

## HAIR DISORDERS PART II: FEMALE PATTERN HAIR LOSS

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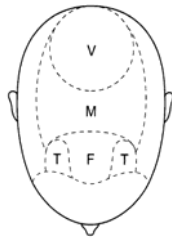
## HAIR LOSS IN WOMEN

Most common types of hair loss

- Caucasian women:
  - Female pattern hair loss
  - Telogen effluvium: acute and chronic
  - Alopecia areata
  - Primary cicatricial alopecia
  - Trichotillomania
- African American women
  - Central centrifugal cicatricial alopecia
  - Hair breakage
  - Alopecia areata
  - Female pattern hair loss
  - Telogen effluvium

## PATTERN HAIR LOSS

- Definition: Hair loss in a predictable distribution of the scalp and in a typical pattern(s) of loss that presents in a post-pubertal male or female



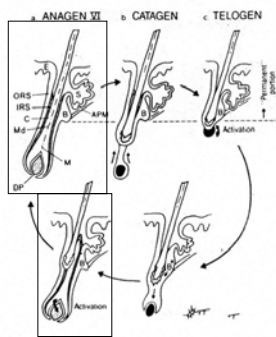
## PATTERN HAIR LOSS

The clinical perception of hair loss in PHL is secondary to three main components:

1. Shrinkage of the size of the dermal papillae and hair matrix leading to miniaturization of the resultant hair shaft.
2. Decreased duration of anagen which in turn leads to increased percentage of hairs in telogen
3. Increased "lag phase" between exogen (the ejection of the telogen hair) and the appearance of a new anagen hair

The net result is finer, shorter, less dense hair in affected areas

## NORMAL HAIR CYCLE



## FEMALE PATTERN HAIR LOSS

Three primary patterns of loss

Male pattern

Diffuse central

Frontal accentuation



## FEMALE PATTERN HAIR LOSS

Two ages of onset:

- Young women, puberty to late 20's: commonly will have signs of hyperandrogenism. This is likely the female counterpart to MPB or true androgenetic alopecia.
- Women 40+ years old with accentuation of hair loss at time of menopause and beyond: signs of hyperandrogenism much less common. May be onset of age-related or senescent alopecia

## FEMALE PATTERN HAIR LOSS

Clinical Clues

- Relative sparing sides of scalp and absolute sparing occiput
- Hair pull
  - Usually negative except in affected areas—not diffusely as in telogen effluvium.
  - Telogen hairs only



## FEMALE PATTERN HAIR LOSS: PRESENTATION AT INITIAL CONSULTATION\*

Clinical Presentation	% Total Patients	% Patients with Frontal Accentuation
Slightly widened part	41%	7%
Obvious thinning central scalp	59%	71%



\*Olsen EA. The midline part: an important physical clue to the clinical diagnosis of androgenetic alopecia in women. *J Am Acad Dermatol* 1999; 40; 106-9

## FEMALE PATTERN HAIR LOSS

Clinical Clues

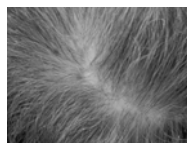
- Fine hair (miniaturization)
- Bitemporal recession (miniaturization and increased lag phase)



## FEMALE PATTERN HAIR LOSS

Clinical Clues: Focal Atrichia

- Pencil eraser sized areas of total hair loss
- Appears to be fairly specific for FPHL particularly late onset FPHL
- Olsen/Whiting unpublished data:
  - 75% of patients with focal atrichia have late onset FPHL. Seen occasionally in other causes of central hair loss including early FPHL, CTE and CCCA (all central hair loss)
  - Of patients with late onset FPHL, 70% have FA

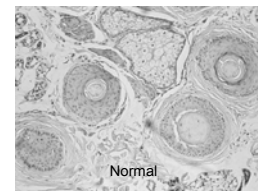


## FPHL

SCALP BIOPSY : not required for diagnosis but may offer supportive information of characteristic changes in scalp hairs

Miniaturization of follicles: ratio terminal/vellus hairs of <4:1 has been suggested as diagnostic measure; normal TV ratio 7:1.

Shorter duration of anagen and increased lag phase after telogen before anagen initiated leads to increased % of telogen hairs



Normal



Pattern hair loss

\*Whiting D. *Derm Therapy* 1998;8:24-33.

**DIFFERENTIAL DIAGNOSIS  
NONSCARRING CENTRAL HAIR LOSS**

- Chronic telogen effluvium
- Alopecia areata
- Trichotillomania
- Syphilis

**FEMALE PATTERN HAIR LOSS**

Etiologic or contributory factors

- Androgens
- Inflammation
- Age related changes

**HYPERANDROGENISM**

Hyperandrogenism can be caused by:

- Increased production of potent androgens (PCOS, tumor)
- Increased production of weak androgens (CAH, Cushing's syndrome, prolactinoma) and interconversion at follicle to more potent androgens
- Hyperinsulinemia which sensitizes ovarian stroma to LH which in turn leads to increased ovarian androgen production
- Blockage of estrogenic pathway (aromatase deficiency) or preferential 5 alpha reductase pathway of testosterone metabolism

**FEMALE PATTERN HAIR LOSS**

POSSIBLE ETIOLOGIC FACTORS:

- Androgen related hair loss (tissue dependent)
  - Androgen receptor (X-linked):
    - Amount of AR
    - Avidity with which hormone is bound to AR
    - Binding of AR-hormone complex to nuclear chromatin
  - Enzymes in the androgen cascade
    - Amount of 5 alpha reductase, 17 OH steroid dehydrogenase, 3B hydroxysteroid dehydrogenase
    - Presence and amount of cofactors
    - Presence of inhibitory or competing factors

Evidence for an androgen dependent process in at least some women with FPHL includes:

- The presence of other androgen related processes (hirsutism, oligomenorrhea) in 20% of women with FPHL, usually early onset. 85% of these women have hyperandrogenemia.
- Some reports of hair regrowth with antiandrogens or 5-alpha reductase inhibitors: primarily in those patients with hyperandrogenism or hyperandrogenemia

Evidence against androgen dependence in all women with FPHL:

- Presence of FPHL in patients with androgen insensitivity syndrome (nonfunctional androgen receptor)
- 80% of women with FPHL do not have any concomitant androgen related problem (hirsutism or oligomenorrhea) and in these women, <15% have hyperandrogenemia
- Relative lack of response of women with FPHL without concomitant hyperandrogenism to cyproterone acetate

**Additional evidence against an androgen related process in most cases of late onset FPHL:**

- Lack of response of postmenopausal women with FPHL to finasteride 1 mg in a placebo controlled trial
- Hair loss occurs when serum androgen (both T and DHT) levels are low.
- Hormone (estrogen) replacement therapy (which increases SHBG and therefore decreases free testosterone) does not effect the process

**CONCLUSIONS RE ANDROGEN RELATEDNESS IN FPHL**

- Female pattern hair loss is a descriptive term for central scalp hair loss
- There is undoubtedly a large percentage of those women with FPHL who have true androgen dependent hair loss, the majority of which have early onset FPHL. These women have FPHL/androgenetic alopecia.
- There is also a large percentage of women, primarily those with late onset FPHL, who do not have evidence of androgen relatedness and may have a different etiology

**FEMALE PATTERN HAIR LOSS**

Etiologic or contributory factors

- Androgens
- Inflammation
- Age related changes

**Mean Inflammation and Fibrosis in Horizontal Sections of 4 mm Scalp Biopsy Specimens**

	Controls	Chronic Telogen Effluvium	Pattern Hair Loss
Mild I/F	32% (7)	28% (99)	35% (142)
Moderate I/F	9% (2)	12% (44)	37% (151)
Total patients with I/F	41% (9)	40% (143)	71% (293)
Mild/moderate I/F ratio	3.5:1	2.3:1	0.94:1
Upper/lower follicular I/F ratio	1.76:1	2.3:1	3.3:1

Whiting. J Am Acad Dermatol 1996; 35: 899-906.

**SOURCES OF POTENTIAL SCALP INFLAMMATION IN FPHL**

- Seborrheic dermatitis
- Infection
  - Fungus
  - Bacterial
- Infestation
- Allergic or irritant reaction to hair care products
- Reparative changes second to scalp insult
- Autoimmune process

**DIFFERENTIAL DIAGNOSIS OF HISTOLOGIC INFLAMMATION/PERMANENT HAIR LOSS IN A PHL DISTRIBUTION**

- Cicatricial pattern hair loss
- Fibrosing alopecia in a pattern distribution
- Central centrifugal cicatricial alopecia

## FEMALE PATTERN HAIR LOSS

### Etiologic factors

- Androgens
- Inflammation
- Age related changes:
  - Menopause: loss of ovarian estrogens and adrenal androgens. Clear that HRT does not reverse late onset FPHL
  - Adrenopause: decrease in adrenal androgens
  - Somatopause: decrease in GH, IGF1

## FEMALE PATTERN HAIR LOSS

### Iron Deficiency:

#### Etiology

- In premenopausal women: must assume menses, diet or absorption abnormality (remember celiac disease)
- In postmenopausal women: must assume GI blood loss until proven otherwise > diet or absorption abnormality

#### Treatment:

- Ferrous sulfate 325 mg (50 mg elemental iron) tid or ferrous lactate, ferrous gluconate
- Absorption is:
  - Decreased with calcium, manganese (in supplements or tea), large doses zinc
  - Increased with citrate, ascorbate
- Target normal ferritin is probably  $\geq 40$  ug/L

## EVALUATION OF THE WOMAN WITH FEMALE PATTERN HAIR LOSS

- Free testosterone is a reasonable minimal screen for hyperandrogenemia: ideally done off of OCPs
- Other tests of potential androgen excess (off OCPs):
  - DHEAS
  - Prolactin
  - 17 hydroxyprogesterone screen for 21 hydroxylase deficiency—ideally should draw during first 14 days of menstrual cycle. More reliable test is a pre and post cortrosyn stimulation test—not cycle specific
  - Dihydrotestosterone

## EVALUATION OF THE WOMAN WITH FEMALE PATTERN HAIR LOSS

- 20% of women with FPHL will have signs of hyperandrogenism ie menstrual irregularity, hirsutism (do not rely on physical exam) and acanthosis nigricans on exam: these women will likely have hyperandrogenemia
- 15% of women with FPHL without signs of hyperandrogenism will have hyperandrogenemia
- If hyperandrogenism is present, consider whether PCOS may be present as well: this should trigger assessment of possible insulin resistance/metabolic syndrome

## POLYCYSTIC OVARIAN SYNDROME (PCOS)

### Current criteria

3-11% of women of reproductive age

NIH 1990: All of the following:

1. Clinical (hirsutism) and/or biochemical signs of hyperandrogenism
2. Oligoovulation ( $\leq 8$  cycles per year)
3. Exclusion of related disorders (hypo or hyperthyroidism, hyperprolactinemia and nonclassical adrenal hyperplasia)

Rotterdam 2003. Two of the following in addition to exclusion of related disorders:

1. Clinical and/or biochemical signs of hyperandrogenism (hirsutism, acne, MPB)
2. Oligo- or anovulation (menstrual cycles longer than 35 days or less than 10 menstruations per year).
3. Polycystic ovaries (12 or more follicles in an ovary with each follicle measuring 2-9 mm in diameter and/or ovarian volume  $>10$ ): ~9% will not have meet this criteria)

## POLYCYSTIC OVARIAN SYNDROME\*

50-60% of patients with PCOS have insulin resistance.

This can be documented best by a GTT with concomitant insulin levels.

- increased fasting glucose ( $\geq 100$  mg/dL) (seen in 20%)
- fasting insulin  $>20$   $\mu$ U/mL (seen in 40%)
- abnormal GTT (seen in 33%)
- glucose to insulin ratio  $<4.5$  (seen in 40%)

Insulin resistance and diabetes in PCOS overlaps with that of the metabolic syndrome and in women with FPHL and PCOS, this should be considered as well

\*Fertility and Sterility 86, 914-933, 2006.

## METABOLIC SYNDROME

- Risk factor for CAD increased 2X
- Risk factor for Type 2 DM increased 5X
- Includes
  - Central obesity
  - Hypertriglyceridemia
  - Low levels of serum HDL cholesterol
  - Hypertension
  - Increased fasting glucose
- In the US, 33% of 18-41 yo non-DM PCOS patients have metabolic syndrome compared to 6.7% of 20-30 yo and 25% of 30-40 yo women in the general population

## TREATMENT OF FPHL

All patients:

- 2% or 5% topical minoxidil

Patients with hyperandrogenism

- Antiandrogens:
  - Spironolactone
  - Cyproterone acetate
  - Flutamide
- 5 alpha reductase inhibitor (finasteride)
- Oral contraceptive pill

## TREATMENT OF FPHL

### Topical Minoxidil Solution 2% or 5%

- Must be used twice daily
- May have initial shedding as newly initiated anagen dislodges telogen hairs
- Efficacy first revealed clinically at about 4-6 months
- 5% TMS has a small but definite efficacy advantage over the 2% TMS but is greasier and more difficult for women to use unless plan to shampoo daily.
- 5% topical minoxidil foam recently FDA approved. No propylene glycol (less greasy)
- Continued use is necessary: telogen effluvium 3-4 months after stop treatment

## TREATMENT OF FEMALE PATTERN HAIR LOSS

### Topical Minoxidil Solution (TMS) 2% or 5%

Adverse effects:

- Hypertrichosis in 5-10% of women with the 5% TMS, less with the 2%: probably a systemic effect but should eliminate exposure to non-scalp areas. Reversible off treatment.
- Irritation vs allergic reaction: the 5% TMS has both more minoxidil and more propylene glycol than the 2% TMS. If in doubt whether a true allergic reaction exists, can patch test. If not minoxidil sensitive, could use the new topical minoxidil foam which does not have propylene glycol

## TREATMENT OF FEMALE PATTERN HAIR LOSS

### Antiandrogens

Spironolactone

Flutamide

Cyproterone acetate

### 5 $\alpha$ -reductase inhibitors

## SPIRONOLACTONE

- Mechanism of Action:
  - Decrease testosterone production through negative effect on cytochrome P450 dependent 17-hydroxylase and desmolase
  - Competitive inhibition DHT/androgen receptor binding
  - Weak progestational activity
- Dose: 100-200 mg qd
- Clinical trial data: largest study to date is 40 women on 200 mg per day for 12 months in an active control trial: 45% responders (Sinclair BJD 2005; 152: 466-473)
- Side effects: hyperkalemia, irregular menses, breast tenderness, mood swings, feminization male fetus

## FLUTAMIDE

- Mechanism of Action
  - Inhibits adrenal 17,20 desmolase activity
  - Inhibits androgen/androgen receptor binding
  - Anti-gonadotropic
- Dose: 250 mg bid to tid
- Efficacy in FPHL only reported in those with hyperandrogenism: Active control trial of 250 mg qd vs observation in 12 women each: statistically significant improvement in the Ludwig score and investigator assessment over observation (Carmina ref 93)
- 6/7 women with hirsutism and FPHL treated with 250 mg bid with OCP showed cosmetically acceptable growth (Ref 94)
- Side effects: GI, hepatotoxicity, feminization male fetus.

## CYPROTERONE ACETATE

- Mechanism of action:
  - block DHT-androgen receptor binding
  - antigonadotropic
  - strong progestagen.
- Dose: given as 25-50 mg CA days 5-15 with 50 mg EE days 15-25 (Diane) or days 1-10 with OCP or if post hysterectomy, can be given alone 25 mg per day
- Clinical trial data:
  - 22 premenopausal women on 50 mg qd +EE and 18 postmenopausal women on 100 mg qd x 12 months: 43% responders (\*Sinclair BJD 2005; 152: 466-473 )
  - 33 women on 52 mg +EE per day 20/28 days X 12 months: no significant improvement (Vexiau BJD 2002; 146: 992-999)
- Side effects: nausea, fluid retention, HA, depressed mood, disruption of menses, reduced libido, breast tenderness, feminization of male fetus

## FINASTERIDE IN FPHL

- Blocks testosterone transformation to DHT
- Does not effect T or DHT binding to AR
- Half life is ~ 6 hours, biological half life longer
- Suppresses DHT ~2/3 in serum and ~40-65% in scalp of men with MPHL: ?????? In women
- May take up to 6-12 months to see response. In men with MPHL, maximum effect of finasteride at 24 months
- Potential adverse effect in women: feminization male fetus

## THERAPY OF FEMALE PATTERN HAIR LOSS: FINASTERIDE

- Efficacy with 2.5 mg qd reported in case reports of post menopausal women with FPHL and hyperandrogenemia and with 1 and 2.5 mg doses in those without hyperandrogenemia
- Camacho reported on effectiveness of 2.5 mg in 41 women with FPHL and SAHA in an open label study
- In an open label study of 37 women with FPHL without hyperandrogenism treated with 2.5 mg and Yasmin, 60% had improvement by global photographs and 32% had an increase in hair density by 12 months\*: no control for OCP
- Finasteride raises both testosterone and estrogen about 10% in men—may have advantages in women regarding libido if can confirm that T not involved in FPHL

\*Iorizzo et al. Arch Dermatol 2006; 142: 298-302.

## TREATMENT OF FPHL

- All antiandrogens or 5 alpha reductase inhibitors may cause feminization of a male fetus in a woman using them during pregnancy therefore effective contraception is obligatory with their use.
- Preference for contraception is OCP
  - Decrease androgen production at ovarian and adrenal source
  - Increased SHBG which decreases unbound serum DHT and T.
  - Some progestins in combination OCPs have greater androgenic effect than others but if using an antiandrogen, of little consequence.
  - Yasmin does have about a 25 mg Spironolactone effect which by itself is not particularly helpful but has an additive effect with additional antiandrogens or 5 alpha reductase inhibitors.

## Female Pattern Hair Loss

### Surgical management:

- Hair transplants, almost exclusively mini- and micro plugs, can be quite effective
- Donor site density and fineness of hair can be an issue in many women

## MY APPROACH TO TREATMENT OF FPHL

### All:

- Topical minoxidil 5% bid or 5%/2% bid
- Zinc pyrithione shampoo

### Early onset FPHL (with or without hyperandrogenism) or premenopausal woman with hyperandrogenism

- OCP for a month before start either
  - Spironolactone 100-200 mg per day
  - Finasteride 1 mg per day

### Postmenopausal woman

- Hyperandrogenism
  - Spironolactone 100-150 mg per day
  - Finasteride or dutasteride

## CONCLUSIONS

- FPHL can be divided by age of onset and by presence or absence of hyperandrogenism into subgroups
  - Early onset FPHL is much more likely to be androgen related
  - Late onset FPHL may be related to hormonal changes but not specifically to androgens
- Etiology is not clear in FPHL in absence of hyperandrogenism and antiandrogens/5 $\alpha$ R inhibitors are not uniformly effective even in patients with hyperandrogenemia
- Cicatricial pattern hair loss and other central scalp types of cicatricial hair loss should be looked for as this effects therapeutic results and patient expectations