Update on hirsutism

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SUMMARY

Hirsutism is an important medical problem affecting about 8% of women. Despite an extensive amount of published work, some aspects of hirsutism are still controversial or understudied. This paper reviews the current data that have been published in recent years on this subject.

Introduction

Hirsutism is the presence of terminal hair in females in a male-like pattern. Furthermore, hirsutism may be a sign of underlying androgen excess (hyperandrogenism) in the majority of sufferers (3). Hence, it is important to evaluate every patient that complains of unwanted facial or body hair and not to dismiss the problem as simply cosmetic.

Prevalence

The prevalence of hirsutism is dependent on the ethnic and racial origin of the population under study but it also depends, to a certain degree, on the method used to diagnose hirsutism. Knochenhauer et al., in a prospective study of 369 consecutive women of reproductive age seeking pre-employment physicals in the southeastern US using the modified Ferriman-Gallwey (mF-G) criteria, reported about an 8% incidence of hirsutism in the US (3). The hirsutism prevalence rates in northern Europe are similar to those in the United States; in other places, rates are not known with certainty (3).

Race and ethnic origin appears to significantly affect terminal hair growth in healthy women. Northern, fair-skinned Europeans have the least amount of terminal hair, whereas southern European, dark-skinned Mediterranean women have the greatest amount of terminal hair. Some studies of scalp hair follicles have indicated that White individuals had a higher density of hair follicles than Blacks, who in turn had more follicles than Asians (4, 5). In a study of facial and body terminal hair growth in an unselected population of Black and White women, DeUgarte et al. addressed the issue of racial differences in terminal hair (6). Their data indicate that the prevalence and degree of facial and body terminal hair growth is similar in Black and White women. The conflicting results of this study compared to the
studies mentioned above (4, 5) have raised the possibility that the number of hair follicles on the scalp, but not on the body or face, is affected by race. Because this study was conducted on White and Black populations only, additional studies in other ethnic or racial groups are needed.

Scoring system

Excess body and facial terminal hair growth is measured objectively using a scoring system such as modified Ferriman-Gallwey (mF-G) hirsutism score (7). This test is done by adding hair scores (0 = none, 4 = frankly virile) in 9 different body locations. However, this system is semi-quantitative in nature and the results are subject to inter-observer variability. Consensus on what score defines hirsutism is lacking. A total score > 8 is considered hirsute based on the 95th percentile of the data originally collected by Ferriman and Gallwey (8). Although the 95th percentile has often been used to define the upper limit of normal, this cutoff limit might not necessarily indicate the populational or natural cutoff value, and may not represent a physiological delineation. Although racial/ethnic differences in the number, distribution, or androgen sensitivity of hair follicles in normal individuals remains to be better defined, information regarding the prevalence of hirsutism in different racial groups is scant.

A change in the form and rate of hair growth is an important determinant in making the diagnosis of hirsutism. A digital imaging technique to record hair development using video equipment and computer software has also been suggested but is not yet widely accepted (10).

Pathogenesis

The growth of sexual hair is entirely under the influence of androgens. Vellus hair is present before puberty. Under the influence of increased levels of androgens at puberty, vellus follicles develop into terminal hair at androgen-sensitive areas (11). Hirsutism can result from an increased androgen level or oversensitivity of the hair follicle to androgen. However, the severity of hirsutism does not correlate well with the level of androgen because the response of hair follicles to androgen excess varies considerably within and among persons (12).

Many hormones have androgenic potential in the human body but testosterone is the key circulating androgen. It is produced by the ovaries and adrenals either as testosterone or prohormones. These prohormones (mainly androstenedione or dehydroepiandrosterone sulfate) are metabolized into testosterone in peripheral tissues, such as fat (13). Large quantities of circulating androgens are bound to specific plasma proteins, including sex hormone-binding globulin (SHBG), cortisol-binding globulin, and albumin. The free fraction of testosterone acts as the main bioactive component of plasma testosterone (14). The SHBG levels can decrease in the body in many conditions such as obesity, hyperinsulinemia, acromegaly, or hypothryroidism, or after administration of androgens, synthetic progestins, glucocorticoids, and growth hormones. Under such circumstances, the level of free testosterone may be elevated even when the total testosterone level is normal in hirsute women (15).

The testosterone is converted into dihydrotestosterone (DHT) in the peripheral tissue by the enzyme 5α-reductase. DHT is the most potent androgen in the body. The phenomenon of increased conversion rate of DHT in the target area may help to clarify the increased sensitivity of hair follicles to androgens (16). The DHT is ultimately converted to 3-alpha- and 3-beta-androstanediol and similar glucuronides in target cells. Some studies have shown significantly increased levels of 3-alpha-androstanediol glucuronide in hirsute women (17).

Extensive research has been performed during the past decades to investigate the molecular basis of polycystic ovarian syndrome (PCOS), hyperandrogenism, and hirsutism. Familial clustering of these disorders strongly suggests a genetic basis, which could be inherited together with insulin resistance and metabolic disorders (18–21). Despite the data suggesting genetic predisposition, the possibility cannot be ruled out that such clustering may be the result of some environmental factors that are present in the affected families. Some studies have suggested that obesity has a triggering role in the development of these disorders (22). Recent experimental evidence strongly supports the hypothesis that the intrauterine environment may influence the development of the hyperandrogenic phenotype in adult life. According to this developmental origin hypothesis, prenatal exposure of the female fetus to hyperandrogenism induced by genetic and environmental factors, or the interaction of both, may program fetal tissues towards the development of PCOS phenotype in adult life (23–25).

Many genes have been tested for their possible linkage in the etiology of hyperandrogenism and hirsutism (Table 1) (26). Among the candidate genes are those related to the regulation of androgen biosynthesis, metabolism, and action. The appreciation of a close relationship of hyperandrogenic disorders with insulin resistance and the metabolic syndrome has prompted many researchers to include genes involved in insulin resistance and associated disorders, and recently also genes involved in chronic inflammation and atherosclerosis (27).

Congenital adrenal hyperplasia (CAH) due to 21-

hydroxylase enzyme deficiency is a common autosomal-recessive disorder caused by mutations in the cytochrome P-45021 (CYP21) gene (28). The CYP21 gene encodes the 21-hydroxylase enzyme, catalyzing the conversion of 17-hydroxyprogesterone (17-HP) into 11-deoxy cortisol (11DC). Witchel et al. have shown that children with premature pubarche and adolescent girls with hyperandrogenism were heterozygous for mutations in CYP21 (29). Genetic mutation studies regarding other genes encoding for various steroidogenic enzymes involved in androgen biosynthesis have reported mixed results. Examples of such genes include cytochrome P-450c17 (CYP17), cytochrome P-45011α (CYP11A), cytochrome P-45011B1 (CYP11B1), cytochrome P-45019 (CYP19), 3β-hydroxysteroid dehydrogenase (HSD17B2), 17β-hydroxysteroid dehydrogenase (HSD17B3), follistatin (FST), and SHBG genes (33–35).

An enzymatic activity that is crucial to androgen action is 5α-reductase, which converts testosterone to the more potent androgen DHT. Ovarian and peripheral 5α-reductase activity appears to be increased in hyperandrogenic women (36). There are two isoforms of 5α-reductase, type 1 and type 2, which are encoded by distinct genes, steroid 5-alpha-reductase 1 (SRD5A1), and steroid 5-alpha-reductase 2 (SRD5A2). These genes and enzymes play an important role in clinical manifestations of hirsutism, acne, and alopecia in hyperandrogenic women. The type 1 isoenzyme is found primarily in the skin and liver, whereas the type 2 isoenzyme predominates in urogenital tissues (37–38). There is some evidence that genetic variation in the genes coding for 5α-reductase may be risk factors for PCOS as well as predictors of the severity of hirsutism within women with PCOS. Goodarzi et al. reported that haplotypes in both SRD5A1 and SRD5A2 are risk factors for PCOS; however, only variants in SRD5A1 are associated with the severity of hirsutism (39).

It has become increasingly evident in recent years that insulin resistance plays a significant role both as a cause and result of hyperandrogenic disorders, especially PCOS. The answer to the question of whether hyperinsulinism or hyperandrogenism is the initiating event is still unclear (40). Current research has focused on identifying a genetic predisposition for insulin resistance in this syndrome (41). Several genomic variants related to insulin resistance and the metabolic syndrome have been studied in these patients, including insulin receptor (INSR), insulin variable number tandem repeats (VNTR), insulin receptor substrate-1 (IRS-1), insulin receptor substrate-2 (IRS-2), calpain-10 (CAPN10), peroxisome-proliferator-activated receptor γ (PPARγ), and protein phosphatase 1 regulatory subunit (PPP1R3) (Table 1) (41–45).

Calpain-10 enzyme plays a role in the secretion and action of insulin. Some recent studies have suggested that the calpain-10 gene (CAPN10) is associated with increased susceptibility to PCOS. However, contradictory results were reported concerning the contribution of certain CAPN10 variants, especially of USCNP-44, to genetic predisposition to type 2 diabetes mellitus, hirsutism, and PCOS (46–47). Escober-Morreale et al. reported that C alleles at the USCNP-45 locus were associated with idiopathic hirsutism in a Spanish population (48). Similarly, studies from southern Spain conducted by González et al. reported an association between PCOS and USCNP-44 (49–50). However, a recent trial of 146 German women with PCOS and 606 population-based controls has revealed an association between USCNP-56 and susceptibility to PCOS (51). Further studies are needed to clarify this issue, especially because the physiological roles of calpain-10 remain mostly unknown (26).

In summary, the genetic studies conducted to date suggest a polygenic etiology for hyperandrogenic disorders but the results are inconsistent. Many studies were undertaken on a small sample size and lack statistical power. The limitation of the genetic techniques used to date is another factor. The recent advances in genomics are exponentially increasing our knowledge of human biology (52, 53). Genomic techniques, such as differential gene expression analyzed by DNA microarrays, are better than molecular genetic analysis because they allow the identification of genes that are differentially overexpressed or suppressed in patients compared with controls.

**Causes**

The causes of increased androgen production in women can be divided into two types: (1) endocrine glands, specifically the adrenals and ovaries; and (2) peripheral tissues (Table 1).

During the past two decades, the criteria for the diagnosis of hyperandrogenic syndromes have changed several times, and these have influenced the classification and relative prevalence of the various androgen excess disorders, especially PCOS and idiopathic hirsutism (IH), which are two major causes of hirsutism. Very strict criteria for the diagnosis of IH (54) and suggestions by some researchers that the hormonal phenotype of non-classic 3β-hydroxysteroid dehydrogenase (HSD3B) deficiency is a variant of PCOS (55) have resulted in a high prevalence of PCOS in the past. Aziz et al. reported an 82% prevalence of PCOS in a large study of 878 women with a clinical diagnosis of hyperandrogenism (56).

The new Rotterdam criteria for diagnosis of PCOS adopted in 2003 have further tilted the diagnostic scale in favor of PCOS (57). With these new criteria, PCOS can be diagnosed in patients with two of these three elements: clinical or biological hyperandrogenism, chronic anovulation, and polycystic ovaries.
In a large study, Carmina et al. (58) assessed the prevalence of different hyperandrogenic syndromes using the new Rotterdam criteria for diagnosis of PCOS. Their results showed that PCOS is by far the most common diagnosis in patients with clinical hyperandrogenism; 56.6% of all patients had PCOS according to previously used NIH criteria, and the Rotterdam criteria added an additional 15%, bringing the total number of patients with PCOS to 72.8%.

There is a consensus among the epidemiologic studies that the most common cause of hirsutism is PCOS, followed by IH (54, 56, 58–60). Other less common causes include congenital adrenal hyperplasia (CAH), non-classic congenital adrenal hyperplasia (NCAH), hyperandrogenism, insulin resistance, acanthosis nigricans (HAIRAN) syndrome, ovarian or adrenal androgen-secreting neoplasms (ASN), androgenic drug intake, Cushing syndrome, and hyperprolactinemia (56, 58).

Congenital adrenal hyperplasia is a group of autosomal recessive disorders resulting from impaired activity of 21-hydroxylase, 3β hydroxysteroid dehydrogenase, or 11β hydroxylase (61, 62). A deficiency of 21-hydroxylase accounts for about 95% of CAH cases. It is characterized by cortisol deficiency, with or without aldosterone deficiency, and androgen excess. The 21-hydroxylase deficiency manifests itself with elevated levels of 17-hydroxyprogesterone (17-HP). The 3β hydroxysteroid dehydrogenase deficiency results in elevated levels of pregnenolone, 17-hydroxypregnenolone, and dehydroepiandrosterone (DHEA). The 11β-hydroxylase deficiency is characterized by elevated levels of 11-deoxycortisol (compound S) and deoxycorticosterone (DOC), a mineralocorticoid. The clinical phenotypes of the disorder show a range of severity and include a severe form classified as classic CAH or a mild form classified as non-classic or late-onset CAH.

Classic CAH is subclassified as salt-losing or non-salt-losing (simple virilizing), reflecting the degree of aldosterone deficiency. The overall incidence of the classic form is one in 15,000 live births (63); however, the non-classic CAH is estimated to be more common than classic CAH, with a prevalence of one in 500 in the White population (64). A higher incidence of all forms of CAH is reported in Middle East, among Arabs and Jews (66).

Female infants with classic CAH are exposed to high concentrations of androgens in utero and are born with ambiguous genitalia including an enlarged clitoris, labial fusion, and a common urogenital sinus in place of a separate urethra and vagina. The internal female organs, the uterus, fallopian tubes, and ovaries, are normal. The salt-losing form typically presents at 7 to 14 days of life with vomiting, weight loss, lethargy, dehydration, hypotension, hyperglycemia, and possibly shock. Children with CAH are usually recognized early in life and a gene-specific prenatal diagnosis is now possible. Patients with NCAH, on the other hand, do not have cortisol deficiency and symptoms of androgen excess are generally manifested later in childhood or in early adulthood (67). These patients can present with early pubarche, or as young women with hirsutism (60%), oligomenorrhea or amenorrhea (54%) with polycystic ovaries, and acne (33%) (68). Recent studies suggest that PCOS may develop in association with conditions with clearly defined adrenal androgen overproduction, such as CAH (59). Polycystic ovaries have been shown frequently in patients with NCAH (65). Research on the pathophysiology of CAH has shown endocrinopathies beyond the characteristic abnormalities of the adrenal cortex, including adrenomedullary dysfunction and insulin resistance. Hyperandrogenism is an independent risk factor for hyperinsulinism in women and might have a role in the development of insulin resistance or polycystic ovaries in patients with CAH (69, 70).

It has been suggested that insulin plays an important role in the development of ovarian hyperandrogenism and related metabolic abnormalities (71, 72).
### Table 1. Causes of hirsutism and clinical features, laboratory findings, and molecular genetic basis.

<table>
<thead>
<tr>
<th>Causes</th>
<th>Clinical features</th>
<th>Lab findings</th>
<th>Additional diagnostic tests</th>
<th>Molecular genetic basis</th>
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<td><strong>OVARIAN</strong></td>
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<td>Polycystic ovary syndrome</td>
<td>Heterogenous presentation — Olgo-anovulation, signs of hyperandrogenism, and polycystic ovaries in various combinations. Metabolic, cardiovascular, and other clinical features may be present.</td>
<td>T = N to ↑&lt;br&gt;DHEAS = N to ↑&lt;br&gt;11α-PHSH = N to ↑&lt;br&gt;LH/FSH = N to ↑&lt;br&gt;17-HP = N</td>
<td>Primarily a clinical diagnosis. TCS = sometimes diagnostic&lt;br&gt;(Finding of 'pearl line' on USG). Consider lap testing and pelvic USG to rule out other disorders/hormones. Consider screening glucose and lipids.</td>
<td>Complex multisystem disorder. None of the genes evaluated seems to play a role in PCOS pathogenesis. Candidate genes are: AR, SHBG, CYP17, CYP11A, 11β-HSD, SRD5A1, FFT, INS, VNR, IRS-1, IRS-2, CAPN10, PPAR-γ2, and PPP1R3</td>
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<td>Ovarian neoplasm</td>
<td>Rapid onset of hirsutism, amenorrhea, clitoromegaly, and acne</td>
<td>T = ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N</td>
<td>USG or CT to image tumors. Selective venous catheterization — unilateral ovarian venous testosterone &gt; 20 ng/mL.</td>
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<td><strong>ADRENAL</strong></td>
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<td>Cushing syndrome</td>
<td>Classical GC tissue effects: moon face, abdominal obesity, red striae, hyperglycemia, and myopathy. Androgen excess features: hirsutism, acne, and menstrual irregularities</td>
<td>Serum cortisol = ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N to ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N</td>
<td>ACTH stimulation test: ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N to ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N</td>
<td>The molecular basis of Cushing disease is not known. A change in overall GR expression or mutations of some functional domains of the GR gene might play a role.</td>
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<td>Congenital adrenal hyperplasia</td>
<td>Clinical picture ranges from genital ambiguity at birth to prematurity pubarche, to hyperandrogenism in adolescents, and infertility in adult women</td>
<td>T = ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N to ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N</td>
<td>ACTH stimulation test: ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N to ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N</td>
<td>Over 40 mutations in the CYP21 gene located in the class III HLA region on the short arm of chromosome 6. The most common haplotypes are HLA-Bw47, HLA-B51 and HLA-B35. The phenotype correlates with specific CYP21 mutations.</td>
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<td>– 21-hydroxylase deficiency</td>
<td>Pregnenolone = ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N to ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N</td>
<td>DHEA = ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N to ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N</td>
<td>ACTH stimulation test: ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N to ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N</td>
<td>Mutations of CYP21B1 gene located at chromosome 8p24.3 typical CYP21 mutations associated with non-classic CAH include V284IL, P304L, P535S, and HLA-B14DR1</td>
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<td>– 11β-hydroxylase deficiency</td>
<td>Mildly elevated levels of adrenal steroids: 17-HP &gt; 2 and &lt; 10 ng/mL.</td>
<td>Cortisol = N to ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N</td>
<td>ACTH stimulation test: ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N to ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N</td>
<td>Mutations in the HSD3B2 gene, mapped to chromosome IP11-13</td>
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<td>Non-class congenital adrenal hypoplasia</td>
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<td>Adrenal neoplasm</td>
<td>Rapid onset of virilization</td>
<td>T = ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N to ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N</td>
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<td>Mutations of CYP17A1 gene located at chromosome 5p15.3, CYP21A2 gene located at chromosome 6p21.3, and CYP11B1 gene located at chromosome 8q22.1. The phenotype correlates with specific CYP11B1 mutations.</td>
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<td><strong>PERIPHERAL</strong></td>
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<td>Idiopathic</td>
<td>Normal ovulatory menstrual cycle</td>
<td>All routine laboratory results normal&lt;br&gt;Free T = may be mildly ↑&lt;br&gt;5α-androstanedione glucuronide may be ↑&lt;br&gt;Serum insulin = N to ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N</td>
<td>Normal ovaries on USG&lt;br&gt;Exclude other causes&lt;br&gt;Androgen receptor (AR) polymorphisms (decreased CAG repeats)</td>
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<td>Insulin resistance – HAIRAN syndrome</td>
<td>Acanthosis nigricans on skin examination, hyperinsulinemia, hyperglycemia, hyperlipoproteinemia, hypertrichosis, and hirsutism</td>
<td>Serum glucose = ↑&lt;br&gt;Serum insulin = N to ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N</td>
<td>INSulin = ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N</td>
<td>Above-mentioned mutation of insulin receptor gene in some cases&lt;br&gt;Homologous mutation in exon I of the CYP19</td>
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<td>Aromatase deficiency</td>
<td>Genital ambiguity, progressive virilization without breast development at the age of puberty. Maternal virilization during pregnancy can occur</td>
<td>T = ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N to ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N</td>
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<td>Mutations in the GR gene</td>
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<td>Glucocorticoid resistance</td>
<td>Absence of features of Cushing syndrome. Androgen excess causes hirsutism, menstrual irregularities, and male type baldness</td>
<td>T = ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N to ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N</td>
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<td>Hypoglycemia MBI for adenoma – diagnostic</td>
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<td>Hyperprolactinemia</td>
<td>Galactorrhea, amenorrhea, infertility</td>
<td>Cortisol = ↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;↑&lt;br&gt;N</td>
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**Note:** SHBG = sex hormone-binding globulin; T = testosterone; DHEAS = dehydroepiandrosterone sulfate; LH/FSH = luteinizing hormone/FSH; 17-HP = 17-hydroxyprogesterone; DOC = deoxycortisol; T = cortisol; TSH = thyroid-stimulating hormone; ACTH = adrenocorticotropic hormone; BMD = bone mineral density; P304L = proline 304 leucine; P535S = proline 535 serine; V284IL = valine 284 isoleucine.
Many studies have shown a higher prevalence of impaired glucose intolerance and diabetes mellitus in hirsute women with PCOS and IH compared to matching healthy women (73, 74). Insulin resistance is generally associated with obese, hirsute, and hyperandrogenic women. Darkening of skinfold sites, acanthosis nigricans, is a manifestation of this condition. Impaired glucose tolerance is characterized by extremely high circulating levels of insulin (greater than 80 µU/mL basal and/or greater than 500 µU/mL after an oral glucose challenge). Hyperinsulinism causes ovarian hyperandrogenism by acting on theca-cell receptors via insulin-like growth factor-1 and decreasing serum SHBG levels, causing a subsequent increase in free testosterone levels in plasma (77). Because of the effect of insulin on ovarian theca cells, the ovaries of many patients with the HAIRAN syndrome are enlarged and hypercistic. Patients with this disorder can be severely hyperandrogenic, and even present with virilization. In addition, these patients are at significant risk for dyslipidemia, type 2 diabetes mellitus, and hypertension. Metabolic syndrome X is characterized by hyperinsulinism, hyperglycemia, hyperlipoproteinemia, hypertension, hirsutism, and polycystic ovary syndrome. Therefore, it may be called the 5H syndrome. Insulin resistance disorders may be divided into prereceptor, receptor, and postreceptor types. The 5H syndrome is caused by a postreceptor type of insulin resistance disorder for which so far the molecular basis and dominant organ site have not yet been defined adequately (78).

Glucocorticoid (GC) overproduction is the hallmark of Cushing syndrome. This results in the classical GC tissue effects such as a moon face, abdominal obesity, striae, hyperglycemia, and myopathy. Hirsutism is rarely the primary complaint in a patient with Cushing syndrome. Its prevalence is quoted from 0 to 1% in various studies (79). No Cushing syndrome patients were reported in two recent large studies (56, 58).

Familial glucocorticoid resistance is a rare syndrome that is characterized by defective GC receptors (GR) in the body resulting in diminished cortisol action. The feedback mechanism increases secretion of adrenocorticotropin hormone (ACTH) by the pituitary gland that results in elevated circulating levels of GCs, mineralocorticoids, and androgens (80, 81). Androgen excess in females results in hirsutism, menstrual irregularities, and male-pattern baldness. In contrast to Cushing syndrome, GC resistant patients do not suffer from the classical GC tissue effects. The majority of the patients with GC resistance have increased plasma ACTH and serum cortisol concentrations but, in contrast to Cushing syndrome, the diurnal rhythm is maintained. Another difference compared to Cushing disease is normal bone mineral density (BMD) in patients with GC resistance. In the past decades several mutations in the gene coding for the GR have been identified in patients with GC resistance, yet in many kindreds the cause is still unknown (80).

Aromatase deficiency is a rare disorder. Only seven males and seven females with this disorder have been reported in the literature. Aromatase enzyme catalyzes conversion of androgens into estrogens. Aromatase deficiency results in defective estrogen biosynthesis. Hyperandrogenism occurs due to peripheral conversion of DHEA into testosterone. A woman pregnant with an affected fetus suffers from hirsutism and acne, which resolves after delivery. Affected female fetuses are born with features of pseudohermaphroditism. Cystic ovaries and delayed bone maturation can occur during childhood. The affected girls present at puberty with primary amenorrhea, failure of breast development, virilization, and hypergonadotrophic hypogonadism. Aromatase enzyme is encoded by CYP19. A homozygous mutation in exon IX of the CYP19 has been detected in cases of aromatase deficiency (82).

It is estimated that about 5 to 15% of hirsute patients suffer from idiopathic hirsutism (56); however, the true prevalence of IH is difficult to estimate because the definition of IH has varied during the last three decades. Currently, IH is defined as hirsutism associated with normal ovulatory function, normal circulating serum androgen concentrations, and no evidence of polycystic ovaries on pelvic ultrasonography. Idiopathic hirsutism is presumed to be the result of increased sensitivity of the pilosebaceous unit to normal circulating androgen levels, presumably caused by increased peripheral 5α-reductase enzyme activity (60, 83). Some studies have incriminated androgen receptor (AR) gene polymorphisms.

Although hirsute patients are commonly tested for thyroid disorders and hyperprolactinemia, these conditions are rare causes of hirsutism. Carmina et al. reported that none of their 950 hirsute women had hyperprolactinemia, and only four patients with a diagnosis of classic PCOS had mildly elevated levels of thyroid-stimulating hormone (TSH) (58). Similarly, hyperprolactinemia was present in only 0.3% of cases in a large series reported by Azziz et al. (56).

**Evaluation**

There is a general consensus among various authorities that a thorough history and physical examination are essential to evaluate women with hirsutism to determine which patients need additional diagnostic testing. Physical examination should distinguish normal amounts of hair growth from hirsutism and hypertrichosis. Amounts, characteristics, and distribution of hair growth should be noted. Patients must be examined for signs of virilization. A thorough abdominal and pelvic examination should be performed to exclude any masses. Acanthosis nigricans, a marker for insulin resistance, is a serious feature of metabolic syndrome X. Impaired glucose tolerance is characterized by extremely high blood glucose levels, causing a subsequent increase in serum insulin levels. Acanthosis nigricans, a manifestation of this condition, is associated with obesity, hyperandrogenism, and insulin resistance. Insulin resistance is generally associated with obese, hirsute, and hyperandrogenic women. Darkening of skinfold sites, acanthosis nigricans, is a manifestation of this condition. Impaired glucose tolerance is characterized by extremely high circulating levels of insulin (greater than 80 µU/mL basal and/or greater than 500 µU/mL after an oral glucose challenge). Hyperinsulinism causes ovarian hyperandrogenism by acting on theca-cell receptors via insulin-like growth factor-1 and decreasing serum SHBG levels, causing a subsequent increase in free testosterone levels in plasma (77). Because of the effect of insulin on ovarian theca cells, the ovaries of many patients with the HAIRAN syndrome are enlarged and hypercistic. Patients with this disorder can be severely hyperandrogenic, and even present with virilization. In addition, these patients are at significant risk for dyslipidemia, type 2 diabetes mellitus, and hypertension. Metabolic syndrome X is characterized by hyperinsulinism, hyperglycemia, hyperlipoproteinemia, hypertension, hirsutism, and polycystic ovary syndrome. Therefore, it may be called the 5H syndrome. Insulin resistance disorders may be divided into prereceptor, receptor, and postreceptor types. The 5H syndrome is caused by a postreceptor type of insulin resistance disorder for which so far the molecular basis and dominant organ site have not yet been defined adequately (78).

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The purpose of laboratory testing is not only to detect the specific androgens involved, but also the source and concentration of the androgens.

Essentially all DHEAS is produced by the adrenal glands and that makes it a good marker of adrenal androgen production. Approximately two-thirds of circulating testosterone originates from the ovary and its levels are used to predict ovarian androgen production. DHT itself is not a good peripheral marker because it is metabolized rapidly and has a very high affinity for SHBG, but its metabolite, 3α-androstanediol glucuronide, serves as a better marker of peripheral androgen action (87).

Decisions regarding the selection of various hormones measured in a specific patient must be individualized. Clinical assessment may demand ordering testing of some additional hormones, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), LH/FSH ratio, 17-HP, serum cortisol or 24-hour urinary free cortisol levels, SHBG, TSH, and prolactin.

The normal ranges of the serum levels of various androgenic hormones are shown in Table 2. It is important to realize, however, that the normal ranges shown in this table may vary considerably if different assay methods are used (88).

Many laboratories are now offering a sensitive radioimmunoassay (RIA) to measure salivary androgens (88). Hormones that can be measured in saliva include testosterone, DHEAS, and cortisol. A good correlation of salivary testosterone is reported with serum testosterone and the degree of hirsutism (89). Practitioners are increasingly using salivary testosterone measurement because of its simplicity, convenience, and cost-effectiveness.

A review of the literature has indicated the following recommendations for evaluation of hirsute women:

1. Patients with slow progressive mild hirsutism, regular menstrual cycles, and no virilization need limited further investigation; laboratory evaluation can be limited to testosterone and DHEAS levels.

2. Patients with slow progressive moderate hirsutism, with or without menstrual cycle disturbances, are mostly cases of PCOS. Further investigation is only required if serum testosterone is elevated or the patient is undergoing infertility treatment.

3. Patients with rapidly progressive hirsutism and virilization, or very severe hirsutism irrespective of symptom duration, require a comprehensive evaluation for an androgen-secreting tumor.

**Table 2: Normal serum levels of various androgenic hormones.**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone*</td>
<td>20–70 ng/dL</td>
</tr>
<tr>
<td>Free testosterone***</td>
<td>1–8 pg/mL</td>
</tr>
<tr>
<td>Androstenedione*</td>
<td>20–250 ng/dL</td>
</tr>
<tr>
<td>DHEA*</td>
<td>30–980 ng/dL</td>
</tr>
<tr>
<td>DHEAS**</td>
<td>50–280 µg/dL</td>
</tr>
<tr>
<td>DHT*</td>
<td>5–30 ng/dL</td>
</tr>
<tr>
<td>Androstanediol glucuronide**</td>
<td>60–400 ng/dL</td>
</tr>
</tbody>
</table>

*Extraction/chromatographic RIA, **Direct RIA, ***Equilibrium dialysis method

Source: 147

**Treatment**

A direct intervention, if possible, is instituted for the underlying disorder. It is easier to prevent hair growth than to treat established hirsutism. Adolescent girls that are beginning to develop hirsutism and have a family history of excessive hair growth should receive early attention to the problem.

Cosmetic measures include mechanical hair removal with the help of shaving, plucking, waxing, depilatory creams, electrical epilation, and laser hair removal. Systemic therapies directed at hirsutism can be divided into those that decrease ovarian or adrenal androgen production and those that inhibit androgen action in the skin. The systemic therapies include: oral contraceptives (OC), Gn-RH analogs, glucocorticoids, antiandrogens (spironolactone, flutamide, finasteride, cyproterone acetate), and insulin sensitizers (metformin, troglitazone, and rosiglitazone).

The response to pharmacologic agents is slow, occurring over many months. The most effective strategy is to combine systemic therapy with mechanical depilation for immediate patient satisfaction.

The response of hirsutism to pharmacological therapy has been the subject of many studies, both with the use of individual agents or as combination regimens. It has been suggested that combination therapy including OC, antiandrogens, or metformin is superior to monotherapy. Unfortunately, reports evaluating the results of these regimens have generally included fewer numbers of patients, limiting the assessment of the efficacy of therapeutic regimens (101–103).

**Oral contraceptives (OC):** These are probably the first choice for young women with hirsutism who do not want to become pregnant. OC are inexpensive and they promote regular uterine bleeding. They inhibit ovarian androgen production by suppressing circulating LH and FSH. They may also decrease adrenal androgen production by a mechanism not yet clear. The progestin in the OC can lead to an antagonism of 5α-reductase and the androgen receptors. In addition, the estrogen content in the OC increases SHBG, decreasing free testosterone levels; alternatively, the progestin in the OC may actually decrease SHBG (91). OCs containing fewer androgenic
Proper hair loss is achieved. The recommended dosage for treatment with cyproterone acetate before the desired mg, ethinylestradiol 35 µg. Ethinylestradiol in a single pill (cyproterone acetate 2 mg) is often combined with a synthetic estrogen androgen-synthesizing enzymes (93). Cyproterone acetate is a progestogen with androgenic properties. It decreases testosterone and androstenedione levels through a decrease in circulating LH levels. It also antagonizes the effect of androgens at the peripheral level. It blocks androgen receptors in the hair follicles. Dosages range between 50 to 300 mg per day (93). It is usually used in combination with OC, but some studies have indicated that it results in better cure of hirsutism if combined with finasteride (103, 114).

**GnRH analogs:** Long-acting GnRH agonists (3.75 mg per month) have been found to be useful in treatment of hirsutism and may be required to suppress the hypothalamic-pituitary-ovarian axis in severe hyperandrogenism. The GnRH analogue increases FSH and SHBG levels and decreases LH, testosterone, and DHEAS levels and results in an improvement in hirsutism scores (109). Two to three months of treatment may be required for the full suppressive effect of the agonist to occur. This therapy is usually combined with estrogen-progestin replacement or an OC, and an androgen blocker (108).

**Glucocorticoids:** Steroids suppress ACTH-dependent adrenal androgen synthesis. Most hirsute women, including those with polycystic ovarian syndrome, have some degree of adrenal hyperandrogenism compared to nonhirsute women. Glucocorticoid is the drug of choice in the treatment of CAH, both classic and nonclassic forms, and its use has been shown to reverse symptoms within 3 months (67, 111).

**Antiandrogens:** These agents may be combined with OC for the treatment of hirsutism. Up to 75% of women report clinical improvement with combination therapy (105). Patients that use antiandrogens alone may experience irregular uterine bleeding and ovulation (113). The commonly used antiandrogens are spironolactone cyproterone acetate, flutamide, and finasteride. Response to antiandrogens is slow and may take up to 18 months. The optimal duration of therapy is unclear, but treatment cessation generally is followed by recurrent hair growth.

**Spironolactone:** This has been used extensively in the treatment of hirsutism because of its safety, availability, and low cost. The spironolactone is a potassium-sparing diuretic, with some antiandrogen action due to its both systemic and peripheral action, competing with androgen receptors in the hair follicles. Dosages range between 50 to 300 mg per day (93). It is usually used in combination with OC, but some studies have indicated that it results in better cure of hirsutism if combined with finasteride (103, 114).

**Cyproterone acetate:** This is a progestogen with antiandrogenic properties. It decreases testosterone and androstenedione levels through a decrease in circulating LH levels. It also antagonizes the effect of androgens at the peripheral level. It blocks androgen receptors and reduces androgen synthesis by inhibiting androgen-synthesizing enzymes (93). Cyproterone acetate is often combined with a synthetic estrogen ethinylestradiol in a single pill (cyproterone acetate 2 mg, ethinylestradiol 35 µg). It can take up to a year of treatment with cyproterone acetate before the desired hair loss is achieved. The recommended dosage for treating hirsutism is usually within the range of 50 to 100 mg daily (91); however, studies regarding its optimal dose are equivocal.

**Flutamide:** This is an androgen receptor blocker used as adjuvant treatment for prostate cancer but also found to be an effective treatment for hirsutism. The clinical dose of flutamide in hirsutism is 250 to 500 mg/day (91). Hirsutism can be treated initially with 250 mg/day daily followed by a long term maintenance dose of 125 mg/day (121). Side effects include the appearance of greenish urine, excessive dryness of skin or scalp hair, liver enzyme abnormalities, and rarely, fatal hepatotoxicity. Flutamide has been shown to be as effective as other antiandrogens; however, hepatic function must be monitored (122, 123).

**Finasteride:** This is a competitive inhibitor of 5α-reductase. It has been shown to be effective in treating hirsutism with relatively few side effects (119, 124). The recommended daily dose is 5 mg. A review of the literature has indicated multiple observational and randomized trials evaluating the relative safety and efficacy of finasteride for treatment of hirsutism. Finasteride lowered hirsutism scores by 30 to 60% in most trials. In comparative trials, finasteride demonstrated efficacy similar to that of other antiandrogens, with fewer adverse effects. Concern over potential teratogenicity and lack of long-term safety information leave finasteride a secondary treatment option for hirsutism (125).

**Insulin-sensitizing drugs (ISD):** These are antidiabetic drugs, not indicated for the treatment of hirsutism alone. ISD are prescribed for symptomatic management of PCOS, particularly in women with additional metabolic and cardiovascular risk factors. Treatment of insulin resistance using metformin, troglitazone, or rosiglitazone can improve many of the hormonal disturbances and restore menses in a considerable proportion of patients with PCOS (128–130). However, its effectiveness in the treatment of PCOS-associated hirsutism is less clear. It has been argued that blood insulin lowering effect of ISD may result in a decrease of free androgen concentration, thereby improving hirsutism as a result (93).

**Topical eflornithine:** Eflornithine hydrochloride cream is the only topical agent to gain US regulatory approval (in July 2001), as the first and only prescription cream clinically proven to slow the growth of unwanted facial hair in women. Data from a randomized, double-blind, placebo-controlled trial show that there is a maximal effect by 8 to 24 weeks, with marked improvement among 32% of patients (as compared with 8% of patients treated with placebo) (137). Another RCT conducted to assess the efficacy and safety of eflornithine as a vehicle with laser therapy in the treatment of unwanted facial hair in women has concluded that eflornithine can be safely used in conjunction with laser hair removal treatments and promotes more rapid hair removal when combined with laser treatment (138).
Mechanical hair removal: For patients with mild hirsutism, local measures such as shaving, bleaching, depilatories, and electrolysis may suffice. The major role of local measures is in combination with pharmacologic treatment. Pharmacotherapy is slow to act and the patient can be managed cosmetically in the interim period. Data from a large series of hirsute patients indicated that patients that used electrolysis in addition to hormonal suppression had a greater decrease in the hair growth than those that did not, suggesting that this hair destruction technique should be encouraged as an adjuvant in the management of the hirsute woman (56).

Laser hair removal: During the past decade we have seen the development of lasers for the removal of unwanted hair. The major objective of laser therapy for hair removal is based on a process termed photothermolysis, which means to selectively cause thermal damage to hair follicles without destroying adjacent tissues. Alternatively, various tissue and skin characteristics also affect the efficacy of lasers, including skin type, hair color, and hair growth phase. The best results are obtained in patients with lighter skin types (Fitzpatrick types I–IV) (140) and dark brown or black hair (141). Some studies have reported successful laser hair removal in patients with Fitzpatrick skin types V and VI as well (142, 143), but the incidence of complications such as burns, scarring, and pigmentary changes increases with the degree of skin pigmentation (144). In addition to the skin type, the melanin content of the hair itself appears to be an important determinant in the efficacy of laser hair removal. Patients with darker hair appear to respond better to laser treatment.

Key points

Hirsutism is usually a benign but extremely distressing symptom for women and affects their quality of life. Polycystic ovarian disease is the commonest cause of hirsutism. Drugs are only partially effective on terminal hair, so management of hirsutism is generally based upon a dual approach: a pharmacological therapy to reduce androgen secretion and/or androgen action, and removal of terminal hair already present. Ovarian suppression of androgen secretion with oral contraceptives is widely used in these women, but its efficacy appears limited. The most effective medical therapy for hirsutism is anti-androgen drugs. Electrolysis and laser photothermolysis are considered the most effective cosmetic procedures, although the effects of these methods should not be considered permanent.

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