CLINICAL REVIEWS

Evaluation and treatment of male and female Pattern hair loss

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Twenty years ago, there were neither specific treatments available for pattern hair loss nor full understanding of the pathophysiology of this common disorder. Male pattern hair loss (MPHL) [or androgenetic alopecia (AGA), male pattern baldness (MPB)] had been clearly recognized as an androgen-dependent hereditary disorder since the 1940's.[1] The principle of donor dominance was first appreciated at that time and led to the development of hair transplantation as a form of treatment.[2] However, it was not until recognition of the phenotype of individuals with the genetic deficiency of 5*a*- reductase (5*a*R),[3] the isolation of the two isoforms of 5*a*-reductase (5*a*R-1 and 5*a*R-2),[4,5] along with the documented utility of 5*a*-reductase inhibitors in male pattern baldness,[6] that the essential role of dihydrotestosterone (DHT) in male pattern hair loss was clearly established.

Much less is known about female pattern hair loss (FPHL) than MPHL, partly because of less recognizable patterns of hair loss in women, but also because of the common presence of other confounding factors.

The purpose of this review is to provide current information on the potential pathophysiology, clinical presentation, and histology of pattern hair loss in men and women. We also present our consensus opinion of an approach to the evaluation and treatment of pattern hair loss.

PATHOPHYSIOLOGY

A. In men

- MPHL is a common age-dependent trait: the frequency and severity increase with age so that at least 8O% of Caucasian men show at least some signs of MPHL by age 70.[7,8] Whether the thinning that occurs after age 50 to 60 is all androgen related or is secondary to some other factor related to aging is not entirely clear.
- Asian, Native American, and many men of African heritage have a decreased frequency of frontal hair loss and less extensive hair loss compared to Caucasians.[9-12]
- Male pattern hair loss is clearly androgen-dependent.
  - — In Hamilton's studies, MPHL was absent in men castrated before puberty. However, MPHL developed in 4 of 12 male castrates treated with testosterone.[1]
  - — MPHL has not been reported in Complete Androgen Insensitivity Syndrome in which there is failure of androgen receptor expression.[13]

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Disclaimer: None of the treatments discussed, particularly those that are not FDA-approved for male pattern hair loss or female pattern hair loss, should be construed as endorsements or specific recommendations for individual patients. These suggestions and opinions are meant to supply an evidence-based record of information from which a physician can make informed judgments about diagnosis and treatment.

Funding sources: Although supported in part by an unrestricted educational grant from Galen Corporation/Merck & Co, neither representatives from Galen or Merck & Co were involved in any aspect of the planning, writing, or editing of this manuscript before or after submission for publication, This was an independent project by the authors.

Disclosure: All authors have been recipients of research grant funding and have served as consultants and/or principal investigators on at least one research study sponsored by Merck & Co, and Pfizer. None of the authors have any financial interest in any of the companies whose products are discussed here.

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Published online November 23, 2004.
J Am Acad Dermatol 2005;52:301-11.
0190-9622/$30.0O

• Although testosterone is the major circulating androgen in men, the testosterone metabolite, dihydrotestosterone, plays a dominant role in MPHL.
— The conversion of testosterone to dihydrotestosterone is catalyzed by 5*a*R.
— There are two isoforms of 5*a*R with different tissue distributions and encoded by different genes.[5]
  — Type I 5*a*R is widely expressed but its physiological function is uncertain.
  — Type II 5*a*R is expressed in androgen-dependent tissues such as the prostate and hair follicle.
— MPHL is absent in men with genetic deficiency of Type II 5*a*R.[3,4]
— Treatment with finasteride, a selective inhibitor of Type II 5*a*R, slows the progression of MPHL and produces some regrowth of hair in about 2/3 of men.[6]
• The primary target of androgen action in the hair follicle is uncertain but there is some evidence that it is mesenchymally derived tissue (dermal papilla [DP] and dermal sheath [DS]).[14-20]
• Genetic factors predispose to MPHL, but their nature and the mode of inheritance is uncertain.
— Inheritance of MPHL is most likely polygenic.[21]
  — There is increased frequency of MPHL in sons of men with MPHL.[8,22] The maternal influence on MPHL is less well defined.
— The early onset of MPHL may be a marker of the carrier status of a gene responsible for polycystic ovarian syndrome in some women.[23] This gene has not been identified.
— Polymorphism in the androgen receptor gene is associated with MPHL, particularly early onset.[24] However, this does not explain the paternal effect in men with MPHL since the androgen receptor gene is located on the X chromosome and, therefore, inherited only from the mother.

B. In women
• As in men, the frequency and severity of FPHL increase with age.[25]
• The role of androgens in all cases of FPHL is less certain and the authors recommend the more general term 'female pattern hair loss' rather than the term androgenetic alopecia.[26]
• FPHL undoubtedly, but not necessarily, occurs in women with hyperandrogenemia.[27]
— These women with hyperandrogenemia may show a 'male' pattern of hair loss,
— These women typically have other signs of hyperandrogenism, eg, hirsutism and/or menstrual disturbance. Hyperandrogenism implies an increased expression of androgen-related conditions but does not require an absolute elevation of serum androgens.
— Women with pattern hair loss in the presence of signs of hyperandrogenism may respond to treatment with finasteride,[28] or cyproterone acetate.[29]
• But:
— The pattern of hair loss in women with FPHL is usually different from that seen in men with MPHL (see clinical findings below).
— Most women with FPHL show no other clinical or biochemical evidence of androgen excess.[27]
— The family histories of women with FPHL are not as straightforward as those of men with MPHL.[30]
— There was no response in postmenopausal women to treatment with finasteride[31] or in women without signs of androgen excess to cyproterone acetate.[29]

General
Whatever the etiology, the follicular changes in MPHL and FPHL appear identical, ie, there is a 'final common pathway' of follicular miniaturization. This includes:
• Progressive reduction in the duration of anagen.
• The prolongation of the latent period of the hair cycle[32] (not yet confirmed in women). Normally, anagen reasserts itself after a fixed period of telogen towards the end of which the hair is shed. The latent period is a period of persistent suspension of growth of the follicle after the hair shaft has been shed.
• Follicular miniaturization
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CLINICAL FINDINGS
A. In men
• Onset:
— May begin anytime post-puberty, usually by age 40.
— 14% of healthy boys aged 15-17 years old show early signs of MPHL. (Trancik RJ, Spindler JR, Rose S et al: Incidence of androgenetic alopecia in males 15-17 years of age. Poster presented at 3rd Intercontinental Meet-

ing of the Hair Research Societies, June 13-15, 2001, Tokyo, Japan.)

— Distribution: Central scalp (this encompasses the frontal, mid, and vertex scalp).[33]

• Pattern:

— Most common: Varying degrees of hair loss in the bitemporal, frontal, mid scalp, and vertex regions that generally fall into one of the Hamilton-Norwood patterns of hair loss.[34]

— Uncommon: Diffuse scalp hair loss or female pattern of hair loss with diffuse central scalp hair thinning.

• Hair pull: May be positive in active early hair loss in the central scalp but generally negative in longstanding hair loss. If there is concomitant telogen effluvium, the hair pull may be positive diffusely over scalp.

• Affected hairs: Miniaturization (finer, shorter hairs) and decreased hair density to the same degree in a given area of the scalp may lead to baldness (no hair) in that area.

• Scalp: Generally normal. Concomitant seborrheic dermatitis is common. If the patient has perifollicular erythema or hyperkeratosis, consider a cicatricial alopecia variant.[35] A scalp biopsy is recommended in the latter case.

• Associated Findings: A higher incidence of coronary artery disease (CAD) has been reported in men with MPHL.[36,37] In one study of 19,112 US male physicians,[36] the relative risk of CAD was 1.32 (95% CI, 1.10-1.59) for moderate vertex baldness and, although independent of age, hypertension, or increased cholesterol, was stronger in men with hypertension or high cholesterol.

• Family history: Commonly positive for MPHL on either side of the family but 20% of patients do not have a family history of MPHL.

B. In women

• Onset:

— May begin any time post menarche or adrenarche.

— Many women also first complain of hair loss in the 40-50-year-old age group: Whether this is an exacerbation of long standing FPHL which has not been previously diagnosed or is truly late onset FPHL is not clear. That these women do not respond to a Type II 5*a*R inhibitor raises questions about the androgen-dependence of this subset of FPHL.[31]

• Distribution: Central scalp + /— sides of scalp.

• Pattern:

— Tends to be one of two patterns in most women: Diffuse central thinning[38] or frontal accentuation ("Christmas tree" pattern).[26,39]

— Fronto-temporal recession/vertex loss, ie, "male pattern," is a third, but uncommon, pattern.

— Bitemporal thinning is commonly associated with, but not necessarily indicative of, FPHL.

— There is not usually any recession of the frontal hairline although the hairs on the frontal margin are commonly miniaturized, ie, finer and shorter

• Hair pull: May be positive in active early loss in the central scalp but generally negative in longstanding hair loss. If there is a concomitant telogen effluvium, the hair pull may be positive diffusely over the scalp.

• Affected hairs: Miniaturization is generally not as uniform nor as profound in specific scalp areas as that in MPHL, and hence, there are no regions of absolute baldness as with MPHL.

• Scalp: Generally normal. Concomitant seborrheic dermatitis is common. If the patient has perifollicular erythema or hyperkeratoses, consider a cicatricial alopecia variant.[35] A scalp biopsy is recommended in the latter case.

• Associated findings: Signs or symptoms of hyperandrogenism should he looked for, ie, hirsuitism, moderate to severe or treatment-refractory acne, irregular menses, infertility, and/or galactorrhea. Acanthosis nigricans is a marker for insulin resistance which is commonly associated hvperandrogenism.[40]

• Family history: Women with FPHL are less likely than men with MPHL to have a history of first-degree relatives with MPHL.[41]

EVALUATION

A. General

• It is important to exclude other causes of hair loss that may mimic pattern hair loss (PHL) since some treatments for PHL are selective (eg, finasteride in MPHL). It is also important to determine if there are other concomitant hair disorders whose untreated presence could ultimately affect the utility of the treatments used for PHL. (eg, iron deficiency in FPHL).[42] The differential diagnosis of PHL should include acute and chronic telogen effluvium, diffuse or reverse ophiasis alopecia areata, and early cicatricial alopecia.

B. **In men**

• Anabolic steroids or supplemental androgens may worsen PHL.

• Consider checking thyroid stimulating hormone (TSH*)* if the hair loss is diffuse and not localized exclusively to typical MPHL areas.

• Consider iron evaluation in men on a strictly vegetarian or otherwise deficient **diet** or where blood loss could be an issue.

C. In women

• Screening blood work is generally recommended in all women. In otherwise healthy women, check TSH and serum ferritin. Hypothyroidism may cause a telogen effluvium[43] and iron deficiency is speculated to both cause a telogen effluvium[44] and **to** interfere with the efficacy of treatment of FPHL.[42] Iron deficiency may be screened by two methods: serum ferritin or serum iron and total iron binding capacity (TIBC). A low serum ferritin is diagnostic of iron deficiency. However, depleted iron stores in patients with chronic disease may not be detected by serum ferritin measurements since ferritin is an acute phase reactant, and active inflammatory disorders, malignancy, and infections increase its synthesis and may, by its elevation in these situations,[45] give a false sense of normal iron stores. Some physicians prefer to have a sedimentation rate drawn with the ferritin to rule out falsely high or normal levels of ferritin in those with underlying active medical problems. If physicians elect to check serum iron and total iron binding capacity instead of ferritin, patients should not be taking concomitant iron-containing preparations (ie, multivitamins with iron or oral contraceptive pills [OCPs] containing iron) for at least 24 hours beforehand since exogenous iron can increase serum iron transiently but mask deficient marrow iron stores. Iron supplements taken for $\geq$3 weeks can falsely elevate ferritin levels in the face of iron deficiency. Iron deficiency is associated with low serum iron and relatively high total iron binding capacity and low percent saturation.

• Other screening tests may he indicated by history including a complete blood cell (CBC) and/or free thyroxine (T4).

• The majority of women with FPHL have no clinical or biochemical evidence of androgen excess.[27] However, a subset of women with FPHL does, and women with concomitant signs/symptoms of hirsuitism, moderate to severe and/or treatment- refractory adult acne, acanthosis nigricans, irregular menses, and or galactorrhea should he adequately screened for hvperandrogenemia. In these cases, blood tests should include:

1. Free and/or total testosterone +/- dehydroepiandrosterone sulfate (DHEAS) at a minimum. Tests ideally should be done off of OCP's since OCP's will inhibit both ovarian and adrenal sources of androgens.[46] If these tests are normal on OCP's, but the suspicion is high for underlying hyperandrogenemia, they should be repeated at least one month after cessation of OCP's.
2. If testosterone is greater than *2.5* X normal or >200 ng/dL, or DHEAS is greater than *2X* normal or >700 ug/dL in premenopausal or >400 ug/dL in postmenopausal women**,** a work-up for a tumor with radiographic tests should be undertaken.[47]
3. Consider checking serum prolactin if galactorrhea is present or if there is increased testosterone or free testosterone.
4. Consider screening for congenital adrenal hyperplasia **(**CAH) if testosterone or DHEAS is elevated. An early morning serum 17-OH progesterone during the follicular phase of the cycle (days 1-14) would be a reasonable screening test for the most common form of CAH, ie, 21-hydroxylase deficiency.[48] However, a serum 17-OH progesterone pre- and post-Cortrosyn (synthetic adrenocorticotropic hormone [ACTH] stimulation test is the most reliable way of screening for 21-hydroxylase deficiency. If either prolactin or 17-OH progesterone is increased, one may wish to refer the patient to an interested endocrinologist for further evaluation and treatment.

HISTOPATHOLOGY

A. Indications for biopsy

• Diagnosis:

—Males: Usually not necessary unless a female pattern of hair loss, diffuse hair loss, or scalp changes suggestive of cicatricial alopecia confuse the diagnosis.

—Females: Sometimes necessary to exclude chronic telogen effluvium, diffuse alopecia areata, or cicatricial hair loss such as early central centrifugal cicatricial alopecia seen commonly in African**i** American women.

• Site of biopsy: The preferred area for biopsy is the central scalp in an area representative of the hair loss

process. Biopsy should not be from bitemporal area as this region may have miniaturized hairs independent of MPHL or FPHL.

- Type of biopsy: A punch biopsy of less than 4 mm in diameter that follows the direction of the hair shafts and is taken deep into the subcutaneous fat where anagen hair bulbs are located is standard. Many dermatopathologists favor horizontal sectioning of biopsies.[49]
- Histologic diagnosis:[49-51]
    1. The key change is miniaturization of terminal hairs into vellus-like hairs. This change is progressive over time. The same changes characterize both male and female pattern hair loss.
    2. The percentage of telogen hairs increases from a normal of 5% - 10% to 15% - 20% on average with a corresponding decrease in the percentage of anagen hairs. The percentage of telogen hairs is slightly less in female pattern hair loss than in male pattern hair loss.
    3. Horizontal sections permit accurate follicular counts of terminal and vellus and vellus-like hairs and characterization of terminal hairs as anagen, catagen, or telogen. Terminal hairs have hair shafts that are > 0.03 mm in diameter and thicker than the follicle's inner root sheath. Vellus or vellus-like (miniaturized) hairs have hair shafts that are $\leq$ 0.03 mm in diameter and thinner than the follicle's inner root sheath.
    4. Vertical sections show a limited number of hair follicles but do allow one to estimate the proportion of anagen, catagen, and telogen hairs and terminal vs vellus or vellus-like hairs.
    5. The ratio of terminal to vellus or vellus-Iike hair normally is 7:1. In PHL, the ratio decreases to 1.9:1 (both sexes combined) or 1.5:1 (males only), 2.2:1 (females only).[52] The amount of vellus or vellus-like hairs is slightly less in FPHL than in MPHL.
    6. The total number of hairs per unit area is usually normal in PHL (normal being approximately 240-400 hairs/cm_ or 30-50 hairs per 4 mm punch biopsy in normal adults)[52,53] but may be reduced in severe baldness or in elderly patients
    7. A perifollicular infiltrate, predominantly lymphohistiocytic, may be present in pattern hair loss, around the upper or lower follicle. The prognostic implications of this finding are uncertain at this time.
    8. Perifollicular fibrosis, usually comprising concentric layers of collagen deposition may be present in pattern hair loss around the upper and lower follicle. This may have negative implications for potential regrowth although further data are needed to corroborate this.

TREATMENT

A. General principles

- The diagnosis should be confirmed. Some treatments are specific to the pathophysiology of PHL, and others are nonspecific hair growth promoters.
- Patients should avoid hair care products likely to damage scalp/hair. This is particularly important African American Women
- Patients should maintain an adequate diet, especially one with adequate protein. The National Institutes of Health (NIH)) recommended daily allowance for protein is 0.35 gm/lb or 0.8 gm/kg, which translates into 45 grams for a 150-lb. person.
- Topical medications work only where the medication is applied; therefore, the entire area at risk of loss (the top of the scalp) should be treated with a given topical agent.
- If possible, any drugs that could negatively affect hair growth should be stopped and alternative substitutes made. Although certain drugs are more commonly associated with hair loss than others, any drug can potentially cause a telogen effluvium. Medications for which hair Ioss is a common potential side effect include retinoids,. cytotoxic agents, and anticoagulants
- Treat any underlying scalp disorder such its seborrheic dermatitis or scalp psoriasis as these conditions can affect the ability to use topical treatments for hair loss without irritation.

B. Medical treatment for men

GENERAL

- Currently, only finasteride 1 mg and minoxidil topical solution (2% and 5%) are FDA-approved for the treatment of male pattern hair loss.
- Both drugs retard further thinning and increase scalp coverage. However, in many patients, the main perceived response may be maintenance of current hair density.

- Neither drug restores all the lost hair. Neither drug is able to reverse total baldness.
- Both drugs require chronic use to maintain effectiveness. If treatment is discontinued the effects of the drug are lost over several months, and the hair density will evolve into what it would have been without treatment.
- Treatment shouId be used for 12 months before making a decision about efficacy although benefit may be seen sooner.

Finasteride (1 MG ORAL DAILY)

- FDA-approved for men ≥ 18 years old.
- Mode of action:
  - Competitive inhibitor of Type II 5*a*R that decreases the conversion of testosterone (T) to DHT. DHT serum and scalp is decreased ~2/3 with treatment.[54]
- Efficacy:
  - — Target area hair counts (TAHC) are generally used to assess efficacy in clinical trials of MPHL. TAHC's are circular target areas 1 cm to 1 inch in diameter typically at the interior leading edge of the vertex balding area where the terminal, non-vellus, or visible hairs are counted pre- and post-treatment.
  - — Target area hair counts increase over the first year and peak by ~ 12 months: In men age 18-41, hair counts increased 16.9/cm_ for those on 1 mg finasteride vs - 4.1/cm_ for those on placebo.[6]
  - — By expert panel review of global photographs, hair growth continues to improve for at least the first 24 months of treatment as the hairs grow longer and thicker. In men aged 18- 41, ~ 50% of men showed an increase in hair growth by 1 year, and 66% by 2 years on finasteride, compared to 7% and 7% at both 1 and 2 years respectively for placebo.[6] In men aged 41-60, 39% on finasteride versus 3% on placebo showed increased hair growth at 2 years.[55]
  - — 5-year placebo controlled trials using both hair counts and expert panel review of global photographs as endpoints confirm that continued use of finasteride helps to maintain this effect and to slow further hair loss.[56]
  - — If treatment with finasteride is discontinued, any positive effect on hair growth will be lost in 12 months.[6]
- Safety
  - — No known drug interactions.
  - — No effects on liver, kidney, bone marrow, or bone or serum lipids.
  - — No effect on spermatogenesis.
  - — Reversible sexually-related side effects (decreased libido, erectile dysfunction, decreased ejaculate volume) were seen in 1.8% of men aged 18- 41 versus 1.1% of those on placebo.[6] In older men aged 41-60, sexually-related side effects were seen in 8.7% on finasteride vs 5.1% on placebo.[54] These side effects often resolve during continued treatment or within days to weeks after treatment with finasteride is discontinued.
  - — The level of finasteride in semen of men taking finasteride is very low and semen from a man taking finasteride poses no risk to a pregnant woman or to her fetus.[57]
  - — Reduction in prostate specific antigen (PSA) is physiologically based on the effect of decreased DHT on the prostate. Recommendation is that any PSA test value should be doubled for any man taking finasteride to compensate for the effect of the drug.[58,59]
  - — Recent data from a long-term (7 year) trial of 18,882 men greater than or equal to 55 years old with normal digital rectal examination and less than or equal to 3.0 ng/ml serum PSA who took 5 mg finasteride (5X the standard dose recommended for MPHL) vs placebo revealed a 25% decrease in prostate cancer for those on finasteride (803 on finasteride vs 1147 on placebo).60 However, 6.4% of men on finasteride developed histologically high grade cancer (defined as Gleason score 7-10) vs 5.1% of those on placebo. This study only monitored changes in the number of prostate cancers and histologic subtype but did not address the biological aggressiveness of the tumors or outcome. Potentia1 hypotheses for the findings include that: (a) finasteride may selectively inhibit low grade prostate tumors, (b) low DHT may induce histologic changes that mimic high grade disease, or (c) low DHT may induce higher grade prostate cancers. Further research and long-term observation of men taking finasteride 1 mg needs to be done on this issue.

MINOXIDIL TOPICAl. SOLUTION 2% AND 5%

- FDA-approved for men > 18 years old. Adolescents have been treated with topical minoxidil solution without any additional problems (Trancik RJ, Spindler JR, Cuddihy RV, et al.: Clinician survey evaluating minoxidil topical solution in the treatment of androgenetic alopecia in patients under 18 years of age. Poster presented at 3rd Intercontinental Meeting of the Hair Research Societies, June 13-15, 2001. Tokyo, Japan).
- Mode of action:

— Increases duration of anagen and enlarges miniaturized follicles.

— Potassium channel opener and vasodilator. The precise mechanism of action is unknown but appears independent of vasodilation.61

• Application: 1 mL twice daily to dry scalp, preferably using a dropper application. Topical minoxidil solution requires approximately 1 hour for absorption. If the patient shampoos or the scalp becomes wet, eg, from excessive sweating or rain, the medication should be re-applied. If gel or hair spray is used, the medication should be applied first so that absorption is not affected.

• Efficacy:

— Target area hair counts and global photographs confirm a significant increase in hair density.62 The hair growth appears to peak at 16 weeks.62 The placebo-controlled trials of both target area hair counts and expert panel review of global photographs at 1 year 62 and hair weight studies over 2 years 63 confirm that continued use of topical minoxidil solution helps to maintain this effect and to slow further loss.

— 5% topical minoxidil solution is superior to 2% topical minoxidil solution by target hair counts, expert panel review of global photographs,62 and hair weight studies in men with MPHL.63 Target area hair count increases are

18.6/cm^2 for 5% topical minoxidil solution, 12.7/cm^2 for 2% topical minoxidil solution and 3.9/cm^2 for placebo at 48 weeks. Expert panel review of global photographs show increased growth at 1 year in 57,9% on 5% topical minoxidil solution**,** 40.8% on 2*%* topical minoxidil solution, and 23.2% on placebo.[62]

— If treatment is discontinued. any positive effect on hair growth will be lost in 4-6 months.[64]

— Topical minoxidil solution may initially cause a telogen effluvium beginning 2-8 weeks after treatment initiation. This temporary shedding, resulting from the minoxidil initiated release of telogen hairs (‘‘exogen’’) as anagen promotion begins, is self-limiting with continued treatment and should not be a cause for concern. Patients should, however, be forewarned so that treatment is not interrupted.

▪ Safety: Adverse effects are mainly dermatologic.[62]

— Scalp irritation, including dryness, scaling, itching, and/or redness, may occur; these are more common with the 5% topical minoxidil solution than the 2% topical minoxidil solution.

– Allergic contact dermatitis is uncommon.[56] Patch test kits are available from Pfizer and may help to sort out whether a rash is an irritant or allergic contact dermatitis and whether it is related to minoxidil or propylene glycol.

• Combination treatment of finasteride and topical minoxidil

— There have been no well-controlled studies in humans. A study in the stumptailed macacque, an animal model for pattern hair loss in both sexes, showed art additive effect when both drugs were used concurrently.[65]

— Men who wish to switch from treatment with one of these agents to the other should continue using the original medication in addition to the new agent for at least 3 months before discontinuing it. The cross over period is needed to provide time for the newer drug to reach a point of effectiveness to avoid excess shedding.

C. Medical treatment for women

WOMEN WITH OR WITHOUT HYPERANDROGENISM:

• If women are on hormone replacement therapy or an OCP, the dose and type should be stabilized, Over-the-counter DHEA or testosterone in hormone replacement therapies should be avoided. In this way, women with FPHL will minimize external additions to any potential underlying androgen sensitivity.

• Minoxidil Topical Solution:

Efficacy:

— currently. only 2% topical minoxidil solution is FDA-approved for the treatment of ‘‘women with thinning hair.’’[66]

— 5% topical minoxidil solution, although not currently FDA—approved for use in women, has been evaluated in women with FPHL and was found to be significantly more effective than placebo by both target area hair counts and subject assessment.[67] There was a trend towards superior efficacy of 5% topical minoxidil solution over 2% topical minoxidil solution but this was not consistently statistically significant. Target area hair counts

at 48 weeks showed a change from baseline of 24.5/cm_, 20.7/cm_, and 9.4/cm^2 in the 5% topical minoxidil solution, 2% topical minoxidil solution, and placebo group respectively. The sensitivity of target area hair counts as a primary endpoint in FPHL has been questioned.[33]

—Treatment should be used for 12 months before making a decision about efficacy although benefit may be seen sooner.

—Topical minoxidil solution works in those women with FPHL both with and without hyperandrogenism and in young and old, pre- a and postmenopausal women alike.

Safety:

—Either 2% or 5%, topical minoxidil solution appears safe to use in women with FHPL, with the only additional risk of the 5% topical minoxidil solution over the 2% topical minoxidil solution being a higher incidence of facial hypertrichosis. The hypertrichosis tends to occur over the cheeks and forehead as vellus, not terminal hair and disappears within 4 months of stopping the drug. Although this may he related to inadvertent spreading to the face after local application to the scalp, this may also be a result of hypersensitivity to low levels of systemic absorption of minoxidil. Other local side effects are the same as in men.

WOMEN WITH HYPERANDROGENISM

- Hvperandrogenism is synonymous with excessive secretion of androgens[68] the indirect evidence of which is the existence of hirsuitism, severe or treatment refractory acne and/or irregular menses (the latter in a woman of childbearing potential off of OCP's), and/or elevation of serum testosterone, free testosterone, or DHEAS. Less than 40% of women FPHL have hyperandrogenism[27] but this population, with clear-cut evidence of androgen hypersensitivity or overproduction, may

respond differently to drugs that block the production or effect of androgens than those women with FPHL and no hyperandrogenism.

- Antiandrogens and 5*a*—reductase inhibitors
  - There are few studies evaluating the effect of antiandrgens or 5*a*R inhibitor in FPHL and only one that is large and placebo—controlled**.** Most studies showing efficacy of these agents have been done in women with hyperandrogenism, particularly those with hirsuitism. Studies of these agents in women with FPHL who do not have overt hyperandrogenism have not specifically shown proven efficacy. In the United States, all of these agents are used off-label for the treatment of hirsutism or female pattern hair loss.

—Since all antiandrogens or 5*a*R inhibitors may cause feminization of a male fetus, all women of childbearing potential should use effective means of contraception while taking any of these drugs. OCPs have the additional advantage of also lowering serum androgens. Women of childbearing potential who use an antiandrogen or 5*a*—reductase inhibitor should be cautioned to stop the medication and call their doctor if their menses are late.

—If of childbearing potential and on an OCP for at least 1 month with a negative pregnancy test, or if of non-childbearing potential, one may try either:

—Spironolactone 100 - 200 mg per day.

1. Only small, uncontrolled studies with spironolactone in FPHL have been published but they support efficacy in the subset of FPHL with hyperandrogenism. [69]
2. For safety purposes, one should check serum potassium at baseline and 1 month after beginning treatment since hyperkalemia is a rare side effect. Patients should keep well hydrated.

—Finasteride 1-1.25 mg per day

1. In a well-controlled study, finasteride I mg per day, was not shown to be useful in post-menopausal women with FPHL.[31] These subjects were not specifically stratified for hyperandrogenism.
2. Some positive reports in women with hyperandrogenism treated with 1.25 mg per day have emerged.[28]
3. There are no anticipated side effects and no blood tests are necessary.

—Cvproterene acetate:

1. 100 mg days 5-15 combined with 50 ug ethinyl estradiol on days 5-25 of the menstrual cycle appears most useful.[70]
2. Only one well-controlled study has been done with FPHL and this proves the value of cyproterone acetate

in women with hyperandrogenism only.[29]

3. Diane (2 mg cyproterene acetate days 5-15 and 50 ug ethinyI estradiol days 5-25 of the menstrual cycle) appears to be less effective in hair loss. [71]

4. No specific blood tests are necessary.

D. Cosmetic aids

- Nonmedical approaches can provide cosmetic relief to men and women with thinning hair if medical treatments are not indicated, not effective, or not desired by the patient. They can also be used as adjuvant therapy if medical or surgical treatments are used.
- Tinted powders, lotions, and hair sprays can all provide a cosmetic covering of the scalp in areas of scalp hair thinning and can be useful in camouflaging it.
- Wigs. hair pieces, and hair extensions can be used to cover a thinning scalp. Advances in the technology of these prostheses have made their use much more acceptable.

E. Surgical treatment[72-74]

HAIR TRANSPLANTS

. Criteria for assessing male candidates:

— Age:

— Patients over the age of 25 years are preferable. The predictive value of future hair loss is much lower for individuals between the ages of 15 and 25 years of age and surgery in this young group of men may result in misplaced hairlines or an unnatural appearance 20 or 30 years later. Young men with early hair loss (Hamilton-Norwood I and II patterns) already have enough hair for facial framing and will receive limited aesthetic benefit from surgery.

- Degree of frontal and vertex hair loss:

Vertex baldness is a progressive process and does not become "stable with time'', and therefore, hair transplantation of the vertex should be approached with extreme caution**.** Ideal candidates are those with just frontal and mid-frontal hair loss. When frontal baldness is corrected, this creates the most dramatic positive change in appearance.

- Density of donor area should he adequate:

Patients with <40 follicular units/cm_ in the donor area are considered poor candidates.

- Hair caliber and color: Thicker hair shafts (>60-70 microns) demonstrate better coverage

compared to finer hair. Lightcr colored hair in Caucasians gives a more natural look compared to dark colored hair since the contrast between hair and skin is not as apparent.

- Criteria for assessing female candidates:

— Women with mild female pattern alopecia (early Ludwig I) arc no**t** optimal surgical candidates since differences in pre-transplanted scalp vs. post-transplanted scalp are difficult to appreciate.

— Those with diffuse unpatterned alopecia are poor surgical candidates for the obvious reason that the entire scalp is suffering hair loss, thus, the donor area is of limited value as it is also susceptible to loss.

— The ideal female patients for hair transplantation are those with high-density donor hair and extensive hair loss or thinning of the frontal scalp.

- Number of sessions:

Experienced surgical teams can create significant coverage in one to two sessions with dense packing of higher number of grafts (1000-2000) being performed per session. Final results are usually seen 5-6 months after the procedure, and thus, timing between sessions, if needed, Is usually a minimum of 6 months.

- Complications:

— Facial edema, scalp erythema, and recipient site crusts of the scalp are common but usually resolve within 3-7 days although crusting may persist a few additional days.

— Other possible complications of hair transplants include nausea and vomiting, post operative bleeding (less than 0.5%), infection (less than 05%), excessive swelling (5%), temporary headache, temporary numbness of the scalp, abnormal scarring around the grafts (less than 1%), poor growth of grafts, fainting (less than 1%), folliculitis, keloid formation, neuroma, persistent scalp pain, telogen effluvium, and arterio-venous fistula formation.

SCALP REDUCTIONS

- Description:

— Hair-bearing skin is brought closer together by removing the center scalp affected by the alopecia.

— Not commonly performed currently.

— Many different designs employed in excising the balding area.

— Reductions may be performed in conjunction with hair transplantation to the remaining bald scalp for a more optimum result.

- Potential complications:

— The efficacy diminishes over time due to the unpredictable progression of hair loss in any given individual.

— Excision scars become noticeable over time.

— The scar may potentially widen secondary to stretching of adjacent scalp skin.

— Usually more than one scalp reduction is necessary to effectively address a person's baldness.

Adjunctive medical therapy with surgery

The use of finasteride and/or topical minoxidil may stabilize underlying hair loss therefore necessitating less donor harvesting and less scalp reductions. This will also allow the patient to maintain a more natural appearance over time.

CONCLUSION

Although the clinical aspects of pattern hair loss are well-recognized in both men and women and the role of DHT and MPHL is well documented, much remains to be determined regarding the genetics and pathophysiology of these common conditions. There are effective treatments, either medical or surgical, available currently for some men and women with pattern hair loss, but clearly further treatment options arc desired, particularly for women with FPHI..

REFERENCES

1. Hamilton JB. Male hormone stimulation is prerequisite and an incitant in common baldness. Am J Anat 1942:71:451-80.
2. Orentreich N. Autografts in alopecias and other selected dermatological conditions. In: St. Whitelock OV, Furness FN, White EW, Lubowe II editors. Hair Growth and Hair Restoration. Ann NY Acad Sci 1959;83:463-79.
3. Imperato-McGinley J, Guerrero L, Gautier T, Peterson RE. Steroid 5*a*-reductase deficiency in man: an inherited form of male pseudohermaphroditism. Science 1974;186:1213-5.
4. Andersson S, Berman DM, Jenkins EP, Russell DW. Deletion of steroid 5-alpha-reductase 2 gene in male pseudohermaphroditism. Nature 1991;354:159-61.
5. Jenkins EP, Andersson 5, lmperato-McGinley J, Wilson JD, Russell DW. Genetic and pharmacological evidence for more than one human steroid 5-alpha-reductase. J Clin Invest 1992; 89:293-300.
6. Kaufman KD, Olsen EA, Whiting D, Savin R, DeVillez R, Bergfeld W. Finasteride in the treatment of men with androgenetic alopecia. J Am Acad Dermatol 1998;39:578-89.
7. Hamilton JB. Patterned loss of hair in man: Types and incidence. Ann NY Acad Sci 1951;53:708-28.
8. Birch MP, Messenger AG. Genetic factors predispose to balding and non-balding in men. Eur J Dermatol 2001;11:309-14.
9. Muller SA. Alopecia. Syndromes of genetic significance. J Invest Dermatol 1973;60:475-92.
10. Hamilton JB. Age, sex, and genetic factors in the regulation of hair growth in man: A comparison of Caucasian and Japanese populations. Montaaqna W, Ellis RA, editors. The Biology of Hair Growth. New York: Academic Press; 1958:399-433.
11 Setty LR. Hair patterns of the scalp of white and Negro males. Am J Phys Antropol 1970;33:49-55.
12. Buechner HA, Brown M, Tretola RJ, Baldness and emphysema. J La State Med Soc 1964;115:329-32.
13. Griffin JE, Wilson JD. The androgen resistence syndromes: 5areductase deficiency, testicular feminization and related syndromes. In: Scrivér CR, Beaudet AL, Sly WS, Valle D, editors. The Metabolic Basis of Inherited Disease, 6th ed. New York: McGraw-Hill; 1989:1919-44.
14. Jahoda CA, Reynolds AJ. Dermal-epidermal interactions. Adult follicle-derived cell populations and hair growth. Dermatol Clin 1996;14:573-83.
15. Van Scott EJ, Ekel TM. Geometric relationships between the matrix of the hair bulb and its dermal papilla in normal and alopecic scalp. J Invest Dermatol 1958;31:281-7.
16. Ibrahim L, Wright EA. A quantitative study of hair growth using mouse and rat vibrissal follicles. I. Dermal papilla volume determines hair volume. J Embryol Exp Morphol 1982;72:209-24.
17. Elliott K, Stephenson TJ, Messenger AG. Differences in hair follicle dermal papilla volume are due to extracellular matrix volume and cell number: implications for the control of hair follicle size and androgen responses. J Invest Dermatol 1999;113:873-7.
18. Choudhry R, Hodgins MB, Van der Kwast TH, Brinkmann AO, Boersma WJ. Localization of androgen receptors in human skin by immunohistochemistry: implications for the hormonal regulation of hair growth, sebaceous glands, and sweat glands. J Endocrinol 1992;133:467-75.
19. ltami S, Kurata S, Sonoda T, Takayasu S. Interaction between dermal papilla cells and follicular epithelial cells in vitro: effect of androgen. Br J Dermatol 1995;132:527-32.

20. Asada Y, Sonoda T, Ojiro M, Kurata S, Sato T, Ezaki T, et al. 5 alpha-reductase type 2 is constitutively expressed in the dermal papilla and connective tissue sheath of the hair follicle in vivo but not during culture in vitro. J Clin Endocrinol Metab 2001;86:2875-80.
21. Küster W, Happle R. The inheritance of common baldness: two B or not two B? J Am Acad Dermatol 1984;11:921-6.
22. Ellis JA, Stebbing M, Harrap SB. Genetic analysis of male pattern baldness and the 5 alpha-reductase genes. J Invest Dermatol 1998;110:849-53.
23. Carey AH, Chan KL, Short F, White D, Williamson R, Franks S. Evidence for a single gene effect causing polycystic ovaries and male pattern baldness. Clin Endocrinol 1993;38:653-8.
24. Ellis IA, Stebbing M, Harrap SB. Polymorphism of the androgen receptor gene is associated with male pattern baldness. J Invest Dermatol 2001;116:452-5.
25. Birch MP, Messenger JF, Messenger AG. Hair density, hair diameter and the prevalence of female pattern hair loss. Br J Dermatol 2001;144:297-304.
26. Olsen EA. Female pattern hair loss. J Am Acad Dermatol 2001;45:570-80.
27. Futterweit MD, Dunaif A, Yeh H-C, Kingsley P. The prevalance of hyperandrogenism in 109 consecutive female patients with diffuse alopecia. J Am Acad Dermatol 1988;19:831-6.
28. Shum KW, Cullen DR, Messenger AG. Hair loss in women with hyperandrogenism: four cases responding to finasteride. J Am Acad Dermatol 2002;47:733-9.
29. Vexiau P. Chaspoux C, Boudou P, Fiet J, Jouanique C, Hardy N, et al. Effects of minoxidil 2% vs. cyproterone acetate treatment on female androgenetic alopecia: a controlled, 12-month randomized trial. Br J Dermatol 2002;146:992-9.
30. Norwood OT, Lehr B. Female androgenetic alopecia: a separate entity. Dermatol Surg 2000;26:679-82.
31. Price VH, Roberts JL, Hordinsky M, Olsen EA, Savin R, Bergfeld W, et al. Lack of efficacy of finastereride in postmenopausal women with androgenetic alopecia. J Am Acad Dermatol 2000;43:768-76.
32. Courtois M, Loussouarn G, Hourseau C, Grollier JF. Ageing and hair cycles. Br J Dermatol 1995:132:86-93.
33. Olsen EA. Current and novel methods for assessing efficacy of hair growth promoters in pattern hair loss. I Am Mad Dermatol 2003;48:253-62.
34. Norwood OT. Male pattern baldness: Classification and incidence. South Med J 1975;68:1359-65.
35. Zinkernagel MS. Trueb RM. Fibrosing alopecia in a pattern distribution. Arch Dermatol 2000;136:205-11.
36. Lesko SM, Rosenberg L, Shapiro S. A case-control study of baldness in relation to myocardial infarction in men. JAMA 1993;269:9987-10003.
37. Lotufo PA. Chae CU, Ajani UA, Hennekens CH, Manson JE. Male pattern baldness and coronary heart disease: The Physician's Health Study. Arch Intern Med 2000;150:154-71.
38. Ludwig E. Classification of the types of androgenetic alopecia (common baldness) occurring in the female sex. Br J Dermatol 1977;97:247-54.
39. Olsen EA. The midline part: An important physical clue to the clinical diagnosis of androgenetic alopecia in women. J Am Acad Dermatol 1999;40:106-9.
40. Torley D, Bellus GA, Munro CS. Genes, growth factors and acanthosis nigricans. {Review}. Br J Dermatol 2002;147:1096-100.
41. Smith MA, Wells PS. Male-type alopecia, alopecia areata, and normal hair in women: Family histories. Arch Dermatol 1964; 89:95-8.
42. Rushton DH, Ramsay ID. The importance of adequate serum ferritin levels during oral cyproterone acetate and ethinyl oestradiol treatment of diffuse androgen-dependent alopecia in women. Clin Endocrinol 1992;36:421-7.
43. Freinkel BK, Freinkel N. Hair growth and alopecia in hypothyroidism. Arch Dermatol 1972;106:349-52.
44. Hard S. Non-anemic iron deficiency as an etiologic factor in diffuse loss of hair of the scalp in women. Acta Derm Venereol 1963;43:562-9.
45. Fairbanks VF, Beutler E. Erythrocyte disorders: Anemias related to disturbances of hemoglobin synthesis. In: Williams WJ, Beutler F, Ersley AJ, Lichtman MA, editors. Hemnatology, 4th ed. New York: McGraw-Hill 1990;482-505.
46. Mestman JH, Anderson GV, Nelson DH. Adrenal-pituitary responsiveness during therapy with an oral contraceptive. Obstet Gynecol 1968;31:378-86.
47. Pittaway DE. Neoplastic causes of hyperandrogenism. Infertil Reprod Med Clin North Am 1991;2:479-94.
48. Azziz R, Zacur HA. 21-Hydroxylase deficiency in female hyperandrogenism. Screening and diagnosis. J Clin Endocrinol Metab 1989;69:577-84.
49. Whiting DA. Diagnostic and predictive value of horizontal sections of scalp biopsy specimens in male pattern androgenetic alopecia. J Am Acad Dermatol 1993;28:755-63.
50. Sperling LC, Lupton GP. Histopathology on non-scarring alopecia. J Cutan Pathol 1995;22:97-114.
51. Lattanand A, Johnson WC. Male pattern alopecia: A histopathologic and histochemical study. J Cutan Pathol 1975;2:58-70.
52. Whiting DA, Waldstreicher J, Sanchez M, Kaufman KD. Measuring reversal of hair miniaturization in androgenetic alopecia by follicular counts in horizontal sections of serial scalp biopsies. Results of finasteride 1 mg treatment of men and postmenopausal women. J Invest Dermatol Symp Proc 1999;4:282-4.
53. Whiting DA. Scalp biopsy as a diagnostic and prognostic tool in androgenetic alopecia. Dermatol Ther 1998;8:24-33.
54. Drake L, Hordinsky M, Fiedler V. Swinehart J, Unger WP, Cotterill PC, et al. The effects of finasteride on scalp skin and serum androgen levels in men with androgenetic alopecia. J Am Acad Dermatol 1999;41:550-4.
55. Whiting DA, Olsen EA, Savin A, Halper L, Swinehart J, Unger WP, Cotterill PC, Rodgers A, et al. Efficacy and tolerability of finasteride 1 mg in men aged 41 to 60 years with male pattern hair loss. Eur J Dermatol 2003;13:150-60.
56. The Finasteride Male Pattern Hair Loss Study Group. Long term (5-year) multinational experience with finasteride 1 mg in the treatment of men with androgenetic alopecia. Eur J Dermatol 2002:12:38-49.
57. Physicians' Desk Reference. 5th Edition Montvale, NJ: Thomson PDR; 2003. 56.
58. Guess HA, Gormley GJ, Stoner E, Oeserling JE. The effect of finasteride on prostate specific antigen: review of available data. J Urol 1992;155:3-9.
59. Oesterling JE, Roy J, Agha A, Shown T, Krarup T, Johansen T, et al. Biologic variability of prostate-specific antigen and its usefulness as a marker for prostate cancer: Effects of finasteride. Urol 1997;50:13-8.

60. Thompson IM, Goodman PJ, Tagen CM, Lucia MS, Miller GJ, Ford LG, et al. The influence of finasteride on the development of prostate cancer. N EngI J Med 2003;349:213-22.
61. Buhl AE, Conrad SJ, Waldon DJ, Brunden MN. Potassium channel conductance as a control mechanism in hair follicles. J lnvest Dermatol 1991;96:735-45.
62. Olsen EA, Dunlap FE, Funicella T, Koperski JA, Swinehart JM, Tschen EH, et al. A randomized clinical trial of 5% topical rninoxidil versus 2% topical minoxidil and placebo in the treatment of androgenetic alopecia in men. J Am Acad Dermatol 2002;47:377-85.
63. Price VH, Menefee E, Strauss PC. Changes in hair weight and hair count in men with androgenetic alopecia after application of 5% and 2% topical minoxidil, placebo, or no treatment. J Am Acad Dermatol 1999;41:717-21.
64. Olsen EA, Weiner MS. Topical minoxidil in male pattern baldness: Effects of discontinuation of treatment. J Am Acad Dermatol 1987;17:97-101.
65. Diani AR, Mulholland MJ, Shull KL, Kubicek MF, Johnson GA, Schostarez HJ, et al. Hair growth effects of oral administration of finasteride, a steroid *5a*-reductase inhibitor, alone and in combination with topical minoxidil in the balding stumptail macaque. J Clin Endocrinol Metab 1992;74:345-50.
66. DeVillez RI, Jacobs JP, Szpunar CA, Warner ML. Androgenetic alopecia in the female: Treatment with 2% topical minoxidil solution. Arch Dermatol 1994;130:303-7.
67. Lucky AW, Piacquadio DJ, Ditre CM, Dunlap F, Dunlap F, Kantor I, Pandya AG, et al. A randomized, placebo-controlled trial of 5% and 2% topical minoxidil solutions in the treatment of female pattern hair loss. J Am Acad Dermatol 2004;50:541-53.
68. Borland's Medical Dictionary. 26th Edition PhiIadeIphia:WB. Saunders Company; 1985.
69. Burke BM, Cunliffe WI. Oral spironolactone therapy for female patients with acne, hirsutism or androgenic alopecia. [Letter]. Br J Dermatol 1985;112:124-5.
70. Dawber RPR, Sonnex T, Ralfs I. Oral anti-androgen treatment of common baldness in women. Br J Dermatol 1982:107:20.
71. Moltz L, Mechies J, Hammerstain J. Die Kontrazeptive Betreuung Androgenisiierter Frauen mit Einen Niedrig Dosierten Cyproteronacetathaltigen Eimphasempraparat. Dtsch Med Wochenschr 1979;104:1376-82.
72. Stough D. Hair replacement. Surgical and Medical. St. Louis: Mosby; 1996.
73. Bernstein RM, Rassman WR. Follicular transplantation: Patient evaluation and surgical planning. Dermatol Surg 1997;23: 771 -84.
74. Unger WP, Unger RH. Hair transplanting: an important but often forgotten treatment for female pattern hair loss. J Am Acad Dermatol 2003;49:853-60.