• Diffuse hair loss can affect both sexes at any age. Anything that affects the normal hair cycle may cause it. Alopecia is a distressing complaint with significant psychopathological comorbidities. Triggers include a wide variety of emotional and biological causes. Loss of telogen-phase hairs appears to be common as diffuse hairloss
• Finding the cause or trigger of the hair loss requires a thorough history, a examination, and testing which may define the trigger or treatment

KEY POINTS
Androgenic alopecia and acne are NOT good markers for hyperandrogenism in PCOS compared with hirsutism
Early androgenic alopecia (AA) can present as episodic telogen hair shedding, before the distinctive pattern of AA is seen
Telogen effluvium (TE) is a sign of an underlying condition, and not itself a complete diagnosis
Androgenic alopecia should not be overlooked as a trigger which may be responsible for diffuse telogen hair shedding


Normal Hair Follicles
Stem cell factor (SCF) is important in embryonic melanocyte migration in hair follicle
Mid-follicle outer root sheath melanocytes implicate SCF in maintaining pigmentation and migration into regenerating new hair bulbs in dermal papilla
Anagen phase- lasts >4-6yrs. (85-90% scalp hairs)
Catagen phase (regression, lasts up to 2 wks). (2-3% of hairs)
Telogen phase- (resting, lasts about 3 mos). (10-15% of hairs)

Androgens inhibit dermal papilla SCE production which may lead to androgenic alopecia. This may also result from abundant androgen skin receptors or non-androgen factors.

Endocrine Aspects of PSU

- Elevated scalp sensitivity to androgens is likely due to the high concentration of the isoenzyme type 1 5α-reductase in hair follicles responsible for DHT formation from testosterone.
- Both normal and hyperandrogenic women of different ethnic origins demonstrate differences in circulating androgens and androgen receptor sensitivity of the PSU.

Rosenfield RL. J Am Acad Dermatol 2001;45:S95-104

- Biochemical hyperandrogenism (HA) may not correlate with the presence or absence of AA. Frequently there is a poor correlation between clinical and biochemical HA.
- Alopecia associated with hirsutism suggests HA, but may often be due to other associated causes: higher quantity of androgen receptors, increased production rates of DHT, lower aromatase levels converting T and androstenedione to estrogens, higher hair follicular 5-alpha-reductase enzymes (less in frontal and occipital scalp hair), and polymorphisms chromosome 20p11.

Deplewski D, Rosenfield RL. Endocr Rev 2000;21:363
Hillmer AM, Am J Hum Genet 2005;77:140
Androgen Receptor Sensitivity

Pathophysiological Overview of AA

• Twin studies confirm a strong genetic predisposition to AA
• Young women with AA have lower level of aromatase compared to males as well as higher levels in frontal hairline
• About 13% of premenopausal women and 37% postmenopausal women demonstrate mild or > bitemporal recession of frontal hairline and diffuse hairloss. Venning VA. J Am Acad Dermatol 1988;18:1073

• Low levels of 5-alpha reductase are seen in occipital hair of women
• Androgen receptor concentration in women is 40% less than men
• Must exclude excessive hair shedding due to chronic telogen effluvium demonstrating typical keratinized club-shape structures in the proximal part of the hair shaft and a positive tug (pull) test

Rathnayake D, Sinclair C. Dermatol Clin 2010;28:611
**Alopecia in PCOS and Hyperandrogenism**

- AA is variably reported 5~70% in PCOS. Scalp biopsy at times helpful
- Frequently associated hirsutism and/or refractory acne and oligomenorrhea
- Onset often midvertex->crown->diffuse short thin hair (gradual process)
- Anterior hair-line usually remains intact, although these hairs may be miniaturized (finer and shorter)
- Rapid development of diffuse hair loss, and/or presence of bitemporal recession are not common. These are most often seen in virilizing syndromes and TE.

Possible Causes or Co-Causes of Alopecia (AA and/or TE)

- **Postmenopausal**: some genetic basis (50-75%); a change in androgenic follicular receptors without change in serum androgens is likely (PCOS)

- **Iron Deficiency and Reserve**: Reduced serum iron and ferritin, blood loss, vegetarians no red meat p.o., iron deficiency anemias. Reduced iron reduces synthesis of ferritin in liver. <40 ng/ml-> follicles go into telogen phase, until ferritin exceeds 70 ng/ml creating basis for a normal anagen phase

- **Trace elements and vitamins**: Zinc, Selenium, B12, biotin deficiency (long-term parenteral nutrition)

- **Genetic susceptibility** (women -> than men, also often paternal role is present). Polygenic. High association with chromosome 20 p11, and the androgen receptor gene in women on chromosome Xq12


- **Drugs** (to follow)

- **Misc**: Eating disorders, vegans, runners, poor hair care, braiding, trichotillomania, traction alopecia, low body fat, crash& lo-protein intake, brazilian nuts (highest concentration selenium)

- **Endocrine Disorders**: Thyroid, hyperprolactinemia, adrenal

- **Discontinuation of estrogen-containing medications**
Medications Associated with Hair Loss

Telogen Effluvium
Interval between Start of Treatment and Hair Loss Medications (2-3 months) (examples of some)

**Estimated Incidence (0%-10%)**
- Heparin, interferon alfa, isotretinoin, lithium, ramipril (Altace), valproic acid (Depakote), warfarin, terbinafine (Lamisil), beta-blockers (propranolol, atanolol, metoprolol), hypervitaminosis A
- Acyclovir (anti-herpes), allopurinol, buspirone (Buspar), captopril (ACE inhibitor), carbamazepine (Tegretol), cetirizine (Zyrtec), cyclosporine, lamotrigine (Lamictal), leuprolide (Lupron), lovastatin (Mevacor), nifedipine (Procardia)

**>5%**
- Amiodarone, amitriptyline (Elavil), azathioprine (Imuran), dopamine, verapamil (Calan), sertraline (Zoloft), naproxen, omeprazole (Prilosec), paroxetine (Paxil)

Shapiro J, NEJM 2007;357:1620

In female pattern alopecia (balding), there is often thinning at the front of the scalp.
Virilizing Adrenal Testesteroma
Ludwig’s Classification of Alopecia

Ludwig E. Br J Dermatol 1977;97:247

Stage II of Ludwig Classification

Figure 1: Marked Thinning of Hair on the Crown of the Scalp in a Woman with Female-Pattern Hair Loss, and Fairly Normal Occipital Density. The centro-parietal portion of the scalp, which shows decreased hair density (Panels A and B), would be classified in Ludwig stage II (a moderately widened central part). In this patient, hair thinning also extends laterally (Panels C and D).
Prevalence of Androgenic Alopecia in PCOS and/or US Polycystic Ovaries (PAO) and Hyperandrogenism

- **Futterweit** et al, 1988. 36.7% PCOS Dx in 109 presenting with AA as main complaint. 10% of nl.population (unaware of PCOS) had CC AA
- **Conway** et al, 1989. 8.0% with PCO morphology
- **O’Driscoll** et al, 1994. 15.2% with PCO morph & hirsutism
- **Vexieu** et al, 2000. 10.0% with alopecia alone had PCOS with biochemical hyperandrogenism (HA), and 84% with clinical HA
- **Cela** et al, 2003. 67% with PCO morphology and 21% of these women with PCO morphology had associated hirsutism
- **Azziz** et al, 2004. 4.7% PCOS with hirsutism
- **Karrer-Voegelli**, 2009. 24.7% with hyperandrogenism, AA with hirsutism and acne 6.0%
- **Carmina** et al, 2009. 3.2% with hyperandrogenic disorders
- **Ozdimir** et al, 2010. 34.7%, and 73.9% of PCOS women with hirsutism

Clinical Analysis

**Case report:**
- 26 yr Caucasian F, irregular menses, with resistant acne to isotretinoin x2, sideburn and chin hair, and male pattern pubic hair and moderate abdominal hirsutism. Recent fewer menses and 25 lb wgt loss. Vegan. Depression. BMI 21.0, hgt 65 inches. Marked further increase in hairloss with finer texture hair. Tug test was positive. T 45 ng/ml with an elevated free T. US ovaries pos. for PCO morphology: numerous bilat. follicles (>10-12), enlarged ovaries.
**Clues to Alopecia Diagnoses**

- **PCOS in pt** after further testing excluding other Dx
- **Clinical clues to type of alopecia:**
  - Rapid onset
  - Positive tug test
  - Prior history of triangle sign and further rapid loss of scalp hair, with several triggers including isotretinoin and major emotional distress and loss. *(vide infra)*

Alopecia appears suggestive of AA and TE combined

Initial Rx may include BCP and spironolactone for AA

Triggers of TE included low iron intake, vegan, and others

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**Possible Causes or Co-Causes of Alopecia (AA and/or TE)**

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- **Iron Deficiency and Reserve**: Reduced serum iron and ferritin, blood loss, vegetarians no red meat p.o., iron deficiency anemias. Reduced iron reduces synthesis of ferritin in liver. <40 ng/ml->follicles go into telogen phase, until ferritin exceeds 70 ng/ml creating basis for a normal anagen phase
- **Trace elements and vitamins**: zinc, Selenium, B12, biotin deficiency (long-term parenteral nutrition)
- **Genetic susceptibility** (women -> than men, also often paternal role is present). Polygenic. High association with chromosome 20 p11, and the androgen receptor gene in women on chromosome Xq12
- **Drugs** (to follow)
- **Misc**: Eating disorders, vegans, runners, poor hair care, braiding, trichotillomania, traction alopecia, low body fat, crash& lo-protein intake, brazilian nuts (highest concentration selenium)
- **Endocrine Disorders**: Thyroid, hyperprolactinemia, adrenal
- **Discontinuation of estrogen-containing medications**
General Statements on Treatment

- About 10% of normal premenopausal women have AA while 50-75% have AA after age 65. Premenopausal women with AA are often genetic, but may react to residual gonadal and adrenal androgens.
- CA (with or without ethinylestradiol), and spironolactone may modify further progression of AA in the postmenopausal woman. Flutamide is more effective than CA-spironolactone, but liver toxicity possible.
- Dutasteride (Avodart) has been found at times helpful where F fails.
- Role of antiandrogen therapy in all ages has not been fully defined and the paucity of effective treatments are quite striking & variable, underscoring the lack of effective universal treatments of AA.
- Somehow, occasional significant responses to treatment occur in non-hyperandrogenic states. Much is being studied on its pathophysiology.
- Rogaine is suggested for most women with AA regardless of cause.

Therapeutic Options Targeting Androgenic Alopecia

- **5-alpha reductase inhibitors** (finasteride, dutasteride) block T to DHT
- **Spironolactone** (Aldactone) 150+ often with oral contraceptives (OCP)
- **Ketoconazole** (2% shampoo). Possible hepatic toxicity.
- **Cyproterone Acetate** (CA), not used in USA. Diane-35 (2mg CA; 35ug ethinylestradiol)
- Minor role for metformin reported, and statins, despite lowering T.
- **GnRH** with OCP for severe hyperandrogenism
- **Combination therapies** including 5a-reductase inhibs, OCP, spiron, CA
- **Glucocorticoids** (low dose DXM) if major adrenal factor is present
- **Flutamide** (Eulexin) 125-500 mg/day, divided dosage, with BCP Pure potent antiandrogen, competitively inhibits the androgen receptor. f/u liver chemistries for hepatic toxicity (~6%). Toxic effects possible with 250 or 125mg/d (recent studies have tried 62.5 mg/d)
- **Minoxidil** (Lonitin) (Rogaine 2%, and 5% topical solutions or foam; with latter od or bid ->often may cause hirsutism, irritative local acne). Effective most time with some hair regrowth with regular use.
Spironolactone in Hyperandrogenism

*Mechanism of Action, and Effects*

- competes and inhibits interaction of DHT with its intracellular androgen receptor
- directly suppresses androgen steroidogenesis
- 150-200 mg daily in divided doses
- possible teratogenicity on male fetus and is often used together with oral contraceptive
- Monotherapy may cause polymenorrhea

**Finasteride**

- 2 isoenzymes of 5aReductase, type I (5aRI) and type II (5aR2) are expressed in skin, scalp, as well as organs such as liver and brain (5aRI), while 5aR2 acts in prostate and seminal vesicles
- Both isoenzymes are expressed in the scalp. 5aRI is mostly found in sebaceous glands, while 5aR2 in connective tissue sheath and dermal papilla. DHT, the most potent androgen (5X > T), has the highest concentration in bald scalp area
- Since males with a 5aR2 deficiency do not develop male pattern alopecia, it has been proposed that 5aR2 is a key enzyme in the genesis of AA. Finasteride (F) inhibits 5aR ~ 50-60%, with a significant effect on 5aR2 -> 5aR1, qualifying it as a therapeutic agent for AA with daily dosage of 5 mg
  

- In men, Rx of 1mg F is Proscar, for excessive thinning hair. It may -> reduced libido, breast tenderness, gynecomastia, and stabilize hairloss.
Finasteride (F) Treatment of AA

*iorizzo M, 2006:* 37 premenopausal women (19-50), 2.5mg/d of F, with a BCP of 3mg drospirenone and 30ug ethinyl estradiol for 12 months. Using global photography and hair density score from videodermoscopy. No TE, nl menses, iron, ferritin, TFT’s, acne, androgens, acne or hirsutism in this cohort. **Results:** After 12 months 23/37 improved alopecia (slightly 8, moderate 8, and 3 greatly). No change in 13 others, 1 got worse. Videodermoscopy distinguishes early AA from telogen effluvium.

*Price VH, 2000:* 1 mg/d of finasteride to 137 normoandrogenic postmenopausal women (41-60 yr) had no effect after 12 months, and similar to controls, studied by scalp biopsies (probably too low dose of F, or senescent postmenopausal scalps may not be very androgen dependent).

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**Figure 1.** Christmas tree pattern of hair loss shows marked improvement compared with baseline (A) after 12 months of oral finasteride treatment (B).
**Dutasteride (Avodart)**

- Treatment dose is one 0.5 mg capsule daily
- Well tolerated. Epigastric discomfort less than finasteride. In males Persistent decr libido, gyneco
- Tends to reduce plasma DHT ~90%. >> finasteride (F)
- Cultured human scalp fibroblasts reveal that 17-a estradiol probably has little effect on androgenic alopecia in view of relatively poor 5-alpha reductase inhibition.
- Better result with dutasteride than finasteride in women with androgenic alopecia after 6 months of therapy (few data). As with F off-label use in women

Rogers NE, Avram NR. J Am Acad Dermatol 2008;59;547

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**5aReductase Inhibitor Treatment of AA**

**Finasteride (F)**
- Inhibits 5aR2> 5aRI
- No known drug interactions
- Strict pregnancy precautions
- In 4 of 1554 men taking F for Ca Prostate -> (breast Ca almost 200 times that of general population)
  - Shen CL. JNCI 2004:96:338-9
- Continued surveillance is suggested
- No breast Ca data reported in women
  - Green L, Wysowski DK, NEJM 1996;335:823

**Dutasteride (D)**
- Reduces serum DHT >F at least 2x
- Increases serum T >>F
- Scalp DHT decreases (NC from F)
- Scalp T increases (NC from F)
- Inhibits 5aRI as well as 5aR2
- Little if any data on Rx D in AA of women in the literature
- Strict pregnancy precautions
- No breast Ca data reported for men or women

Rogers NE. J Am Acad Derm 2008;59:507
Pharmacologic Treatment Choices of Androgenic Alopecia

Moderate Premenopausal:
- Spironolactone, OCP  *(often in combination in all)*  
- Spironolactone, Finasteride (or Dutasteride), OCP

Severe Premenopausal:
- Dutasteride, Spironolactone, OCP, hair transplant

Moderate Postmenopausal:
- Spironolactone, OCP & Dutasteride, or Finasteride

Severe Postmenopausal:
- Dutasteride and Spironolactone ?? Hair transplant.
  *(selectively Rx estrogens in early stages menopause)*
  *(Personal observations and choices)*