CLINICAL UPDATES IN HAIR

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Androgenetic alopecia (AGA) is relatively common in both men and women; however, the severity of hair loss in women is usually much less than in men. Hair loss for both men and women may begin as early as the teen years but can even start in later decades of life. In men with AGA, one of the earliest findings is an increase in the percentage of hairs in a telogen phase of the hair cycle, so that initial hair loss may appear indistinguishable from a telogen effluvium. As in men, AGA in women can be psychologically devastating to accept, giving overall less body-image satisfaction and making it difficult to cope and retain integrity of personality functioning. AGA has been reported to be an autosomal dominant trait with partial or variable penetrance for both men and women.

BIOCHEMICAL ADVANCES FOR MALE AND FEMALE ANDROGENETIC ALOPECIA

Although for many years it had been assumed that the hormonal basis for AGA in women was the same as for men, no studies confirmed this. Recent work has shown that on the scalp there are local differences in the amounts of enzymes that convert weak androgens to more potent androgens (Fig. 1). This is important because the skin is an endocrine target tissue for androgen hormone action, similar to ovaries, testes, and adrenals. Studies have shown that persons using anabolic-androgenic steroids show hypertrophy of sebaceous glands, with systemic hirsutism, and AGA. In Figure 1, the hormone pathway describes the potential of a relatively weak, yet abundant hormone called dehydroepiandrosterone (DHEA) to be metabolized to more potent androgens such as testosterone and dihydrotestosterone (DHT). The enzymes have been localized in sebaceous glands and hair follicles of scalp skin. Therefore, the skin has the potential to mediate androgen action without relying on elevated systemic levels or production of testosterone or DHT.

An important enzyme in this pathway of Figure 1 is 5a-reductase, which mediates reduction of testosterone to DHT. Although many antiandrogens described in this article are known to interfere with this enzyme, it should be noted that there may be two forms of 5a-reductase and that the use of antiandrogens may not be specific for the 5a-reductase in skin, and therefore have limited effects in treating androgen-related skin conditions.

Another important enzyme that has come to recent attention is the aromatase enzyme (Fig. 1). Because it is known that androgen metabolism occurs within the hair follicle structure, finding aromatase to be specifically located in the outer root sheath of hair follicles adds to the importance of studying the entire hair follicle and not just the dermal papilla cells. Aromatase has been shown to convert androgens such as testosterone and

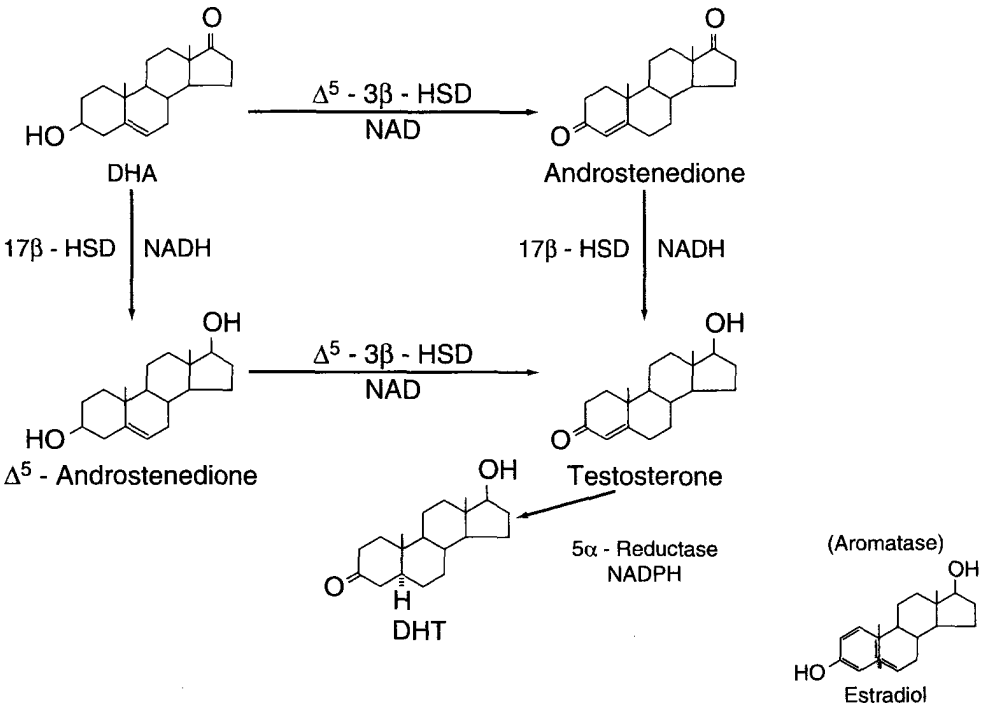

Figure 1. Metabolic pathway of androgens in skin. Conversion of DHA to potent androgens T and DHT, via the 3p- and 170-hydroxysteroid dehydrogenase enzymes, and 5a-reductase; also the conversion of androgens to estrogens, via aromatase enzyme. DHA = dehydroepiandrosterone; DHT = dihydrotesterone.

androstenedione to the estrogens, estradiol and estrone, respectively. It was also found that in women, there may be a two- to fivefold greater amount of aromatase in female scalp versus male scalp, perhaps explaining why women may have a sparing of the frontal hairline in AGA, and as well, why women may have a less severe pattern of hair loss than men. It is uncertain if the estrogens formed from aromatase are playing a role in suppressing the severity of hair loss, or whether aromatase is primarily reducing the overall load of androgens formed locally in the hair follicle.

The next important step in understanding androgen action in skin is the binding of the target tissue active androgens, testosterone and DHT, to the androgen receptor (Fig. 2). The androgen receptor has been purified and located in specific skin structures, such as hair follicle and sebaceous gland. AIthough the mechanism described in Figure 2 depicts the hormone testosterone binding to the androgen receptor, we are now realizing that very complex enzyme mechanisms such as phosphorylation and sulfhydryl reduction of this receptor are important for forming an activated hormone-androgen receptor complex that has the ability to bind to specific hormone response elements at gene sites in the nucleus to stimulate or alter cellular processes mediating hair growth.

CLINICAL OBSERVATIONS OF ANDROGENETIC ALOPECIA

In genetically predisposed men the balding process is triggered by exposure to androgens at puberty. In women, the relationship between systemic elevated androgen levels and alopecia is difficult to determine, because approximately 30% to 40% of women who experience AGA have a systemic endocrine problem, classifying the condition in the majority of women as idiopathic.

Most women with AGA have a diffuse hair loss, maintaining the frontal hair line, with accentuating hair loss at the crown in particular. Over time, further miniaturization of affected hairs results in usually two populations of hairs, one normal and the other shorter, thinner, and finer. It should be noted that if one sees a deep frontotemporal

recession on the scalp as seen typically in men with AGA, a hyperandrogen state may be taking place systemically, warranting further inspection for other signs of virilization, such as acne and hirsutism or hypertrichosis. Again, a workup of potential causes of an excess androgen state in these women is necessary.

There are two major sites of androgen production in women, the adrenal gland and the ovaries, with either a source for overproducing systemic androgens. It has also been postulated that in women there is an increased local sensitivity of the hair follicle to androgens in AGA and idiopathic hirsutism, because plasma androgen concentrations may be normal (Table 1) Only through expensive and time-consuming adrenocorticotropic hormone stimulation tests was it found that some women who show normal blood androgen levels have subtle defects in the steroidogenic pathway (i.e., llb-hydroxylase, 21-hydroxylase defects, etc.), which may be contributing to the androgen-related skin diseases. So, even though most clinicians evaluate basal blood hormone levels as shown in Table 1, finding normal levels does not exclude the possibility of one of the subtle enzyme defects now thought to occur more commonly in women with hirsutism and AGA.

TREATMENT FOR MEN AND WOMEN WITH ANDROGENETIC ALOPECIA

Many of the treatments listed in Tables 2 and 3 are used to treat AGA in men and women; however, it must be kept in mind that there is no hard evidence for any of these agents to cause cosmetically acceptable hair growth. Many of the drugs listed have been thought to retard hair loss, but not totally prevent hair loss, with an antiandrogen mode of action inhibiting, to variable degrees, the enzymes in the metabolic androgen pathway or the androgen receptor protein

Spironolactone is a drug approved for use in primary aldosteronism, as well as for edematous conditions such as congestive heart

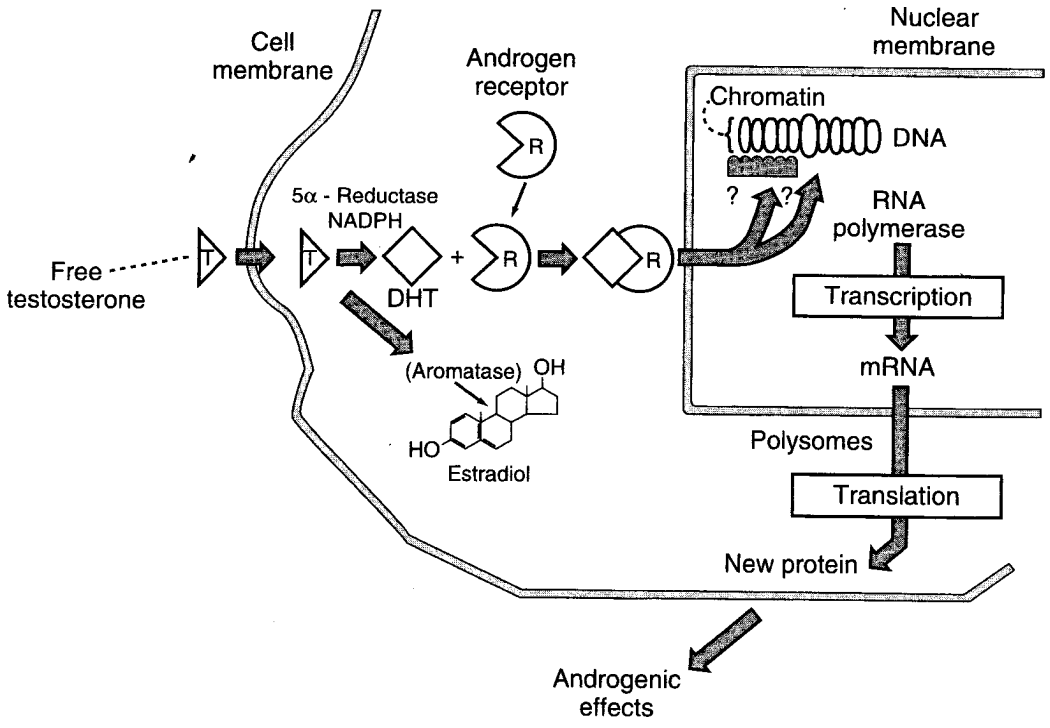

Figure 2. Cellular mechanism for androgens in skin. Steroid hormones passively diffuse through the cell membrane (as shown for testosterone [T]) and may enzymically convert to more potent androgens to bind to the androgen receptor (R). The hormone-androgen receptor complex is sulfhydryly reduced and undergoes phosphorylation to bind to specific gene sites, altering RNA polymerase activity, which affects hair growth.

Table 1. LABORATORY VALUES FOR EVALUATION OF FEMALE ANDROGENETIC ALOPECIA

	Female-Pattern AGA	Female-Pattern AGA with Hirutism	Male-Pattern AGA (Frontotemporal Recession)
DHEAS	Normal/elevated	Normal/elevated	Elevated
Testosterone	Normal	Normal/elevated	Elevated
TeBG	Normal	Decreased/normal	Decreased/normal
Testosterone/TeBG	Normal	Elevated	Elevated

DHEAS = dehydroepiandrosterone-sulfate; AGA - androgenetic alopecia; TeBG = testosterone-binding globulin, also known as sex-steroid binding globulin.

Data from Kasick JM, Bergfeld WF, Steck WD, et al: Adrenal androgenic female-pattern alopecia: Sex hormones and the balding woman. Cleve Clin 0 50:111, 1983.

failure, cirrhosis, hypertension, and hypokalemia. Because it was found to decrease testosterone production by the adrenal gland by affecting the cytochrome P450 enzyme system, many physicians started to use it as an antiandrogen. Spironolactone is also known to be a mild competitive inhibitor against DHT for binding to the androgen receptor. Treatment consists of oral doses of 100 to 200 mg/day, with monitoring of potassium levels, blood pressure, menstrual changes, breast tenderness, and mood swings. Although no large controlled clinical trials have been performed for spironolactone's efficacy in hair loss, physicians often consider using this drug in patients who are highly motivated as well as in those with associated androgen skin disorders such as hirsutism, where it has been noted to show some improvement in 25% of hirsute female patients after 6 months of use .

Flutamide (also known as Eulexin), a nonsteroidal compound used in the treatment of prostatic cancers, is also thought to work as an antiandrogen given in oral doses of 250 mg three times a day alone or in combination with an oral contraceptive (OCP).

Flutamide has been used in patients with hirsutism, where 20 patients showed an increase in testosterone-binding globulin during therapy, with minimal side effects observed. Further trials are necessary to determine its efficacy for scalp hair growth in women with AGA.

Cimetidine (Tagamet) is a gastric H2-receptor antagonist also found to act as a weak antiandrogen by competing with DHT. Patients are given doses of 300 mg, five times a day, for 5 months or longer. Keep in mind that no controlled clinical trials have been done in men or women to show the efficacy of this drug in AGA.

Dexamethasone or glpcocorticoids in general have been used to suppress adrenal and ovarian androgen production. Prescribed oral doses of **0.25 to 0.75** mg each night are given to reduce adrenocorticotropic hormone stimulation. Even though some patients have shown improvement of their hair loss or hirsutism, no large-scale clinical trials have been performed with this drug to show its effectiveness in alleviating androgen-dependent hair loss versus the multiple side effects that can occur with prolonged glucocorticoid use.

Table 2. DRUGS USED TO TREAT ANDROGENIC DISORDERS IN MEN AND WOMEN

Treatment	Dose
Spironolactone	100-200 mg orally every day
Flutamide	250 mg orally three times a day
Cimetidine	300 mg orally five times a day
Dexamethasone	0.25-0.75 mg/night
Cyproterone acetate*	50-150 mg/day
Minoxidil (Rogaine)	2% topical solution, applied twice a day for >32 weeks; soon available over the counter, with 5% awaiting approval
Propecia (finasteride)	Oral drug, 1 and 5 mg/day trials in men and women
Roussel's RU58841	Topical antiandrogen, still in testing trials anticipated for 1997
ProCyte (ionic copper)	In development
AntiSense technology for 5a-reductase and androgen receptor	In development

*Not available in the United States.

Table 3. DRUGS USED TO TREAT WOMEN

Oral contraceptives (listed from least to more androgenic)
Desogestrel: Desogen, Ortho-Cept
Norgestimate: Ortho-Cyclen, Ortho Tri-Cyclen
Norethindrone: Micronor, Nor-OD, Ovcon-35, Brevicon, Modicon, Ortho-Novum 7/7/7, Ortho-Novum 10-11, Tri-Norinyl, Norinyl and Orthol/35
Ethynodiol diacetate: Demulen 1/35
Levonorgestrel: TriphasilfTri-Levlen, Nordette
Norgestrel: Lo/Ovral, Ovrefte, Ovral
Norethindrone acetate: Loestrin 1/20, Loestrin 1.5/30
Gonadotropin -releasing hormone agonists*
Leuprolide (Lupron-Depot), 3.75 mg/month intramuscularly, plus 0.625 mg conjugated estrogens and cyclic medroxyprogesterone acetate 10 mg (from days 1-12 of each month)
Nafarelin (400 [Lg intranasally twice a day), plus Norinyl 1/35 tablets daily for 21 of 28 days, orally

***From trials completed for hirsutism, but may have application for androgenetic alopecia and acne as well.**

Again, dexamethasone is also used in women with the other associated androgen-dependent skin conditions, such as acne and hirsutism.

OCPs are commonly prescribed to alleviate AGA, hirsutism, or acne in female patients. OCPs should be selected based on the estrogen and progestin components, which can have a sebum-inhibiting effect if the correct derivatives are used (Table 3). OCPs are usually used if the physician attributes the systemic elevated level of androgens to the ovaries.

An important aspect to choosing an OCP is the progestin component, because some progestins can act as an androgen. Progestins of low androgen index are desogestrel (Desogen, Ortho-Cept) and norgestimate (OrthoCyclen, Ortho Tri-Cyclen). OCPs combined with 35 or 50 ug of ethinyl estradiol or mestranol are found in Ortho-Novum or Norinyl may be prescribed. Brands containing low estrogen, 35 ug with 1 mg of norethindrone, may be better tolerated by some patients. If treated in the early phases of hair loss, some patients may show some improvement after 6 to 12 months.

Cyproterone acetate (CPA) is a potent antiandrogen used in Europe and elsewhere. CPA acts peripherally by competing with androgens for binding to the androgen receptor and can also act as a strong progestin, maintaining normal releasing hormones and gonadotropin levels. This drug has been widely used in Europe to treat men and women with AGA, hirsutism, and acne and is available as a treatment for prostate enlargement (benign prostate hypertropy) in men, called Androcur, and in women an OCP called Diane, which contains 2 mg of CPA with an estrogen. Investigators have reported a marked improvement in women when treating patients with 100 mg of CPA and 50 Rg of ethinyl estradiol daily, versus the untreated control group. Another study in women 18 to 47 years of age showed that 50 mg of CPA once daily from day 5 to 24 of the menstrual period given with 30 ug of ethinyl estradiol from day 5 to 24 of the menstrual period improved hair growth in women with AGA, as long as serum ferritin levels were above 40 ug/L. The side effects of this drug are important to consider: loss of libido, mood swings, and weight gain.

Rogaine (minoxidil) has now been used for several years in the United States and abroad. Even though the mechanism of action is still under investigation, in women it has been shown to increase the nonvellus hairs when used for 32 weeks or more. A drawback to minoxidil therapy is that "spontaneous reversal to the pretreatment state can be expected 1 to 3 months after cessation of therapy," indicating that minoxidil has a direct effect on the hair follicle, sensitizing it and making it dependent on the drug for future growth .

Newer drugs currently being tested are Propecia (finasteride), an oral 5a-reductase type 11 inhibitor from Merck Co. This drug developed from prostate research for the type II 5a-reductase enzyme, and, already available as Proscar for benign prostatic hypertrophy, is in current clinical trials throughout the United States, with reports showing improved hair growth in the vertex of young men with early hair loss at oral doses of 5 mg and even 1 mg/day. New trials are under way for women with AGA. Again, more information is needed to assess the efficacy of this oral drug versus any systemic side effects it may have for men and women with AGA.

Another new drug from the French company Roussel Uclaf (Romainville, France) is a topical antiandrogen receptor blocker called RU58841. This drug has been in rigorous laboratory testing,33, [10] showing it to be a promising topical antiandrogen for promoting hair growth on scalp as well as retarding hair growth from beard and body hair follicles. Human clinical trials are anticipated to start in mid to late 1997.

Gonadotropin-releasing hormone agonists are now coming into investigation for their use in treating hirsutism and other associated

cutaneous androgen conditions, such as AGA and acne. Recent trials with leuprolide in combination with OCPs, and nafarelin with OCPs, respectively, have suggested their improved use in comparison with OCPs alone, for treating androgen-related skin conditions, i.e., hirsutism. Investigations may suggest a new role for these drugs in AGA and acne.

CONCLUSION

Even though research continues to provide information about hair growth regulation, clinically treating women and men with hair loss is frustrating. At present, no drug or compound or procedure has been found to be worthwhile for the majority of individuals who suffer with AGA hair loss. Even when some success of regrowth (or retarding hair loss) is achieved, the problem of maintaining this state has not been solved.

The opinion by many in the field regarding future treatments is positive, hopeful, and bright for discovering new drugs or products that can give cosmetically acceptable results to treat AGA. Based on further research in the molecular processes involved in androgen regulation of the hair follicle, such a drug would have to satisfy the criteria of being safe, i.e., the ability to target local scalp hair follicles while having.minimal to no side effects on other target tissues or sex organs. Thus far, the Roussel drug, RIJ58841, comes close to this, but even this drug may not be the perfect cure. Variations in response to treating patients with this drug will have to be considered because aging, duration of hair loss in the individual, and scarring or fibrotic “changes'" that may have taken place will be important in predicting if a patient will respond successfully. In any case, the window of opportunity for further drug discovery in this area remains wide open.