
بسم الله الرحمن الرحیم

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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.

Case presentation

- 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.

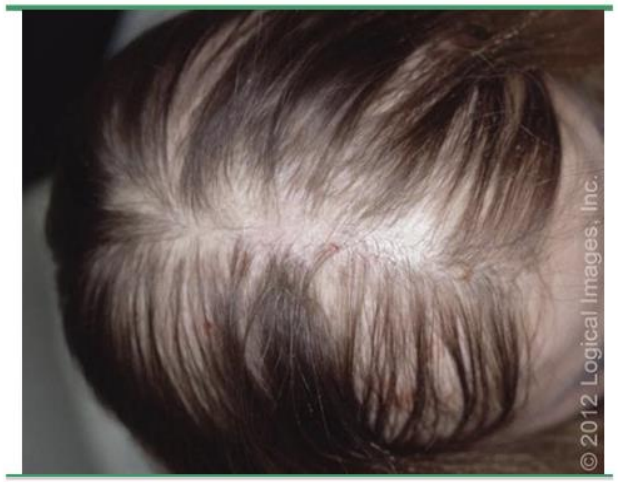
How would you treat this patient?

Female pattern hair loss (FPHL)

- common form of nonscarring hair loss that primarily occurs in adult females.
- The condition is characterized by the
  - *progressive* **loss of terminal hairs over the frontal and vertex regions** *of the scalp, resulting in a* ***visible reduction in hair density*** *.*
- Unlike many cases of androgenetic alopecia in males (male pattern hair loss), the loss of terminal hairs in affected areas is usually incomplete,

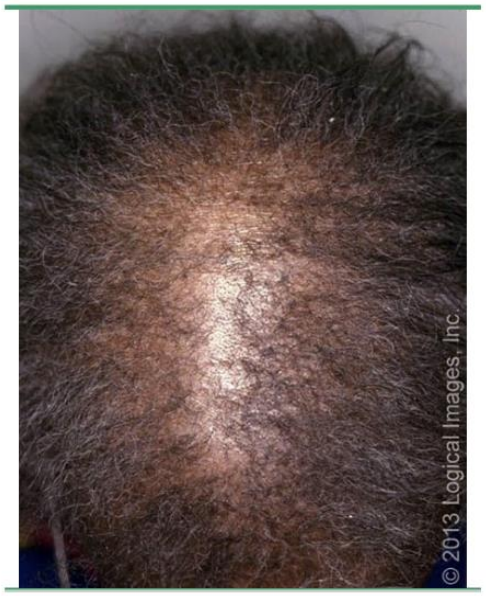
  and the frontal hairline is often spared

Female pattern hair loss



A marked reduction in terminal hair density is present on the crown of the scalp.

Female pattern hair loss



A marked reduction in terminal hair density is present on the crown of the scalp.

uptodate

prevalence

- 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,*
  - *56% among those older than 70 years of age.*
- The prevalence is lower among Asian women — 12 to 25% among those older than 70 years of age
- is unknown among women of African descent owing to the common overlap with those of early central centrifugal cicatricial alopecia.

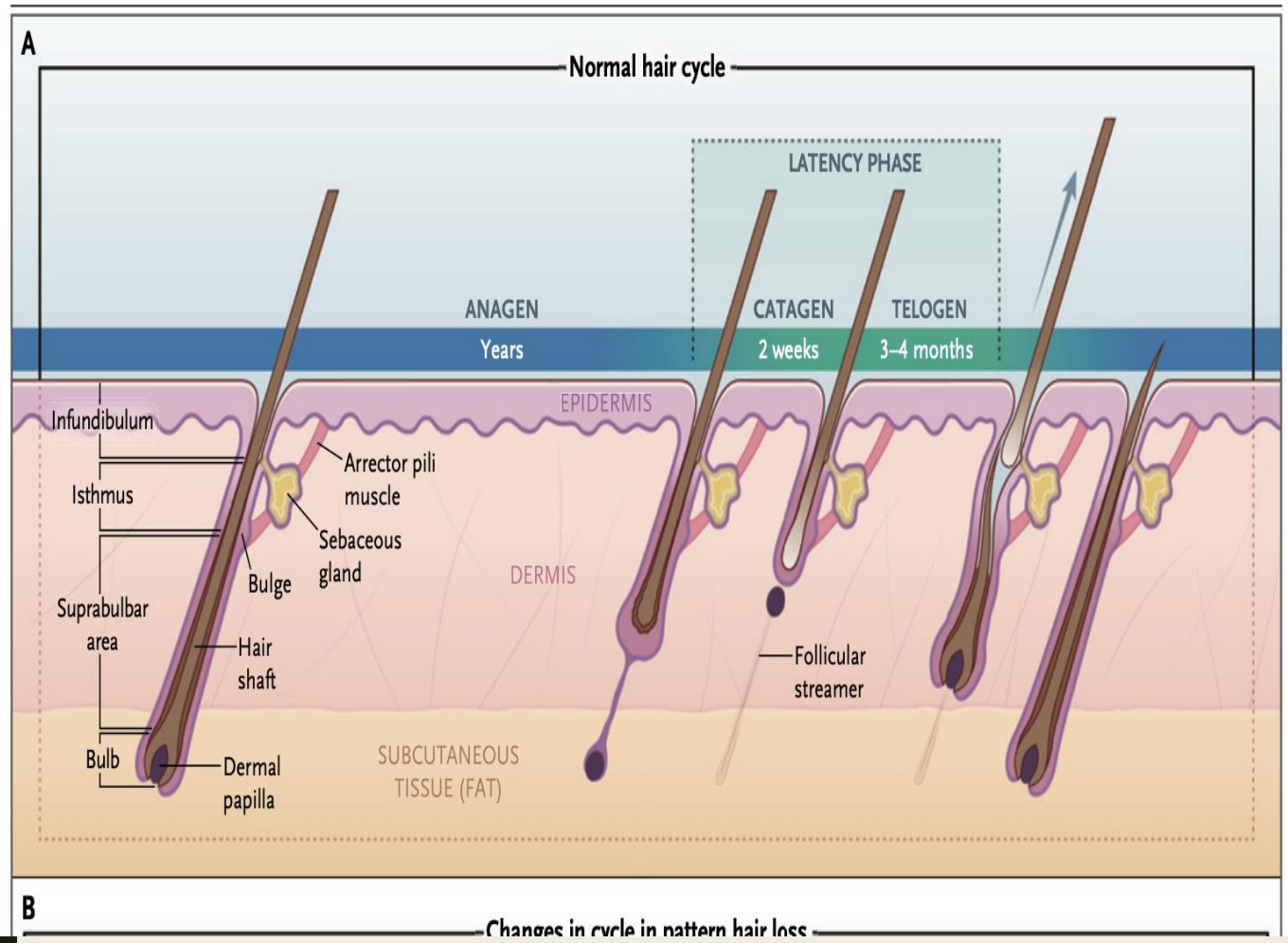
- Both male-pattern hair loss and female-pattern hair loss are characterized by progressive miniaturization of the hair follicle,
  - *a shortened anagen (growth) phase,*
  - *a prolonged latent phase.*
- Scalp hair is arranged in **follicular units** of
  - *two to four terminal hairs (>60 µm in diameter) and*
  - *one or two vellus hairs (<30 µm in diameter),*
- This miniaturization process leads to a progressive, but variable, decrease
  - *in the caliber, length, and number of hairs in an affected follicular unit.*

The cycle includes 3-to-6-year periods of active hair growth (anagen) separated by periods of inactivity.

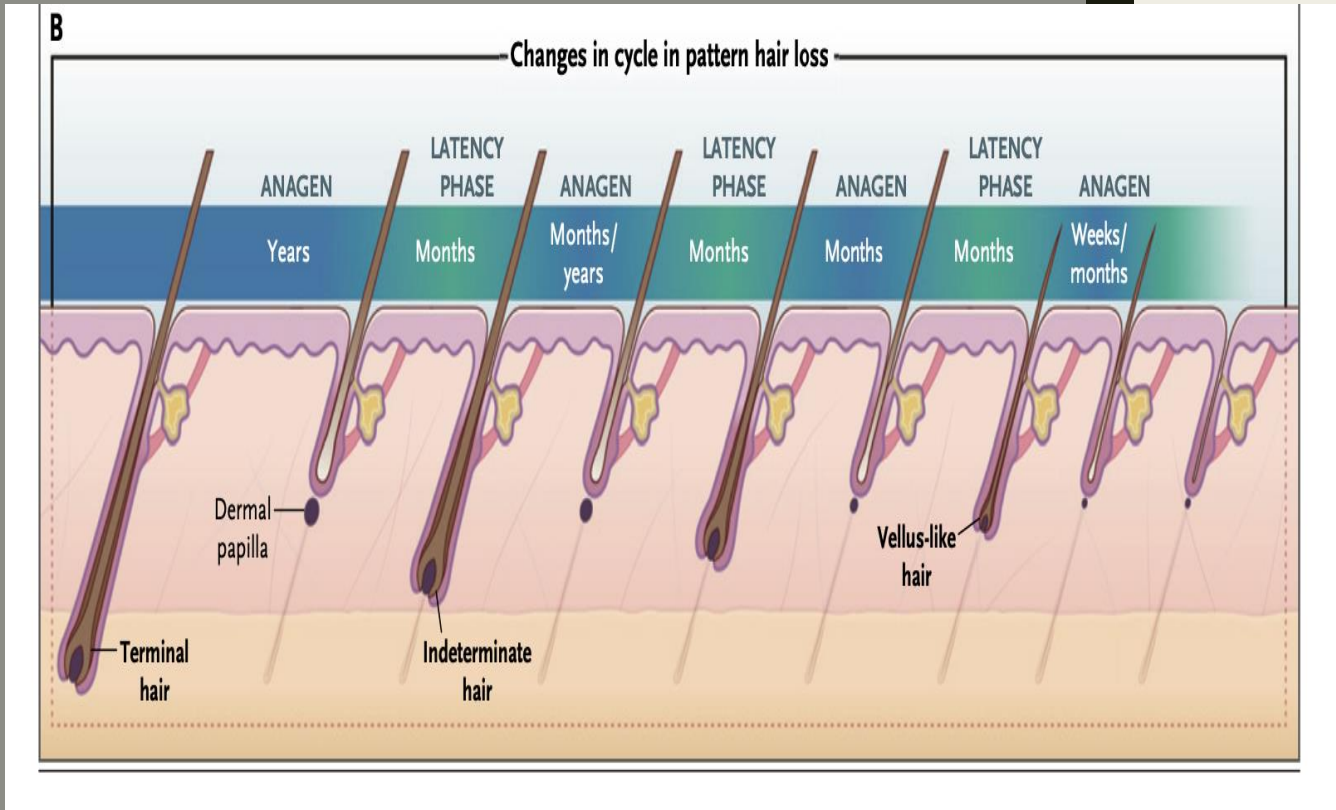
This latency phase is initiated by a brief period of apoptosis driven regression of the inferior portion of the hair follicle and upward movement of the remaining follicle and its dermal papilla to the area immediately below the arrector pili muscle.

This brief transition period (catagen) is followed by a quiescent period (telogen) that lasts several months.

hair cycle of a normal-scalp terminal hair



hair cycle in pattern hair loss



In male 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

the duration of the anagen phase, which determines the length of the hair shaft, becomes shorter over several cycles.

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.

- Female-pattern hair loss manifests as decreased hair density in a diffuse central or frontal accentuation pattern but without baldness .
  - The rare manifestation in women that mimicks that of male-pattern hair loss usually related to marked hyperandrogenemia and,

    if accompanied by virilization,

    should arouse suspicion for a tumor.
- may first manifest between
  - *puberty and the late 20s (early-onset female-pattern hair loss) or*
  - *the late 40s through menopause (late-onset female-pattern hair loss).*

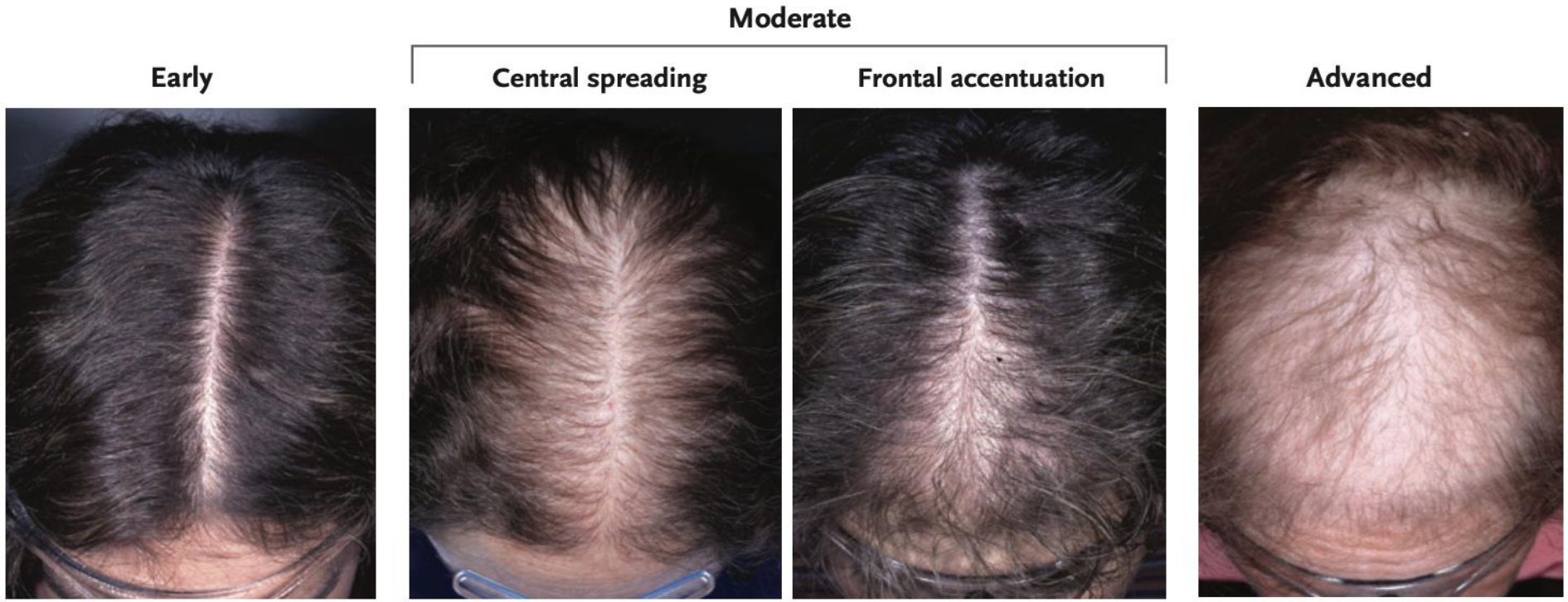


Figure 2. Severity Scale for Female-Pattern Hair Loss.

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.

ethiology

- the causes of female-pattern hair loss appear to be more complex,
  - *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**.
- 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, **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.*

- Among those with female-pattern hair loss and hirsutism,
  - *more than 80% will have hyperandrogenemia, and*
  - *polycystic ovarian syndrome is not uncommon.*

- 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.

- 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.*

- A female-pattern hair loss phenotype indistinguishable from naturally occurring female-pattern hair loss develops in women taking antiestrogen agent

- 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.

diognose

- 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),*
    - confirming the presence of intact folliculosebaceous units and a potentially reversible process.
- Clinical inflammation is absent unless the patient has an additional scalp condition.

differential diagnosis

- **Telogen effluvium**, which is characterized by
  - *a history of increased shedding of scalp hair*
  - *a diffuse decrease in hair density,*
  - *is associated with a reversible increase in the percentage of hair in the telogen phase.*

- **Frontal fibrosing alopecia**, which was first described in 1994, is now the most common type of cicatricial alopecia.
  - *postmenopausal White women as*
  - *recession of the anterior and parietal hairlines,*
  - *perifollicular erythema,*
  - *loss of follicular ostia,*
  - *loss of eyebrows,*
  - *each of which may appear independently and in any temporal order*

- **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.*
    - 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

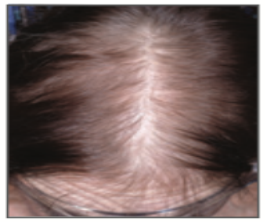
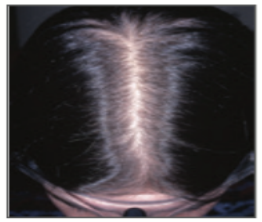
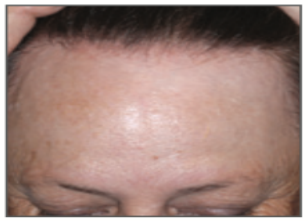
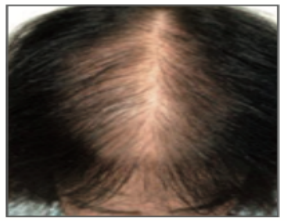
	 Female-Pattern Hair Loss (FPHL)	 Chronic Telogen Effluvium	 Frontal Fibrosing Alopecia	 Fibrosing Alopecia in a Pattern Distribution	 Central Centrifugal Cicatricial Alopecia
Patient Population	After puberty through menopause, all races	Any age or race, more commonly middle-aged women	Typically postmenopausal 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 Spares occiput Scalp biopsy if uncertain of diagnosis or if focal atrichia	Present >6 mo Diffusely positive hair pull for telogen hairs May overlap with FPHL	Possible isolated or concomitant eyebrow loss Prominent facial veins and facial papules in some cases Scalp biopsy diagnostic if clinical diagnosis uncertain	May be present with frontal fibrosing alopecia May mimic FPHL, especially FPHL with follicular depletion Scalp biopsy recommended	Early stage may be difficult to distinguish from FPHL 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.

history

- A targeted history that help determine further evaluation and treatment
  - *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,*
  - *hair-care practices .*

blood tests

- Also useful are blood tests to identify the major potential factors that may affect hair regrowth.
  - *assess androgen levels*
  - *complete blood count,*
  - *iron and vitamin D levels,*
  - *thyroid profile*

biopsy

- 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
    - **terminal hair to vellus hair**.
  - ***lymphohistiocytic infiltrate at the infundibulum or isthmus*** *(upper part) of the follicle*
    - is present in approximately 70% of biopsy specimens,
    - which raises the **potential relevance of microinflammation** in female-pattern hair loss.

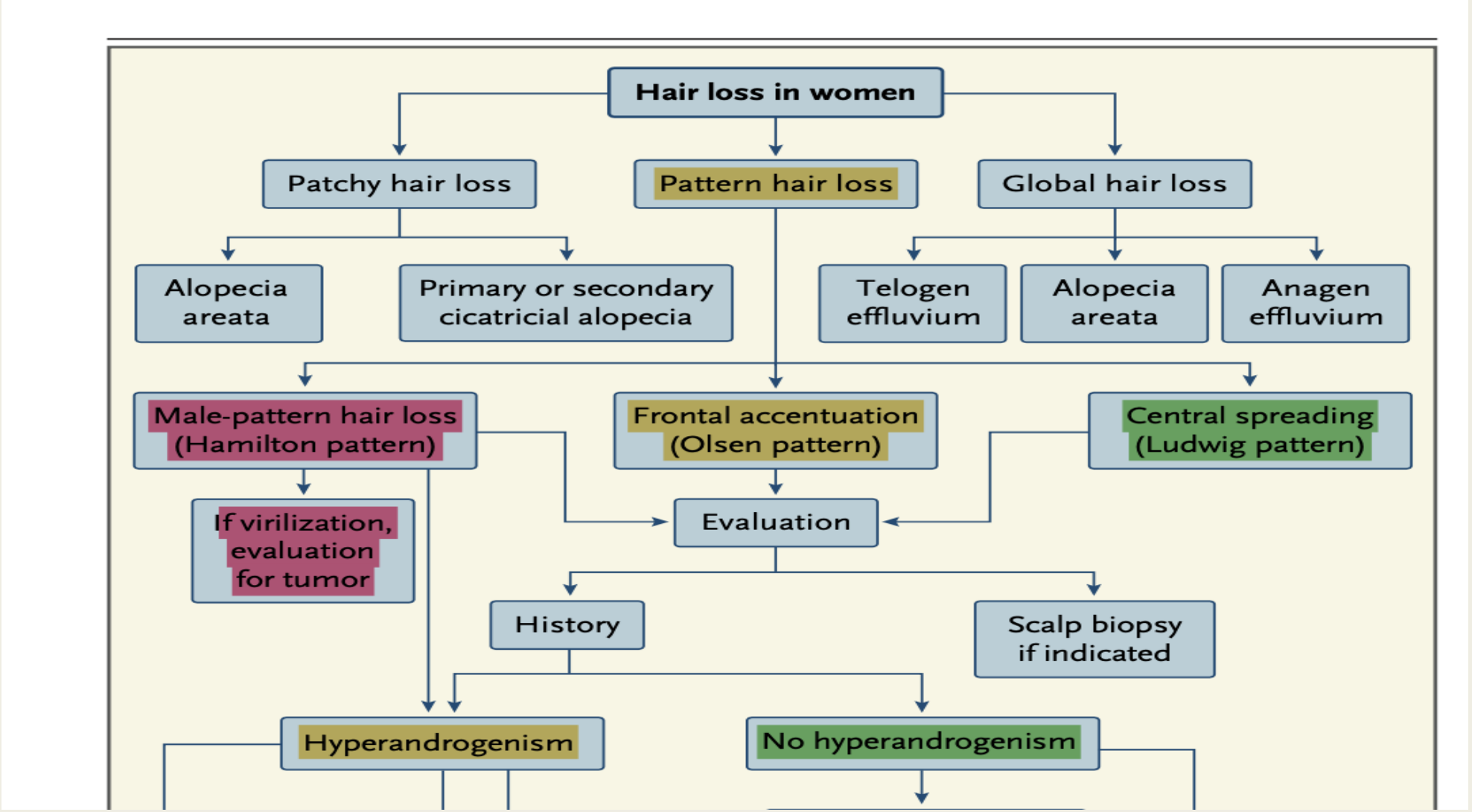
- A biopsy can also identify any
  - ***resident microflora in the infundibulum*** *(bacteria, fungus, or demodex),*
    - related to the microinflammation and benefit from treatment.
- Both inflammation and follicular density have been shown to affect response to treatment.

Treatment of Female-Pattern Hair Loss

- The decision on which treatment to administer first is dependent on the
  - *patient's childbearing potential*
  - *anticipation of pregnancy in the near future*
  - *coexisting conditions including any hyperandrogenism*
  - *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,
  - *limited data on whether these combinations provide superior efficacy as compared with monotherapy.*

treatment


Hair loss in women
Patchy hair loss
Pattern hair loss
Global hair loss
Alopecia areata
Primary or secondary cicatricial alopecia
Telogen effluvium
Alopecia areata
Anagen effluvium
Male-pattern hair loss (Hamilton pattern)
Frontal accentuation (Olsen pattern)
Central spreading (Ludwig pattern)
If virilization, evaluation for tumor
Evaluation
History
Scalp biopsy if indicated
Hyperandrogenism
No hyperandrogenism

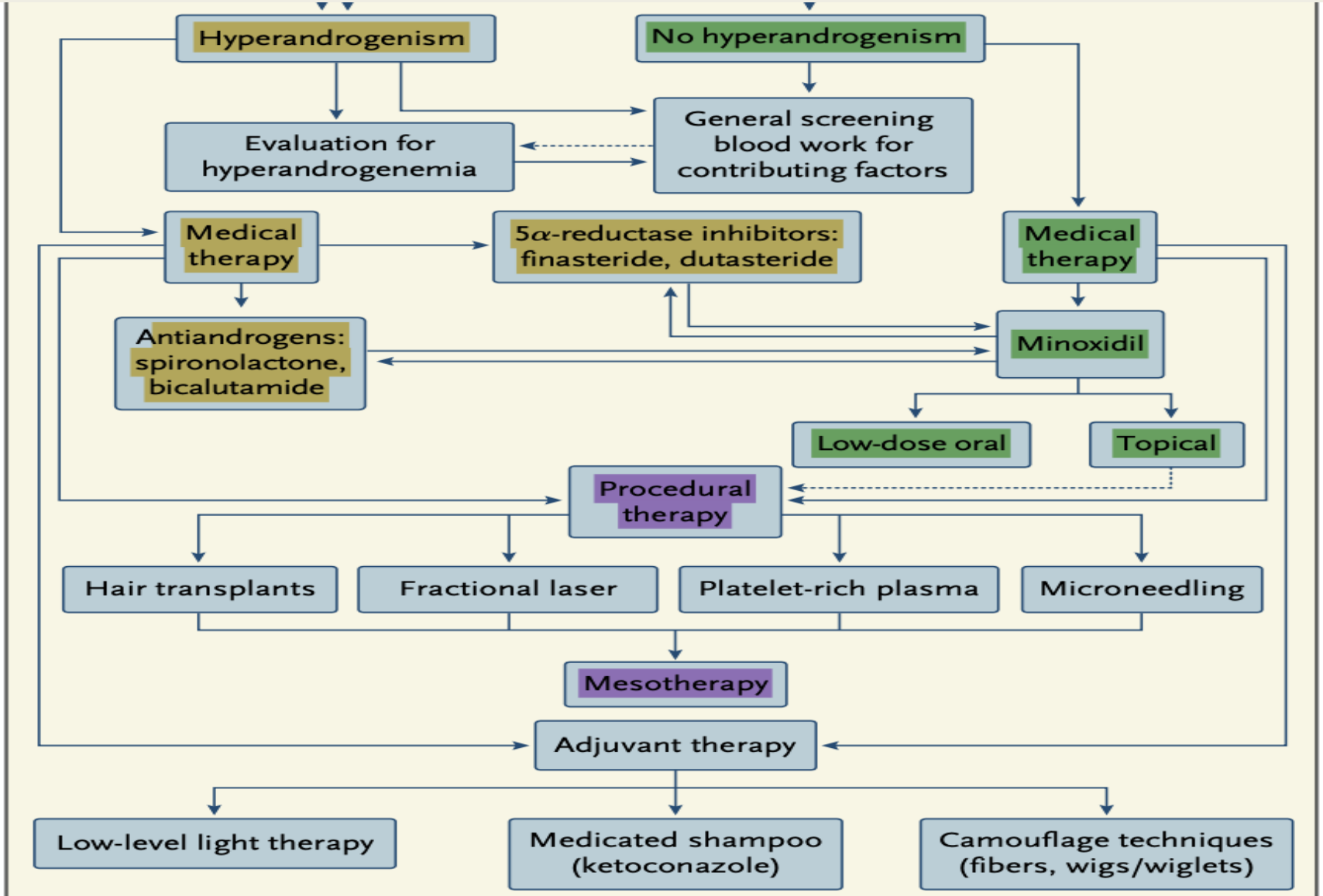


Figure 4. Evaluation and Treatment of Female-Pattern Hair Loss.

Minoxidil

- The only treatments 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.
- Minoxidil is converted to its active metabolite , minoxidil sulfate ,

  by sulfotransferases in skin , platelets, and liver.
- 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,*
  - *down-regulation of the androgen receptor on follicular dermal papillae is unclear*

side effects

- *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,*
- *facial hypertrichosis.*
- *decrease in blood pressure*
- *Peripheral edema*
- *pericardial effusion*

- 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.

- 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.*

- 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.*

- The incidence of pericardial effusion, a rare side effect of oral minoxidil
  - *when prescribed for hypertension, for low-dose oral minoxidil,*
  - *but both symptomatic and asymptomatic cases have been reported.*

- Concomitant use of microneedling or low-level light therapy may increase the efficacy of topical minoxidil.

- 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 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,
  - dutasteride, which inhibits both type 1 and type 2 5α-reductase isoenzymes.
- lead to a
  - decrease in serum dihydrotestosterone and an
  - increase in testosterone and,
  - potentially, increase in estradiol.
- Neither treatment is FDA-approved for use in women.

finasteride

- showed no significant differences between at a dose of 1 mg and placebo in hair counts,
  patient or investigator assessment of response to treatment, or scalp-biopsy results.

- 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.

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**
- approximately 90% of men treated with dutasteride and in 70% treated with finasteride.

- 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 5α-Reductase Inhibitors
  - *less reduction in serum dihydrotestosterone levels with topical.*

- 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 multi center, prospective, randomized clinical trials are lacking.*

- Flutamide and bicalutamide are nonsteroidal antiandrogens
- Spironolactone is a steroidal antiandrogen and aldosterone antagonist

- Flutamide and bicalutamide that appear to be more effective for female-pattern hair loss than either spironolactone or finasteride.

- they are generally not considered to be first-line treatments because of the potential for fatal liver toxicity, which is greatest with flutamide.

- flutamide at doses of 62.5 to 250 mg per day,
- side effects including gastrointestinal symptoms, dry skin, reduced libido, and hepatic toxic effects.

Bicalutamide

- longer half-life than flutamide, allowing administration once per day
- typically at doses of 10 to 50 mg per day
- side effects such as
  - *mild increases of 2.9 to 11.4% in levels of aminotransferases*
  - *peripheral edema,*
  - *gastrointestinal symptoms,*
  - *and breast tenderness.*

Spironolactone

- 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 include
  - *breast tenderness,*
  - *irregular menses,*
  - *hyperkalemia,*
  - *polyuria,*
  - *postural hypotension,*
  - *and light headedness or dizziness.*
- A minimal dose of spironolactone of 100 mg per day

Cyproterone acetate

- is an antiandrogen that may be effective for FPHL.
- is not available in the United States:
- The dosing regimen for cyproterone acetate for FPHL is not standardized.
- When used in the treatment of FPHL, some authors have suggested the following regimens for premenopausal patients
  - *100 mg per day on days 5 to 15 of the menstrual cycle and 50 mcg of ethinylestradiol on days 5 to 25*

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Patients with hyperandrogenism

- Treatment of the underlying, hyperandrogenic state is important for improving FPHL associated with hyperandrogenism.
- FPHL therapies that are not antiandrogenic, such as topical minoxidil, may also be beneficial .

- A frequent approach to FPHL related to polycystic ovarian syndrome (a common cause of hyperandrogenism in females) is the addition of topical minoxidil and spironolactone when oral contraceptive therapy yields insufficient improvement.

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Patients with concomitant scalp disorders

- Treatment of coexisting inflammatory scalp conditions,
  - *such as seborrheic dermatitis,*
    - is generally advised to minimize additional hair loss related to scalp inflammation.
- In our experience,
  - *successful treatment of seborrheic dermatitis seems*
    - to reduce risk for skin irritation from topical minoxidil.

uptodate

- Topical antiandrogens for treatment of male- and female-pattern hair loss are currently in clinical trials.
- Ketoconazole, an imidazole anti- fungal 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.
- The shampoo is commonly prescribed for female hair loss

Procedural Treatments

- 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.
- 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.

Female-Pattern Hair Loss in Survivors of Breast Cancer

- minoxidil (topical or low-dose oral) is an effective frontline therapy.
- On the basis of large-scale studies , spironolactone is considered to be a low-risk treatment in survivors of estrogen receptor–positive cancers,
- 5α-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 rasonable additional treatments in this population.

Conclusions

- 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.


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