Female Diffuse Alopecia: Exploration and Management

Professor Ralph M. Trüeb, M.D.
Center for Dermatology and Hair Diseases
Zentrum Wallisellen
Bahnhofplatz 1a
CH-8304 Wallisellen (Zurich)
Switzerland
Hair loss is frequent

Hair loss causes considerable distress

Treatment options are available, though limited, both in terms of indications and of efficacy

Success depends on unpatronizing sympathy from the side of the physician and comprehension of the underlying pathology

Treatment must meet patients‘ expectations, otherwise patients must be informed on what to expect
Hair Follicle Cycle

Hair cycling in a random mosaic pattern

Control of hair cycling within the hair follicle itself

Influence of systemic and external factors:
- hormones
- cytokines
- toxins
- deficiencies (nutrients, vitamins, energy)

Mildred Trotter (1899-1991)

Anagen (2-6 years)

Teloptosis

Catagen (2 weeks)

Telogen (3 months)

Daily telogen shedding: 35-100 depending on amount of hair on the head!
**Diffuse Alopecia: Dystrophic Anagen Effluvium**

Direct insult to the rapidly dividing bulb matrix cells

LM: Tapered proximal end and lack of root sheath

Within days to few weeks loss of 90% of scalp hair

- **antineoplastic drugs:** chemotherapy-induced alopecia
- **x-ray:** radiation-induced alopecia:
  - temporary $>3$-4 Gy
  - permanent $>30$ Gy deep x-rays, $>50$ Gy soft x-rays

- **environmental or occupational toxin exposure:** toxic alopecia

- **immunologic injury:** alopecia areata

**Diffuse Alopecia: Telogen Effluvium**

**Definition:**
Disruption of the hair cycle resulting in increased proportion (> 20%) and shedding of telogen hair

Hair loss < 50% of scalp hair: Diffuse thinning of hair, most conspicuous at the temples

Positive pull test of telogen club hairs

< 6 months: acute telogen effluvium:
- Fever: postfebrile telogen effluvium
- Childbirth: postpartum telogen effluvium
- etc.

> 6 months: chronic telogen effluvium:
- Primary disorder
- Secondary to a variety of systemic disorders

Kligman. Arch Dermatol 1961;83:175-198
Telogen Effluvium: Pathologic Dynamics

With synchronization:

- **Diffuse Telogen effluvium:**
  - Immediate anagen release
  - Delayed anagen release
  - Immediate telogen release
  - Delayed telogen release

Without synchronization:

- Short anagen:
  - **Androgenetic alopecia**
  - **Senescent alopecia**

**Headington JT. Telogen effluvium. New concepts and review.**
Arch Dermatol 1993;129:356-363
Chronic Telogen Effluvium

Diffuse shedding of telogen hair > 6 months

Secondary to a variety of systemic disorders:
- iron deficiency, other dietary deficiencies
- thyroid disease, other metabolic diseases
- systemic lupus erythematosus, other connective tissue disorders
- syphilis, HIV
- drug-induced hair loss

Primary disorder:
- First described 1960 as „Diffuse cyclic hair loss in women“
  Guy and Edmundson. Arch Dermatol 1960;81:205-227
- Revived in 1996, since then focus of interest again
- Diagnosis of exclusion!

Differential diagnosis:
- Androgenetic alopecia/Female pattern hair loss (FPHL)
- Diffuse alopecia areata („alopecia areata incognita“)
## Differential Diagnosis: Androgenetic Alopecia

Genetically determined, androgen induced, age-dependent progressive loss of hair with sex-dependent differences in pattern of alopecia

### Men:
- 18 - 29: 12%
- 30 - 39: 38%
- 40 - 49: 45%
- 50 - 59: 52%
- 60 - 69: 65%
- 70 - 79: 64%
- > 80: 70%

### Women:
- 20 - 29: 3%
- 30 - 39: 17%
- 40 - 49: 16%
- 50 - 59: 23%
- 60 - 69: 25%
- 70 - 79: 28%
- 80 - 89: 32%

---

**Hamilton-Norwood I-VII**

- 18 - 29: 12%
- 30 - 39: 38%
- 40 - 49: 45%
- 50 - 59: 52%
- 60 - 69: 65%
- 70 - 79: 64%
- > 80: 70%

**Ludwig I-III**

- 20 - 29: 3%
- 30 - 39: 17%
- 40 - 49: 16%
- 50 - 59: 23%
- 60 - 69: 25%
- 70 - 79: 28%
- 80 - 89: 32%

---

Androgens + Androgen metabolism

Genetics

Progressive shortening of anagen phase + Reduction of volume of dermal papilla

Follicular microinflammation → Perifollicular fibrosis

Hair follicle miniaturization/hair growth arrest

Increased shedding of hair: Telogen effluvium

Decreased hair growth: Terminal-to-vellus hair transformation
Differential Diagnosis: Diffuse Alopecia Areata

Most frequent cause of hair loss in childhood. Before age 2 <2%, before age 20 32,5-63 %, and after age 40 20% of cases

May cause diffuse hair loss (2% of patients, women > 40 years)!

Organ specific autoimmune disease of hair follicle with usually focal alopecia and unpredictable course with tendency to recurrence or chronicity, depending on age of onset, disease associations, duration of disease, and extent of hair loss (prognostic factors)

Diagnosis:

• Non-cicatrizing alopecia with dystrophic hairs and empty follicles: typical dermascopic findings

• Nail changes in 20-40% (more frequent in children)

• Trichogram: telogen or dystrophic anagen effluvium

• Histology: peribulbar lymphocytic infiltration

• Immune serology: Frequently circulating autoantibodies (thyroid, intrinsic factor)
Value of Scalp Dermoscopy (Trichoscopy)

Normal finding

Diversity of hair shaft diameter > 20% in androgenetic alopecia


Yellow dots typical for alopecia areata

Seasonality of Hair Growth and Shedding

Reports 3 women in New York who experienced maximum hair loss in November


Demonstrate in 14 men over a period of 18 months that the proportion of telogen hair and of hair shedding were maximal in September


Demonstrate in 10 men with or without alopecia during a period of 8-14 years a maximal proportion of telogen hairs at the end of summer

Fluctuations in frontal telogen rates (n = 823) in relation to the day of the year:

Telogen rates showed an overall annual periodicity, manifested by a maximal proportion of telogen hair in July.

A second telogen peak seems to exist, although less pronounced, in April.

Seasonality of Hair Growth and Shedding

Subsequent images taken in January 2007, August 2007, and February 2008

Seasonal fluctuations in telogen rates may be significant enough to be clinically apparent, especially in women with female pattern hair loss!

The existence of seasonal fluctuations in hair growth and shedding complicates the assessment of pharmacological effects.

Awareness of these fluctuations is prerequisite to providing the correct cause and prognosis to the patient, ensuring patient compliance with therapy.

Ultimately, awareness of these fluctuations also has potentially serious implications for investigations with hair growth promoting agents: Depending on the stage of periodicity in growth and shedding of hair for a particular subject, the heterogeneity of included subjects may be enough to distort the clinical efficacy results and the perceived benefit of an investigational agent.

Investigating Hair Loss in Women

**Family history of hair loss**

**Personal history:**
- of hair loss
- of medical problems and drug intake
- of diet habits

**Clinical examination:**
- hair loss pattern
- hair loss activity (pull test)
- dermoscopy

**Biochemical investigations:**
- for hematinic deficiencies (CRP, ferritin, vitamin B12, folic acid)
- thyroid stimulating hormone
- estradiol (in menopausal), extended hormonal studies as indicated
- extended biochemical studies as indicated

**Trichogram and scalp biopsy as indicated:**
- CTE versus FPHL (trichogram)
- Loss of follicular orifices (biopsy)
Anagen hair loss

LM

Dystrophic anagen effluvium

Patient history
Toxicologic studies

Pulltest positive

Telogen hair loss

< 6 months:
Acute telogen effluvium

Patient history

Patient history
Laboratory investigations

Secondary CTE or Differential diagnosis

Imaginary hair loss

Primary CTE

Androgenetic alopecia

Diffuse alopecia areata
Psychocutaneous Disorders of Scalp

Imaginary Hair Loss
(Psychogenic Pseudoeffluvium)

Adjustment Disorders

Feeling of Disfigurement
(Body Dysmorphic Syndrome)

Abnormal Scalp Sensations
(Cutaneous Sensory Disorder)

Self-Induced Injury
(Trichotillomania, Factitious Disorder)

Psychogenic Pseudoeffluvium: Diagnosis of Exclusion

Imaginary Hair Loss (Psychogenic Pseudoeffluvium): Fear or conviction of hair loss without objective findings

Etiology and Pathogenesis:

- **Heterogeneous underlying mental disorders:**
  - Depressive disorder (ICD-10 F34.1)
  - Hypochondrial and body dysmorphic disorder (ICD-10 F45.2)
  - Delusional disorder (ICD-10 F22.0)

Diagnosis:

- Clinical examination (no alopecia)
- Hair calendar (normal counts of hair shed)
- Trichogram (normal anagen and telogen rates)
- **Nosologic classification of underlying psychopathologic condition!**

Eckert G. Acta Dermatol Venereol (Stockh) 1975;55:147-149
Cotterill JA Dermatol Clin 1996;14:457-463
Adjustment Disorders (To Hair Loss)

- Prolonged depressive reaction (ICD-10 F43.21)
- Mixed anxiety and depressive reaction (ICD-10 F43.22)
- With predominant disturbance of conduct (ICD-10 F43.24)
- With mixed disturbance of emotions and conduct (ICD-10 F43.25)

The best way to treat the adjustment disorder is to effectively treat the underlying hair disorder!
Managing Hair Loss

Trichological and biochemical characterization of hair loss

Quantitating hair loss:
• Daily count
• Wash test
• Combining epiluminiscence microscopy with digital imaging (TrichoScan)

Causal treatment, wherever possible!

Specific treatments for the scarring alopecias

Specific treatments for alopecia areata:
• Acute: Corticosteroids (pulse therapy, intralesional)
• Chronic: Topical immunotherapy

Specific treatments for androgenetic alopecia:
• Topical 2-5% minoxidil
• 5-alpha reductase inhibition

Role for hormonal and nutritional treatments?
Efficacy of Topical Minoxidil in Androgenetic Alopecia/FPHL

Price et al. Changes in hair weight and hair count in men with androgenetic alopecia, after application of 5% and 2% topical minoxidil, placebo, or no treatment. J Am Acad Dermatol 1999;41:717-21
Effect of **estrogen therapy** on postmenopausal women?

**Antiandrogen therapy** not effective in normoandrogenic women


**Gestagens with androgenic action** may precipitate hair loss in women: norethisterone, levonorgestrel, tibolone contraindicated!

**DHEA** may cause hair loss in women in a dose-dependent manner!
Finasteride in Postmenopausal Women

Randomized, double-blind, placebo-controlled study with 1 mg oral finasteride during 12 months in 137 postmenopausal age 41-60 Y.

Study endpoints:
- Hair count
- Global photographic assessment
- Biopsy (morphometric)

Results: For all endpoints no difference in comparison to placebo


5 normoandrogenic postmenopausal women treated with 2.5 – 5 mg oral finasteride for up to 18 months showed improvement on global photographic assessments.

Trüeb et al. Dermatology 2004;209:202-207

Iorizzo et al. Arch Dermatol 2006;142:298-302
Pharmacy aisles and Internet drugstores are full of nutrients promising full, thick, luscious hair -- for prices that range from suspiciously cheap to dishearteningly exorbitant.

What are the facts?

- Unless the hair is falling out due to a nutritional deficiency, there's only so much that nutrients can do to increase the size of individual hairs. This is because hair thickness is largely genetic.

- Nevertheless, there are external factors that influence hair health to a great degree, and nutrients can boost hair that's suffering from these problems.
Role of Nutritional Deficiency: Iron

**Iron deficiency most common nutritional deficiency:** 12-16% prevalence in adolescent girls and women of childbearing age (16-49 years of age) and 6-9% in women 50 years of age and older in the USA.

Most laboratories use **10 - 15 µg/l as lower limit of normal for menstruating women, and 30 µg/l for children, men and non-menstruating women.** In women of childbearing age, a cutoff of 10-15 µg/l yields a sensitivity of 75% and specificity of 98%, a cutoff of 30 µg/l yields a sensitivity of 92% and a specificity of 98%.

**Most common causes of iron deficiency:**
- in premenopausal women: menstrual blood loss, pregnancy and lactation
- in postmenopausal women: decreased absorption and gastrointestinal loss.
- **Risk factors:** heavy menstrual bleeding (> 80 ml per month), use of an IUD, history of iron deficiency anemia, insufficient dietary iron intake.

From: Bregy and Trüeb. Dermatology 2008;217:1-6
Role for Iron Supplementation

Decreased serum ferritin is associated with alopecia in women ("Rushtonians"):  

There is no clear association between low serum ferritin and chronic diffuse telogen hair loss ("Sinclairians"):  
- Aydingoz et al. 1999;13:65-7  
- Sinclair R. Br J Dermatol 2002;147:982-4

No association between serum ferritin levels >10 microg/L and hair loss activity in women (trichogram).

From: Bregy and Trüeb. Dermatology 2008;217:1-6
Ageing of Hair

Rare premature aging syndromes with alopecia (Hutchinson-Gilford, Curshmann-Steinert, Rothmund-Thomson, Laron syndrome)

Androgenetic alopecia (AGA)
Female pattern hair loss (FPHL)

Senescent alopecia
<table>
<thead>
<tr>
<th>Androgenetic alopecia</th>
<th>Senescent alopecia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td></td>
</tr>
<tr>
<td>Early (teens, twens)</td>
<td>Late (60 years +)</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td></td>
</tr>
<tr>
<td>Patterned</td>
<td>Diffuse</td>
</tr>
<tr>
<td><strong>Pathophysiology</strong></td>
<td></td>
</tr>
<tr>
<td>Increased activity of 5-α reductase (DHT) in men</td>
<td>Senescence (decreased activity of 5-α reductase)</td>
</tr>
<tr>
<td><strong>Genetics</strong></td>
<td></td>
</tr>
<tr>
<td>Polygenic</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Association or risk factor for other diseases</strong></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>Age-related disorders?</td>
</tr>
<tr>
<td>Benign prostatic hyperplasia</td>
<td></td>
</tr>
<tr>
<td>Prostate cancer</td>
<td></td>
</tr>
<tr>
<td><strong>Gene expression profiles</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased expression of genes required for anagen onset and maintenance / increased expression of catagen and telogen inducers</td>
<td>Increased expression of markers for mitochondrial dysfunction and oxidative stress</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
</tr>
<tr>
<td>Minoxidil</td>
<td>Minoxidil</td>
</tr>
<tr>
<td>Finasteride</td>
<td>Nutritional supplements</td>
</tr>
<tr>
<td>Estrogens (anecdotal)</td>
<td>hGH (anecdotal)</td>
</tr>
</tbody>
</table>

Biology of Hair Aging

Intrinsic (Chronologic) Aging:
- **Genetic**: AGA, familial premature graying (AD), progerias (rare)
- **Hormones und hormone metabolism**: AGA
- **Replicative senescence**: Graying, senescent alopecia?
- **Oxidative metabolism** (melanogenesis): Graying

Extrinsic (Accelerated) Aging:
- **Oxidative stress from UV-R**
- **Oxidative stress from tobacco smoking**
- **Others**?

Trüeb RM. Is androgenetic alopecia a photaggravated dermatosis? Dermatology 2003;207:343-348

Trüeb RM. Association between smoking and hair loss: another opportunity for health education against smoking? Dermatology 2003;206:189-191
External Factors: Smoking

Premature senescence of balding DPC in vitro in association with expression of p16(INK4a)/pRB suggests that balding DPC are sensitive to environmental stress and identifies alternative pathways that could lead to novel therapeutic strategies for treatment of AGA.


Active compound led to statistically significant improvement and normalization of mean anagen hair rates within 6 months of treatment, independent of age (smoking status not examined).

Hair count and cumulative hair shaft diameter did not show any change in both groups (as opposed to studies with topical minoxidil).
# Pilot Study With Oral Combination of Cystine and B-Vitamins in Female Senescent Hair Loss

Demographic data and preliminary 3-months-results (unpublished data)

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Initials</th>
<th>Sex</th>
<th>Age</th>
<th>T0 % Anagen</th>
<th>T0 Haircount</th>
<th>T3mo % Anagen</th>
<th>T3mo Haircount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EZ</td>
<td>Female</td>
<td>83</td>
<td>67</td>
<td>125</td>
<td>86</td>
<td>137</td>
</tr>
<tr>
<td>2</td>
<td>IE</td>
<td>Female</td>
<td>76</td>
<td>68</td>
<td>155</td>
<td>77</td>
<td>128</td>
</tr>
<tr>
<td>3</td>
<td>VH</td>
<td>Female</td>
<td>78</td>
<td>61</td>
<td>93</td>
<td>78</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>DC</td>
<td>Female</td>
<td>71</td>
<td>64</td>
<td>128</td>
<td>77</td>
<td>135</td>
</tr>
<tr>
<td>5</td>
<td>NS</td>
<td>Female</td>
<td>64</td>
<td>71</td>
<td>140</td>
<td>81</td>
<td>175</td>
</tr>
</tbody>
</table>
Efficacy of Oral Supplementation with Combination of Cystine and B-Vitamins in Female Senescent Hair Loss

Before treatment

After 6 months of treatment

Personal observation
Summary and Conclusions: Female Diffuse Alopecia

The complaint of hair loss is frequent in women and causes considerable distress.

In a minority of patients hair loss is imaginary.

The number of hair lost per day depends on the amount of hair on the scalp and seasonal effects.

There are effective therapies of hair loss, though with limitations with respect to indications and efficacy.

The role of nutrition is overemphasized by the lay and underestimated by physicians.

Iron deficiency is overestimated as a single cause of hair loss in women, as well as the role of antiandrogens in the treatment of female pattern hair loss.

Androgenetic alopecia and ageing of hair are two distinct entities, though with some common denominators.

Treatment should target multiple factors responsible for hair loss.

Treatment success depends on comprehension of the underlying pathology and unpatronizing sympathy on the part of the physician.
Thank you for your attention!

References:


www.derma-haarcenter.ch