Pathophysiology and causes of hirsutism

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INTRODUCTION

Hirsutism, defined as excessive terminal hair growth, affects between 5 and 10 percent of females of reproductive age. Hirsutism may be the initial and possibly only sign of androgen excess, the cutaneous manifestations of which may also include acne and male-pattern hair loss (androgenetic alopecia). The pathophysiology and causes of androgen-mediated hair growth are reviewed here. Hyperandrogenism in postmenopausal females and the evaluation and treatment of hirsutism in premenopausal females are discussed separately. (See "Evaluation and management of postmenopausal hyperandrogenism" and "Evaluation of premenopausal women with hirsutism" and "Management of hirsutism in premenopausal women".)

PATHOPHYSIOLOGY

Hair growth cycle — Humans are born with approximately five million hair follicles, and it is estimated that 80,000 to 150,000 of them are located on the scalp. Hair can be categorized as either vellus (fine, soft, and not pigmented) or terminal (long, coarse, and pigmented) [1]. 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.

The hair growth cycle is comprised of three phases [2]:

- The growth phase (termed anagen), which varies by body area, is approximately four months for facial hair. Therefore, it takes approximately six months to detect the effects of hormonal therapy for facial hirsutism.

- The involutional phase (catagen), which lasts two to three weeks.
- The resting phase (telogen), which lasts three to four months. Hair is released from the hair follicle and shed at the end of telogen, and the next cycle is initiated. Telogen hairs are characterized by a mature root sheath or "club" at the proximal end.

Role of androgens in hair growth — Hair on the scalp, eyebrows, and eyelashes grow, in the absence of androgens. At other body sites (eg, face, axilla, pubis, arms, legs, trunk, ears), androgens increase hair growth as manifested by an increased hair follicle size, hair fiber diameter, and the proportion of time terminal hairs spend in the anagen phase [1,3]. Androgen excess in females leads to increased hair growth in most androgen-sensitive sites (eg, upper lip, chin, midsternum, upper abdomen, back, and buttocks) but to loss of hair in the scalp region, in part by reducing the time scalp hairs spend in anagen phase.

Androgens are necessary for terminal hair and sebaceous gland development and cause differentiation of pilosebaceous units (PSUs) into either a terminal hair follicle or a sebaceous gland (figure 1) [1]. In the former case, androgens transform the vellus hair into a terminal hair (a large medullated hair); in the latter, the sebaceous component proliferates and the hair remains vellus. In androgen-sensitive areas before puberty, the hair is vellus and the sebaceous glands are small. In response to increasing levels of androgens, PSUs become large terminal hair follicles in sexual hair areas or they become sebaceous follicles (sebaceous glands) in sebaceous areas. Androgens promote growth of sexual hair by recruiting a population of PSUs to switch from producing vellus hairs to initiating terminal hair growth.

Male-pattern hair growth occurs in sites where relatively high levels of androgen are necessary for PSU differentiation. Although androgen excess underlies most cases of hirsutism, there is only a modest correlation between the quantity of hair growth and serum testosterone concentrations [4,5]. 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 and local conversion of testosterone to dihydrotestosterone (DHT) [1]. Some data suggest that serum free or bioavailable testosterone concentrations correlate positively with hirsutism scores, while sex hormone-binding globulin (SHBG) concentrations correlate negatively with hirsutism scores [6,7].

Nearly all hirsute females 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. This is because the carrier protein for testosterone, SHBG, is suppressed when androgen production is increased.

Androgens and androgen action — Hirsutism is a result of the interaction between circulating serum androgens and the sensitivity of the hair follicle to androgens and local growth factors. Several different androgens may be secreted in excess:

- Testosterone, which is usually of ovarian origin
- Dehydroepiandrosterone sulfate (DHEAS), which is of adrenal origin
- Androstenedione, which can be of either adrenal or ovarian origin

In some females, hirsutism may be due to increased conversion of testosterone to DHT within the PSU by the enzyme 5-alpha-reductase [8]. The rate of intracellular conversion of testosterone to DHT is variable (figure 1).

DHEAS is a general marker of adrenal androgen production, as 90 percent of circulating DHEAS is derived by the sulfation of DHEA within the zona reticularis. While the intrinsic androgenic activity of DHEAS is limited, small amounts are converted to androstenedione and then to testosterone (and to estrone and estradiol) 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.

Generalized hair growth — There are at least two forms of 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 growth. This is a rare condition that is usually caused by a drug, examples of which 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. (See "Cutaneous manifestations of internal malignancy", section on 'Hypertrichosis lanuginosa'.)

EPIDEMIOLOGY

Hirsutism may affect between 5 and 10 percent of females of reproductive age [9,10]; most females with hirsutism have polycystic ovary syndrome (PCOS) [11,12]. (See 'Polycystic ovary syndrome' below.)

A commonly used method to grade hair growth is a modified scale of Ferriman and Gallwey [9]. (See 'Ethnicity' below.)

In a 1961 study of 430 British females aged 15 to 64 years attending a general medical clinic, 49 percent had hair above the lip, 22 percent had hair on the chin, 10 percent had hair on the chest, and no woman had terminal hair on the upper back or upper abdomen [9]. In most of the females 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 nine sites (modified Ferriman-Gallwey scoring system), only 1.2 percent of females aged 18 to 38 years had scores above 10, and only 5 percent had a score ≥8. As such, approximately 95 percent of reproductive age females have a score of <8, but cutoff scores considered to be abnormal vary by race and ethnicity. Although a total score is typically used to indicate hirsutism, lower scores have been associated with androgen excess disorders [13,14].

Ethnicity — The definition of normal must also consider race and ethnicity. Most East Asian and Native American females have little body hair, while Mediterranean females on average have substantially greater quantities of body hair even though serum androgen concentrations are similar in the three groups [15]. These differences must be kept in mind in determining whether a woman has a pathologic degree of hirsutism and whether she should be evaluated further. While a Ferriman-Gallwey score ≥8 is considered to be abnormal in Black and White females, the scores considered to be abnormal in other groups are ≥9 to 10 in Mediterranean, Hispanic, and Middle Eastern females and ≥2 to 3 for East Asian and Native American females.

Thus, an East Asian woman with a few peri-areolar hairs may warrant further evaluation, whereas a Mediterranean woman with some hair growth on her upper lip might well be considered normal and consider herself normal. 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.

CAUSES

Polycystic ovary syndrome (PCOS) is the most common cause of hirsutism. Other causes of androgen overproduction occur less frequently [11,12].

Polycystic ovary syndrome — PCOS is the most common cause of hirsutism in females (table 1). The syndrome is characterized by menstrual irregularity and hyperandrogenism, and the cutaneous manifestations may include clinical (hirsutism, acne, or male-pattern hair loss) and/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" and "Diagnosis of polycystic ovary syndrome in adults" and "Treatment of polycystic ovary syndrome in adults".)

In most populations of females with PCOS studied to date, testosterone is the predominant steroid secreted in excess; less often, androstenedione may be the predominant androgen that characterizes PCOS (table 1) [16]. (See "Evaluation of premenopausal women with hirsutism", section on 'Hirsutism with oligomenorrhea/amenorrhea'.)

One study prospectively evaluated 350 British females: 319 with hirsutism and 31 with frontal hair loss [17]. Only 2.3 percent (eight patients) had an identifiable endocrine disorder other than PCOS (congenital adrenal hyperplasia, ovarian tumor, virilizing adrenal carcinoma, prolactinoma, or acromegaly). (See "Diagnosis of polycystic ovary syndrome in adults".)

In two other series of 873 and 950 females presenting with androgen excess symptoms [11,12], PCOS was diagnosed (using the original criteria of oligomenorrhea and hyperandrogenism) in 82 and 57 percent, respectively. (See "Diagnosis of polycystic ovary syndrome in adults".)

The androgen excess in females with PCOS 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). Other diagnoses such as ovarian or adrenal tumors should be considered in older females, particularly those who have rapid development of hirsutism and/or other signs of hyperandrogenism or even virilization, or have a sudden onset of menstrual irregularity.

The evaluation of hirsutism is complicated by the lack both of reliable androgen assays and robust normative data in females. (See "Evaluation of premenopausal women with hirsutism", section on 'Biochemical testing'.)

Idiopathic hirsutism — The diagnosis of idiopathic hirsutism is given to females with hirsutism but normal serum androgen concentrations, no menstrual irregularity, and no identifiable cause of the hirsutism [4,18,19]. In some females, there may be a steroidogenic abnormality despite the apparently normal serum androgen levels [20]. The distinction between idiopathic disease and PCOS may be one of degree. As noted, many females who were previously considered to have idiopathic hirsutism would now be considered to have PCOS if using the newer Rotterdam PCOS diagnostic criteria. This is because most would meet two criteria for PCOS: clinical hyperandrogenism (hirsutism) and polycystic ovaries on ultrasound, which has been reported in over 90 percent of females with "idiopathic hirsutism" [21]. (See "Diagnosis of polycystic ovary syndrome in adults".)

Nonclassic 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 nonclassic (also called late-onset) forms (primarily 21-hydroxylase deficiency) have been identified. Affected females present peripubertally with

hirsutism and sometimes menstrual irregularity or primary amenorrhea; they have no manifestations of cortisol deficiency.

The prevalence of nonclassic congenital adrenal hyperplasia (NCCAH) among hirsute females has varied from 1 to 15 percent in different studies [22-25]. 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 (figure 2). (In nonclassic adrenal hyperplasia, cortisol production is not decreased due to an increase in corticotropin [ACTH] secretion.) (See "Genetics and clinical presentation of nonclassic (late-onset) congenital adrenal hyperplasia due to 21-hydroxylase deficiency" and "Adrenal steroid biosynthesis".)

Females with virilization or severe hyperandrogenemia — Virilization of recent onset and rapid progression, a serum total testosterone >150 ng/dL (5.2 nmol/L), or a serum dehydroepiandrosterone sulfate (DHEAS) >700 to 800 mcg/dL (18.9 to 21.7 micromol/L) is usually due to an androgen-secreting tumor (ovarian or adrenal) or ovarian hyperthecosis (although both are more common in postmenopausal than premenopausal females). Females with hyperthecosis have high serum testosterone (not DHEAS), and symptoms tend to develop more gradually than in females with androgen-secreting tumors. (See "Evaluation and management of postmenopausal hyperandrogenism", section on 'Women with virilization or severe hyperandrogenemia' and "Ovarian hyperthecosis".)

Androgen-secreting tumors — Hirsutism caused by an androgen-secreting tumor usually occurs later in life and progresses rapidly when compared with PCOS. 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. Many androgen-secreting ovarian tumors can be identified by transvaginal ultrasonography. (See "Sex cord-stromal tumors of the ovary: Epidemiology, clinical features, and diagnosis in adults".)

Most of the females have serum testosterone concentrations greater than 150 to 200 ng/dL (5.2 to 6.9 nmol/L) and many present with virilization [26-28]. The upper limit of normal for serum testosterone in females is now in the 45 to 60 ng/dL range (1.6 to 2.1 nmol/L) using an accurate and specific method: liquid chromatography-tandem mass spectroscopy (LC-MS/MS). The importance of using proper assays for measuring serum testosterone in females is reviewed separately. (See "Evaluation and management of postmenopausal hyperandrogenism", section on 'Women with virilization or severe hyperandrogenemia'.)

Adrenal tumors are a rare cause of androgen excess [11,12]. A few are adrenal adenomas that secrete mostly testosterone, but most are carcinomas that often secrete not only androgen (mostly DHEA and DHEAS) but also cortisol; therefore, the woman may have clinical manifestations of androgen excess and Cushing syndrome. Some of the carcinomas

may lose the ability to sulfate DHEA, so a normal serum DHEAS value does not exclude the diagnosis [29]. Nevertheless, an unequivocally elevated serum DHEAS value (>700 to 800 mcg/dL [18.9 to 21.7 micromol/L]) is suggestive of an adrenal carcinoma. (See "Clinical presentation and evaluation of adrenocortical tumors".)

Ovarian hyperthecosis — Ovarian hyperthecosis is a nonmalignant ovarian disorder characterized by increased production of testosterone by luteinized thecal cells in the stroma, leading to markedly increased serum testosterone concentrations. It is still unclear if hyperthecosis is a distinct disorder or is part of the spectrum of PCOS. The woman's history is usually one of gradual onset of hirsutism and frank virilization. Hyperthecosis is seen primarily in postmenopausal females, but it can occur in premenopausal females. (See "Ovarian hyperthecosis".)

Other — Other uncommon causes of hirsutism include a number of endocrine disorders (including Cushing syndrome) and drugs.

- **Endocrine disorders**
  - Cushing disease – Adrenal overactivity due to a corticotroph adenoma secreting ACTH excessively results not only in excessive secretion of cortisol but also of adrenal androgens, typically resulting in hirsutism. Although the majority of females who have Cushing disease have hirsutism, only a very small fraction of females with hirsutism have Cushing disease. (See "Epidemiology and clinical manifestations of Cushing syndrome", section on 'Signs of adrenal androgen excess'.)
  - Hyperprolactinemia, acromegaly, and hypothyroidism are uncommon causes of hirsutism. Females typically present with the features specific to these disorders in addition to their hirsutism.
  - Syndromes of severe insulin resistance – Females 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 and insulin-like growth factor-1 (IGF-1) (figure 3). Insulin also decreases SHBG 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", section on 'Hyperandrogenism and reproductive abnormalities'.)
- **Drugs** – Androgen therapy (testosterone or DHEA) may be associated with hirsutism. Danazol, a drug commonly used in the past for the treatment of endometriosis, is also

associated with hirsutism. (See "Overview of androgen deficiency and therapy in females".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hirsutism".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Hirsutism (excess hair growth in women) (The Basics)" and "Patient education: Sertoli-Leydig cell tumor (The Basics)")
- Beyond the Basics topics (see "Patient education: Hirsutism (excess hair growth in females) (Beyond the Basics)")

SUMMARY

- **Hirsutism** – Hirsutism, defined as excessive terminal hair growth, affects between 5 and 10 percent of females 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 hair loss (androgenetic alopecia). (See "Male pattern hair loss (androgenetic alopecia in males): Management".)
- **Hair growth cycle** – 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.)

- **Determinants of body hair distribution** – Race and ethnicity are important determinants of body hair distribution in females. (See 'Ethnicity' above.)

- **Causes**

  - **Polycystic ovary syndrome** – Polycystic ovary syndrome (PCOS) is the most common cause of hirsutism. (See 'Polycystic ovary syndrome' above.)

  - **Idiopathic hirsutism** – The diagnosis of idiopathic hirsutism is given to females with hirsutism with normal serum androgen concentrations, no menstrual irregularity, and no identifiable cause of their hirsutism. However, if using the Rotterdam criteria for PCOS diagnosis, many females with idiopathic hirsutism would be considered to have a subtle form of PCOS. (See 'Idiopathic hirsutism' above.)

  - **Other** – Other causes of hirsutism include nonclassic congenital adrenal hyperplasia (NCCAH) due to 21-hydroxylase deficiency, ovarian and adrenal androgen-secreting tumors, medications, and other rare disorders. (See 'Causes' above.)

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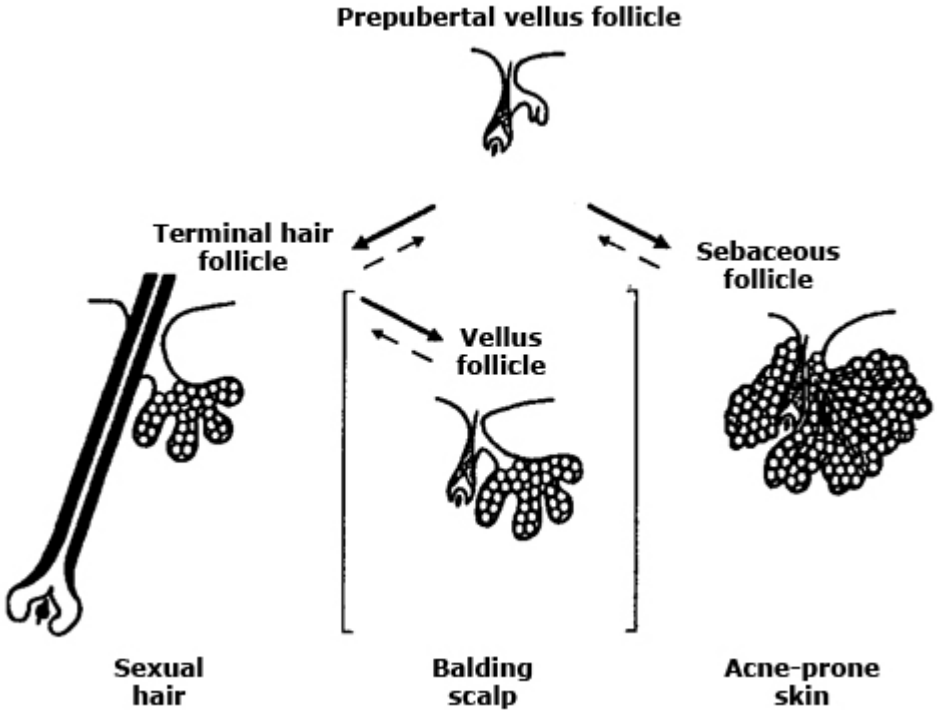
GRAPHICS

Androgens in the development of the pilosebaceous 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.

Graphic 52814 Version 3.0

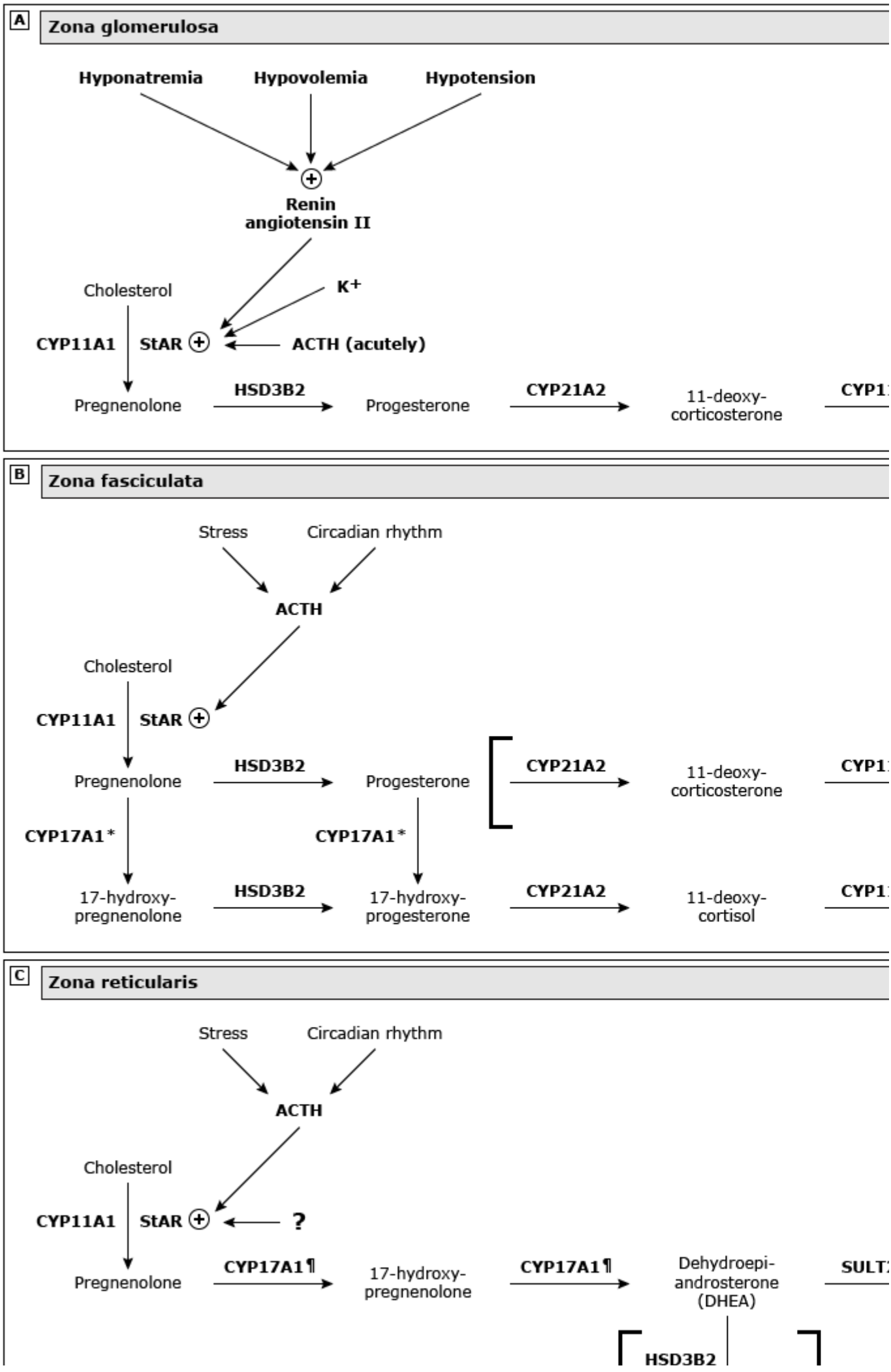
Causes of hirsutism in women

Etiology	Clinical features
Common	
PCOS	Peripubertal onset of symptoms, oligomenorrhea obesity, polycystic ovaries on ultrasound.
Nonclassic 21-hydroxylase deficiency	Similar presentation to PCOS, high serum 17-hydroxyprogesterone concentration, more common in certain ethnic groups.
Uncommon	
Classic 21-hydroxylase deficiency	Diagnosed during infancy, ambiguous genitalia.
Androgen-secreting ovarian tumors (Sertoli-Leydig cell, granulosa-theca cell, hilus cell)	Onset in third decade or later (usually postmenopausal), rapidly progressive hirsutism, virilization.
Androgen-secreting adrenal tumors	Some women with adrenocortical cancer present with just virilization, but a mixed Cushing's and virilization syndrome is more common.
Ovarian hyperthecosis	Onset in third decade or later (usually postmenopausal), rapidly progressive hirsutism, virilization.
Severe insulin-resistance syndromes	Virilization, amenorrhea, infertility, and the ovary shows histologic changes of hyperthecosis.
Cushing's disease	Corticotroph adenoma secreting ACTH results in excess cortisol and adrenal androgens.
Drugs	Use of exogenous androgens (testosterone or DHEA) can cause hirsutism and acne.
Acromegaly	Enlarged jaw (macrognathia) and enlarged, swollen hands and feet, which result in increasing shoe, glove, and ring sizes. Patients with large pituitary tumors may have headaches, visual field defects, and cranial nerve palsies.

PCOS: polycystic ovary syndrome; ACTH: corticotropin; DHEA: dehydroepiandrosterone.

Graphic 65205 Version 10.0

Normal adrenal steroidogenesis


A
Zona glomerulosa
Hyponatremia
Hypovolemia
Hypotension
Renin
angiotensin II
Cholesterol
K+
CYP11A1
StAR
ACTH (acutely)
Pregnenolone
HSD3B2
Progesterone
CYP21A2
11-deoxy-
corticosterone
B
Zona fasciculata
Stress
Circadian rhythm
ACTH
Cholesterol
CYP11A1
StAR
Pregnenolone
HSD3B2
Progesterone
CYP21A2
11-deoxy-
corticosterone
CYP17A1*
CYP17A1*
17-hydroxy-
pregnenolone
HSD3B2
17-hydroxy-
progesterone
CYP21A2
11-deoxy-
cortisol
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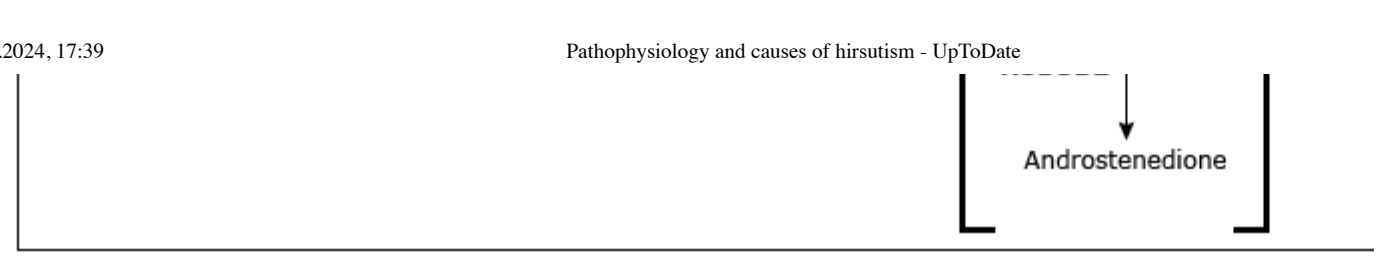
Zona reticularis
Stress
Circadian rhythm
ACTH
Cholesterol
CYP11A1
StAR
?
Pregnenolone
CYP17A1¶
17-hydroxy-
pregnenolone
CYP17A1¶
Dehydroepi-
androsterone
(DHEA)
HSD3B2



(A) Zona glomerulosa (ZG): Controlled primarily by the renin-angiotensin system through angiotensin II as well as potassium ion and ACTH (acutely). Renin secretion is stimulated by hyponatremia, hypovolemia, and hypotension. The ultimate increase in angiotensin II causes vasoconstriction and stimulates aldosterone, thereby increasing renal sodium reabsorption resulting in an expansion of plasma volume.

(B) Zona fasciculata (ZF): Cortisol is the major product because CYP17A1 (17-hydroxylase activity*) predominates. The square brackets ([ ]) indicate that corticosterone synthesized from progesterone by CYP21A2 and then CYP11B1 is usually a minor pathway (except in CYP17A1 [17-hydroxylase*] deficiency).

(C) Zona reticularis (ZR): The question mark (?) indicates that there are other as yet defined factors involved in the control of steroidogenesis in the ZR. The square brackets ([ ]) indicate that HSD3B2 production of androstenedione is a minor pathway in the ZR. However, not shown is that DHEA from the ZR is converted to androstenedione (and then testosterone) in peripheral tissues.

ACTH: corticotropin.

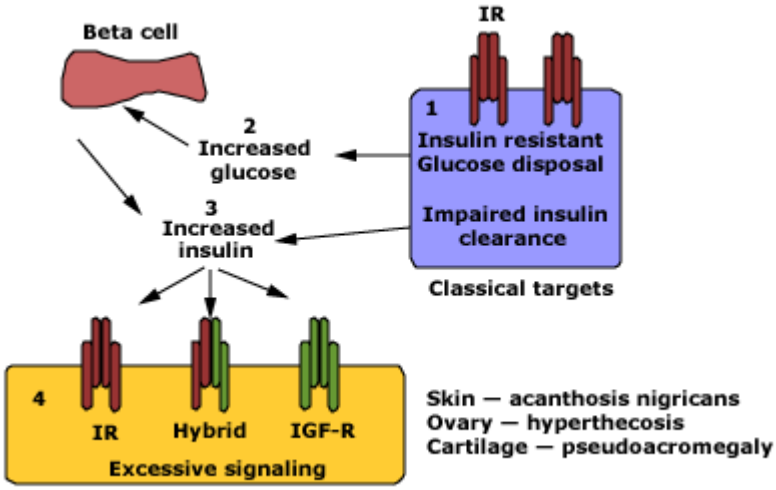
* CYP17A1 has high 17-hydroxylase activity in the zona fasciculata, but has minimal 17,20-lyase activity because of low expression of a cofactor (cytochrome b_5) necessary for full 17,20-lyase activity. Therefore, the ZF is not a source of significant adrenal androgen precursors as in the ZR (C).

¶ In the ZR, CYP17A1 catalyzes 17-hydroxylase and 17,20-lyase activity because of the presence of a cofactor (cytochrome b_5).

Courtesy of Hershel Raff, PhD.

Graphic 71558 Version 8.0

Possible mechanisms by which insulin resistance leads to the clinical manifestations of 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 IGF-1 receptors or hybrid receptors formed by covalent linkage of subunits of the homologous receptors for insulin (IR) and IGF-1 (IGF-R).

IGF-1: insulin-like growth factor 1; IR: insulin receptor; IGF-R: insulin-like growth factor receptor.

Adapted from: Mantzoros CS, Flier JS. Insulin resistance: the clinical spectrum. Adv Endocrinol Metab 1995; 6:193.

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