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Seminars in Cutaneous Medicine and Surgery

Hair Loss in Women

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Female pattern hair loss (FPHL) is a clinical problem that is becoming more common in women. Female alopecia with androgen increase is called female androgenetic alopecia (FAGA) and without androgen increase is called female pattern hair loss. The clinical picture of typical FAGA begins with a specific "diffuse loss of hair from the parietal or frontovertical areas with an intact frontal hairline." Ludwig called this process "rarefaction." In Ludwig's classification of hair loss in women, progressive type of FAGA, 3 patterns were described: grade I or minimal, grade II or moderate, and grade III or severe. Ludwig also described female androgenetic alopecia with male pattern (FAGA.M) that should be subclassified according to Ebling's or Hamilton-Norwood's classification. FAGA.M may be present in 4 conditions: persistent adrenarche syndrome, alopecia caused by an adrenal or an ovarian tumor, posthysterectomy, and as an involutive alopecia. A more recent classification (Olsen's classification of FPHL) proposes 2 types: early- and late-onset with or without excess of androgens in each. The diagnosis of FPHL is made by clinical history, clinical examination, wash test, dermoscopy, trichoscan, trichograms and laboratory test, especially androgenic determinations. Topical treatment of FPHL is with minoxidil, 2-5% twice daily. When FPHL is associated with high levels of androgens, systemic antiandrogenic therapy is needed. Persistent adrenarche syndrome (adrenal SAHA) and alopecia of adrenal hyperandrogenism is treated with adrenal suppression and antiandrogens. Adrenal suppression is achieved with glucocorticosteroids. Antiandrogens therapy includes cyproterone acetate, drospirenone, spironolactone, flutamide, and finasteride. Excess release of ovarian androgens (ovarian SAHA) and alopecia of ovarian hyperandrogenism is treated with ovarian suppression and antiandrogens. Ovarian suppression includes the use of contraceptives containing an estrogen, ethinylestradiol, and a progestogen. Antiandrogens such as cyproterone acetate, always accompanied by tricyclic contraceptives, are the best choice of antiandrogens to use in patients with FPHL. Gonadotropin-releasing hormone agonists such as leuprolide acetate suppress pituitary and gonadal function through a reduction in luteinizing hormone and follicle-stimulating hormone levels. Subsequently, ovarian steroid levels also will be reduced, especially in patients with polycystic ovary syndrome. When polycystic ovary syndrome is associated with insulin resistance, metformin must be considered as treatment. Hyperprolactinemic SAHA and alopecia of pituitary hyperandrogenism should be treated with bromocriptine or cabergoline. Postmenopausal alopecia, with previous high levels of androgens or with prostatic-specific antigen greater than 0.04 ng/mL, improves with finasteride or dutasteride. Although we do not know the reason, postmenopausal alopecia in normoandrogenic women also improves with finasteride or dutasteride at a dose of 2.5 mg per day. Dermatocosmetic concealment with a hairpiece, hair prosthesis as extensions, or partial hairpieces can be useful. Lastly, weight loss undoubtedly improves hair loss in hyperandrogenic women.
Semin Cutan Med Surg 28:19-32 © 2009 Elsevier Inc. All rights reserved.

Introduction

Hair loss in women is an increasingly frequent problem. The clinical aspects of female pattern hair loss differ according to the origin. When the problem is typical female androgenetic alopecia (FAGA), it starts by a specific diffuse loss of hair of the parietal or frontovertical regions ("in the crown") maintaining the frontal hairline. The woman needs to be reassured that the hair loss never

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doi:10.1016/j.sder.2009.01.001

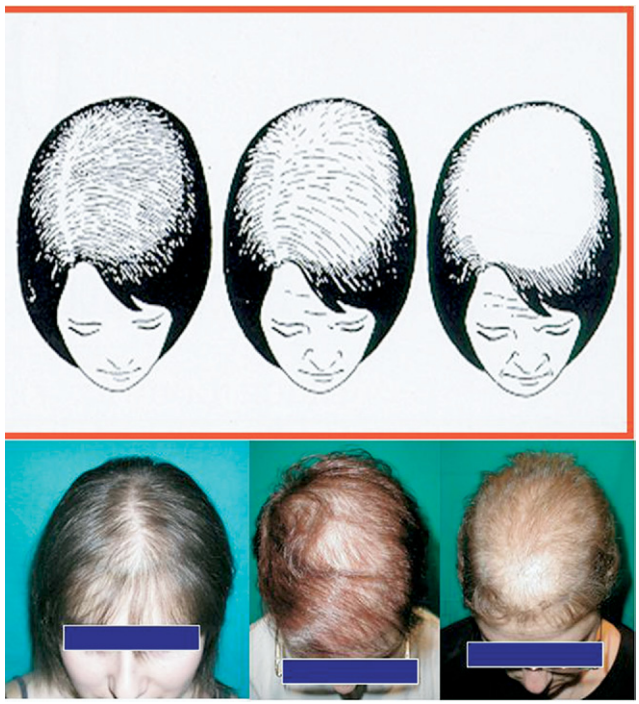

Figure 1 Ludwig's classification. Three progressive stages of hair loss. Reprinted with permission from Ludwig et al.[29]

reaches total alopecia; however, the diameter of her hair will be progressively smaller, with the hair becoming more fine, short, and depigmented, permitting the scalp to be seen.[1] This process, named "rarefaction" by Erick Ludwig,[2] means that female alopecia starts by a uniform miniaturization of the hairs from centroparietal regions or "crown" and reaches diffuse alopecia of oval form that is surrounded by a circular band of hair with normal density. This band has variable dimensions in accordance with the area; in the frontal region it is 1 cm-3 cm, in temporoparietal areas a little wider, from 4 cm to 5 cm, and in the occipital region the area of alopecia is separated from the normal hairy occipital zone by a wide line that is located between vertex and occipital area. FAGA differs from a completely developed MAGA (male androgenetic alopecia), or "Hippocratic alopecia," because it always maintains the frontal hairline.

Classifications of Female Alopecia

Ludwig's Classification

In Ludwig's classification, the 3 patterns represent stages or progressive types of FAGA (Fig. 1). All have a moderate increase of circulating androgens.[2,3]

FAGA Degree I (Minimal)

It is considered as the beginning of FAGA. There is a perceptible thinning of hair from the anterior part of the crown with minimal widening of the part width. Women hide the frontovertical area of hair loss by combing the hair forward, thus, exposing a visible area of alopecia in the anterior centroparietal area while the frontal hairline is maintained. This type of alopecia is observed in young women with SAHA syndrome (ie, seborrhea, acne, hirsutism, alopecia), generally of ovarian origin. It is accompanied by other hyperandrogenism manifestations as seborrhoea, acne, hirsutism, seborrheic dermatitis, and slight menstrual alterations. Because SAHA syndrome is constitutional, there are not increases of blood biochemical levels.

FAGA Degree II (Moderate)

Some time later, the "crown" area of thinning will be more evident because of an increase in the number of thin and short hairs. This makes it more difficult, although still possible, to camouflage the alopecia with combing the hair forward. This pattern of alopecia is a marker of excess androgens, generally of ovarian origin. The stage of SAHA syndrome has passed. Blood biochemical studies can demonstrate an excess of androstenedione, free testosterone, and androstanediol glucuronide.

FAGA Degree III (Intense)

Finally, in some perimenopausal or menopausal women, the "crown" becomes practically total alopecia or "denuded," with significant widening of the part width, but the frontal hairline is maintained. Although women comb their hair forward trying to cover the alopecia, it will always be possible to see the alopecia. This type of alopecia also can be seen in women with adrenal diseases, tumoral or not, with very high levels of androstenedione, DHEA-S, free testosterone, sometimes of prolactin, and always of androstanediol glucuronide.

Recently, female alopecia in frontovertical area and in temporoparietal supra-auricular areas has been recognized. These regions must be examined in all women that seek consultation for alopecia. Sometimes, this area is the only one involved with alopecia. The 3 Ludwig patterns of FAGA are similar to those of Olsen (Fig. 2) the Olsen patterns incorporate the accentuation of the frontovertical alopecia, which has a triangular or "Christmas tree" form.[3]

Female Androgenetic Alopecia of Male Pattern (FAGA.M)

This type of alopecia was also described by Ludwig in 1977.[2] Although Ludwig only referred to Hamilton IV to VIII patterns, he considered them as diagnostic of women with circulating androgen levels similar to men. When using Ebling's classification, this type of alopecia increases from I to V. It may be observed in women with increased testosterone levels or with a hypersensibility of target follicular organ to androgens. To find Ebling's degrees II or III is rare because if the women have persistent adrenarche syndrome or adrenal SAHA, they present with a single line of the frontal hairline, representing, Ebling's I (Fig. 3). Excess androgen production by adrenal or ovarian tumors causes severe alopecia, Ebling's IV to V, which is of interest in medical practice. When the alopecia is

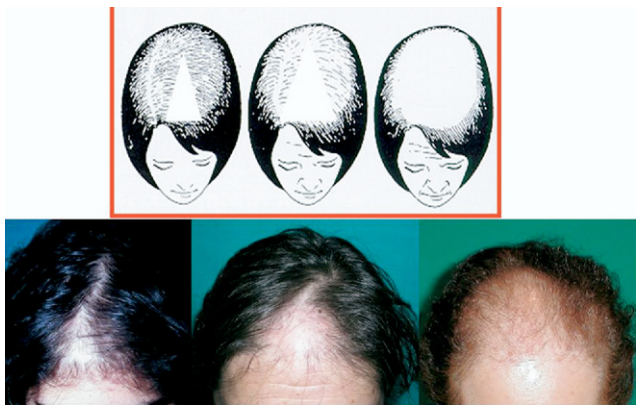

Figure 2 Olsen's classification: 3 triangular progressive stages of hair loss.

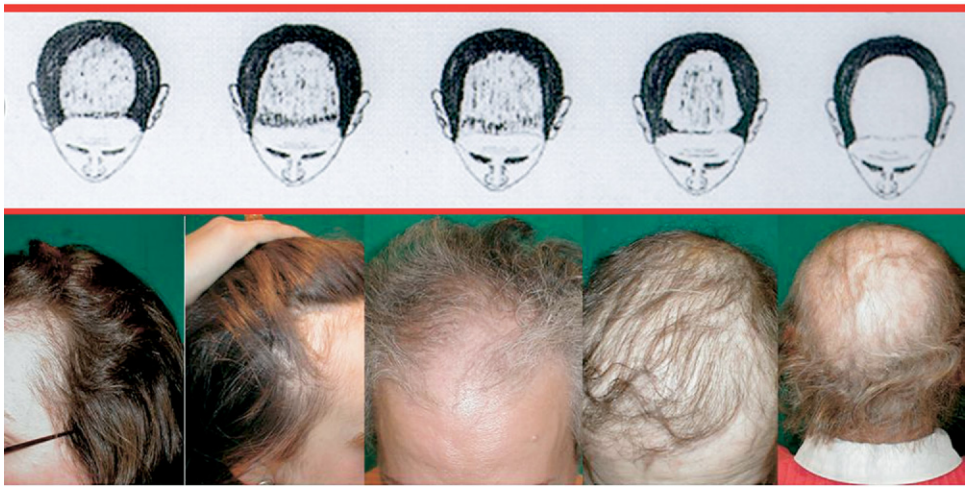

Figure 3 Ebling's classification: 5 progressive stages of hair loss. The final example is Hippocratic alopecia as in men. Reprinted with permission from Ludwig et al.[29]

FAGA.M.I, a functional alteration must be suspected. When the alopecia is Ebling's degree IV or V, laboratory tests must be performed urgently. Depending on the results of the laboratory tests, diagnostic imaging tests, such as magnetic nuclear resonance or computed tomography to find the tumor are indicated. Ludwig did not observe cases of FAGA.M. II and III, and he did not write about them in his report.

Classically, it is considered that this type of FAGA can also be observed in hypoestrogenic alopecia and after hysterectomy. Women with FAGA.M, who progress from FAGA.II to FAGA.M.V, producing a gradual loss of the frontal hairline, may develop hair loss because of a genetic predisposition as well as alterations in androgen metabolism at the level of the hair follicle and systemic hormonal changes. FAGA.M can be observed in 4 circumstances[4]: (1) persistent adrenarche syndrome; (2) adrenal or ovarian tumoral alopecia; (3) posthysterectomy alopecia; and (4) involution alopecia. FAGA.M.II and III could be observed in women with a high production of adrenal or ovarian androgens and also can be observed in diseases, such as congenital adrenal hyperplasia, Cushing syndrome, and polycystic ovary syndrome (PCOS).

Persistent Adrenarche Syndrome

Adrenarche begins in girls at 8 years of age, starting with the secretion of the hormones, DHEA and DHEA-S, manifested by the presence of microcomedones in acneiform areas. When the secretion of adrenal hormones is produced in major quantities and DHEA-S is transformed in testosterone, hyperandrogenism at follicular levels is observed. Patients show intense seborrhea, papulopustulous acne located on the face and back, hirsutism generally of central distribution, male pattern alopecia with hairline loss in parietal-temporal areas, menses with long cycles or occasionally amenorrhea, and a tendency toward thinning hair. The young woman experiences continuing stress from the dermatological disease.[5] Patients with persistent acne of late onset show an increase of adrenal androgens.[6]

Adrenal or Ovarian Tumoral Alopecia

Adrenal or ovarian tumoral alopecia is the consequence of an important increase of androgens that can reach a FAGA.M.V. The alopecia and other manifestations of hyperandrogenism disappear when the tumor is removed. These other manifestations include hirsutism that reaches a value greater than 15 in the Ferriman and Gallwey scale, amenorrhea, change in the tone of voice, and modification of muscle mass and body measurements.

Posthysterectomy Alopecia

This type of alopecia is caused by decreasing levels of estrogen that alter the estrogen/androgen ratio. It starts 1 or 2 years after the hysterectomy with diffuse thinning of hair, which is more evident if the patient previously had alopecia. Because there is loss of the frontal hairline, the alopecia is transformed into a male pattern, including tonsure alopecia. This condition does not improve with estrogen replacement therapy.

Involution Alopecia

This type of alopecia is similar to male alopecia, which has a genetic predisposition. It has a variable onset and probably is not dependent on hormonal influences (Fig. 4A). It is seen in relation to general cutaneous atrophy and with the nutritional deficiencies of aging. In some families, it appears at 60 years of age, in others around 70 to 80 years. In those without genetic predisposition, it does occur.[7]

FAGA.M.II-IV Patterns

This pattern can be observed when the hyperandrogenism does not originate from a tumor. It may also be observed in congenital adrenal hyperplasia (CAH), including the late-onset CAH, and in the Cushing syndrome. When the hyperandrogenism is caused by ovarian sources, it can present as PCOS or HAIRAN syndrome. Woman also can present with diffuse alopecia in other regions as eyebrows, pubis, and axillar areas as well as seborrhoea and an itching and burning scalp.

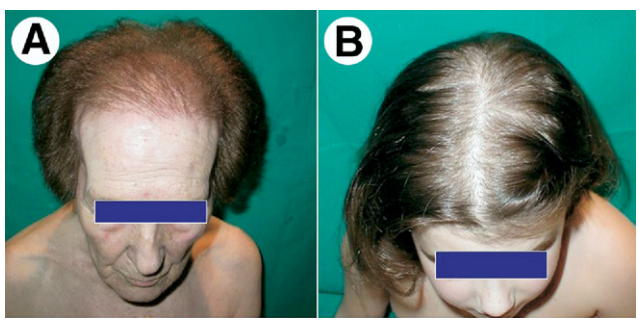

Figure 4 (A) Involution alopecia. Diffuse hair loss in frontovertical area. (B) Alopecia in girl. A wide frontovertical line is observed.

Classification System with Five Levels of Severity

Another classification system, the Women's Alopecia Severity Scale, has 5 classes with the objective of measuring the severity with photographic methods.[8]

Classification System with Eight Levels

Savin in the 51st Annual Meeting of the American Academy of Dermatology, in 1992, proposed in posters 23 and 24 a scale of 8 levels similar to Hamilton–Norwood's classification with frontal and lateral views of the hair loss patterns. Computer analysis of the temporal-parietal supra-auricular alopecia is based in the "density of hairs by unit of area." This classification system of female alopecia was not successful because not all dermatologists have computers on their desks to do this measurement. Clinicians use the easiest classification system: either Ludwig or Olsen scales.[9]

Olsen's Classification

Because most women with alopecia show no other clinical or biochemical evidence of androgen excess, and family histories of women with alopecia are not as straightforward as those of men with alopecia, Olsen[1] proposed a classification with 3 degrees of severity with hair loss in a triangular form in frontovertical area. This classification permits differentiation of early onset from late onset and with or without excess androgens (Table 1).

Other Types of Alopecia

Alopecia in Girls

Although this type of alopecia can be observed in all children, it is more frequent in girls. In our experience,[9] it is relatively rare as reported by Tosti et al.[10] Hamilton, in his excellent and transcendental work on alopecia,[11] commented that alopecia in newborns of both sexes develops in frontal, frontoparietal, and tonsure areas. During the end of the first year or during the second year of life, new hair appeared in these areas. Children of 1 or 2 years have an alopecia type I or I.a that lasts until puberty. Then, in adolescence the hair loss started in the frontal hairline in both sexes.

Alopecia in children appears at 6 to 10 years of age in the adrenarche phase. Because adrenarche is earlier in girls than in boys, we must consider that this is the reason it is found earlier in girls. It is observed as thinning of hair and widening of the central part of the scalp in the form of a clear line from the frontal hairline to the tonsure (Fig. 4B) and less frequently presenting in the triangular pattern of Olsen.[3] Usually, antecedents of alopecia are found in the mother or in both parents, but it is exceptional to find antecedents only in the father. Almost all mothers state that they had the same pattern of alopecia in their infancy and that they still have it. In one case in twins, we demonstrated increased levels of DHEA-S and 17-OH-progesterone that were maintained after puberty, which was treated with spironolactone. Although generally hormone alterations are not found, biochemical examination looking for high levels of adrenal hormones, testosterone, and dihydrotestosterone are conducted.

Diagnosis is easy with the pull test, trichogram, and trichoscan. We do not consider biopsy necessary in female alopecia.[9] Androgenization signs are usually not seen. Cases have normal Tanner degrees. Topical treatment is usually adequate. Parents and other relatives are anxious over transmitting the problem to their daughters.

Table 1 Female Pattern Hair Loss

Alopecia of early onset:
With excess androgens
Without excess androgens
Alopecia of late onset:
With excess androgens
Without excess androgens

Alopecia and Menopause

Menopausal women do not necessarily have hair loss. When a menopausal woman develops sudden hair loss, other causes of alopecia must be considered. Nevertheless, when the woman has a genetic predisposition, it is likely that she will develop male pattern alopecia, with 63% showing a Ludwig pattern and 37% an Ebling pattern. Postmenopausal or adrenopausal FAGA[1] can also be produced because of a functional alteration of follicular androgenic receptors without a change in the serum androgen levels. In the UK, 42% of women older than 70 years of age show FAGA.[12]

Postpartum Alopecia

Almost all women have postpartum hair loss, which is androgen-dependent. The women's risk factors for FAGA may predispose her to develop postpartum alopecia. Postpartum alopecia is related to the decrease of estrogens that were maintained at high levels during the last months of pregnancy. These high estrogen levels kept follicles in anagen. During pregnancy there is very little hair loss, an increase in the diameter of the hair,[13] a reduction in seborrhoea, and the cutis is eudermic.

Iron Deficiency Alopecia

Women can develop alopecia from iron deficiency as the result of the blood loss that occurs in delivery that can add to postpartum alopecia. Nevertheless, alopecia in women can also be consequence of a decrease in iron reserves. This is not uncommon in women that have abundant menses and do not eat red meats or have vegetarian diets.[1] When iron deficiency develops, the synthesis of ferritin by the liver ceases. Ferritin that was located in growing follicles is released to serum to support other organ function, such as the bone marrow. As a consequence of this loss of ferritin, the follicles go into telogen phase.[14] Ferritin levels less than 40 ng/mL (90 pmol/L) are associated with an increase of telogen phase. When the levels are between 40 ng/mL and 70 ng/mL (90 and 156 pmol/L), an excess of telogen hair loss is also observed.[1] Only when serum levels are greater than 70 ng/mL the hair is in normal anagen phase. Studies have confirmed that low serum levels of ferritin have an influence in FAGA and in alopecia areata but not in telogen effluvium or total or universal alopecia areata.[15]

Alopecia and Vitamin B_{12}

Although vitamin B_{12} does not have a known action on hair growth, its depletion may be associated with depression. Neuropsychiatric alterations can be present when its serum levels are lower than 300 ng/L, which is observed in women with FAGA treated with cyproterone acetate and ethynyl estradiol.[1] Although some authors think that women with FPHL tend to underestimate the severity of their hair loss,[8] we found that most Spanish women with hair loss were worried or depressed.[16] A health-related quality of life questionnaire for women with androgenetic alopecia demonstrated a high incidence of social and psychological changes in these women.[17]

Other Types of Hair Loss in Women

Some cases of biotinidase deficiency may develop alopecia.[18,19] Hair loss has also been observed in anorexia nervosa.[20] Women following hypocaloric diets may start or exacerbate alopecia. Diets with neg-

Table 2 Incidence of Female Alopecia in United States and Spain by Age of Onset

Age	Percent
20-29 years	3
30-39 years	17
40-49 years	19
50-59 years	25/27
60-69 years	28/34
80-89 years	32/36
Total	19/20

ative nitrogen balance increase alopecia. Low protein diets decrease the percentage of anagen, and appear like pseudomonilethrix type of hair. After 2 to 4 months of lipid-free diets, there is an increased telogen, decreased anagen and the appearance of the hair is "dishevelled." Hair loss in women can be increased in autumn as the result of seasonal shedding.[21]

Epidemiology

In Spain epidemiological studies show that 36% of women have FAGA, of which 19.7% is FAGA.I-III and 16.3% FAGA.M. These percentages are similar to those in United States (Table 2). In 17% of those with FAGA, it occurs before 40 years of age and increases to 32% in postmenopausal women.[22] In the United Kingdom, 6% of women younger than 30 years of age have FAGA, and for those older than 70 years, it reaches 42%.[12]

Pathophysiology

Female and male pattern androgenetic alopecia are a consequence of increased central or peripheral androgens and/or a fault in the follicle hormonal transformation coupled with a genetic predisposition to permit these to act on follicular target cells which are specially sensitized by binding to specific intracellular androgen receptors. The androgen receptors are on the X chromosome, which would explain why women show a mosaic pattern of alopecia and are relatively mildly involved, whereas men are more severely involved. A high percentage of women with FPHL without any overt clinical sign of hyperandrogenism had no biochemical evidence of androgen excess.[23] Because early and late FPHL are genetically distinct, it seems that hair loss in women is polygenic and multifactorial with the additional influence of environmental factors.

Two genes have been shown to be related to alopecia. CYP17 is a steroid metabolism gene that codifies P450 aromatase enzyme helping to release more estradiol. This gene was found in women with PCOS and their brothers with early balding.[24,25] A new gene on chromosome locus 3q26 has been found in androgenetic alopecia families.[26]

The mechanism of androgen action in hair follicles is well known in female androgenetic alopecia. FAGA is related to the excess of Δ-4-androstenedione serum levels of ovary or adrenal origin and FAGA.M with the increase of dehydroepiandrosterone (DHEA) or DHEA-S of adrenal origin. Androstenedione and DHEA-S are peripherally transformed into testosterone (T), and this in turn is converted into 4 main metabolites, of which we are mainly interested in 5-α-dihydrotestosterone (DHT). This enzymatic conversion is mediated by steroid sulfatase (DHEA-S to DHEA), 3β-hydroxysteroid dehydrogenase (DHEA to androstenedione), 17β-hydroxysteroid-oxidoreductase (DHEA to androstenediol and androstenedione to testosterone), and 5α-reductase (free-testosterone to 5α-DHT). Conversion of T in DHT requires free T that is not bound to sex-hormone-binding globulin (SHBG).

In balding scalp hair follicles, the androgen receptor is a specific protein known as "caspase," which binds 5-α-DHT. Once the hormone has bound, the receptor complex undergoes a conformational change, exposing DNA binding sites, and the hormone-receptor complex, in conjunction with other coactivating proteins, to specific hormone response elements in the DNA altering the expression of specific androgen-dependent genes[21,27] and starting apoptosis. Once DHT has been metabolized in the follicular target organ, it is transformed into its metabolite 3α-androstanediol glucuronide by the enzyme 3α-hydroxysteroid dehydrogenase; therefore, the serum level of this metabolite is an indicator of the intracellular androgenic metabolism. Prolactin may be also involved in FAGA. It is thought that hyperprolactinemia is associated with an increase in DHEA-S as the result of the action of prolactin on the adrenal cortex.

Another important enzyme is aromatase (P450arom), which is specifically located in outer root sheath. Aromatase converts androstenedione to estrone and testosterone to estradiol, decreasing the levels of circulating and tissue T and DHT. This explains the difference between androgenetic alopecia of male and female pattern. In women there are 2- to 5-fold greater amounts of aromatase in the scalp than in men. In FAGA there is 3 to 5 times more aromatase in frontal and occipital scalp areas than in MAGA explaining the maintenance of the frontal hairline in women.[28]

As an etiopathogenic factor of FAGA, one should also consider the decrease of SHBG, as this would result in free T, which could act at the follicular level. For some authors, the biochemical marker of FAGA would be the decrease of SHBG and the increase of 3α-androstanediol glucuronide. For others it is the decrease of SHBG that would proportionally increase the T/SHBG ratio.[29] In hypothyroidism, there is decreased synthesis of SHBG, which is why, in theory, women with hypothyroidism with a history of FAGA could see an increase of their alopecia.

Diagnosis

A correct diagnosis, which is based on the clinical history, clinical examination, and biochemical investigation, is essential for successful treatment.[30]

1. The clinical history will be an in-depth examination of possible factors that may precipitate or exacerbate the alopecia, such as chronic illnesses, nutritional alterations, metabolic and endocrinologic alterations, and recent surgical interventions and medical treatment. If the patient is taking oral contraceptives containing progesterone with a high androgenic potential, such as norethindrone, or has recently discontinued an estrogenic oral contraceptive that was taken for a long time, hair loss may occur. It is always important to take a menstrual history and to ascertain the products used to care for the hair.[31]
2. In the clinical examination, a photograph is taken to document the baseline condition. This photograph is indispensable in evaluating the therapeutic results. Neither the patient nor the physician can remember the presenting condition 5 months later. The patient, who keeps looking at her scalp every day, may not realize how much she improved. Physical examination should include all aspects of the scalp, especially to see whether hair loss excludes the occipital area.[32,33] The specific maneuvers that may be performed include noninvasive, semi-invasive, and invasive methods.

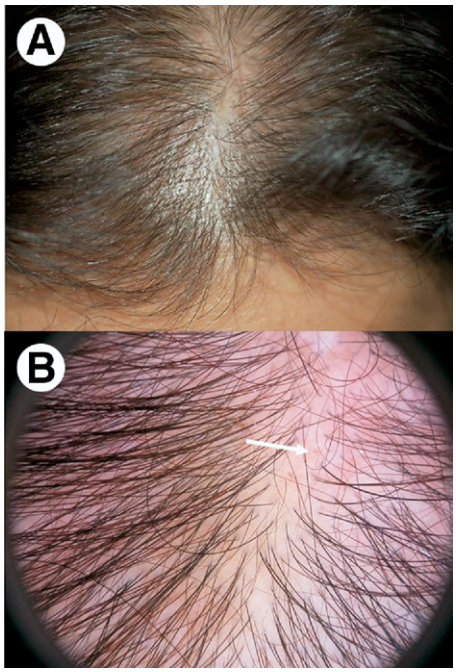

Figure 5 Dermoscopy. (A) Photograph of a wide frontovertical balding area. (B) With dermoscopy hairs of different diameter and pigmented areas can be clearly observed.

Noninvasive Methods

We perform the "traction test" or "Sabouraud's sign," evaluating the number of hair shedding after slight traction on scalp hair, "pull-out sign" to know the strength of a tuft of hairs, and "standardized wash test." In the wash test the woman refrains from shampooing for 5 days, and then she shampoos and rinses her hair in the basin with the hole covered by gauze. She collects all the hairs remaining in the water and the gauze, and sends them for examination.[34] Hairs must be counted and divided into ≤3 cm and >5 cm in length. This is an important technique to differentiate telogen effluvium from female pattern hair loss. The "modified wash test" demonstrates that in FAGA 58.9% of the hair is vellus, whereas in chronic telogen effluvium there are only 3.5%.[34]

Other photographic methods, such as macrophotographic analysis in microcalibrated hair tubes, phototrichogram,[35] traction phototrichogram,[36] and the methods that use an image analyzer,[37] are obsolete. Dermoscopy has replaced them in the diagnosis of androgenetic alopecia. Dermoscopic features are (1) Hairs with different caliber reflecting progressive hair miniaturization (Fig. 5). (2) Brown halo, roughly 1 mm in diameter, at the follicular ostium around the emergent hair shaft. (3) Small bald areas with numerous empty follicles in postmenopausal women. (4) Scalp pigmentation because of sun exposure.[38]

Semi-Invasive Methods

Semi-invasive methods include the trichogram, unit area trichogram, and trichoscan. The trichogram is the most criticized technique, especially by those who do not perform it with scientific rigor.[39] To perform the technique correctly, one must observe 50-100 hairs from the temporoparietal, occipital, and vertex areas (some 25 hairs from each area). Once the dermatologist has experience, he/she can evaluate FAGAs with approximately 10 to 15 hairs from the vertex.[37] It is a quantitative technique that provides information about the growth capacity of hair and the alterations of its growth. The trichogram also permits measurement of the diameter of the hair shaft that usually varies between 0.05 mm and 0.07 mm. What really is of value is the "coefficient of variability" of the hair shaft diameter, because it expresses the percentage of variation between the diameters of each individual. The coefficient of variation in women without hair problems is 20.41%, with a standard deviation of 6.3%, whereas in women with FAGA.M, the coefficient of variability reaches 41.7% with a standard deviation of 4%.[40]

Rushton, et al[41] described the "unit area trichogram" in 1983. It consists of depilating the area framed by a macrophotograph using a Canon Fin camera with a Canon macro of 100 mm fixed at 1:1. The hairs found inside this frame are depilated using traction forceps and are transferred to a slide, in the same way as in a classic trichogram. With this technique one can determine the hair density in a specific area (hairs/cm^2), the diameter of the hair (mm), and the linear growth (mm/d), with an error margin of less than 5%.

Trichoscan is a new technique consisting in shaving a transitional balding area of 0.661 cm^2 and evaluating several parameters with an epiluminescence microscopy[42]: number of hairs in the area, density of hairs (hairs/cm^2), anagen hairs, telogen hairs, density of vellus (vellus/cm^2), density of terminal hairs (terminal hairs/cm^2), and vellus and terminal hairs. This technique is only a screening tool; it is not diagnostic (Fig. 6).

Invasive Methods

Although scalp biopsy and folliculogram are 2 invasive methods, we shall only refer to biopsy because folliculogram is used to evaluate the action mechanism of several treatments in animals used as models in alopecia.[43] Biopsies from the involved area can be taken when

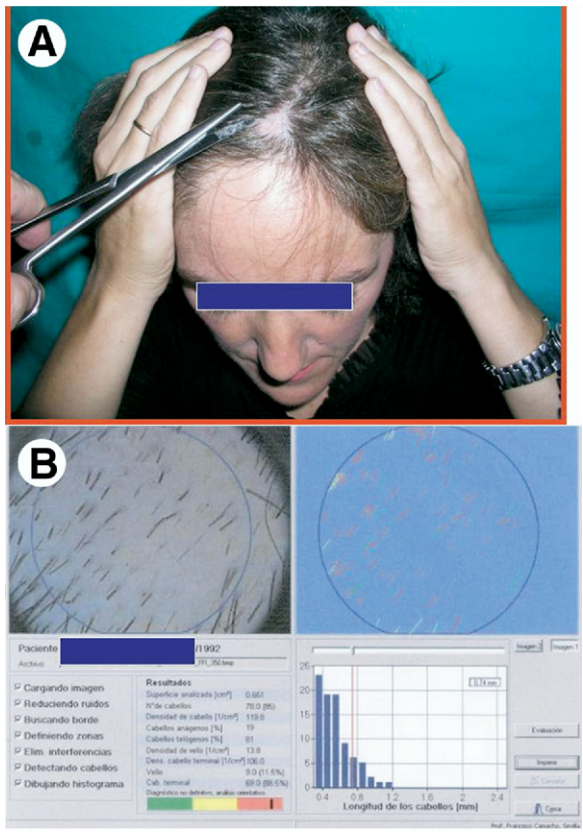

Figure 6 Trichoscan. (A) An intermediate balding area is being prepared by shaving. (B) Trichoscan with different parameters investigated.

the diagnosis is in doubt, especially to differentiate from chronic telogen effluvium[44] or to know the possibility of reversing hair loss. With biopsy, Whiting[44] demonstrated the different features between controls, chronic telogen effluvium and androgenetic alopecia: terminal hairs: 35/35/25, vellus: 5/4/12, terminal hair/vellus ratio: 7/1, 9/1, 2/1, and percentage of telogen: 6.5/11/16.8.

Biopsy of FPHL has similar features to male pattern hair loss. A decrease of terminal hair and anagen hair and an increase of vellus-like hair, telogen hairs, and fibrous residual tract must be found. Slight perifollicular inflammation is another microscopic feature. Combining photographic methods and transverse orientation of scalp biopsies yields "hair diameter diversity," which is a clinical sign reflecting follicle miniaturization. This feature is only statistically significant in advanced stages of Ludwig's patterns of hair loss.

Biochemical Test

Among the laboratory tests, androgenic determination has priority. In our protocol, we consider levels of free testosterone, 5-α-DHT, DHEA-S, 17-β-hydroxyprogesterone, prolactin, Δ-4-androstenedione, SHBG, and 3-α-androstanediol glucuronide essential. In 2001, prostatic-specific antigen (PSA) became known as a marker of androgenization[45-47] in both, premenopausal (normal levels $\leq$ 0.02 ng/mL) and postmenopausal women (nL $\leq$ 0.04 ng/mL); therefore, we added this to our protocol. We found greater levels of PSA in ovarian and adrenal FAGAs, whereas women without clinical hyperandrogenism or women with clinical hyperandrogenism and normal hormonal serum levels had lower PSA levels.[48]

Cortisol levels will be normal in CAH and adrenal tumors and increased in Cushing's disease. If CAH is considered, then levels of 17-hydroxyprogesterone before and after the "ACTH stimulation test" may be investigated. When cutaneous signs of Cushing's disease are present, a 24-hour urinary free cortisol and creatinine excretion must be determined, and the overnight "dexamethasone (Dx) suppression test" also can be performed.

Gonadotropins luteinizing hormone (LH), follicle-stimulating hormone (FSH), and the ratio of LH:FSH must be determined to confirm PCOS because an increase in serum LH is pathognomic of, but not required for, a diagnosis of PCOS, and ratio LH:FSH $\geq$ 3 can be increased in up to 95% of subjects.[49] Given the prevalence of impaired glucose tolerance in PCOS, all the women with PCOS must be screened for type 2 diabetes mellitus.[50] When HAIRAN syndrome is suspected, insulin serum levels must be also determined.[50] When androgen levels are normal, screening should include TSH, T4, antimicrosomal and antithyroglobulin antibodies, and ferritin or total iron binding capacity.[37]

Table 3 Medical Treatment of Female Pattern Hair Loss

- Topical treatments:
  - Minoxidil 3-5%
  - VEGF stimulants
  - Spironolactone 3%, canrenone 2%
  - Spironolactone/progesterone
- Systemic treatments:
  - Treatment of persistent adrenarche syndrome (adrenal SAHA), FPHL in adrenal hyperandrogenism, and FPHL in postmenopausal hyper- or normoandrogenic women
    - Adrenal suppression
      - Dexamethasone
      - Prednisone
      - Deflazacort
    - Antiandrogens
    - Antagonists of the androgen receptors (central antiandrogens).
      - Cyproterone acetate
      - Spironolactone
      - Flutamide
      - Drospirenone
    - Peripheral antiandrogens (5α-reductase inhibitors-antienzymes):
      - Finasteride
      - Dutasteride
  - Treatment of excess release of ovarian androgens (ovarian SAHA), FPHL in ovarian hyperandrogenism, and FPHL in normoandrogenic postmenopausal women
    - Ovarian suppression:
      - Oral contraceptive pills (OCP): ethinyl estradiol (EE).
    - Gonadotropin-releasing hormone agonists (GnRH-a).
    - Antiandrogens.
    - Endocrinological or gynecological PCOS treatment
  - Treatment of hyperprolactinemic SAHA (pituitary SAHA) and pituitary hyperandrogenism.
    - Bromocriptine
    - Cabergoline
- Complemmentary treatments
- Vitamins, iron, phytoestrogens
- Lifestyle
- Dermocosmetic measurement

Treatment

Because FPHL is a biological process determined by a sensitivity to androgens that is genetically mediated, we use 3 treatments to interrupt its course: (1) modification of the biological response through nonhormonal mechanisms; (2) modification of the androgen action by altering the production, transport, or metabolism of androgens, such as preventing binding to androgenic receptors[51]; and (3) transplanting follicles to balding areas by surgical procedures. Surgical treatment with follicular unit transplants will not be discussed (Table 3).

Topical Treatment

Modifiers of the Biological Response

Minoxidil is a potent peripheral vasodilator which, when administered orally, is used in the treatment of arterial hypertension. One of its main side effects is a non-virilizing hypertrichosis, which affects the face, shoulders, arm, and legs of women and the entire body in men, including the scalp.[52] Its action mechanism is through its active metabolite, minoxidil-sulfate, which has potassium channel-opening activity.

Minoxidil in Female Pattern Hair Loss. In the American multicenter study sponsored by the Upjohn Laboratory, 256 women with hair loss between the ages of 17 and 45 were followed. In week 32 there was a minimal or moderate hair growth in 63%; this response was also observed in 39% of the patients treated with placebo. At the end of the study, it was found that women treated with minoxidil had improved their "hair count by unit area" from 140 to 163, an improvement of 16%. The hair count of the placebo groups went from 140 to 149, an improvement of 6%, which is a significant difference in favor of topical treatment with minoxidil. There were

no side effects. The Food and Drug Administration approved its use in women in 1991.[52] Jacobs, et al[53] confirmed that FPHL treated with 2% minoxidil improved their initial count by 44%, whereas those treated with a placebo only did so in 29%. After 32 weeks of treatment, DeVillez et al[54] concluded that topical minoxidil treatment in women is superior to the treatment with placebo when they found moderate growth in 13% and discrete growth in 50% of cases.

Although there is a formulation of 5% topical minoxidil in a foam vehicle, we prefer using 2% or 3% concentrations twice daily[55] because at these concentrations it presents fewer side effects. The most frequent side effects are facial hypertrichosis, irritation dermatitis, contact eczema, pruritus, scaling, dryness, and headaches. Minoxidil is not recommended during pregnancy or lactation. Some start the treatment of female pattern hair loss with 5% minoxidil for 6 months and then continue with 2% or 3% concentrations. It is the drug of choice in normoandrogenic premenopausal women. It is also useful in postmenopausal women with spectacular results (Fig. 7A and 7B).

Other Modifiers of the Biological Response Used Locally

Many attempts have been made to use different biological response modifiers, but none of these have exceeded the effects of minoxidil, which is why they have not been commercialized. Minoxidil associated with tretinoin stimulated the growth of terminal hairs in 66% of the subjects. These results are similar or superior to those of minoxidil alone. Tretinoin increases the amount of minoxidil that reaches the follicle.[56] Another study demonstrated that when 2% minoxidil is associated with 0.05% tretinoin, the absorption of the former is 3 times greater.[57] The combination of 0.01% tretinoin with 2% or 3% minoxidil achieves an acceptable response in 53.2% of those treated.[58] The chance of side effects, especially irritation dermatitis, is greater with this combination. Other modifiers of biological response, such as diazoxide, viprostol, or cyclosporin, have effects lower than those of minoxidil.

Vascular Endothelial Growth Factor Stimulants. Our experience with eighty normoandrogenic women first treated with 1% alpha-tocopherol nicotinate for 3 months, followed with 5% minoxidil at night and 3% in the morning versus 80 men treated with the same procedure demonstrated that 25% of women and 10% of men showed an increased vascular supply.[52] Although it is clear that minoxidil up-regulates the expression of VEGF 6-fold in human hair dermal papilla cells, the effect is dose related. VEGF increases angiogenesis which produces hair growth, and increases the size of hair and follicles.[59] We have no explanation for the difference in the response of women and men.

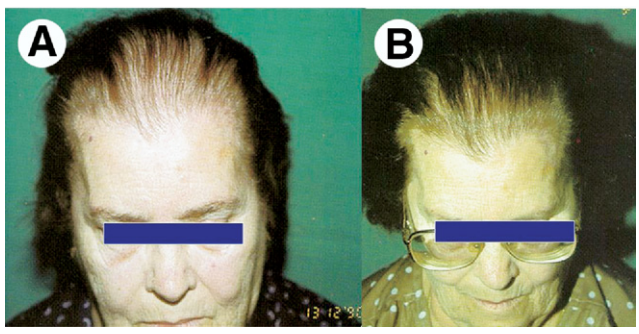

Figure 7 Normoandrogenic postmenopausal woman treated exclusively with 3% minoxidil twice a day. (A) Before treatment. (B) After 1 year of treatment.

Other Local Therapeutics. Twice-daily applications of 1% to 5% tincture of progesterone are useful in women. It should not be used at concentrations greater than 2% or in amounts greater than 1 mL twice a day because it may cause menstrual alterations. Although both 3% spironolactone and its metabolite 2% canrenone are useful for the topical treatment of FPHL, we prefer to use 0.025% progesterone with 0.05% spironolactone because they appear to complement each other synergistically with a greater effect on FPHL than either alone.[60] In menopausal women, a solution of 0.03% estradiol valerate used during 12 weeks and 24 weeks has demonstrated improvement of anagen/telogen ratio and a decrease in hair loss at 12 weeks and 24 weeks.[61] Finally, 0.05% topical finasteride showed a 40% decrease of DHT serum levels, but does not increase the hair growth.[62]

Systemic Treatment

The treatment of hyperandrogenic women with their different possibilities of androgen origin and normoandrogenic women with FPHL is the same that we used in other dermatological hyperandrogenic diseases, such as hirsutism.[50,63,64]

Treatment of Persistent Adrenarche Syndrome (Adrenal SAHA) and FPHL in Adrenal Hyperandrogenism and FPHL in Postmenopausal Hyper- or Normoandrogenic Women

Two types of drugs must be used, corticosteroids for adrenal suppression and antiandrogens, central or peripherals, to avoid the production of adrenal androgens or their effects on the target follicular organ. In postmenopausal women, hair loss has a male pattern.

Adrenal Suppression. Adrenal suppression is achieved with glucocorticosteroids. In the past, we used dexamethasone at an initial dose of 0.5 mg every night for 3 months and then alternate nights for another 3 months. If the dexamethasone doses were greater than 0.75 mg daily and continued for 6 months or longer, Cushingoid changes could be observed.[50] Prednisone at a dose of 7.5 mg daily for 2 months, reduced to 5 mg daily for 2 months, and then 2.5 mg daily for 2 months or 6 months of treatment is an alternative. At present we use deflazacort at an initial dose of 30 mg daily for 1 month with a maintenance dose of 6 mg daily for up to 2 years. Deflazacort has the advantage that at this dose it does not produce side effects. These doses of glucocorticosteroids are enough to reduce the level of DHEA-S, Δ-4-androstenedione and testosterone.[63] The only secondary effect is that obese women tend to gain more weight. Adrenal hyperplasia is treated with substitute corticosteroid therapy, regardless of the enzymatic deficiency. Cushing's syndrome benefits from substitute therapy with corticosteroids associated with surgery and/or irradiation.[64]

Antiandrogenic Therapy. Antiandrogenic therapy includes cyproterone acetate (CA), spironolactone, drospirenone, flutamide, finasteride, and dutasteride. Central antiandrogens competitively inhibit binding of 5-α-DHT to the androgen receptor,[49] and peripheral antiandrogens acts by inhibiting the 5-α-reductase, blocking the conversion of testosterone to 5-α-DHT.[65]

Antagonists of the Androgen Receptors. CA acts by interfering with the binding of 5-α-DHT to the androgen receptor and by inhibiting the secretion of FSH and LH as the result of its progesterone action. The "Hammerstein schedule" is 50 to 100 mg/d of CA from the fifth to the 15th day of the menstrual cycle for a 6-month period, which is the time of the glucocorticosteroid suppression. The 2 mg/d is given from the first day of the cycle to the 21st, with

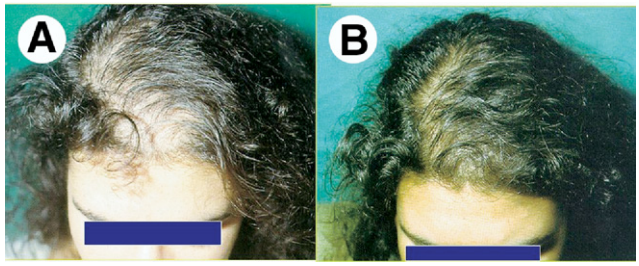

Figure 8 FPHL in adrenal SAHA treated for 2 years with minoxidil, 3% twice a day, 100 mg for 6 months of cyproterone acetate from the fifth to the 15th days of the menstrual cycle followed by 2 mg/d for 18 months during the cycle, always with 0.035 mg of ethynyl estradiol. (A) Before treatment. (B) After treatment.

a week of rest, for 18 more months (Fig. 8A and 8B). Because CA usually causes feminization in the male fetus, as well as menstrual alterations, even at doses of 50 mg a day, it is best to add oral contraceptive pills such as ethinyl estradiol. In postmenopausal women with slight hair loss, cyproterone acetate can be administered in doses of 50 mg daily without interruption.[64] Side effects include loss of libido, mood swings, fatigue, mastodynia, hypertension, and weight gain. It is absolutely contraindicated in patients with liver disease. In the author's opinion, CA is the best treatment for the FPHL.[65]

Spironolactone is an antagonist of aldosterone that also has antiandrogenic activity, decreasing the levels of total testosterone. It is used at a dose of 50 mg d^{-1}-200 mg d^{-1} for at least 6 months,[66] starting at a low dose of 50 mg d^{-1}, which is enough in adrenal SAHA, and increasing the monthly dose by 50 mg to a final dose of 200 mg d^{-1}. Improvement after the sixth month of treatment has been demonstrated.[67] Lethargy, upset stomach, and menorrhagia are common and transient side effects, which tend to resolve spontaneously after 2 or 3 months of therapy. Nevertheless, to decrease the incidence of menorrhagia, low-dose OCP may be used.[49] Other potential side effects include a decrease in libido, an increase in breast size, headache, and hyperkalemia.[50] Although the risk of hyperkalemia is very low in healthy young women, some advise patients against excessive intake of bananas and diet soda and periodically check the serum potassium levels. This drug is category X for pregnancy. Cutaneous side effects, such as pruritus, xerosis, maculopapulous eruptions, urticaria, *Melasma*-type facial pigmentation, contact dermatitis, erythema annulare centrifugum, vasculitis, erythema multiforme, Raynaud's phenomenon, alopecia, lupus-type eruption[63,68] and, on 2 occasions, a lichenoid eruption,[69] have been described.

Flutamide is a pure, nonsteroidal antiandrogen. It is used at a dose of, 250 to 500 mg twice a day for 6 to 9 months for the treatment of prostatic hyperplasia. At present, this is considered the most effective antiandrogen for the treatment of adrenal hirsutism but has less efficacy in hair loss. It is the treatment of choice when hair loss and hirsutism are associated with each other.[70] In this case, low doses of 62.5 to 125 mg daily can be used.[71,72] In 1993, we used doses of 250 to 375 mg daily during 6 months to 2 years in the treatment of SAHA syndrome with evident hair loss demonstrating improvement of hair loss, seborrhea, and acne from the third month of treatment but, with this dose,we observed dry skin in 75% and severe hepatotoxicity in 13% of the women. Other side effects described include lethargy, mood change, and loss of libido. Because it may also cause feminization of the male fetus, contraceptives must be used.

Drospirenone is 17-α-spironolactone derived with progestagenic, antiandrogenic and antialdosteronic activities. During a 21-day cycle, 3 mg/d of drospirenone given with 30 μg of ethinyl estradiol is considered the treatment of SAHA. Because drospirenone does not cause the retention of fluids, the patient does not increase weight.[65] Its efficacy in the treatment of CAH and Cushing's syndrome has not been demonstrated.

Cimetidine is a H2 blocker that could also act as a peripheral antiandrogen by inhibiting the binding of 5-α-DHT to the androgenic receptor.[63] Although one uncontrolled study of 300 mg 5 times a day suggests some utility in FPHL,[73] we think that cimetidine is of anecdotal value because its use causes an increase in the androgen secretion through a negative feedback mechanism.[63]

α-Reductase Inhibitors (Antienzymes). There are 2 types of isoenzymes 5-α-reductase. Type 1 is reported to be found predominantly in the sebaceous gland and type 2 predominantly in the prostate and certain regions of terminal hairs. Approximately 70% to 80% of serum 5-α-DHT is produced by the type 2 isoenzyme and 20% to 30% by the type 1 isoenzyme.[74] Nevertheless, there is no pure inhibitor of specific type of 5-α-reductase isoenzyme. Finasteride is predominantly a 5-α-reductase type 2 inhibitor but it also has activity on the sebaceous gland.[65] Currently, finasteride, dutasteride, and isotretinoin are available. Other antiandrogens of steroid configuration, such as desoxycorticosterone, androstenedione, and progesterone, which would act as 5-α-reductase inhibitors, have a limited use because of their systemic androgenic hormonal effects. Newly synthesized steroid 5-α-reductase inhibitors (dienones and trienones) inactivate the enzyme by an irreversible Michael type addition of the nucleophilic portion of the enzyme to the conjugated double bond of the steroid.[75,76]

Finasteride is considered a potent nonsteroidal antiandrogen that acts by inhibiting the 5-α-reductase isoenzyme 2, blocking the conversion of free-T to 5-α-DHT. This lowers serum and scalp levels of DHT while increasing scalp levels of testosterone.[77] These effects on scalp and serum DHT and testosterone levels were demonstrated in 2 studies of men. Dallob et al[78] studied these levels in 17 patients who underwent scalp biopsy before and after 28-day treatment with either placebo or finasteride 5 mg daily. In the bald scalp of patients receiving finasteride, the mean DHT concentration decreased from 6.4 pmol/g at baseline to 3.62 pmol/g. Scalp testosterone levels increased in 6 of 8 subjects treated with finasteride. Finasteride also decreased the mean serum DHT concentration from 1.36 nmol/L to 0.46 nmol/L, but serum testosterone levels were not modified.

Drake et al[79] studied 249 patients that were randomized to placebo or finasteride at doses ranging from 0.01 mg/d to 5 mg/d to find the lowest possible dose that could modify scalp and serum DHT levels. They found that after 6 weeks, doses as low as 0.2 mg/d could significantly decrease scalp DHT levels by 60% to 75% without significantly affecting serum testosterone levels. The optimal dose of finasteride for male androgenetic alopecia was identified as 1 mg/d.[77] Randomized, placebo controlled trials using finasteride 1 mg d^{-1} in men showed significantly greater hair count in the balding vertex[80] and in the anterior and mid scalp area.[81] Because finasteride is metabolized in the liver, it should be used with caution in patients who have liver abnormalities. No drug interactions of clinical importance have been recognized.[77] Finasteride is pregnancy category X, and this contraindicates its use in females of childbearing age unless they are using birth control measures. If they became pregnant, the finasteride might cause the feminization of a male fetus. In addition, finasteride and dutasteride were considered doping drugs of Section S5 corresponding to "Diuretics and other masking agents," but they did not appear as masking drugs in the new

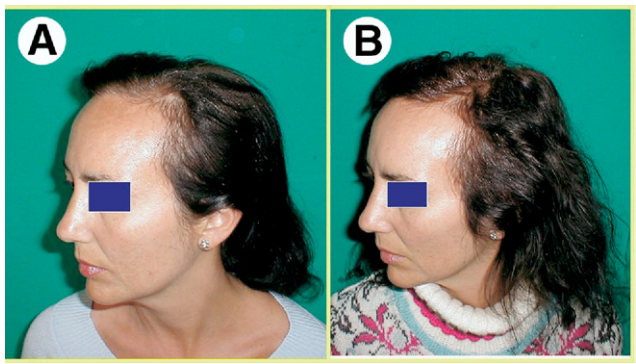

Figure 9 FPHL in adrenal SAHA treated with minoxidil, 3% twice a day, 2.5 mg d^{-1} finasteride and 0.035 mg ethinyl estradiol. (A) Before treatment. (B) After 1 year of treatment.

World Anti-Doping Code. The 2009 prohibited list states that "Alpha reductase inhibitors are no longer prohibited. They have been rendered ineffective as masking agents by closer consideration of steroid profiles."

Finasteride is considered an efficient antiandrogen in women with improvement in hirsutism and hair loss. In men, it treats benign prostatic hyperplasia and male androgenetic alopecia. Our team published the first publication about the treatment of hair loss in women with adrenal SAHA syndrome in 2001.[82] Eighty-nine patients with persistent adrenarche syndrome were treated with 2.5 mg daily of finasteride and 30 μg of ethinyl estradiol during 2 years, achieving improvement of hair loss in 84.27% women (Fig. 9A and 9B), with significant decrease of serum levels of 5α-DHT and no prominent side effects. But other authors, in a 1-year, double blind, placebo-controlled trial treated 137 postmenopausal women with 1 mg/d or placebo and failed to demonstrate any improvement.[83]

Four reports indicate that doses of 1 mg/d-2.5 mg/d were effective in postmenopausal women without hyperandrogenism and in hyperandrogenic women.[84-87] Recently, Iorizzo et al[88] demonstrated increased hair growth in 23 of 27 premenopausal women treated with finasteride 2.5 mg with drospirenone and ethynyl estradiol. This is the same dose that we used in adrenal SAHA[82] and in postmenopausal women with fibrosing frontal alopecia and FPHL.[89] Other authors also used 2.5 mg finasteride in frontal fibrosing alopecia.[90,91] Doses of 5 mg were also used in normoandrogenic women to reduce hair loss and acne.[90] The explanation for why normoandrogenic women would benefit from finasteride at high doses could be that some women have excessive activity of 5α-reductase enzyme.[77]

Dutasteride is a potent nonsteroidal antiandrogen that acts by inhibiting both 5-α-reductase isoenzymes 1 and 2 in humans, lowering serum and scalp 5-α-DHT levels. There are few reports about the use of dutasteride in the treatment of androgenetic alopecia in men[91,92] and women.[93] The first report in men was a phase II trial in 416 men showed that dutasteride increased scalp hair growth in a dose-dependent fashion and that dutasteride 2.5-mg group was superior to the finasteride 5-mg group at both 12 weeks and 24 weeks in increasing target hair growth and in decreasing scalp and serum DHT levels. An adverse event was decreased libido in 13% of patients receiving 2.5 mg of dutasteride, and 50% of these patients resolved their decreased libido while receiving therapy. Other side effects include ejaculation disorders in 4% of patients receiving 0.1 mg, of which 33% were resolved during therapy, and impotence in 3% of patients receiving 0.05 mg. Curiously, the greater percentage of impotence was produced by "nocebo phenomenon"* in placebo group.[91]

Another study in 17 sets of male twins with male androgenetic alopecia demonstrated that after 1 year of dutasteride 0.5 mg daily, the treatment group had significantly more hair regrowth than did the placebo group.[92] Dutasteride to treat male pattern hair loss is not approved by the Food and Drug Administration, probably because of concerns about side effects, including gynecomastia;[94-96] although only a case of gynecomastia has been published.[96] There is evidence that dutasteride is processed in the liver by the CYP3A4 enzymes, thus, it could affect the clearance of other potent CYP3A4 inhibitors, such as ketoconazole, diltiazem, cimetidine, ciprofloxacin, ritonavir, and troleandomycin. No drug interactions of clinical importance have been recognized.[77] Men treated with dutasteride should not donate blood for at least 6 months.

A woman with FAGA that had been treated previously with cyproterone acetate and ethinyl estradiol without response had significant improvement after dutasteride treatment.[93] Dutasteride is contraindicated in women of childbearing age unless they are using birth control measures because of the potential feminizing effects on a male fetus. Twenty-five postmenopausal women with female androgenetic alopecia of male pattern (FAGA.M) were treated off-label with 0.25 mg/d of dutasteride. They demonstrated improvement, starting in the frontotemporal region, followed by vertex and frontal areas in 60% at 1 year of treatment and in 80% at 2 years.[52] In all cases serum 5-α-DHT and PSA levels were reduced.

Recently, 14 postmenopausal women with FAGA.M[28] and 5 premenopausal women with FAGA.M, central hirsutism, and nodulocystic acne corresponding to persistent adrenarche syndrome were treated off-label with a 0.5 mg daily dose of dutasteride and 2.5 mg/d of finasteride for 6 months. Improvement of alopecia was achieved in all the cases (Fig. 10A and 10B), and of hirsutism and acne in 80% of cases. The aim of using this combination is to obtain 100% reduction of 5α-reductase, and consequently of 5α-DHT, alopecia, central hirsutism, and seborrhea-acne. The reduction was demonstrated with 5α-DHT serum levels and trichoscan, Ferriman and Gallwey score, and Sebumeter at baseline, 3 months, and 6 months. With the exception of menopausal women, dutasteride should not be used in women. Hepatic function must be monitored when using this drug.

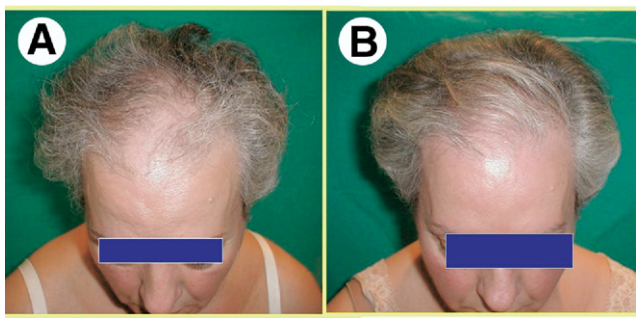

Figure 10 Postmenopausal female androgenetic alopecia of male pattern stage II treated with 5% minoxidil twice a day, 0.5 mg/day dutasteride, and 2.5 mg/day finasteride. (A) At the beginning of treatment. (B) At 6 months after treatment.

**Nocebo phenomenon* is when an adverse side effect is not a direct result of the pharmacologic action of a drug but rather of the patient knowing that it is a side effect (Mondaini N, Gontero P, Giubilei G, et al. Finasteride 5 mg and sexual side effects: How many of these are related to a nocebo phenomenon? J Sex Med 4:1708-1712, 2007).

Treatment of Excess Release of Ovarian Androgens (Ovarian SAHA) and FPHL in Ovarian Hyperandrogenism and FPHL in Normoandrogenic Postmenopausal Women

Three types of treatment can be used: contraceptives for ovarian suppression, gonadotropin-releasing hormone agonists (GnRH-a) for pituitary and gonadal suppression, and antiandrogens.

Ovarian Suppression with OCP. This is the first-line therapy for hair loss and acne in women with ovarian SAHA syndrome and PCOS.[49] The choice of OCP is important because they contain an estrogen, ethinyl estradiol (EE), and a progestin. The estrogenic component suppresses LH and ovarian androgen production and enhances SHBG production in the liver, thus reducing free testosterone and consequently 5-α-DHT.[64] Estrogens can also decrease sebum production but at doses greater than those used for oral contraception.[49] The difficulties in the selection of OC are the progestins because some of them are proandrogenic and some antiandrogenic. Thus, the least-androgenic progestins are norgestimate and desogestrel, whereas the most androgenic progestins are norgestrel and levonorgestrel. The association of EE with norgestrel and/or levonorgestrel should be avoided. The association of EE with norgestimate or desogestrel is recommended. These should not be used in women with insulin resistance, thrombophlebitis, cerebrovascular disease, coronary occlusion, abnormal vaginal bleeding, impaired liver function, migraine, or in smokers older than 35 years of age, or in individuals with increased risk of breast cancer.[49,75] If the patient does not tolerate OCP, medroxyprogesterone acetate, synthetic progesterone, can be used at 5-mg daily or twice a day. This anovulatory agent reduces the production of testosterone and Δ-4-androstenedione in the ovaries.[63] In women older than 40 years, the administration of 4 mg of estradiol valerate orally, may substitute for EE. For an oral intolerance to estrogens, one can administer 10 mg of estradiol valerate intramuscularly on days 5 and 15 of the cycle.[63]

Gonadotropin-Releasing Hormone Agonists (GnRH-a). Although their use in hair loss of the SAHA syndrome is not usually considered, they are useful in the treatment of other manifestations of SAHA syndrome, such as hirsutism, acne and seborrhea seen in severe forms of ovarian hyperandrogenism and especially in HAIRAN syndrome. Treatment of HAIRAN syndrome has focused on lowering insulin levels with a combination of weight loss, OCPs, antiandrogens, and a GnRH agonist known as metformin, which can also be effective in the treatment of PCOS[97] and improve hirsutism.[98] Doses of metformin between 500 mg and 855 mg 3 times daily have been demonstrated to be effective in doubling the frequency of menses in those patients with oligomenorrhea. Metformin has shown modest improvement in markers of insulin resistance,[99] most evident in the 2550-mg/d dose group; marked reduction of circulating serum Δ-4-androstenedione levels, also was most evident in the high doses group. Neither circulating testosterone nor SHBG showed changes, but there were significant reductions in total cholesterol and low-density lipoprotein cholesterol without effect on circulating triglycerides or high-density lipoprotein; highly significant reductions in leptin that were not reflected by changes in circulating C-reactive protein, and a modest reduction in circulating LH was found.[50] Patient weight loss correlated strongly with the change in the glucose/insulin ratio.[50] Metformin may be useful for inducing ovulation in anovulatory women who do not have hyperandrogenism. This effect may be independent of a lowering of androgen or insulin levels. Doses of 1500 mg/d metformin have demonstrated efficacy, tolerability, and safety.[100]

Antiandrogens. Antiandrogens used in the FPHL of ovarian SAHA and PCOS are the same as those used in the treatment of adrenal SAHA and adrenal hyperandrogenism. The experience is greater because ovarian diseases with hair loss and hirsutism have a high incidence. Gynecologists use this type of treatment, especially to treat hirsutism. For the last 8 years (2000-2008) we have treated ovarian SAHA with 2.5 mg/d finasteride and PCOS with 5 mg/d, always monitoring the serum 5α-DHT and PSA levels.[9,28,50] Of 41 hirsute women with nodulo-cystic acne, 34 were diagnosed with ovarian SAHA syndrome. Seven with SAHA type HAIRAN syndrome were treated with a 2.5 mg/d finasteride for 2 years. The results obtained in hirsutism were excellent, with the score decreasing from a mean of 17.4 $\pm$ 4.4 to 8.3 $\pm$ 3.9. Acne improved in 96% of women; and hair loss although decreased was not so evidently approved. Significant decreases of serum levels of 5-α-DHT, 3-α-androstanediol glucuronide, and PSA[48] were also observed.

We also treated 31 women with PCOS who presented as FAGA.I–II with 5 mg/d finasteride and 5% topical minoxidil. At these doses a reasonable clinical improvement was obtained in 23 women (74.1%; Fig. 11A and 11D) and moderate improvement in another 8 cases (25.8%), which was reported by the women themselves. We did not agree with this improvement because our interpretation and that of other 2 external dermatologists demonstrated no clinical change and even worsening in 2 cases (6.4%).[9] The modified wash test demonstrated in 100% of women a decrease in hair loss with a baseline of 134 hairs every 2 days and of 38.2 hairs 1 year later. DHT had a mean serum level at baseline of 0.975 ng/mL, which is greater than 0.5 ng/mL that is the normal level in woman, in 90.3%. The DHT decreased to less than 0.5 ng/mL at 6 months in 51.6% of women and after 1 year in 83.8%. The 3 women that had normal level of DHT before treatment maintained their normal levels. PSA level that at baseline was over 0.02 ng/mL, decreased in 74.1% at 6 months and in 96.7% at 1 year.[9] These results are in accordance with Falsetti et al.[101]

In our work with dutasteride, we used off-label doses of 0.5 mg/day in a group of 23 normoandrogenic postmenopausal women with MAGA.F. Twelve (52.1%) of these women had had cosmetically evident improvement, especially in the occipital regions, at 6 months and 14 (60.8%) at 1 year.

We also treated another group of 33 women with frontovertical FPHL in ovarian hyperandrogenism (Fig. 12A and 12B) with

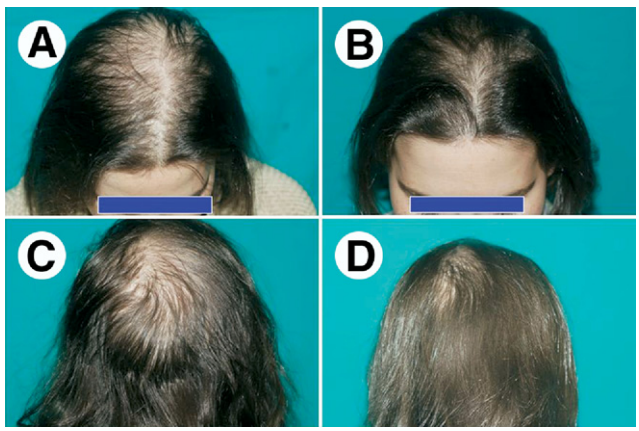

Figure 11 Polycystic ovary syndrome. Treatment with 5% minoxidil twice a day, 5 mg/d finasteride and 0 mg, 0.30 mg/cycle of EE and 3 mg/cycle of drospirenone. (A) Frontal view before treatment. (B) Frontal view 1 year after starting treatment. (C) Occipital view before treatment. (D) Occipital view 1 year later.

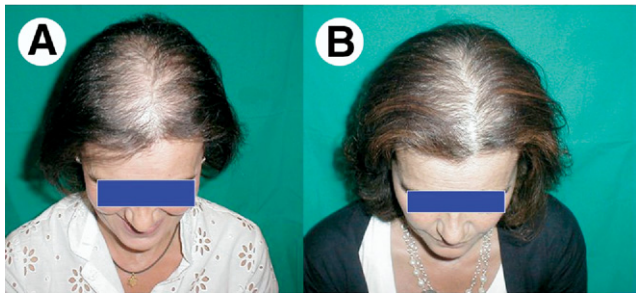

Figure 12 Frontovertical FPHL in ovarian hyperandrogenic woman treated with 2.5 mg/d of finasteride and 0.5 mg/d dutasteride, 5% minoxidil twice a day, and COP of 3 mg drospirenone/cycle and 0.035 mg EE. (A) Before treatment. (B) Moderate cosmetic improvement after 1 year of treatment.

lateral hirsutism and acne, and 9 normoandrogenic postmenopausal women with 2.5 to 5 mg/d of finasteride and 0.5 mg/d dutasteride. When the PSA in premenopausal women was greater than 0.02 ng/mL and in postmenopausal women greater than 0.04 ng/mL, they were treated with 5 mg/d finasteride. In all groups, we always used 5% minoxidil twice a day, and premenopausal women received OCP of 3 mg drospirenone and 0.035 mg ethynyl estradiol. In all cases hepatic tests were investigated at baseline, 6 months, and after 1 year of treatment.

PSA and DHT were decreased in all the 42 cases (100%) at 6 months and 12 months. Clinical improvement was different in premenopausal and postmenopausal women. In 33 premenopausal women, slight improvement was observed in 18 (54.5%) and 4 (12.1%) women at 6 months and 12 months, respectively, and cosmetically evident improvement in 10 (30.3%) and 18 (54.5%) at 6 months and 12 months (Fig. 12A and 12B). Significant improvement was seen in 5 (15.2%) and 11 (33.3%) women at 6 months and 12 months. In the postmenopausal group, there was slight improvement at 6 months and 12 months with 2 (22.2%) and 1 (11.1%), respectively, cosmetically evident 3 (33.3%) and 1 (11.1%) at 6 months and 12 months, and significant improvement in 4 (44.4%) and 7 (77.7%) at 6 month and 12 months, respectively.[9]

Endocrinologist or Gynecologist PCOS Treatment. Treatment of dyslipidemia and hyperinsulinemia by endocrinologists and restoration of ovulation/fertility is performed by gynecologists. Dyslipidemia is treated with statins plus OCP, showing significantly lowered testosterone levels and normalized gonadotropin levels, and insulin resistance is treated with metformin and 2 types of thiazolidinediones (rosiglitazone and pioglitazone). Using these thiazolidinediones, we found that ovulation was significantly increased, free testosterone levels decreased, and SHBG levels increased. Thus, insulin-sensitizing agents are the subject of research on improving ovulation, as well as improving the cardiovascular risk factors associated with hyperandrogenemia, in PCOS. To increase ovulation in PCOS, clomiphene citrate alone or with metformin is useful. Newer ovulation induction agents include the aromatase inhibitor letrozole, which decreases estrogen production, leading to an increase of FSH and consequently to ovulation and delivery.[50]

Treatment of Hyperprolactinemic SAHA (Pituitary SAHA) and Pituitary Hyperandrogenism

A gynecologist with endocrinologic expertise or an endocrinologist should treat these patients. However, when the predominant clinical picture is dermatological, 2.5 mg/d^{-1} of bromocriptine may be prescribed. PCOS with hyperprolactinemia may be treated with clomiphene citrate to restore ovulation. Cabergoline is also used in the hyperprolactinemic hirsutism with the advantage that it is only used once weekly and at a dose of 0.5 mg.[102] Side effects include fatigue, lethargy, hypotension, depression, vomiting, and abdominal pain.[50]

Complementary Treatments

Vitamins

Because treatment with cyproterone acetate and ethinyl estradiol produce a decrease of vitamin B_{12}, women treated for FPHL with these agents must be treated with supplemental vitamin B_{12}. Biotin (vitamin B_7 or H) can be also necessary.

Iron. Women with sideropenic anemia need iron, but it also will be necessary in the treatment of FPHL in vegetarian women. When the quantities of iron ingested are lesser than those lost in menstrual cycle, or in other types of blood loss, a negative serum balance is created and ferritin synthesis in liver is not stimulated. Then, the ferritin of growing follicles is released to serum to cover the needs of other more important organs, thus, anagen follicles go into telogen.[103] Ferritin serum levels less than 40 ng/mL (90 pmol/l) are related to a telogen increase. A recent report confirms that ferritin has an influence in FPHL.[104]

Saw Palmetto (Serenoa Repens). This is a botanic product that inhibits the conversion of testosterone to 5α-DHT in follicles. It has shown increased hair growth in 60% of men with moderate androgenetic alopecia.[105]

Phytoestrogens. Phytoestrogens are plant compounds that are structurally and functionally similar to mammalian estrogens. The 3 main classes found in the human diet are isoflavones (daidzein, genistein, and glycitein), lignans (enterodiol and enterolactone), and coumenstans.[106] The primary food sources of isoflavones are soy and soy products, and sources for lignans are cereals, flaxseed, and berries.[107] Plasma concentrations of phytoestrogens in Europeans are low compared with Asian populations.[106] Because the incidence of breast cancer is much lower in Asian countries, it has been hypothesized that phytoestrogens protect against breast cancer[107] and against menopausal hot flashes, cardiovascular risk, and osteoporosis.[108] An inverse association between plasma genistein and the risk of breast cancer has been demonstrated.[107,109]

Lifestyle

Weight loss of only 2% to 7% has been showed to improve manifestations of hyperandrogenism,[110] decrease hyperinsulinemia, and restore ovulation and fertility in up to 75% of obese women. Therefore, healthy eating, regular exercise, and weight reduction are encouraged.[49]

Dermatocosmetic Concealment

Concealment with wigs or hairpieces, and extensions or partial hairpieces is useful when women wish for more density than can be achieved with medical treatment alone. Another possibility is camouflage with powders, dyes, sprays, and keratin-based fibers (Toppik®).[111] Table 3.

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