CLINICAL PRACTICE

# Hair Loss in Women

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*This* Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

**A 46-year-old premenopausal woman presents with a 3-year history of progressive thinning and shedding of her scalp hair. She has well-controlled hypertension and relates no recent surgery, weight loss, or change in her medications or medical conditions. She has mild hirsutism treated with plucking. On examination, she has a decrease in hair density in the central scalp with frontal accentuation, retention of her anterior hairline, absence of scalp inflammation, and release of multiple hairs on a gentle hair pull. Eyebrows and eyelashes are intact. How would you treat this patient?**

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CME

## THE CLINICAL PROBLEM

Female-pattern hair loss is the most common cause of hair loss in women.[1] The prevalence of this condition is 3 to 12% among women of European descent in their 20s and 30s, 14 to 28% among those in their 50s, and 56% among those older than 70 years of age.[2,3] The prevalence is lower among Asian women — 12 to 25% among those older than 70 years of age[2] — and is unknown among women of African descent owing to the common overlap of the clinical findings of female-pattern hair loss with those of early central centrifugal cicatricial alopecia. It is unclear whether the decrease in hair density or diameter (or both) commonly seen in older persons, known as senescent or involutional alopecia, is a distinct entity or a part of pattern hair loss (i.e., pattern hair loss that occurs in men or women).

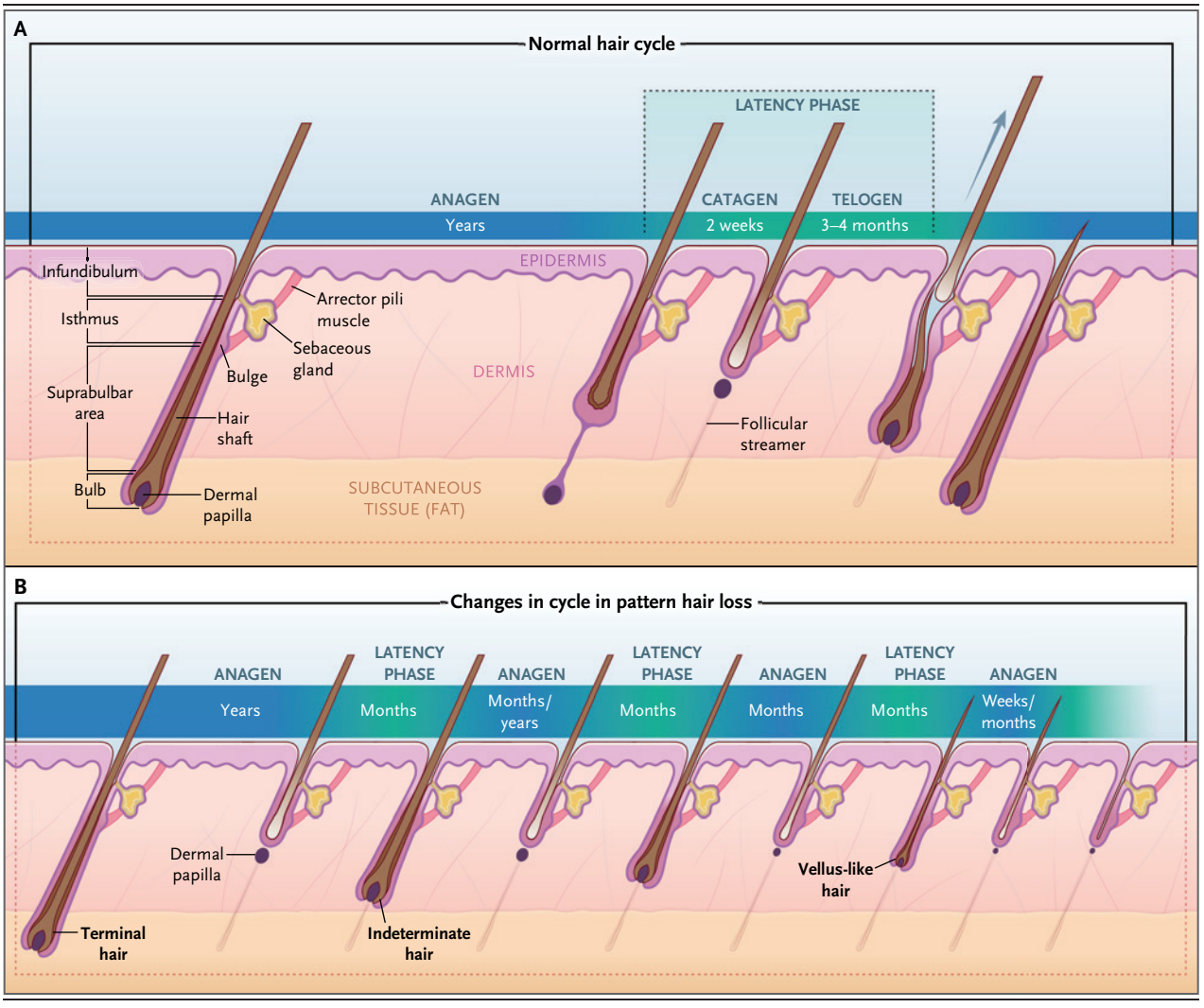
Both male-pattern hair loss and female-pattern hair loss are characterized by progressive miniaturization of the hair follicle, a shortened anagen (growth) phase, and a prolonged latent phase[1] (Fig. 1). Scalp hair is arranged in follicular units of two to four terminal hairs (>60 μm in diameter) and one or two vellus hairs (<30 μm in diameter), with the degree of miniaturization specific to each individual hair. This miniaturization process leads to a progressive, but variable, decrease in the caliber, length, and number of hairs in an affected follicular unit.[1,4] Female-pattern hair loss manifests as decreased hair density in a diffuse central or frontal accentuation pattern but without baldness[1,5] (Fig. 2). The rare manifestation of female-pattern hair loss in women that mimicks that of male-pattern hair loss is usually related to marked hyperandrogenemia and, if accompanied by virilization, should arouse suspicion for a tumor. Female-pattern hair loss may first manifest between puberty and the late 20s (early-onset female-pattern hair loss) or in the late 40s through menopause (late-onset female-pattern hair loss).

Whereas male-pattern hair loss is a genetically determined, androgen-dependent

KEY CLINICAL POINTS

**HAIR LOSS IN WOMEN**

- Female-pattern hair loss is common and increases with age. Distinguishing between early-onset and late-onset female-pattern hair loss and establishing the presence or absence of hyperandrogenism or hyperandrogenemia may identify subpopulations of patients with varied etiologic factors and response to treatment.
- The major clinical features of female-pattern hair loss are a pattern of central-scalp hair loss with or without frontal accentuation, preservation of follicular ostia, and variation of hair-shaft diameter. A scalp biopsy can confirm the disorder and determine the potential for regrowth.
- One treatment strategy for female-pattern hair loss is to start with either 5% topical minoxidil twice a day or a low dose of oral minoxidil and escalate the latter if no unacceptable side effects occur (e.g., symptomatic low blood pressure, peripheral edema, or hypertrichosis).
- Antiandrogen agents or 5$\alpha$-reductase inhibitors are effective treatments in women with female-pattern hair loss and are useful in combination with minoxidil.
- For patients with female-pattern hair loss who prefer to avoid medications or wish to augment their medical therapy, microneedling, platelet-rich plasma, nonablative fractional laser treatment, and low-level light therapy may be useful.



process, the causes of female-pattern hair loss appear to be more complex, involving hormonal, genetic, and environmental factors. Follicular androgen sensitivity in both male- and female-pattern hair loss appears to be related to increased expression of the androgen receptor and 5α-reductase in affected scalps.[6,7] 5α-Reductase converts testosterone to the more potent, avidly bound dihydrotestosterone. In genetically sensitive follicles, the binding of androgen to the X-linked androgen receptor, which is strategically located on the dermal papilla of the follicle, leads to reduced proliferation of the dermal papilla cells and the closely aligned matrix cells that form the hair shaft. Signs of hyperandrogenism are common in women with female-pattern hair loss, especially in those with early-onset female-pattern hair loss.[1] Among those with female-pattern hair loss and hirsutism, more than 80% will have hyperandrogenemia,[1] and polycystic ovarian syndrome is not uncommon.[3]

**Figure 1 (facing page). The Hair Cycle with Normal Hair Growth and with Pattern Hair Loss.**

Panel A shows the hair cycle of a normal-scalp terminal hair. The cycle includes 3-to-6-year periods of active hair growth (anagen) separated by periods of inactivity. This latency phase is initiated by a brief period of apoptosis-driven regression of the inferior portion of the hair follicle and upward movement of the remaining follicle and its dermal papilla to the area immediately below the arrector pili muscle. This brief transition period (catagen) is followed by a quiescent period (telogen) that lasts several months. At the conclusion of telogen, the hair shaft is shed (exogen), anagen is reinitiated, and the anagen follicle moves downward along the collapsed follicular streamer to its former location in the subcutaneous tissue. Panel B shows the hair cycle in pattern hair loss. In male-pattern or female-pattern hair loss, the process of miniaturization of individual hairs in affected follicular units drives the degree and location of the hair loss. The dermal papilla and the bulb of affected hairs, which determine the diameter of the hair shaft, synchronously become smaller and the duration of the anagen phase, which determines the length of the hair shaft, becomes shorter over several cycles. An additional period of quiescence called kenogen follows telogen in pattern hair loss, which lengthens the latency phase between active anagen phases and increases the time that affected follicles and follicular ostia may remain empty of hair shafts. In severe pattern hair loss, this miniaturization process can evolve into actual follicular loss. The net result is a decrease in follicular density and volume.

However, female-pattern hair loss has neither a clear association with any of the various loci identified in male-pattern hair loss nor the strong paternal relation with hair loss seen in male-pattern hair loss.[2,3,8-11] Most women with female-pattern hair loss have no clinical or biochemical evidence of androgen excess, and the response to antiandrogens or 5α-reductase inhibitors among women with this condition is inconsistent. The female-pattern hair loss phenotype has also been reported in the complete androgen insensitivity syndrome and in the absence of androgens.[10] In addition, waning plasma androgen levels are present in women with late-onset female-pattern hair loss.

Aromatase, a key enzyme regulating both estradiol and testosterone levels, is decreased in the affected scalp of those with female-pattern hair loss.[7] This fact suggests not only a potential relationship of estrogen with this condition but another mechanism for increased tissue androgen in women with female-pattern hair loss. A female-pattern hair loss phenotype indistinguishable from naturally occurring female-pattern hair loss develops in women taking antiestrogen agents. Several studies have suggested associations, inconsistently confirmed, between female-pattern hair loss and polymorphisms of the genes *CYP19A1* and *ESR2*, which encode aromatase and the target receptor for estrogen, respectively.[11,12] Because the relation of androgens to the female-pattern hair loss phenotype is complex and androgen-independent factors may also play a role, the term "female-pattern hair loss" has largely supplanted the term "androgenetic alopecia" with respect to women.[3]

## STRATEGIES AND EVIDENCE

The pattern of decreased hair density on the central or frontal scalp (or both) and the general sparing of hair on the occiput are key features of female-pattern hair loss. Parietal and bitemporal areas may also be involved. Trichoscopic evaluation shows variation of hair-shaft diameter and preservation of follicular openings (ostia), the latter confirming the presence of intact follicular sebaceous units and a potentially reversible process. Focal atrichia — 2-to-4-mm hairless areas commonly seen in late-onset female-pattern

hair loss — may reflect the prolonged latent period after hair shafts have been shed or the loss of follicles seen on scalp biopsy in advanced pattern hair loss.[13] Clinical inflammation is absent unless the patient has an additional scalp condition.

The differential diagnosis of female-pattern hair loss includes types of reversible as well as cicatricial (scarring) hair loss[3] (Fig. 3). Telogen effluvium, which is characterized by a history of increased shedding of scalp hair and a diffuse decrease in hair density, is associated with a reversible increase in the percentage of hair in the telogen phase. Chronic telogen effluvium may occur in concert with female-pattern hair loss.[14] Frontal fibrosing alopecia, which was first described in 1994, is now the most common type of cicatricial alopecia. It manifests predominantly in postmenopausal White women as recession of the anterior and parietal hairlines, perifollicular erythema, loss of follicular ostia, and loss of eyebrows, each of which may appear independently and in any temporal order.[15] Fibrosing alopecia in a pattern distribution is a type of cicatricial hair loss that appears specifically in areas of the scalp where pattern hair loss occurs. Central centrifugal cicatricial alopecia, seen predominantly in women of African descent, manifests as a progressive decrease in hair density in the central or vertex scalp with loss of follicular ostia and potential balding.[16] Scalp-biopsy specimens from patients with these conditions have characteristic histopathological findings but also commonly show follicular miniaturization suggestive of underlying female-pattern hair loss. Previously published articles have suggested female-pattern hair loss as one etiologic factor in each of these conditions.[17,18]

If a diagnosis of female-pattern hair loss is suspected, a 4-mm scalp biopsy will help to confirm the diagnosis and can provide information on follicular density. Typical histologic findings include a decreased ratio of anagen hair to telogen hair and of terminal hair to vellus hair. A lymphohistiocytic infiltrate at the infundibulum

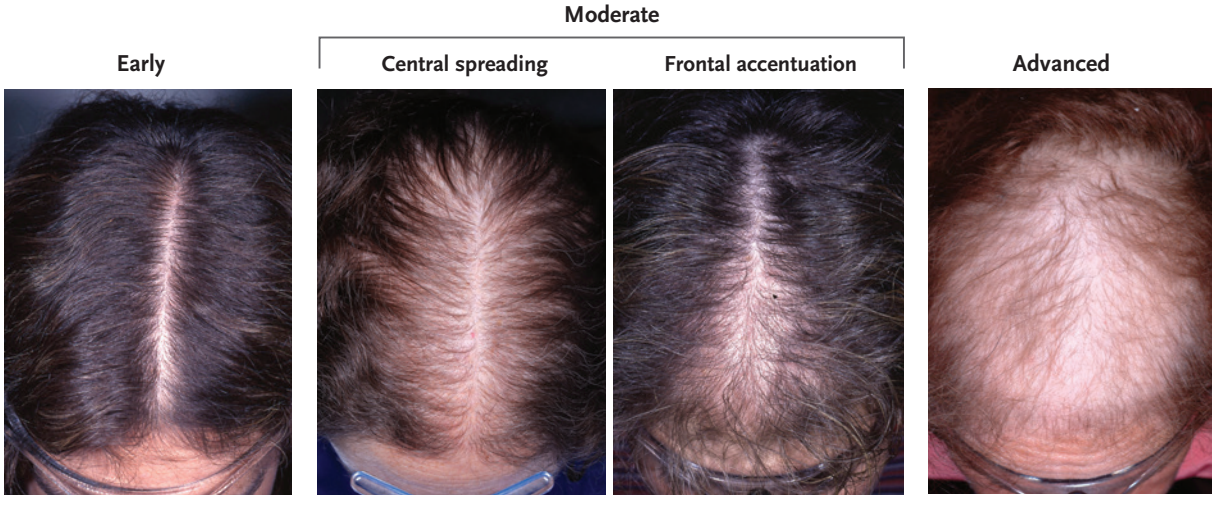



**Figure 2. Severity Scale for Female-Pattern Hair Loss.**

Patients with female-pattern hair loss may present with minimal evidence of scalp hair loss. A midline part in early female-pattern hair loss usually will show an increase in part width and a decrease in hair density (left panel) that are especially notable when compared with that in the occiput. An increasing part width from the vertex toward the anterior hairline, even if subtle, will help to differentiate the condition from telogen effluvium. As female-pattern hair loss progresses, one of the two primary patterns becomes obvious — a central spreading (Ludwig) pattern (left-middle panel) or a "Christmas tree" or frontal accentuation (Olsen) pattern (right-middle panel). The degree of hair loss may occasionally progress to a marked decrease in density across the entire top of the scalp (right panel), simulating a primary cicatricial alopecia; a scalp biopsy is recommended in these cases.

or isthmus (upper part) of the follicle is present in approximately 70% of biopsy specimens,[14] which raises the potential relevance of microinflammation in female-pattern hair loss. A biopsy can also identify any resident microflora in the infundibulum (bacteria, fungus, or demodex), which could be related to the microinflammation and benefit from treatment. Both inflammation and follicular density have been shown to affect response to treatment.[17]

A targeted history that includes age at onset, evolution of the hair loss, menopausal status, signs and symptoms of potential hyperandrogenism (hirsutism, irregular menses, infertility, or cystic acne), current medications or supplements that have androgenic properties, and hair-care practices is key to help determine further evaluation and treatment. Also useful are blood tests to assess androgen levels in persons with signs of hyperandrogenism and assessment of complete blood count, iron and vitamin D levels, and thyroid profile to identify the major potential factors that may affect hair regrowth.

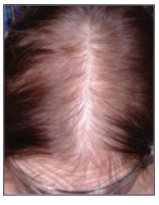
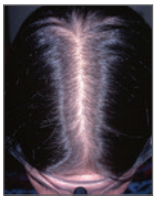
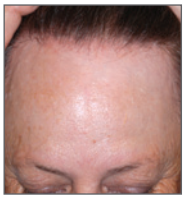
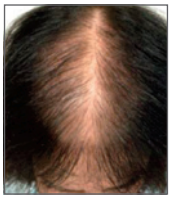
| |  Female-Pattern Hair Loss (FPHL) |  Chronic Telogen Effluvium |  Frontal Fibrosing Alopecia |  Fibrosing Alopecia in a Pattern Distribution |  Central Centrifugal Cicatricial Alopecia |
|---|---|---|---|---|---|
| **Patient Population** | After puberty through menopause, all races | Any age or race, more commonly middle-aged women | Typically postmenopausal White women but any age or race | Typically middle-aged or older women but any age or race | Typically women of African descent, any age |
| **Pattern of Loss** | Central or frontal accentuation | Global hair loss | Anterior hairline recession with or without bitemporal and parietal hairline recession | Central hair loss | Central- or vertex-spreading hair loss, balding common |
| **Loss of Follicular Ostia** | No (unless advanced with depletion of follicular-sebaceous units) | No | Yes | Yes | Yes |
| **Perifollicular or Interfollicular Erythema** | No | No | Common | Common | Variable |
| **Perifollicular Hyperkeratosis** | No | No | Common | Variable | Variable |
| **Additional Key Points** | Variation in hair-shaft diameter<br>Spares occiput<br>Scalp biopsy if uncertain of diagnosis or if focal atrichia | Present >6 mo<br>Diffusely positive hair pull for telogen hairs<br>May overlap with FPHL | Possible isolated or concomitant eyebrow loss<br>Prominent facial veins and facial papules in some cases<br>Scalp biopsy diagnostic if clinical diagnosis uncertain | May be present with frontal fibrosing alopecia<br>May mimic FPHL, especially FPHL with follicular depletion<br>Scalp biopsy recommended | Early stage may be difficult to distinguish from FPHL<br>Scalp biopsy recommended |

**Figure 3. Differential Diagnosis of Female-Pattern Hair Loss.**

The conditions listed in the four right columns may warrant a scalp biopsy to distinguish them from female-pattern hair loss. In addition, miniaturization may be present histologically in each of these conditions, which would suggest concomitant female-pattern hair loss.

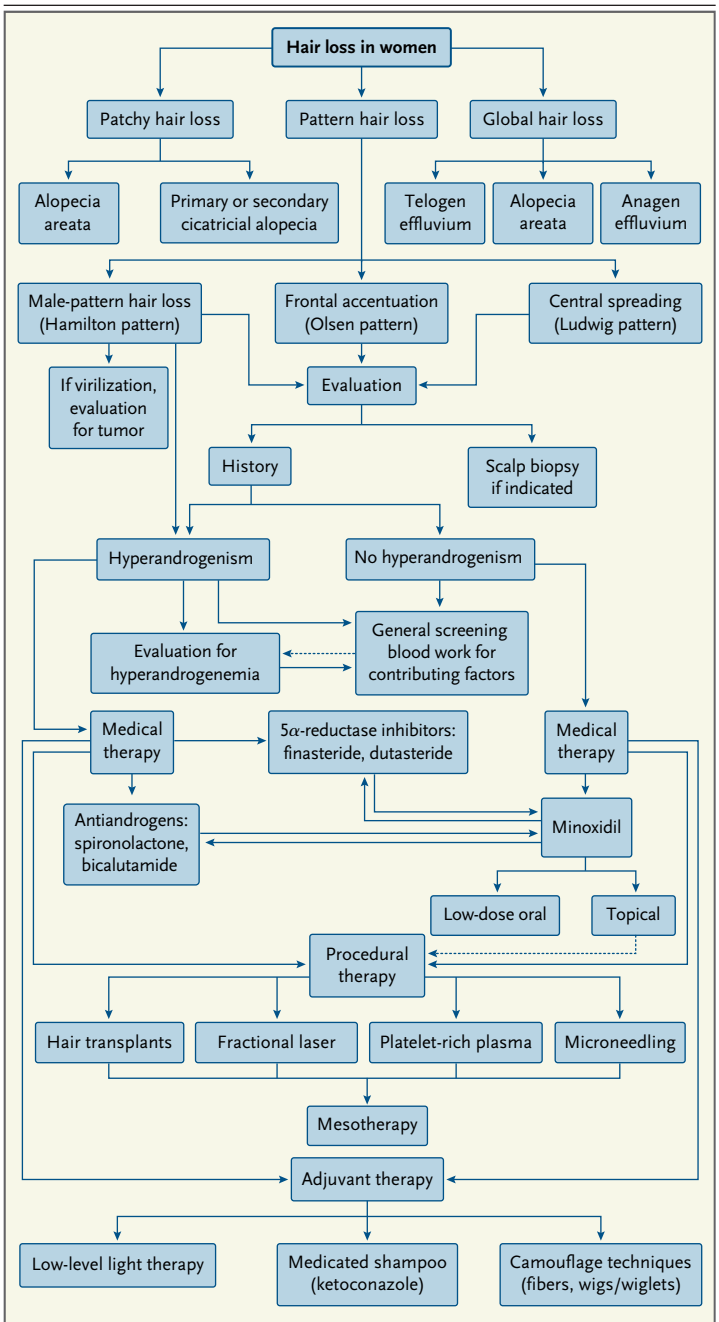



**Figure 4. Evaluation and Treatment of Female-Pattern Hair Loss.**

## TREATMENT OF FEMALE-PATTERN HAIR LOSS

The decision on which treatment to administer first is dependent on the patient's childbearing potential and anticipation of pregnancy in the near future, coexisting conditions including any hyperandrogenism, and history of breast cancer. Most of the treatments used for female-pattern hair loss have not been subjected to randomized, placebo-controlled clinical trials, and comparative assessment of efficacy is difficult. A combination of medications with different mechanisms of action is commonly used, albeit with limited data on whether these combinations provide superior efficacy as compared with monotherapy.[3,19] An algorithm for the evaluation and treatment of female-pattern hair loss is presented in Figure 4.

### MEDICAL THERAPY

#### *Minoxidil*

The only treatments for female-pattern hair loss currently approved by the Food and Drug Administration (FDA) are a 2% topical minoxidil solution administered twice daily and a 5% topical minoxidil foam administered once daily. Both resulted in hair growth in more than 50% of the participants in a controlled 48-week trial.[20] A 5% topical minoxidil solution administered twice a day, approved only for male-pattern hair loss, is regularly used for female-pattern hair loss, with data to support enhanced efficacy.[21] Minoxidil is converted to its active metabolite, minoxidil sulfate, by sulfotransferases in skin, platelets, and liver.[22] Whether the mechanism by which minoxidil sulfate reverses the miniaturization process is related to the opening of ATP-sensitive potassium channels, prostaglandins, increased expression of vascular endothelial growth factor, downstream activation of the β-catenin–Wnt pathway,[22] or down-regulation of the androgen receptor on follicular dermal papillae[23] is unclear. Common side effects include transient shedding of scalp hair (a positive sign of the transition from the telogen phase to the anagen phase that is shared with oral minoxidil), irritant or contact dermatitis, and facial hypertrichosis.[20,21] Concomitant use of microneedling[24] or low-level light therapy[25] may increase the efficacy of topical minoxidil.

Although oral minoxidil at doses of 10 to 40 mg per day is an FDA-approved treatment for resistant hypertension, low-dose oral minoxidil (defined as a dose of ≤5 mg per day) is commonly used off label to treat a variety of hair-loss conditions. A randomized, prospective trial

involving participants with female-pattern hair loss showed that 1 mg of oral minoxidil per day was at least as effective as a daily application of a 5% topical minoxidil solution.[26] Oral minoxidil is rapidly absorbed and, through peripheral vasodilation, may cause a decrease in blood pressure and a potential compensatory increase in pulse rate and cardiac contractility, with these effects peaking at 1 to 2 hours after dose administration. Although low-dose oral minoxidil has no substantial effect on blood pressure in most persons, women may benefit from starting at a dose of 1.25 mg per day or less and escalating slowly as long as unacceptable side effects do not occur.[22] Peripheral edema and hypertrichosis, both of which can manifest after approximately 2 to 4 months of treatment and are dose related, have been reported in 1.1% and 15.1% of patients, respectively.[22] The incidence of pericardial effusion, a rare side effect of oral minoxidil when prescribed for hypertension, is unknown for low-dose oral minoxidil, but both symptomatic and asymptomatic cases have been reported.[22] A sublingual and an extended-release preparation of minoxidil are in clinical trials for pattern hair loss.

### *5α-Reductase Inhibitors*

Both type 1 and type 2 5α-reductase isoenzymes are present in the hair follicle. There are two FDA-approved 5α-reductase inhibitors: finasteride, which primarily inhibits the type 2 5α-reductase isoenzyme, and dutasteride, which inhibits both type 1 and type 2 5α-reductase isoenzymes. Both lead to a decrease in serum dihydrotestosterone and an increase in testosterone and, potentially, estradiol.[27] Neither treatment is FDA-approved for use in women.

A double-blind, randomized, placebo-controlled trial involving 137 postmenopausal women with mild-to-moderate female-pattern hair loss diagnosed clinically, with stratification according to hormone-replacement therapy, showed no significant differences between finasteride at a dose of 1 mg and placebo in hair counts, patient or investigator assessment of response to treatment, or scalp-biopsy results.[28] However, subsequent retrospective case series and nonrandomized prospective studies have documented improvement with daily finasteride at a dose of 2.5 mg or 5 mg in more than 60% of pre- and postmenopausal women with female-pattern hair loss with or without concomitant hyperandrogenism or hyperandrogenemia.[3,29,30]

In a randomized, placebo-controlled trial involving men with male-pattern hair loss, dutasteride at a dose of 0.5 mg per day showed enhanced efficacy as compared with finasteride at a dose of 5 mg per day, with dihydrotestosterone suppression occurring in approximately 90% of men treated with dutasteride and in 70% treated with finasteride.[27] Although oral dutasteride is used regularly in women with hair loss, data on its efficacy for female-pattern hair loss are limited.

Reports of side effects in women receiving finasteride are infrequent but include decreased libido, headache, dizziness, gastrointestinal disorders, depression, increased body hair, dry skin, increased liver-enzyme levels, and irregular menses.[31] Safety issues associated with dutasteride in women appear to be similar to finasteride, but because of the long half-life of dutasteride, its use is best reserved for women of nonchildbearing potential. Topical finasteride may add a level of safety as compared with oral finasteride, with some data suggesting similar increases in hair count but lower levels of plasma finasteride and less reduction in serum dihydrotestosterone levels with topical as compared with oral finasteride.[32] Multiple non–FDA-approved topical preparations of various vehicles and concentrations of finasteride, minoxidil, and other agents that purport enhancement of hair growth are promoted and sold directly to patients online or are available in compounding pharmacies. Because feminization of a male fetus is possible if a 5α-reductase inhibitor or antiandrogen is taken during pregnancy, contraception measures are recommended for women of childbearing potential.

### *Antiandrogens*

The antiandrogens flutamide, bicalutamide, and spironolactone have all shown efficacy for female-pattern hair loss, but multicenter, prospective, randomized clinical trials are lacking. Flutamide and bicalutamide are nonsteroidal antiandrogens that appear to be more effective for female-pattern hair loss than either spironolactone or finasteride.[3,33] However, they are gen-

**Table 1. Procedural or Device-Related Options for the Treatment of Female-Pattern Hair Loss.***

| Treatment | Potential Mechanism of Action | Controlled Clinical Trials | Limitations of Studies | Side Effects |
|---|---|---|---|---|
| Microneedling[24] | Induction of percutaneous wounds purportedly leads to release of growth factors that promote angiogenesis, reversal of fibrosis, initiation of anagen, and proliferation of dermal papillae and stem cells. It may also enhance transdermal delivery of topical agents. | Trials have shown equivocal results with microneedling as monotherapy. Most trials showed significant improvement with topical minoxidil and microneedling as compared with topical minoxidil alone. | Limitations have included variation of methods used (depths of microneedling vary between 0.25 and 2.5 mm), delivery method (needling stamps, manual rollers, or automated pens with or without fractional radiofrequency), and frequency of treatments. Studies have been small, and those involving persons with FPHL or that are placebo-controlled are limited. | In general, few side effects are reported. Pain and lymphadenopathy are possible. |
| Low-level light therapy[25,41] | Devices include lasers (630–660 nm), light-emitting diode, or combination devices in comb, hat, or helmet form. The mechanism for hair growth is unclear, but photobiomodulation promotes anagen and a potential anti-inflammatory effect. | Double-blind, randomized, sham-controlled trials have shown an increase in hair density.[41] Use of a 650-nm low-level laser device with 5% topical minoxidil had greater efficacy than monotherapy with either treatment.[25] | Only a few devices have FDA clearance specifically for MPHL or FPHL, and all are sold online directly to patients. A comparison of results among devices is limited owing to inherent variation in light absorption of skin and hair color, variation in wavelength, and treatment specifics including frequency of use. | Side effects are few but include pruritus, pain or tenderness, paresthesia, urticaria, dermatitis, irritation, dry skin, and headaches. |
| Platelet-rich plasma[38-40] | Platelet-rich plasma is a blood-derived product with a concentration of platelets that is 3 to 5 times that of whole blood, ideally 1,000,000 per microliter. Therapeutic potential lies with the release from activated platelet alpha granules of various growth factors, cytokines, and cell-adhesion molecules, enhancing a transition of telogen to anagen and prolonging anagen. | Many single-site trials (including half-head-controlled trials†) have shown an increase in hair-shaft diameter from baseline. | All devices are FDA-cleared, but there is no standardization of process (anticoagulants, single or double centrifugation, spin rate, force or duration of centrifugation, activation of platelets, and number of red cells or leukocytes) or treatment specifics (platelet concentration; volume injected; number, depth of, and distance between injections; and frequency of treatments). There are few multisite, paired-comparison, randomized, placebo-controlled trials and few studies of FPHL in which there was a period of washout of other current hair-related treatments. | Local discomfort is the most commonly reported side effect. |
| Fractional laser treatment[42-44] | Nonablative fractional lasers stimulate hair growth through fractional photothermolysis (i.e., controlled dermal damage) while maintaining the integrity of the epidermis with minimal thermal effect. Ablative fractional lasers penetrate deeper and may have more efficacy but greater risk of side effects than nonablative fractional lasers. Lasers may assist topical drug delivery as well. | A prospective, open-label, single-blind, controlled trial involving patients with FPHL treated with a nonablative 1550-nm fractional laser (10 treatments 2 weeks apart) documented an increase in hair density.[43] In a single-center, retrospective trial, an FDA-cleared nonablative 1565-nm laser resulted in visible hair growth in participants with either FPHL or MPHL.[44] | Studies of fractional laser treatment for pattern hair loss vary with respect to use of ablative or nonablative lasers, wavelength, spot size, energy, interval of treatment, and recommended number of sessions. Because no medication or invasive treatment is involved, fractional lasers have a wide range of applicability to diverse populations with hair loss. | Side effects are related to laser type and treatment specifics and range from mild erythema and warmth to pruritus, dryness, mild ulceration, and pigmentary changes. |

| Treatment | Potential Mechanism of Action | Controlled Clinical Trials | Limitations of Studies | Side Effects |
|---|---|---|---|---|
| Mesotherapy[45,46] | Microinjection of medications (minoxidil, dutasteride, or bicalutamide), botulinum toxin, or various purported growth promoters into the mesoderm (mid-dermis) may bypass systemic reactions of medications and enhance local efficacy. | A trial involving 126 women with FPHL who received dutasteride mesotherapy or saline (12 sessions over 18 weeks) showed significant photographic improvement (62.8% vs. 17.5%) and an increase in mean hair diameter and patient self-assessment with mesotherapy as compared with placebo.[45] | Limitations include variability in agent, concentration, vehicle, solvent, frequency and number of sessions, and injection technique; few placebo-controlled trials or comparisons with an oral agent; a lack of data on blood or plasma levels of the agent used; small studies with or without washout of other hair treatments; and few studies involving participants with FPHL. | Side effects include headache, injection-site pain, local site reactions, infection, frontal edema, and hair loss. |
| Hair transplants | The goal is to add hair from the occipital scalp that is uninvolved with pattern hair loss to areas with low hair density. | Follicular unit extraction is the preferred method. | Success of treatment depends on the density and caliber of hair in the donor area and control of ongoing pattern hair loss. | Continued medical therapy is warranted to prevent further loss. |

* FDA denotes Food and Drug Administration, FPHL female-pattern hair loss, and MPHL male-pattern hair loss.
† Half-head-controlled trials involve administering an active agent on one half of the head and an active control, placebo, or no treatment on the other half.

erally not considered to be first-line treatments for this condition because of the potential for fatal liver toxicity, which is greatest with flutamide. Efficacy has been reported for flutamide at doses of 62.5 to 250 mg per day, with side effects including gastrointestinal symptoms, dry skin, reduced libido, and hepatic toxic effects.[3] Bicalutamide has a longer half-life than flutamide, allowing administration once per day as compared with three times per day, respectively. Retrospective studies of bicalutamide, typically at doses of 10 to 50 mg per day, have shown mild increases of 2.9 to 11.4% in levels of aminotransferases as well as side effects such as peripheral edema, gastrointestinal symptoms, and breast tenderness.[34] Spironolactone is a steroidal antiandrogen and aldosterone antagonist that affects hair growth through interference with ovarian production or secretion of androgens and through peripheral androgen action. Potential adverse reactions associated with spironolactone include breast tenderness, irregular menses, hyperkalemia, polyuria, postural hypotension, and lightheadedness or dizziness.[33,35] A minimal dose of spironolactone of 100 mg per day appears to be necessary for efficacy in female-pattern hair loss.[3] Cyproterone acetate, a synthetic steroidal antiandrogen and progestin, is not approved in the United States but is used in other countries for the hyperandrogenism spectrum of disorders.

Topical antiandrogens for treatment of male- and female-pattern hair loss are currently in clinical trials. Ketoconazole, an imidazole antifungal agent that is FDA-approved as a 2% cream, foam, and shampoo for superficial fungal infections, tinea versicolor, and seborrheic dermatitis, also has antiandrogen properties. An open-label study of a lotion formulation of ketoconazole and a controlled comparative trial of a 2% ketoconazole shampoo as compared with a nonmedicated shampoo have shown hair regrowth with topical ketoconazole in participants with male-pattern hair loss.[36,37] The shampoo is commonly prescribed for female-pattern hair loss.

### PROCEDURAL TREATMENTS

Among the procedural treatments for female-pattern hair loss, platelet-rich plasma is one of the most commonly used. Platelet-rich plasma may augment the efficacy of hair-growth medications or provide an alternative treatment option.

Multisite, well-controlled studies are lacking, but many single-site studies have shown an increase in hair-shaft diameter or density (or both) as compared with baseline. The general consensus is that at least three treatments with platelet-rich plasma, administered 1 month apart, are needed to determine efficacy, and continued treatments are necessary to maintain response.[38-40] Procedural treatment options are given in Table 1.[24,25,38-46]

### FEMALE-PATTERN HAIR LOSS IN SURVIVORS OF BREAST CANCER

For survivors of breast cancer with female-pattern hair loss, minoxidil (topical or low-dose oral) is an effective frontline therapy.[47] On the basis of large-scale studies,[48] spironolactone is considered to be a low-risk treatment in survivors of estrogen receptor–positive cancers, whereas 5$\alpha$-reductase inhibitors and other antiandrogens should be avoided in this group of patients until further safety data are available. Low-level light therapy, microneedling, nonablative fractional laser treatment, and hair transplants are reasonable additional treatments in this population.

## AREAS OF UNCERTAINTY

Well-controlled clinical trials involving women with a firm clinical and histopathological diagnosis of female-pattern hair loss that take into account key variables, including age at onset, race or ethnic group, the presence or absence of hyperandrogenism or hyperandrogenemia, and menopausal status, will help to identify potential new genetic, hormonal, and environmental factors that are key to prognosis and effective treatment. Comparative-effectiveness trials are warranted to assess the relative efficacy of individual agents as well as the benefits and safety of combinations of agents with different mechanisms of action.

## GUIDELINES

The most recent guidelines for female-pattern hair loss are based largely on consensus expert opinions. The guidelines highlight the lack of high-quality data for the treatment of female-pattern hair loss outside of topical minoxidil.[49,50]

## CONCLUSIONS AND RECOMMENDATIONS

The patient in the vignette has a combination of late-onset female-pattern hair loss, chronic telogen effluvium, and hirsutism. Her workup revealed mildly elevated free and total testosterone levels but did not indicate the source of telogen effluvium, as is often the case. A biopsy was not essential for diagnosis.

I would start treatment with combination therapy, either spironolactone or finasteride for both the hirsutism and the female-pattern hair loss and either topical or oral minoxidil to address both the female-pattern hair loss and the chronic telogen effluvium, providing counsel on the continued need for contraception while she is still of childbearing potential. Standardized photographs of the central scalp with a midline part (as shown in Fig. 2) are a simple and effective measure to help both the physician and the patient determine the efficacy of treatment, and trichoscopic evaluation of changes in hair-shaft diameter and density documents the mechanism of improvement.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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