Bleaching facial hair, and sometimes body hair, is a popular approach to hiding hirsutism for light skinned individuals. The bleaching is intended to reduce the color contrast between the hair fiber and the skin. The less contrast in color, the less visible the hair is. For dark skinned individuals bleaching is usually more of a disadvantage as it can actually increase the color contrast between the hair fiber and the surrounding dark skin.

CHEMICAL DEPILATION

Chemical depilatories can be an effective way to remove hair and the results last longer than with shaving. In essence, the chemicals are very alkaline in nature. The alkaline chemicals weaken the hair fiber so that it breaks off a little below the skin surface when the cream is rubbed or washed away.

PLUCKING

Plucking hair to remove can work quite well. Small areas may be individually plucked with tweezers. Larger areas of hair can be plucked using battery operated epilators that mechanically pluck the hair. The result can be very good. However, one of the main disadvantages of plucking hair is that it will grow back and sometimes it can grow back thicker than it was before. Plucking hair injures the hair follicles.

Threading is a particular form of hair plucking. Some cosmetics salons now offer this. Threading involves passing twisted threads across the skin such that the catch hair between the threads which is then plucked. It's a quick way to pluck hair and in experienced hands it can be a good way to remove smaller hairs on the face.

PERMANENT HAIR REMOVAL

There are two types of permanent hair removal: Electrolysis and Photoepilation (using Laser and intense pulse light (IPL)). Photoepilation seems to be superior to the conventional methods, such as shaving, waxing and electrolysis. A Cochrane review of photoepilation of unwanted hair growth showed that alexandrite and diode lasers are more effective, whereas little evidence was obtained for the effect from IPL, Nd: YAG, or ruby lasers[13]. However, some longer wavelength lasers (Nd:YAG), or IPL, appear to provide benefits in patients who have darker skin types and therefore have less risk of burning and dyspigmentation, but rare, adverse effect of photoepilation, particularly in dark-skinned individuals[14,15].

1. ***ELECTROLYSIS:*** It is the method in which a very fine needle is inserted into the hair follicle. A mild electric current is sent through the needle to permanently destroy the hair follicle's ability to produce hair. Since follicles are treated one at a time, it is somewhat impractical to use electrolysis to treat very large areas of the body.
2. ***LASER METHOD:*** This method is used on large areas of body. This involves a beam of light is passed through the skin to the hair follicle to destroy it. People with light skin and dark hair usually achieve the best results with laser hair removal[8].

PHARMACOTHERAPY ANTIANDROGENS

Spironolactone (Aldactone), a diuretic or "water pill," is often prescribed in combination with birth control pills. It has been found to directly block the effects of androgens in hair follicles and has been used to treat hirsutism[8], an aldosterone antagonist, has several actions

including inhibition of the androgen receptor, suppression of adrenal androgen biosynthesis, and inhibition of the 5α-reductase enzyme. Spironolactone is generally well tolerated with few side-effects, such as menorrhagia, lethargy, stomach upset, dry skin, heart burn, fatigue[16]. Spironolactone should not be prescribed to patients with renal insufficiency or hyperkalemia. As spironolactone usually causes feminization of the male fetus as well as menstrual alterations, it is best to add oral contraceptive pills[17].

Flutamide is a pure nonsteroidal antiandrogen that acts as an androgen receptor blocker. Studies have shown that flutamide 250-500mg/d is more effective than finasteride[18] and triptorelin, [19] a long acting gonadotropin-releasing hormone antagonist.

Finasteride is a potent inhibitor of the type 2 isoenzyme of 5-α-reductase, which blocks the conversion of testosterone to 5-α-dihydrotestosterone. Finasteride has been shown to lower hirsutism scores by 30%-60% in addition to reducing the average hair diameter[20].

GONADOTROPIN-RELEASING HORMONE (GnRH) AGONISTS

GnRH agonists suppress luteinizing hormone, and to a lesser degree follicle stimulating hormone secretion, leading to a decline in ovarian androgen production. GnRH agonist therapy seems to have no therapeutic advantage over OC and antiandrogens[21, 22]. As GnRH agonist therapy is expensive, requires injections, and estrogen needs to be added to the therapy, its use should be reserved for severe forms of hyperandrogenemia, such as patients with ovarian hyperthecosis who have a suboptimal response to OCs and antiandrogens.

CONCLUSION

Hirsutism is usually a benign, but extremely distressing condition. Although several treatment options exist, we recommend the use of oral contraceptives (OCs) with antiandrogenic activity as first-line therapy for the majority of premenopausal women. An antiandrogen can be added if the response to OCs is suboptimal after 6 months of use. Laser/photoepilation are the preferred direct hair removal methods. Logical combinations tailored to the individual clinical profile can accomplish the best results in most patients. Hirsute patients frequently have either elevated androgen levels or clinical conditions associated with hyperandrogenemia. Eumenorrhea does not rule out endocrine abnormality and particularly polycystic ovary syndrome which is a common cause of hirsutism. We recommend performing endocrinologic work up, investigation of coexisting hyperandrogenic states, and evaluation of polycystic ovary syndrome in all patients with hirsutism.

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