Treatment of female pattern hair loss with combination therapy

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■ **Abstract**

Female pattern hair loss (FPHL) is a common nonscarring alopecia characterized by progressive loss of terminal hairs. FPHL is a major concern for women and has a high impact on quality of life. Therapeutic regimen is often challenging and requires multiple combinations of topical, systemic, and interventional therapies to control hair loss and produce satisfactory hair regrowth. This article reviews common treatments of FPHL and their efficacy.

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Female pattern hair loss (FPHL), or androgenetic alopecia (AGA), is a common cause of alopecia in women characterized by nonscarring, progressive loss of terminal hairs over the frontal and vertex regions of the scalp.[1] The hair loss occurs due to a process called follicular miniaturization, in which there is shortening of anagen phase and an increase in vellus hairs over frontal and vertex scalp.[1] FPHL may occur at any age with varying severity, and it becomes clinically detectable in about 3% of women by 29 years of age, in 13% by 49 years, in 19% by 69 years, and in 25% among those over 69.[2,3] Clinical severity and progression tends to be more intense with earlier onset. Prevalence appears to be lower among women of Asian descent.[1]

Typically, women complain of a thinning ponytail, scalp visibility in frontal and vertex areas, and gradual thinning of hair density on the central scalp. Patients frequently relate an increased sunburn in those thinned areas. Clinically, there is a gradual transition of terminal scalp hairs to vellus hairs over the areas of frontal and vertex of scalp, without scaling, inflammation, or scarring. However, scalp seborrhea and seborrheic dermatitis may be associated with FPHL. Loss of scalp hair density is progressive but slow, and usually there are no areas of complete baldness.

FPHL is a major concern for women and is associated with reduced quality of life. Herein, we review the various treatments used for FPHL and their efficacy.

Diagnosing FPHL

The approach to any hair loss is challenging and involves a combination of a patient's medical and family history, trichoscopy, laboratory evaluation, and potential biopsy to further examine the possibility of an inflammatory and scarring alopecia. Patient history should include questions regarding duration and progression of hair loss; amount of shedding; hair habits such as coloring or bleaching, heat styling, or the use of perms and keratin treatments; any additional symptoms such as itching, scaling, or burning; recent changes in medication; hospitalizations or new stresses; dietary habits; and general personal and family medical conditions. To assess current amount of hair shedding, the hair-pull test, in which 50 to 60 hairs are grasped at the scalp and pulled away from the head, should be performed. By doing this, loose telogen hairs are removed, and removal of more than 10% of hairs indicates excess shedding. Examining the differences between left and right parietal, frontal, and occipital scalp can give further clues to the disease.[4] Trichoscopy can be further used to assess loss of terminal hairs within follicular units and variations in hair diameter due to follicular miniaturization (>20% reduction in hair shaft diameter) characteristic of male and female pattern hair loss.[5-7] Other signs that may be present are follicular atrichia, yellow dots (due to filling of follicular ostia with keratin and sebum), and white peripilar signs.[5,8] If a biopsy is needed, local anesthetic is applied, and 4-mm scalp punch biopsies—preferably from the midline—are obtained and sectioned horizontally. Terminal-to-vellus hair ratio of less than 3:1 and lack of other pathologic signs are indicative of FPHL.[4] In our practice, we routinely perform laboratory analyses for complete blood count, metabolic panel, ferritin, zinc, and vitamin D levels, as well as thyroid-stimulating hormone, total and free testosterone, and dihydroepiandrosterone sulfate. Additional testing is relative to the patient's history but can include more extensive thyroid evaluation, microsomal antibodies, and antinuclear antibodies.

Topicals

A summary of topical treatments is presented in Table 1.

Minoxidil

First-line treatment for FPHL is minoxidil, a potassium channel opener that is hypothesized to enhance angiogenesis and vasodilation, in addition to having anti-inflammatory and anti-androgenic effects.[9] Of note, only 2% and 5% minoxidil are US Food and Drug Administration approved for FPHL; all other therapies discussed are off-label. The resulting anagen phase is prolonged while telogen is shortened and miniaturized follicles are enlarged, resulting in increased hair counts and weight. Minoxidil is available in 2% and 5% solution or 5% foam.[10] Minoxidil solutions should be applied to the affected scalp 1 to 2 times a day, while foam is applied once a day. A randomized placebo-controlled trial demonstrated superior efficacy for hair count and patient and physician assessment of hair growth for 5% and 2% topical minoxidil after 48 weeks.[10] Similarly, a phase 3 trial comparing 5% minoxidil and placebo improved regrowth and scalp coverage after 24 weeks in

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TABLE 1. Topical treatments for female pattern hair loss

	Mechanism of Action	Dosage	Side Effects
Topical minoxidil	K^+ channel opener with anti-inflammatory, antiandrogenic properties	2% solution; 5% solution; 5% foam	Hair shedding during the first 2-8 weeks, scalp pruritus, flaking, facial hypertrichosis
Zinc pyrithione	Releases zinc ion, inhibits 5α reductase		Irritation, itching
Ketoconazole	Reduction of dihydrotestosterone in the hair follicle	1% shampoo; 2% shampoo	Irritation, scalp oiliness or dryness, pustules, discoloration, abnormal hair texture

both physician and patient assessment.[11] Recently, a phase 3 trial of 5% and 2% minoxidil for FPHL showed similar effects in hair regrowth after 24 weeks, but minoxidil was unable to meet non-inferiority criteria.[12] For nonresponders to 5% minoxidil, there is some evidence that using 15% topical minoxidil could induce hair growth in 60% of patients without increasing adverse events; however, further investigation is necessary.[13] In our practice, we recommend 5% minoxidil for its effect on hair regrowth and higher patient satisfaction. During the initial treatment period of 2 to 8 weeks, there can be transient increase in shedding, of which patients must be informed.[14] Additional adverse effects include scalp pruritus, flaking, and facial hypertrichosis, which are more likely to occur with 5% minoxidil.[10] Minoxidil should be used for at least 12 months for optimal results.[9]

Shampoo

Ketoconazole is an imidazole antifungal with anti-inflammatory and anti-androgenic properties. The anti-androgenic mechanism is due to a decrease in dihydrotestosterone at the level of the hair follicle.[15] It comes in 1% (over the counter) and 2% (prescription) solutions. The patient is supposed to lather the shampoo and leave it on for 5 minutes before rinsing off. Limited data are available for females; however, in a study of 6 Japanese males, 2 experienced hair growth at 6 and 10 months with ketoconazole alone.[15] Another study examining 39 patients using ketoconazole and 2% minoxidil and ketoconazole alone found similar improvement in hair density as well as size and proportion of anagen follicles.[16] Side effects include irritation, scalp oiliness or dryness, pustules, discoloration, and abnormal hair texture. There is no evidence regarding safety profile during pregnancy or breastfeeding.

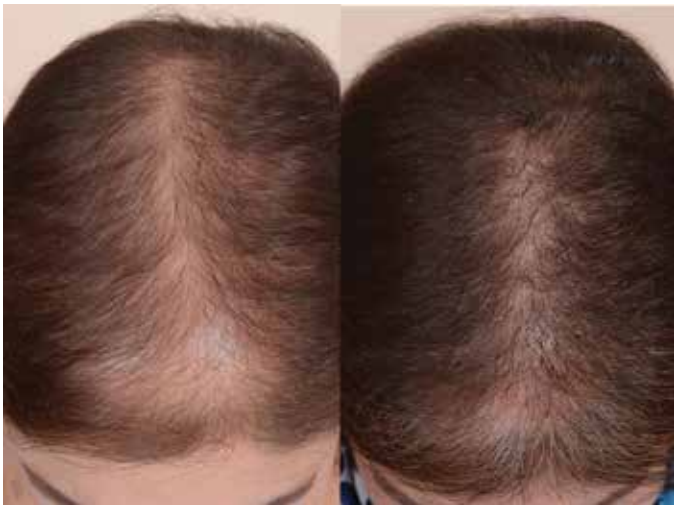

FIGURE 1. A 46-year-old woman with FPHL, before and after spironolactone 100 mg daily, minoxidil 5% once daily, daily multivitamin, and ketoconazole shampoo 3 times weekly. Photos courtesy of Melissa Piliang, MD. Abbreviation: FPHL, female pattern hair loss.

Zinc pyrithione is another antimicrobial shampoo used for seborrheic dermatitis. It likely releases zinc ion, causing a reduction in inflammation. It is also a skin antioxidant and has been demonstrated to inhibit 5-alpha reductase in vitro.[17-19] Limited data on efficacy are available. In a randomized controlled trial of 200 males on placebo, zinc pyrithione shampoo, minoxidil, or a combination, there was a significant increase in total hair counts compared with placebo; however, this was about half of the increase seen in the group treated with minoxidil.[20] Despite this, the effects of zinc pyrithione were apparent only to the investigator.[20] Side effects include irritation and itching.

Others

Several other less used topical therapies exist, including 17α estradiol and methyl vanillate. A study of 53 women using 0.025% 17α estradiol, which inhibits conversion of androstenedione to testosterone, demonstrated significant improvement by physician and patient assessment.[21] In addition, a randomized controlled trial demonstrated a 63% reduction in telogen hairs, and another study reported maintaining 88% of anagen hairs but no hair regrowth.[21,22] However, in comparison to minoxidil, 17α estradiol demonstrates lower efficacy for hair regrowth.[23]

A newer treatment option is topical methyl vanillate, which activates the WNT/α-catenin signaling pathway. A 0.2% spray was used on 20 women, and there was a 6% increase in hair count and 12% increase in hair density after 6 months.[24]

Systemic

A summary of systemic treatments is presented in Table 2.

Anti-androgens

Anti-androgen therapy is used in FPHL if there is presence of hyperandrogenism or if there is a poor response to minoxidil; however, information on their efficacy is limited.[25] The most commonly used anti-androgenic drugs are 5-alpha reductase inhibitors (fin-

TABLE 2. Systemic treatments for female pattern hair loss

	Mechanism of Action	Dosage	Side Effects
5α reductase	Blocks conversion of testosterone to dihydrotestosterone		
Finasteride	Blocks type 2 5α reductase	2.5 mg/day-5 mg/day	Depression, allergic reactions and loss of libido, teratogenic
Dutasteride	Blocks type 1 and 2 5α reductase	0.25-0.5 mg/day postmenopausal	Depression, allergic reactions and loss of libido, teratogenic
Spironolactone	Aldosterone antagonist, weak 5α reductase inhibitor, decreases microsomal cytochrome p450 activity	50 mg/day increased by 50 mg per month to up to 200 mg/day	Breast tenderness, lethargy, headache, nausea, menorrhagia, hyperkalemia, and orthostatic hypotension
Flutamide	Competitive blockage of androgen binding to its receptor, decreases microsomal cytochrome p450 activity	62.5 mg/day	Headache, dry skin, reduction in libido, gastrointestinal distress, liver function test abnormalities, and hepatic failure
Cyproterone acetate	Direct inhibition of androgen receptors and gonadotropin-releasing hormone	Premenopausal: 100 mg/day for 10 days per month; postmenopausal: 50 mg/day	Weight gain, menstrual irregularities, loss of libido, depression, and gastrointestinal upset

asteride, dutasteride), spironolactone, flutamide, and cyproterone acetate (progesterone), which are typically used in conjunction with minoxidil.

Oral contraceptives

Systemic estrogens up-regulate sex-hormone-binding globulin, resulting in decreased circulating testosterone.[26] In addition, they can increase the anagen phase and decrease telogen, which is supported by telogen effluvium following cessation of oral contraceptives. Little information exists on usage of oral contraceptives alone in FPHL, and we recommend using them as an adjunctive therapy for premenstrual women, particularly if there's a history of hormonal imbalance or polycystic ovarian syndrome or if patients are taking finasteride.

5-alpha reductase inhibitors

Finasteride is a type 2 5-alpha reductase inhibitor that works by blocking conversion of testosterone to dihydrotestosterone.[27] Variable efficacy has been demonstrated in studies, with some retrospective studies showing no significant improvement with 1.25 mg/day and one large, multicenter placebo-controlled trial of postmenopausal women concluding that 1 mg of finasteride does not increase hair growth or slow progression.[28,29] However, other case reports and retrospective studies demonstrated that dosage between 1.25 mg/day, 2.5 mg/day, and 5 mg/day are associated with increase in hair thickness and improvement in hair regrowth.[30-35] An additional retrospective study of 112 premenopausal and postmenopausal females on 2.5-mg finasteride found significant improvement of hair loss in 65.2% and slight improvement in 29.5% and that patients with a lower Ludwig score and older age at onset demonstrated better response to therapy.[33] Potential side effects include depression, allergic reactions, and loss of libido; however, limited data are available in women.[36] This treatment is not advisable in those with a history of breast cancer and requires use of contraception in women of childbearing age because finasteride is teratogenic.[36,37] Liver function tests should be performed as finasteride is metabolized in the liver.[37] Finasteride treatment should be continued for 12 months to establish efficacy.

Dutasteride is superior to finasteride in inhibiting conversion of testosterone to dihydrotestosterone due to blocking type 1 and 2 of 5-alpha reductase.[37,38] It has effectively been used off-label in doses of 0.25 to 0.5 mg/day in postmenopausal women.[38] In addition, patients undergoing 12 sessions of mesotherapy with dutasteride demonstrated a 62.8% improvement from baseline compared with 17.5% in controls, with no difference in side effects between the 2 groups.[39] Treatment should continue for 6 months to achieve effect.

Spironolactone

Spironolactone is an aldosterone antagonist with weak 5-alpha reductase inhibitor activity that depletes cytochrome p450, thus decreasing testosterone production. Starting dose is usually 50 mg per day and is increased as needed by 50 mg per month as tolerated, until dosage reaches 200 mg per day.[40] In a retrospective study, 74.3% of female patients on spironolactone reported stabilization or improvement of hair loss.[41] In a comparison study of spironolactone and cyproterone acetate efficacy, about 44% of females experienced hair regrowth and 12% had continued hair loss.[42] Another study examined efficacy of oral minoxidil 0.25 mg and spironolactone 25 mg and found reductions in hair shedding and hair loss severity at 12 months.[43] Side effects of spironolactone only include breast tenderness, lethargy, headache, nausea, menorrhagia, hyperkalemia, and orthostatic hypotension, while urticarial, hypertrichosis, and postural hypotension were seen in the oral minoxidil and spironolactone combination. Blood pressure and serum potassium should be monitored.[43,44] Efficacy should be assessed after 6 months of usage.

Flutamide

Flutamide competitively blocks the binding of androgen to its receptor and decreases testosterone production by depleting microsomal cytochrome p450.[45,46] It is rarely used in FPHL, typically only if women failed to improve with another anti-androgen. A

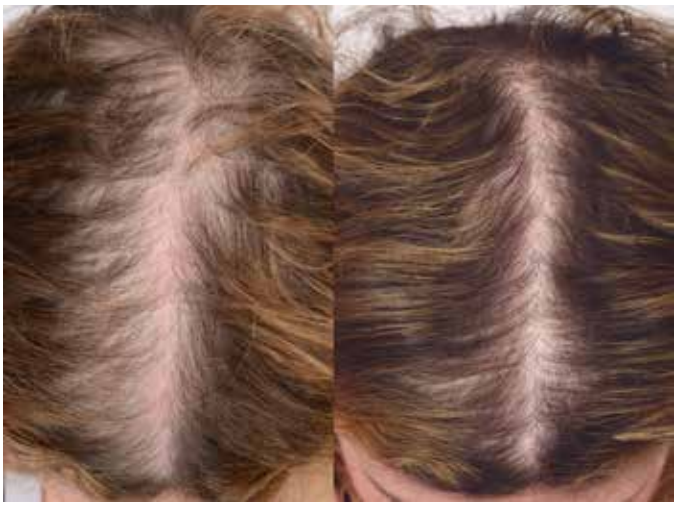

FIGURE 2. A 41-year-old woman with FPHL who had been stable on 5 years of spironolactone 50 mg daily, 5% minoxidil daily, and 3 mg of biotin daily (left). She desired additional hair growth, so she underwent 3 monthly sessions of PRP (right). Photos courtesy of Shilpi Khetarpal, MD. Abbreviations: FPHL, female pattern hair loss; PRP, platelet-rich plasma.

prospective cohort study of premenopausal women demonstrated a 15% improvement in hair loss severity within 6 months, 20% improvement after 1 year, and 28% improvement after 2 years.[45] Dosage of 62.5 mg per day has proven safe and effective.[45,46] Side effects are headache, dry skin, reduction in libido, gastrointestinal distress, liver function test abnormalities, and hepatic failure.[45] Efficacy can be assessed after 6 months.[45]

Cyproterone acetate

Cyproterone acetate, which acts as a progesterone, directly blocks androgen receptors and inhibits gonadotropin-releasing hormone.[14] It was found to be more effective in women with signs of hyperandrogenism compared with 2% minoxidil.[47] In women without hyperandrogenism, it is effective in conjunction with oral contraceptives.[48] Dosage is 100 mg/day for 10 days per month in premenopausal women and 50 mg/day for postmenopausal women.[49] Side effects include weight gain, menstrual irregularities, loss of libido, depression, and gastrointestinal upset.[47,48] This medication is not available for use in the United States.

Interventional treatments

A summary of interventional treatments is presented in Table 3.

Low-level laser light therapy

The initial discovery of low-level laser light therapy (LLLT) in hair loss followed reports of hypertrichosis in patients undergoing intense pulsed light to remove unwanted hair. This was termed paradoxical hypertrichosis and is hypothesized to occur when the laser fluence is suboptimal for thermolysis but sufficient for stimulating hair growth by acting on hair follicle stem cells or follicular keratinocytes and thus accelerating mitotic rate.[50,51] In addition, it reduces inflammation by increasing transforming growth factor beta 1 and interleukin 10 and reducing proinflammatory cytokines and prostaglandin E2. Usually, wavelengths between 600 and 1,400 nm in the infrared spectrum are used.[52] There are various devices that can be used, including excimer, helium–neon, fractional erbium glass lasers, laser combs, and head caps. HairMax was the first approved device for FPHL, and a study of 7 female patients reported an increase in hair count and strength in the temporal and vertex area.[53] Similarly, a helmet-shaped device reported an increase in mean hair diameter after 23 weeks of daily treatment for 18 minutes; however, patients did not perceive the improvement.[54] Another randomized controlled trial of a 655-nm helmet-shaped device for utility in 47 FPHL patients found a 37% improvement after 16 weeks of treatment every other day.[55] Adverse effects include headache, erythema, pruritus, burning, pain, and mild paresthesia.[56] This is a good adjunct for patients who do not respond to other therapies and do not wish to undergo hair transplantation.[50]

Platelet-rich plasma

Platelet-rich plasma (PRP) is produced by centrifuging patient blood, thus increasing platelet concentration 300% to 700% from baseline and injecting it into androgen-dependent areas of the

TABLE 3. Interventions for female pattern hair loss

	Mechanism of Action	Dosage	Side Effects
PRP	Growth factors, chemokines, cytokines induce hair growth	Monthly sessions for the first 3 months, then every 3 months for the first year	Swelling, bruising, headache, pain
Low-level laser light therapy	Vasodilation, anti-inflammation; mitochondria activation	600-1,400 nm; ~25 minutes every other day	Headache, erythema, pruritus, burning, pain, mild paresthesia
Microneedling	Mechanical disruption of collagen fibers resulting in increased growth factors and cytokines in the area	Same as PRP	Itching, erythema, pain, headache, and infection
Mesotherapy	Microinjection of medication	Same as PRP	Itching, erythema, pain, headache, and infection
Hair transplant		Depends on patient	

Abbreviation: PRP, platelet-rich plasma.

scalp.[57] Platelets in the centrifuged solution become activated when injected into the scalp and release numerous growth factors from alpha granules as part of the wound-healing process.[58] The growth factors bind to the bulge area of the hair follicles and promote hair growth through fibroblast activation, collagen synthesis, stimulation of the extracellular matrix, and overexpression of endogenous growth factors. A study of 20 FPHL patients undergoing 1 session of PRP and 11 sessions of polydeoxyribonucleotide demonstrated improvement in hair thickness compared with 20 patients undergoing just polydeoxyribonucleotide injections.[59,60] Microneedling combined with PRP once a month for 6 months was compared to 5% minoxidil monotherapy in 40 FPHL patients, and both groups showed similar improvement in hair counts; however, minoxidil produced faster hair regrowth.[61] Finally, in a meta-analysis examining 6 studies of both male and female pattern hair loss, there was a significant increase in hair density and thickness.[58]

PRP has become a promising treatment modality for FPHL; however, no standard practice for PRP preparation and administration or methods for evaluation of results have been established. In our practice, we recommend the use of PRP as a co-adjuvant treatment for FPHL and encourage patients to continue topical and/or oral therapies because PRP does not suppress the hormonal component of FPHL. Based on review of the published studies, we suggest PRP preparation by a single-spin centrifugation method to produce pure PRP with a mean platelet enrichment 3- to 6-fold the mean concentration of whole blood and minimize the granulocytes. We recommend administration of PRP as subdermal depo bolus injections, which allow for diffusion of PRP and result in fewer injections because this is less painful and an overall more efficient injection technique. Injections should be spaced out in the thinning area, which is typically along the hairline, part, vertex, and crown of the scalp. Side effects include pain at injection site, swelling, bruising, and rarely headaches, all of which are mild and transient. Treatment intervals should include monthly sessions for the first 3 months, then every 3 months for the first year (6 treatment sessions in first year—months 1, 2, 3, 6, 9, and 12). However, 3 monthly sessions followed by sessions at 6-month intervals has also been effective. Overall, our male and female patients have had positive results from PRP injections in AGA in terms of regrowth, increased hair density, and improved quality of life.

Mesotherapy and microneedling

Mesotherapy involves microinjection of various vitamins, minerals, lipolysis agents, and medications into the middle layer of skin. Microneedling is another technique that involves creating multiple punctures in the skin using dermal rollers or stamp devices and can be followed by application of various solutions to improve their absorption.[62] Prior to either technique, a topical anesthetic is applied 15 to 45 minutes prior to starting, followed by disinfection if needed. If using the microneedling stamp, linear movement over the treatment area is necessary with lifting of the device between strokes. In the case of dermal rollers, 0.5- to 1.5-mm needles are used, and the rolling motion is performed in a vertical, horizontal, and diagonal direction 15 to 20 times until there is mild erythema of the scalp. Once treatment is completed, antibiotic should be applied.[63] Potential complications include itching, erythema, pain, headache, and infection.[62] In addition, there have been reported cases of cicatricial and reversible alopecia following mesotherapy for AGA (patterned alopecia), indicating that caution needs to be taken with technique and quality of injectable solutions.[64,65] Contraindications include pregnancy, history of stroke or cancer, and anticoagulation medication.[66]

Hair transplantation

Hair transplantation is an important alternative if response to pharmacological therapy is unsatisfactory; however, realistic goals must be set. The results depend on technique used, donor area, quality of harvested hair, amount of hairs transplanted, and recipient area.[67] Other therapies must be continued post-transplant, or progression of hair loss will continue to occur. Adjuvant use of PRP as a direct injection to the scalp, or in conjunction with hair transplant procedures, has shown better results compared with hair transplant alone.[67,68]

Combination therapy

Combination therapy is often necessary for hair loss treatment; however, few studies examine the efficacy of various combinations. Most often, topical minoxidil is combined with some form of cosmetic coverage, and/or anti-androgenic therapy is employed. More recently, at-home treatment with LLLT is added along with PRP once every 3 to 6 months.[69]

A recent study evaluating combination 2% minoxidil and botanical hair solution demonstrated improvement in hair growth, as well as patient satisfaction with hair volume and quality within 6 weeks.[70,71,72] Similar findings were present in men using 5% minoxidil and botanical hair solution.[73] Another study evaluated effects of a combination of 3% minoxidil and 0.025% 17α estradiol on 34 women and found increases in hair count and density after 6 months of treatment.[74] However, none of these studies had comparison groups available.

Combination low-dose oral minoxidil (0.25 mg) and spironolactone (25 mg) demonstrated decrease in severity of hair loss and shedding in 100 women.[43] Side effects were present in 8 women and included urticarial, facial hypertrichosis, and postural hypertension; however, no hyperkalemia or hematological abnormalities were noted.[43]

LLLT for 25 minutes 3 days a week for 4 months combined with 5% minoxidil in 45 patients demonstrated a significant increase in hair follicles using ultrasound biomicroscopy after 2 months and a significant increase in hair follicle regrowth after 4 months using dermoscopy.[75] Patient satisfaction was highest in the combined minoxidil and LLLT group compared with either modality alone. Side effects included warm sensation, irritation, and scalp tenderness.[75] In contrast, a study of LLLT at 655 nm containing 32 patients demonstrated no differences between LLLT alone and combination with minoxidil or finasteride.[76]

Mesotherapy with 0.05-mL dutasteride was used in 86 FPHL patients, and mesotherapy with saline was used in 40 controls.[39] Treatments were received once a week for 8 weeks, then every other week for 4 weeks, and finally once every 4 weeks. Improvement was present in 62.8% of patients and 17.5% of controls. Better response was seen in FPHL patients with shorter duration of

disease. There is some evidence that increasing the protocol time to 3 months could be effective and maintain adherence.[77]

Another study evaluated 11 women for whom one-half of the scalp was treated with 5 weekly sessions of growth factors followed by microneedling with 0.5 mm while the other side received saline followed by microneedling.[78] The growth-factor-treated side had >10% increase in hair count compared with the control side; however, it is important to note that growth factors likely had an effect on the other side of the scalp. No adverse events were noted.[79,80]

In our practice, we generally prescribe 5% minoxidil daily with spironolactone starting at 50 mg (Figure 1). The maintenance dose is usually 100 mg of spironolactone due to dose-dependent risk of adverse events. For adjunctive therapy, we prescribe daily multivitamin—biotin 3 mg and vitamin D3 2,000 international units—particularly if patients have nutritional deficiencies or are on vegetarian or vegan diets. In addition, we prescribe ketoconazole shampoo at least 2-3 times a week, alternating with their personal-choice shampoo. If a patient's hair loss is stable but hair regrowth is unsatisfactory, additional recommendations include a trial of PRP, LLLT, or combination PRP and LLLT and possibly microneedling with and without minoxidil (Figure 2).

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