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REVIEW ARTICLE

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Updates on Hirsutism: A Narrative Review

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Abstract

Hirsutism is described as an abnormal amount of hair development in females in a male-like way. Excessive hair growth is frequently associated with severe emotional discomfort. Hirsutism is a frequent presentation to dermatologists, as women seek both aesthetic and therapeutic treatment options for their condition. Hirsutism is caused by an excess of androgens, most frequently from the ovary or adrenal glands. Hirsutism is frequently linked with metabolic disorders such as polycystic ovary syndrome (PCOS); it can also occur idiopathically, as a side effect of medicine, or, rarely, due to a serious underlying condition. This article discusses the diagnosis and treatment of hirsutism concisely.(**International Journal of Biomedicine. 2022;12(2):193-198.**)

Key Words: polycystic ovary syndrome • hirsutism • treatment

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Abbreviations

CAH, congenital adrenal hyperplasia; **DHEA-S**, dehydroepiandrosterone sulfate; **FSH**, follicle-stimulating hormone; **GnRH**, gonadotropin-releasing hormone; **LH**, luteinizing hormone; **NCAH**, nonclassic CAH; **OCPs**, oral contraceptive pills; **PCOS**, polycystic ovary syndrome; **SHBG**, sex hormone–binding globulin.

Introduction

Hirsutism is the abnormal development of dense, black hair in locations where women's hair development is generally modest or non-existent. Men's body hair pattern development is more common in androgen-stimulated areas, including the face, chest, and areolae.(1) In women, hirsutism generates severe anxiety and low self-esteem. Although it is a benign disorder in and of itself, it is frequently a symptom of a more serious underlying endocrine issue. In the majority of cases, hirsutism is a harmless disease that is mostly of aesthetic importance. However, hirsutism might be a signal of an ovarian or adrenal tumor if it is accompanied by masculinizing signs or symptoms, especially if they appear after puberty. Fortunately, these conditions are uncommon. Hypertrichosis, which is an increase in body hair that is not restricted to androgen-dependent regions, must be separated from hirsutism. Hypertrichosis is characterized as abnormal hair development in areas other than androgen-dependent parts, whether terminal or vellus hairs. Hypertrichosis is a condition that can be either congenital or acquired. Acquired hypertrichosis can occur as a side effect of some medications, such as phenytoin, penicillamine, L-thyroxine, and others, or as a result of systemic disorders, including hypothyroidism and malnutrition. Depending on the amount of hair, hirsutism can be classed as I (hirsutism) or IV (virilization).(2) The most essential factor in determining the diagnosis is a change in hair growth type and rate. Recently, camera equipment and computer software were used to establish a procedure for evaluating hirsutism. There is a considerable variation in hair

structure and growth rate between hirsute and non-hirsute women, as evidenced by digital imaging of hair development.[3] Following a comprehensive clinical assessment, laboratory work and radiology are performed to verify or exclude underlying reasons. Hair removal and pharmacological therapy of any associated etiology are among the first steps in management, which also involve patient education and support.

Hirsutism affects around 5% to 10% of women in the childbearing period.[4,5] Excess hair is a cosmetic problem for women, and it may have a negative impact on self-esteem.[6] Hair growth that is normal or acceptable is determined by a female's ancestry, family, cultural, and social hair volume, and distribution norms. Females of the Mediterranean region have a fair quantity of face and body hair, while Asian females have very little. Hirsutism is clinically rated using the Ferriman-Gallwey (FG) scale, with an FG score of 8 or above indicating the person is hirsute.[4]

PATHOPHYSIOLOGY

Numerous variables, including growth factors, mediators, and reproductive hormones, influence hair development. Hair growth patterns have been demonstrated to be affected by thyroid and growth hormones. Sex hormones, especially androgens, influence the kind of hair that develops and distributes throughout the body. Vellus follicles in certain regions grow into terminal hair when testosterone levels rise throughout adolescence.[8] This is determined by the degree and length of androgen exposure, local 5-alpha-reductase function, and the inherent hair follicle susceptibility to androgen action.[9] In most androgen-sensitive areas, high androgen levels result in enhanced terminal hair growth (e.g., regions of the upper lip/chin/chest/back). Despite the fact that androgen excess is at the basis of the majority of hirsutism instances, hair development and androgen volumes are only slightly linked.[7] Hirsutism is produced by hair follicles that are more responsive to normal or unusually high androgen levels.[10] As a result, excessive hair growth is frequently seen in people with endocrine problems defined by hyperandrogenism (ovaries or adrenal gland abnormalities). Three stages are postulated for the physiologic process of androgenic action: (1) Adrenal and ovarian production of androgens; (2) Transport of androgen in the blood by carrier proteins (most notably SHBG); (3) Androgen receptor binding and intracellular modification.

In brief, hirsutism could be induced by central androgen overproduction, increased peripheral androgen conversion, reduced metabolism, and increased receptor binding. Circulating testosterone must be transformed into dihydrotestosterone, a more powerful follicle-active derivative, in order to have an enhancing effect on the hair follicle. This conversion is carried out by the 5-alpha-reductase enzyme, which is present in the hair follicle. Due to individual differences in hair follicle androgen reactivity, the degree of hirsutism does not correspond to the amount of elevated serum androgens. Testosterone promotes hair development by enhancing the size and pigmentation of hair. Estrogens work against testosterone, decreasing hair development and resulting in finer, lighter hairs. Hair growth is unaffected by progesterone. SHBG regulates the quantity of available testosterone (the physiologically active androgen, which induces hair development following conversion to dihydrotestosterone). Low SHBG concentrations increase free testosterone bioavailability. SHBG levels decline as a result of the following: External androgens, PCOS, Cushing syndrome, Hyperinsulinemia, Overweight, Hypothyroidism, Elevated prolactin, and Overproduction of growth hormone. SHBG concentrations, on the other hand, rise in response to greater estrogen levels, such as those seen during oral contraceptive medication. As a result of the elevated SHBG levels, circulating testosterone activity is reduced.[9]

Polycystic ovary syndrome

PCOS is a prevalent cause of hirsutism that usually appears throughout puberty. Menstrual abnormalities or infertility are symptoms of PCOS, as are insulin resistance (metabolic syndrome or diabetes), indicators of increased androgen (such as hirsutism and acne), and laboratory proof of excess androgens. PCOS can be diagnosed without polycystic ovaries. Although the cause is unclear, it is believed that the etiology of PCOS is complex. PCOS develops whenever the ovaries are prompted to generate high androgen amounts. Increased LH secretion or hyperinsulinemia can induce this. Hyperinsulinemia increases GnRH pulse frequency, LH over FSH dominance, and androgen synthesis, while decreasing SHBG levels.[11] This disease is thought to be caused by gonadotropin-dependent functional ovarian hyperandrogenism, but a modest, functional adrenocorticotropic-dependent increase in androgens has been seen in several patients. PCOS can appear with a solitary DHEA-S increase in rare situations.[12]

Idiopathic hirsutism

Idiopathic hirsutism refers to hirsutism that arises for no apparent reason, such as in women who have regular menses, normal androgen levels, and no other symptoms that suggest other causes of hirsutism.[4] Whereas this phrase is often used, it can be deceptive, particularly if idiopathic hirsutism is diagnosed using routine laboratory testing, which does not usually show androgen excess.[7] Idiopathic hirsutism is believed to be caused by a small increase in androgens secreted from the ovary or adrenal gland, enhanced activity of 5-alpha reductase in the hair follicle, or androgen receptor anomalies.[10]

Other conditions of excess androgen

HAIR-AN (hyperandrogenism, insulin resistance, and acanthosis nigricans) syndrome is a set of genetic diseases characterized by significant insulin and glucose metabolic abnormalities as well as symptoms of hyperandrogenism. It is distinct from PCOS.[13] SAHA (seborrhea, acne, hirsutism, and acanthosis nigricans) syndrome is a clinical spectrum linked to high androgen levels. These symptoms can occur as a result of the HAIR-AN syndrome or a different source of elevated androgens, such as ovarian, adrenal, hyperprolactinemic, or idiopathic sources. Exogenous variables such as androgenic medicines (Progestins, Diazoxide, Minoxidil, Phenytoin, Danazol, Glucocorticoids, Anabolic steroids, Testosterone, Cyclosporine) and NCAH can also cause hirsutism. Premature pubarche, hirsutism, and menstrual abnormalities are all symptoms of NCAH, which is caused by a 21-hydroxylase

insufficiency.[14-16] Adrenal or ovarian androgen-secreting tumors, both benign and malignant, are uncommon causes of hirsutism. In such circumstances, hirsutism may appear suddenly or progress quickly, and it may be accompanied by virilization symptoms such as a deeper voice, greater muscular mass, clitoromegaly, and increased libido.[13]

CLINICAL AND INSTRUMENTAL ASSESSMENT OF HIRSUTISM

Women's excessive hair that exceeds regionally acceptable levels could be just as unpleasant as hair loss on the scalp. Hirsutism can manifest itself in a variety of ways. It commonly arises during adolescence in women with familial hirsutism, for example. In individuals with PCOS and CAH, hirsutism typically develops over time. When an androgen-secreting tumor forms, hirsutism emerges suddenly. Obtaining a proper menstrual history is critical since women with high androgen will experience irregular menstrual periods. Menstrual irregularities are typical in women with PCOS. Idiopathic hirsutism can affect women who have regular periods. When collecting a history, ethnicity should also be considered. In comparison to many Asian women, who have very little hair, women of Mediterranean heritage have more body hair, on average. Finally, a review of hirsutism, infertility, and obesity in the family, as well as medication usage, should be conducted.[10]

Excess terminal hair in a male pattern characterizes a woman with hirsutism; however, hirsutism might be difficult to detect in women with blond hair. The FC model, a quantitative way of evaluating hair growth, permits assessing hirsutism severity by analyzing hair growth in nine main anatomical areas: Moustache, temple, and beard regions on the face; Central chest; Areolae; Linea alba; Back (upper); Lower back; External genitalia; Buttock area; Inner thighs.[1] Other signs include Acanthosisnigricans; Obesity; Virility and Cushing's symptoms; Alopecia and acne.[17]

The purpose of biochemical testing of hirsute women is to find those with significantly high androgen levels, which might indicate the presence of androgen-secreting tumors. After ruling out hereditary and drug-induced causes of hirsutism, androgen excess hirsutism must be considered. The serum DHEA-S and total testosterone values are often acquired to exclude adrenal and ovarian cancers. Baseline testosterone (total or free) evaluation, as well as DHEA-S, may typically identify if additional testing is required. These hormones may reveal the cause of increased androgen secretion.[17]

Regarding serum testosterone, it is debated whether total testosterone or free testosterone is a more efficient screening test. Total testosterone testing is less costly and perhaps easier to interpret. Free testosterone, on the other hand, may be a more sensitive sign of hormonal imbalances. Tests for testosterone levels should be done first thing in the morning. The highest acceptable limit for testosterone in plasma differs per laboratory; however, it often falls between 70ng/dL and 90ng/dL. It's also worth noting that testosterone levels change by about 25% during different parts of the menstrual cycle. Because hirsutism is caused by dihydrotestosterone, the much more powerful testosterone metabolite, there is no direct association between testosterone levels and the degree of hirsutism. Most women with anovulation and hirsutism have increased free serum testosterone(>80 ng/dL). A tumor workup is recommended for most individuals with total testosterone >200 ng/dL (>100 ng/dL in post-menopause). Pelvic and ultrasound examinations are generally sufficient to confirm PCOS in this workup. An adrenal computed tomography scan is conducted if the test findings are negative.[17]

The DHEA-S level is high in certain hirsute people. Moderate increases point to hirsutism being caused by the adrenal glands. Normal DHEA-S levels and high testosterone levels suggest that the excess androgen is produced by the ovaries rather than the adrenals. Most individuals with a DHEA-S greater than 700 mcg/dL (400 mcg/dL in post-menopause) should have a tumor workup. Adrenal hyperplasia, rather than the exceedingly uncommon adrenal carcinomas, causes a rise in this level.

Consider the following additional tests if a woman has significant or fast progressing hirsutism or indications of virilism (e.g., irregular or missed cycle, acne, deep voice, androgenetic alopecia, increased muscle mass circumfluous, enhanced libido, clitoral enlargement):

•Androstenedione in the blood: Androstenedione is produced by the adrenal glands or the ovaries, and its levels are frequently increased in hyperandrogenic individuals. A serum androstenedione level of 100 ng/dL indicates an ovarian or adrenal tumor.

•LH and FSH: LH is often increased while FSH is decreased in women with PCOS, resulting in high LH/FSH ratios (>2).

•17-Hydroxyprogesterone: Morning 17-hydroxyprogesterone levels are measured as a screening test for late-onset CAH. DHEA-S and 17-ketosteroids levels are normal or slightly increased. Precursors of testosterone and cortisol are at an all-time high. Patients with PCOS have slightly increased urinary 17-ketosteroid levels. The most prevalent defect linked with CAH is a 21-hydroxylase deficiency, which is diagnosed by a 17-hydroxyprogesterone level >800 ng/dL.

•A dexamethasone suppression test is required for an intermediate 17-hydroxyprogesterone level (200-800 ng/dL); however, this level is normal in many females with adult 21-hydroxylase insufficiency, and corticotropin stimulation could lead to overdiagnosis of the illness.

•Prolactin level: PCOS is more common in oligomenorrheic patients. Sensitivity and specificity problems affect LH, FSH, and prolactin tests. Testing almost never improves the patient's result.

•Urine cortisol testing: If Cushing's syndrome is suspected, urine cortisol testing for 24 hours is required.[18]

Imaging investigations of the adrenal and ovarian organs may be necessary for patients with suspected PCOS or a potential tumor.[18] A biopsy of a hirsute area will reveal terminal hairs; however, a biopsy is not really required for diagnosis.[13]

TREATMENT

When an underlying problem is discovered, it is critical to treat it. PCOS is seen in the majority of individuals with

severe hirsutism, and the most essential therapies are to reduce the chances of endometrial hyperplasia and cardiovascular diseases. Hirsutism management is only essential if the extra hair is cosmetically bothersome to the patient. Simple hair bleaching is an economical alternative to hair removal that works effectively when hirsutism is not severe. Bleaches lighten the hair color, making it less apparent.[19] The patient should be informed about cosmetic and pharmacological therapy, as well as the possibility of long-term treatment and the negative effects of certain medications or surgeries. At the start of treatment, the patient should have realistic expectations. Patients should be informed that, rather than completely eliminating hair follicles, pharmacologic treatment will most likely result in reduced hair development, and hair removal will be less frequent. Obtaining an FG score at baseline and, if feasible, at each visit should be used to track therapy response. The patient's opinion of improvement is most likely the most relevant consequence. During therapy, no recommendations for monitoring testosterone are required. Therapy could be maintained as long as the patient chooses during the reproductive years but should be stopped if pregnancy is planned.[18]

Hair removal

Depilation

Depilatories are products that remove hair from the skin's surface. Shaving and applying thioglycolic acid are examples of depilatory procedures. Shaving eliminates all hairs; however, it is followed by the return of anagen hairs, generating scratching as they grow in. Shaving does not appear to accelerate or coarsen future hair development. The majority of women, on the other hand, avoid shaving facial hair. Chemical depilation could be the ideal option for treating big regions in people who can't afford more expensive procedures like electrolysis or laser epilation. Chemical depilatories work by diminishing the sulfide bonds contained in hairs, which helps to detach the hair from its follicle. Irritant responses and folliculitis are possible side effects.[4]

Temporary epilation

Epilation is the removal of unbroken hair from the root. Tweezing or plucking is a standard procedure. Irritation, hair follicle damage, folliculitis, hyperpigmentation, and scarring are all possible side effects of this approach. Waxing is the cutaneous application of melted wax. It is peeled away from the skin as it cools and hardens, eliminating any attached hair. This procedure is inconvenient and can lead to folliculitis. Waxing on a regular basis may cause hair shrinkage and, in the long run, a permanent reduction in the quantity of hair. Natural sugars, which have long been utilized in regions of the Middle East, are gaining popularity as a substitute for waxes. They epilate like waxes but with less abrasion. Threading is a method of removing hair from the root using cotton threads, which is popular in several Arab nations. Home epilating devices that use a rotational or frictional approach to remove hair are available. Traumatic folliculitis can be caused by any method. In the past, radiation treatment was a common way of hair removal. It has, however, lost popularity and is no longer acceptable.[4]

Permanent epilation

Hair is destroyed via electrolysis, thermolysis, or a combination of the two methods, which use a tiny, flexible electrical wire that generates electricity when inserted into the hair. Thermolysis is a quick form of electrolysis that employs a high-frequency alternating current rather than a direct galvanic current. Thermolysis and electrolysis are slow procedures that may be used on any skin or hair color, but they require several sessions. These methods can cause pseudofolliculitis, folliculitis, and postinflammatory pigmentation in the skin, which can be painful. Lasers have the ability to treat greater areas more quickly than thermolysis or electrolysis. They contain skin-cooling systems that help to keep the epidermis from being destroyed throughout the operation. The color of one's skin and hair may frequently indicate whether or not a laser should be utilized. On fair-skinned persons, lasers are more effective on dark hairs. The laser, which only targets the melanin, does not compete with darker hairs in lighter skinned people. In dark-skinned people, a new procedure that gives hairs greater energy over longer periods of time may be safe and effective. Multiple sessions are required for long-term hair elimination. Laser treatment can cause folliculitis, pseudofolliculitis, pain, and pigmentary changes. It's still unclear if lasers are more successful than more traditional procedures for permanent hair removal. They are unquestionably more expensive.[18]

Pharmacologic treatment

Typically, pharmacologic therapies for hirsutism are chosen depending on the underlying etiology. Medications (antiandrogens) are frequently used together with cosmetic hair reduction procedures. Because androgens rebound to their previous levels when these medicines are stopped, they must be taken continually. These drugs are not recommended during pregnancy, because there is a danger of feminizing a male fetus. These substances can be used alone or in combination.[18]

Oral contraceptives

Oral contraceptives are frequently the first line of defense in ovarian hyperandrogenism and idiopathic hirsutism. Oral contraceptives also aid in enhancing antihirsutism benefits and preventing the negative effects of spironolactone and other antiandrogen-therapy-induced menstrual period irregularities. The combinations of estrogen and progestin in OCPs are generally thought to be safe and cost-effective. The capacity of progestin to decrease LH production and, as a result, ovarian androgen production, is its mode of action. Estrogen raises SHBG levels, which lowers free testosterone and other androgens bound to it. OCPs also work by interfering with the production of adrenal androgens. A combination of ethinyl estradiol (0.03 to 0.035 mg) plus a progestin (CPA or drospirenone) with low androgenic or antiandrogenic characteristics is commonly used to start OCPs.[19]

Antiandrogenic drugs

Many antiandrogenic medications are used off label, to treat hirsute women. Spironolactone, a competitive inhibitor of 5-alpha reductase and androgen receptors, has been shown to be useful in the treatment of hirsutism. When initiating antiandrogen treatment, reliable contraception should be utilized in women of reproductive age. Spironolactone is commonly used in doses of 100mg to 200mg per day to treat hirsutism. Potential side effects include polyuria,

postural hypotension, irregular cycle, hyperkalemia, and liver problems. Spironolactone has been shown to be tumorigenic in animal experiments; however, this has not been shown in people.[18]

Cyproterone inhibits androgen receptors and 5-alphareductase activity in a competitive manner. It can be taken with an oral contraceptive pill for only the first 10 days of the cycle (50 or 100 mg dosage) or in a low dose with a combination oral contraceptive pill (Diane-35). Tiredness, emotional changes, risk of venous thrombosis, and lower libido are among the side effects, which are comparable to the risks associated with oral contraceptives. Importantly, there is a possibility of feminizing a male fetus in women of reproductive age; thus, reliable contraception must be utilized.[10,20]

Flutamide, an experimental antiandrogen, has shown promise in the treatment of hirsute women. Flutamide is a competitive, nonsteroidal androgen receptor inhibitor. It has a high chance of causing hepatotoxicity.[4,18]

Finasteride 1mg is rarely used to treat hirsutism (off label). It suppresses dihydrotestosterone levels by inhibiting type II 5-alphareductase. Hepatotoxicity, gastrointestinal disturbances, reduced desire, and male fetus feminization are the risk factors (pregnancy category X). As with all antiandrogens, dependable contraception is recommended for all women of reproductive age. The treatment of hirsutism with dutasteride, a type I and II 5-alpha-reductase inhibitor, has still not been explored (pregnancy category X).[4]

Insulin-sensitizing agents

Metformin, like other insulin sensitizers, is less successful than antiandrogens at decreasing hirsutism. On the other hand, it is beneficial in inducing ovulation in polycystic ovarian syndrome patients. Metformin (Glucophage) lowers insulin levels, which lowers ovarian testosterone levels by inhibiting ovarian insulin receptors in a competitive manner. This medication is useful in treating hirsutism in PCOS patients. Gastrointestinal discomfort is a typical side effect, and lactic acidosis is a significant but uncommon complication.[18,21]

Other drugs

Cimetidine and ketoconazole are two more antiandrogen medications. Cimetidine is ineffective for the treatment of hirsutism, while ketoconazole is linked with a considerable risk of hepatotoxicity, as well as various medication interactions.[18]

In individuals with severe hyperandrogenism, GnRH is only used if antiandrogen and oral contraceptive medications have failed. They inhibit luteinizing hormone release and ovarian androgen production. Because GnRH analogs lead to menopausal-level estrogen decline, these medications are administered intramuscularly every month, generally with an estrogen-progestin supplement. Menopausal symptoms, such as vaginal atrophy, hot flushes, and osteoporosis, are among the side effects. Because these medicines totally block ovulation, many gynecologists do not recommend further contraception in women of reproductive years. GnRH analogs, on the other hand, are not authorized as a contraceptive and are classified as pregnancy category X.[18]

In women with typical 21-hydroxylase insufficiency, steroids are frequently required for a long time. They sustain ovulatory cycles while suppressing adrenal androgen production and controlling hirsutism. In females with NCCAH 21-hydroxylase deficiency, trials comparing glucocorticoids to antiandrogens and OCPs have indicated that glucocorticoids are more successful in reducing adrenal androgens but less efficient in treating hirsutism. According to the Endocrine Society, glucocorticoids should not be used to treat hirsutism in women who do not have a classic or nonclassic type of CAH caused by a 21-hydroxylase deficiency. Glucocorticoids are recommended for women with NCCAH who do not react to or cannot take OCPs or antiandrogens, or who want to induce ovulation.[18]

Topical, surgical treatment, and lifestyle

Eflornithine is a topical cream that serves as a development suppressor rather than a depilatory. Ornithine decarboxylase, a hair development enzyme, is inhibited by this drug. It's for ladies who wish to get rid of their undesirable facial hair. Application twice a day for at least 4-8 weeks is mandatory before the result is realized.[4,18] When ovarian or adrenal tumors are confirmed to be the cause of excessive body hair, the tumor may usually be removed. Many tumors, however, are cancerous and lethal.[18]

Although many hirsute females are obese, the link between fatty tissue and hair development is unknown. Clinically, for obese hirsute women with monthly abnormalities, losing weight may control menses and decrease hirsutism.[12,23]

In conclusion, treating hirsutism sometimes necessitates an interdisciplinary approach. Frequently, many specialties are involved in this process. The purpose of this multifaceted approach is to treat not only cosmetic problems via medical treatment and hair removal, but also the female's self-image anxieties and emotional stress caused by excessive body hair.

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Competing Interests

The authors declare that they have no competing interests.

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