Pathogenesis and causes of hirsutism

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INTRODUCTION — Hirsutism, defined as excessive male-pattern hair growth, affects between 5 and 10 per cent of women of reproductive age [1,2]. Hirsutism may be the initial, and possibly only, sign of an underlying androgen disorder, the cutaneous manifestations of which may also include acne and male-pattern balding (androgenic alopecia). Virilization refers to the state in which androgen levels are sufficiently high to cause not only hirsutism, but additional signs and symptoms such as deepening of the voice, breast atrophy, increased muscle bulk, clitoromegaly, and increased libido. This card will cover the pathophysiology and causes of androgen-mediated hair growth. Evaluation and treatment of hirsutism are discussed elsewhere. (See "Evaluation of women with hirsutism" and see "Treatment of hirsutism").

HAIR GROWTH CYCLE — The hair growth cycle is comprised of three phases: anagen (growth phase), catagen (involution phase), and telogen (rest phase) [3]. Depending upon the body site, hormonal regulation plays an important role in the hair growth cycle [4]. Androgens increase hair follicle size, hair fiber diameter, and the proportion of time terminal hairs spend in the anagen phase [5]. Androgen excess in women leads to increased hair growth in most androgen sensitive sites, but will manifest with loss of hair in the scalp region, in 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) [4]. The number of hair follicles does not change over an individual's lifetime, but the 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 (show figure 1) [4]. 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.

Male-pattern hair growth occurs in sites where relatively high levels of androgen are necessary for pilosebaceous unit differentiation. Although androgen excess underlies most cases of hirsutism, there is only a modest correlation between the quantity of hair growth and androgen levels [6]. This is thought to result from the fact that stimulation of hair growth from the follicle does not depend solely on circulating androgen concentrations, but also depends upon local factors and variability in end-organ sensitivity to circulating androgens [4]. The term "idiopathic hirsutism" has been used to describe the circumstance in which hirsutism is present with circulating androgen levels within the normal range [6]. (See "Idiopathic hirsutism" below).

DEFINITION — Hirsutism is the development of androgen-dependent terminal body hair in a woman in places in which terminal hair is normally not found [1,7]. As noted above, terminal body

hairs are the stiff, pigmented hairs normally seen in men on the face, chest, abdomen, and back, and which are not normal in women. The individual woman's definition of hirsutism may differ depending upon her ethnic background and upon her interpretation of normal, which is often influenced by popular images of hairless female beauty. A commonly used method to grade hair growth is a modified scale of Ferriman and Gallwey [1]. Approximately 95% of women have a Ferriman Gallwey score of less than 8. (See "Evaluation of women with hirsutism").

Nearly all hirsute women have an increased production rate of androgens, usually testosterone, but the increase may not be sufficient to raise the serum total testosterone concentration above the normal range because the carrier protein for testosterone, sex hormone binding globulin, is suppressed when androgen production is increased [8-11]. In the remaining women, the hirsutism may be due to increased conversion of testosterone to dihydrotestosterone in peripheral tissue, including hair follicles [12].

There are two conditions characterized by generalized hair growth that do not represent true hirsutism:

- Androgen-independent hair, which is the soft vellus unpigmented hair that covers the entire body. In infants, this hair is called lanugo.

- Hypertrichosis, which refers to diffusely increased total body hair. This is a rare condition that is usually caused by a drug; examples include phenytoin, penicillamine, diazoxide, minoxidil, and cyclosporine. Hypertrichosis also can occur in patients with some systemic illnesses, such as hypothyroidism, anorexia nervosa, malnutrition, porphyria, and dermatomyositis, and as a paraneoplastic syndrome in some patients with cancer. (See "Cutaneous manifestations of internal malignancy", section on Hypertrichosis lanuginosa).

EPIDEMIOLOGY — Hirsutism may affect between 5 and 10 per cent of women of reproductive age [1,2]. In a classic study of 430 British women aged 15 to 64 years attending a general medical clinic, no woman had terminal hair on the upper back or upper abdomen, 10 percent had hair on the chest, 22 percent had hair on the chin, and 49 percent had hair on the lip [1]. In most of the women who had hair in any region, however, there were rarely more than a few scattered hairs; thus, graded on a scale of 0 to 4 at 9 sites, (modified Ferriman-Galwey scoring system), only 1.2 percent of women aged 18 to 38 years had scores above 10.

Ethnicity — The definition of normal must also consider race and ethnicity. Most Asian and Native American women have little body hair, while Mediterranean women on average have moderately heavy body hair; serum androgen concentrations are similar in the three groups [13]. These differences must be kept in mind in determining whether a women has a pathologic degree of hirsutism and whether she should be evaluated further. Thus, an Asian woman with a few peri-areolar hairs may warrant further evaluation, whereas a southern European woman with some hair growth on her upper lip might well be considered normal, and consider herself normal. However, further evaluation may still be indicated in such women. The most important consideration, whatever the woman's background, is whether the pattern of hair growth has changed or the rate of growth has increased.

ETIOLOGY — Hirsutism is caused by either increased androgen production by the ovaries or adrenal glands, or rarely increased target organ production of androgen. Some hirsute women also have menstrual dysfunction, ranging from anovulatory cycles to amenorrhea, and a few have virilization. Several different androgens may be secreted in excess. (See "Steroid hormone metabolism in polycystic ovary syndrome"):

- Testosterone excess is usually of ovarian origin
- Dehydroepiandrosterone sulfate (DHEA-S) excess is of adrenal origin
- Androstenedione excess can be of either adrenal or ovarian origin

Although DHEA and DHEA-S are general markers of adrenal androgen production, they have little if any intrinsic androgenic activity. Small amounts are converted to androstenedione and then to testosterone (and to estrogen) in both the adrenal glands and peripheral tissues, including hair

follicles and external genitalia. Thus, the hirsutism and virilization that may be seen with adrenal hyperandrogenism are caused by androstenedione and testosterone. (See "Adrenal hyperandrogenism").

Polycystic ovary syndrome — The polycystic ovary syndrome (PCOS) is the most common cause of androgen excess in women (show table 1). The syndrome is characterized by menstrual irregularity, evidence of hyperandrogenism whether clinical (hirsutism, acne, or male pattern balding) or biochemical (elevated serum androgen concentrations). The diagnostic criteria, clinical manifestations, and treatment of PCOS are discussed in detail elsewhere. (See "Clinical manifestations of polycystic ovary syndrome in adults", see "Diagnosis and treatment of polycystic ovary syndrome in adults" and see "Metformin for treatment of the polycystic ovary syndrome").

One study prospectively evaluated 350 British women: 319 with hirsutism and 31 with frontal balding [14]. Among the 282 women who had ovarian ultrasonography, 170 (60 percent) had polycystic ovaries; one-half of these women also had menstrual irregularity, and therefore met the original criteria for the polycystic ovary syndrome (see below); the remainder would have originally been considered to have idiopathic hirsutism, but could perhaps now be considered to have PCOS if using the newer Rotterdam PCOS diagnostic criteria (See "Diagnosis and treatment of polycystic ovary syndrome in adults"). Only 2.3 percent (8 patients) had an identifiable endocrine disorder other than the polycystic ovary syndrome (congenital adrenal hyperplasia, ovarian tumor, virilizing adrenal carcinoma, prolactinoma, acromegaly).

The women with polycystic ovaries in this report had a mean serum testosterone concentration of 71 ng/dL (2.5 nmol/L), as compared with 59 ng/dL (2.0 nmol/L) in those with normal ovaries. No upper limit of normal was cited, but this value varies from 60 to 80 ng/dL (2.1 to 2.8 nmol/L) in most laboratories. Only 13 (3.7 percent) women with PCOS had serum testosterone concentrations above 145 ng/dL (5.0 nmol/L).

In two other series of 873 and 950 women presenting with androgen excess symptoms [15,16], PCOS was diagnosed (using the original criteria of oligomenorrhea and hyperandrogenism) in 82 and 57 percent, respectively. (See "Diagnosis and treatment of polycystic ovary syndrome in adults")

The androgen excess in women with the polycystic ovary syndrome usually becomes evident about the time of puberty or soon thereafter, because androgen production is increased by both puberty (increased ovarian steroid production) and adrenarche (increased adrenal androgen production). In general, the symptoms gradually worsen with age. Other diagnoses such as ovarian or adrenal tumors should be considered in older women, particularly those who develop hirsutism rapidly or have a sudden onset of menstrual irregularity.

Idiopathic hirsutism — The diagnosis of idiopathic hirsutism is given to women with hirsutism with normal serum androgen concentrations, no menstrual irregularity, and no identifiable cause of their hirsutism [6,17,18].

There may be a steroidogenic abnormality despite the apparently normal serum androgen levels [19]. The distinction between idiopathic disease and the polycystic ovary syndrome may be one of degree.

Congenital adrenal hyperplasia — Excess androgen production is a key feature of most forms of congenital adrenal hyperplasia. These disorders are usually recognized at birth or in early infancy, but late-onset (also called non-classical) forms of several of them have been identified. Affected women present peripubertally with hirsutism and sometimes menstrual irregularity or primary amenorrhea; they have no manifestations of cortisol deficiency. The prevalence of late-onset congenital adrenal hyperplasia among hirsute women has varied from 1 to 15 percent in different studies [20-23]. It is nearly always due to 21-hydroxylase (P450c21) deficiency, which leads to increased production of both 17-hydroxyprogesterone (the substrate for 21-hydroxylase and an androgen precursor) and androstenedione; (in non classical adrenal hyperplasia cortisol production is not decreased due to an increase in ACTH secretion) (show figure 2). (See "Overview of congenital adrenal hyperplasia due to CYP21A2 (21-hydroxylase) deficiency" and see "Adrenal steroid biosynthesis and congenital adrenal hyperplasia").

Ovarian tumors — Hirsutism caused by an androgen-secreting tumor is most likely to occur later in life and progress more rapidly than when the cause is the polycystic ovary syndrome. Androgen-secreting tumors constitute only 5 percent of all ovarian tumors; histologically they are Sertoli-Leydig cell tumors (androblastoma, arrhenoblastoma), granulosa-theca cell (stromal cell) tumors, and hilus-cell tumors. Most of the women have serum testosterone concentrations greater than 150 to 200 ng/dL (5.2 to 6.9 nmol/L) [24-27]. (The upper limit of normal for serum testosterone in women varies from 60 to 80 ng/dL [2.1 to 2.8 nmol/L] in most laboratories.) Many of these tumors can be identified by transvaginal ultrasonography. (See "Sex cord-stromal tumors of the ovary", section on Sertoli-Leydig cell tumor).

Adrenal tumors — Adrenal tumors are a rare cause of androgen excess. A few are adrenal adenomas that secrete mostly testosterone, but most are carcinomas that often secrete not only androgen - mostly DHEA and DHEA-S - but also cortisol; therefore, the woman has clinical manifestations of androgen excess and Cushing's syndrome. Some of the carcinomas may lose the ability to sulfate DHEA, so that a normal serum DHEA-S value does not exclude the diagnosis [28]. Nevertheless, an unequivocally elevated serum DHEA-S value is suggestive of an adrenal carcinoma. (See "Clinical presentation and evaluation of adrenocortical tumors").

Drugs — Androgen therapy (testosterone or DHEA) may be associated with hirsutism. (See "Androgen production and therapy in women"). Danazol and the androgenic progestins present in some oral contraceptives such as levonorgestrel can cause hirsutism.

Hyperthecosis — Hyperthecosis is a nonmalignant ovarian disorder characterized by increased production of testosterone by luteinized thecal cells in the stroma, leading to increased serum testosterone concentrations. It is still unclear if hyperthecosis is a distinct disorder or is part of the spectrum of the polycystic ovary syndrome. The woman's history usually is one of gradual onset of hirsutism and other manifestations of androgen excess. (See "Ovarian hyperthecosis").

Severe insulin resistance syndromes — Women who have one of the syndromes of severe insulin resistance and marked hyperinsulinemia often have hirsutism. The marked hyperinsulinemia causes ovarian hyperandrogenism, possibly acting via the theca-cell receptors for insulin-like growth factor-1 (show figure 3). Insulin also decreases serum sex hormone-binding globulin concentrations, thereby increasing the fraction of serum testosterone that is free at any serum total testosterone concentration.

The syndromes of severe insulin resistance include genetic defects in the insulin receptor, the production of antibodies to the insulin receptor, and several syndromes of lipoatrophy and lipodystrophy. (See "Insulin resistance: Definition and clinical spectrum").

Hyperprolactinemia — Some women with hirsutism have mild hyperprolactinemia, but whether it alone can cause hirsutism is not clear. The elevation in serum prolactin is sometimes associated with increased serum DHEA-S concentrations [29,30], prolactin receptors have been identified in human adrenal cells, and prolactin can increase adrenal DHEA secretion in vitro [31]. However, the underlying problem in many of these women is probably the polycystic ovary syndrome, with the hyperprolactinemia being caused by the increases in serum estrone concentration that occur in women with this disorder. DHEA-S is such a weak androgen that the hirsutism associated with hyperprolactinemia is probably due more to the ovarian hyperandrogenism characteristic of the polycystic ovarian syndrome than any effect of hyperprolactinemia. (See "Steroid hormone metabolism in polycystic ovary syndrome").

SUMMARY — Hirsutism, defined as excessive male-pattern hair growth, affects between 5 and 10 per cent of women of reproductive age. It may be the initial, and possibly only, sign of an underlying androgen disorder, the cutaneous manifestations of which may also include acne and male-pattern balding (androgenic alopecia).

- Depending upon the body site, hormonal regulation plays an important role in the hair growth cycle. Androgens increase hair follicle size, hair fiber diameter, and the proportion of time terminal hairs spend in the anagen phase. (See "Hair growth cycle" above).

- Race and ethnicity are important determinants of body hair distribution in women. (See

"Ethnicity" above).

- Polycystic ovary syndrome is the most common cause of hirsutism. (See "Polycystic ovary syndrome" above).

- The diagnosis of idiopathic hirsutism is given to women with hirsutism with normal serum androgen concentrations, no menstrual irregularity, and no identifiable cause of their hirsutism. (See "Idiopathic hirsutism" above).

- Other causes include congenital adrenal hyperplasia, ovarian and adrenal androgen-secreting tumors, medications, and other rare disorders. (See appropriate sections above).

- It is not known if hyperprolactinemia per se causes hirsutism. (See "Hyperprolactinemia" above.

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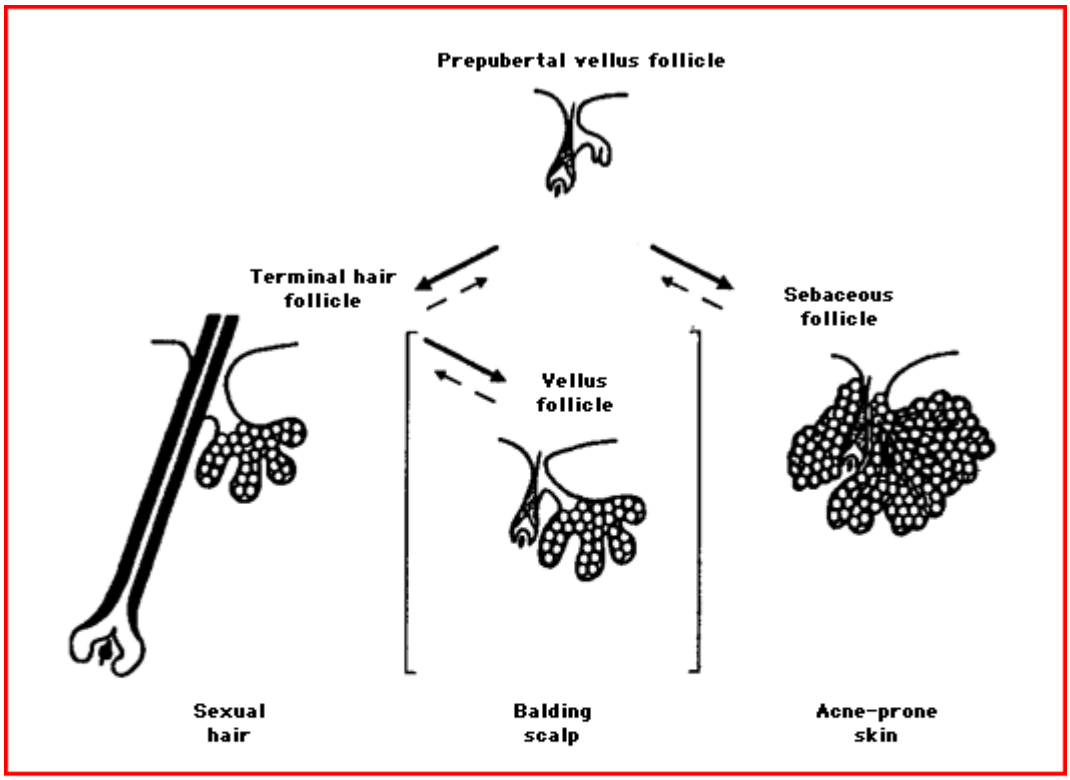
GRAPHICS

Androgen pilosebaceous



Androgens in the development of the pileosebaceous unit
Solid lines indicate effects of androgens; dotted lines indicate effects of antiandrogens. Hairs are depicted only in the anagen (growing) phase of the growth cycle. In balding scalp (bracketed area), terminal hairs not previously dependent on androgen regress to vellus hairs under the influence of androgen. Reproduced with permission from: Rosenfield, RL, Deplewski, D. The role of androgens in the development of biology of the pilosebaceous unit. Am J Med 1995; 98:80S.

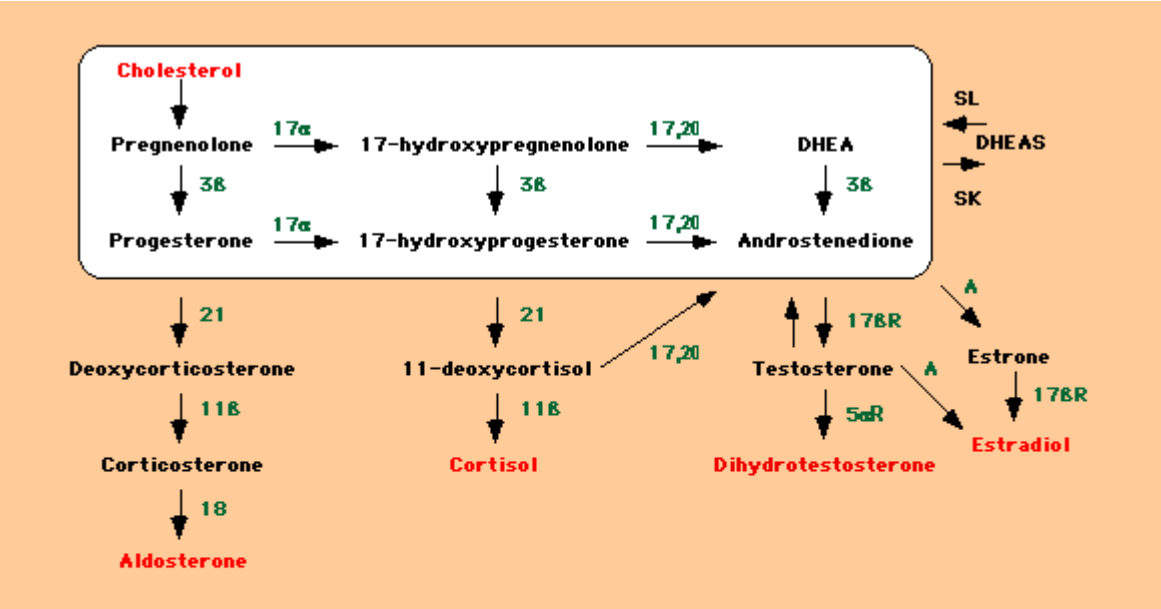
Causes of hirsutism

Causes of Hirsutism in Women

Common
- Idiopathic hirsutism
- Polycystic ovary syndrome

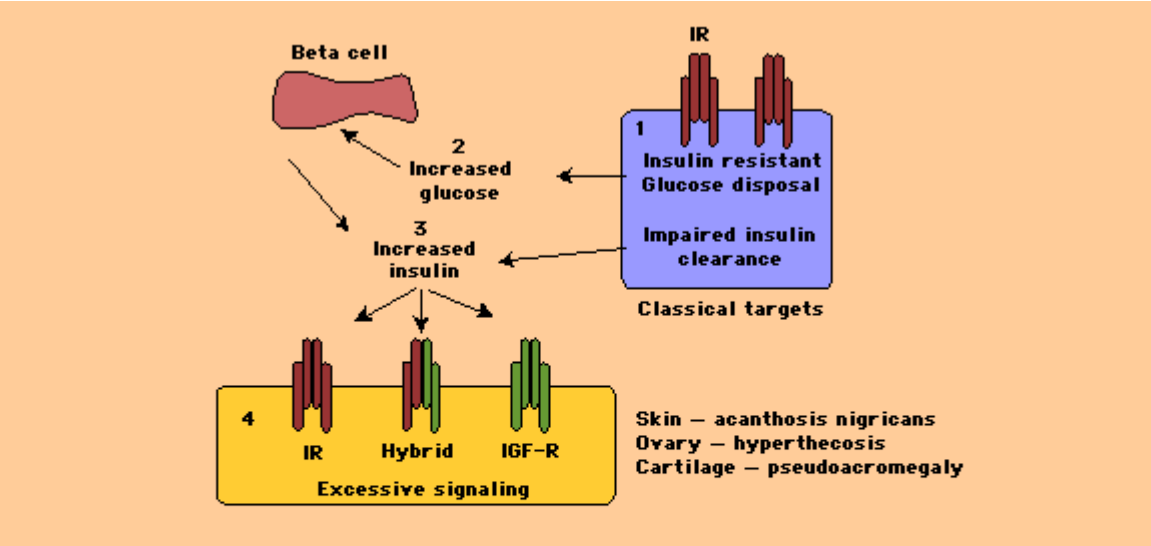
Uncommon
- Drugs
  - Danazol
  - Oral contraceptives containing androgenic progestins
- Congenital adrenal hyperplasia (most often 21-hydroxylase deficiency)
- Hyperthecosis
- Ovarian tumors
  - Sertoli-Leydig cell tumors
  - Granulosa-theca cell tumors
  - Hilus-cell tumors
- Adrenal tumors
- Severe insulin resistance syndromes
- Hyperprolactinemia

Adrenal steroid synthesis



Synthetic pathways for adrenal steroid synthesis The first step in adrenal steroid synthesis is the combination of acetyl CoA and squalene to form cholesterol, which is then converted into pregnenolone. The enclosed area contains the core steroidogenic pathway utilized by the adrenal glands and gonads. The numbers at the arrows refer to specific enzymes: 17α = 17α-hydroxylase (CYP17, P450c17); 17,20 = 17,20 lyase (also mediated by CYP17); 3ß = 3ß-hydroxysteroid dehydrogenase; 21 = 21-hydroxylase (CYP21A2, P450c21); 11ß = 11ß-hydroxylase; (CYP11B1, P450c11); 18 refers to the two-step process of aldosterone synthase (CYP11B2, P450c11as), resulting in the addition of an hydroxyl group that is then oxidized to an aldehyde group at the 18-carbon position; 17ßR = 17ß-reductase; 5αR = 5α-reductase; DHEA = dehydroepiandrostenedione; DHEAS= DHEA sulfate; and A = aromatase (CYP19).

IGF receptors in insulin resis



Possible mechanisms by which insulin resistance leads to the clinical manifestations of the polycystic ovary syndrome Insulin resistance in muscle and adipose tissue leads to hyperglycemia and thus increased insulin secretion from the pancreatic beta cells. This insulin can cause changes in the skin, ovary, and cartilage via activation of insulin-like growth factor-1 (IGF-1) receptors or hybrid receptors formed by covalent linkage of subunits of the homologous receptors for insulin (IR) and IGF-1 (IGF-R). (Adapted from Mantzoros, CS, Flier, JS, Adv Endocrinol Metab 1995; 6:193.)