Therapy Update for Management of Androgenetic Alopecia in Women

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Introduction

• Common:
  • By menopause about ½ of women experience hair loss
  • Incidence increases with age

• Psychologically distressing:
  • Women feel it is unnatural for their hair to thin
  • Despite high prevalence, feel they ‘are the only one’

• Limited treatment option:
  • Poorly studied
  • Mildly efficacious at best
  • Unpredictable response
Clinical Presentation

- Slow, progressive reduction in hair density on the crown of the scalp
- Spares of the frontal hairline - temporal recession much less in women

- Widening part width - anteriorly first
- Thinning rather than baldness

- Family history – male and female relatives
Nota bene

• Diffuse, rapid onset is uncommon in AGA
• Should raise suspicion for:
  • Systemic illness:
    • Nutritional deficiency (iron, vitamin D, zinc)
    • Thyroid disease
    • Syphilis
    • Medication exposure
  • Autoimmune etiology
    • Lupus
    • Alopecia areata – diffuse type
Psychologic Effect

• Despite a significantly large prevalence
  • Many women feel the condition is rare
  • Affected socially and psychologically
• Despite high prevalence, many women feel the condition is rare
• Leads to high levels of stress, anxiety and social effects
• Women with FPHL:
  • Had more negative body image
  • A pattern of less adaptive functioning
  • 55% of patients who had FPHL displayed symptoms of depression (vs anxiety, aggressiveness or hostility in men)
• Treatment of hair loss produced an improvement in 89% of women and 76% of men

Pathogenesis – Genetically Determined

• Shortening of the anagen phase

• Telogen phase – constant duration

• Result: gradual conversion of terminal (large, thick, and pigmented) hairs into vellus (short, thin, nonpigmented) hairs
Pathogenesis of Androgenic Alopecia

- Follicular miniaturization
- Anagen shortens
- Increased percentage of follicles in telogen (10-20%)
- Loss of follicles, replaced by fibrous tracts
Miniaturization

- Process driven by:
  - Testosterone
  - Age
  - Genetics
- Hair follicles become progressively smaller with each anagen cycle
- Anagen phase shortens
- Proportion of hairs in telogen increase
Work-Up

• Evaluate for androgen excess
  • DHEAS
  • Testosterone – free and total
  • Fasting blood glucose
  • HbA1C

• Others:
  • Sex hormone binding globin
  • Androstenedione
  • 24 hour urine cortisol
  • Prolactin

• Health/nutrition
  • Complete metabolic panel
  • Blood cell count
  • TSH
  • Ferritin
  • Zinc
  • Vitamin D
Polycystic Ovary Syndrome

• 5-10% of woman

• Variable definitions
  • Irregular menses
  • Infertility
  • Cysts on ovaries
  • Acne
  • Hirsutism
  • Metabolic syndrome
Genetics

• Sisters of patient with PCOS:
  • 1/3 of sisters of PCOS patients have elevated testosterone levels
  • ½ of those patients will later develop PCOS

• Parents:
  • 1/3 of PCOS patients had a parent with metabolic syndrome or diabetes mellitus

• No specific genes have been identified that cause PCOS

• Proposed genes likely regulate the hypothalamic-pituitary-ovarian axis

• High frequency of PCOS and metabolic syndrome in family members -> family be screened for PCOS and metabolic syndrome, esp the obese
When to Refer?

• Pre-diabetes, diabetes
• Obese
• Young and thin with high androgens
• Family history of DM2, metabolic syndrome
Treatments

- Antiadrogen
  - Spironolactone
  - Cyproterone acetate
  - Flutamide
- Reductase inhibitors
  - Finasteride
  - Dutasteride
- Estrogen
- Prostaglandin analogs

- Topical
  - Minoxidil
  - Ketoconazole
  - Zinc Pyrithione
- Hair transplant
- Nutritional supplements
- Others:
  - Platelet rich plasma therapy
  - Low intensity light therapy
  - Microneedling
Minoxidil

• Only FDA approved treatment for hair loss in women
• 5% foam once daily or 2% solution twice daily
• Safe, effective, well-tolerated
• Takes 4-6 months to see results – patients must be patient!

• Prolongs anagen
• Converts telogen -> anagen (initial shed)
• Reverses miniaturization (early)
Minoxidil

• The good:
  • Relatively inexpensive, readily available, easy to use
  • Effective treatment in restoring the number of non vellus hairs

• The challenges:
  • Clinical effects are unpredictable
  • Results may be mild and unappreciated by the patient
  • If the treatment is not continued continuously and indefinitely, improvements will be lost
Estrogens – As part of OCP

• Decreases the duration of the telogen phase
• Increases the duration of the anagen phase
• Biological activity at hair follicle is likely a result:
  • Complex interplay between genetic factors
  • Hormonal influence on a multitude of signaling pathways
Estrogens/OCP – Improvement in Hormone Profile

• Suppresses ovarian testosterone
• Increases SHBG -> decreases circulating free testosterone
• Positively impacts PCOS lab profile
• Reverse/protects against many PCOS associated risks (endometrial carcinoma)
• Many other treatments are teratogenic
OCP – Progesterone Component

• Differentiates available formulations
• Range: very androgenic to anti-androgen
• Best (available in US OCP formulations)
  • Norgestimate
  • Drospirenone – equivalent to 25 mg spironolactone

• Avoid (commonly used)
  • Norethindrone
  • Desogestrel
## Progesterone: androgenic potential

<table>
<thead>
<tr>
<th>Anti-androgenic</th>
<th>Neutral</th>
<th>Androgenic</th>
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<tbody>
<tr>
<td>Cyproterone acetate</td>
<td>Norethindrone</td>
<td>Norgestrel</td>
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<tr>
<td>Chlormadinone acetate</td>
<td>Ethynodiol diacetate</td>
<td>Levonorgestrel</td>
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<tr>
<td>Dienogest</td>
<td>Norethynodrel</td>
<td>Desogestrel</td>
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<tr>
<td>Drospirenone</td>
<td>Norgestimate</td>
<td>Gestodene</td>
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Spironolactone

• Not approved for any dermatologic conditions
• Accepted use in acne, hirsutism, and FPHL
• Anti-androgenic properties
  • Decreases androgens (testosterone and DHEAS)
    • Depletes cytochrome p450
    • Decreases cytochrome p450-dependent enzyme 17a-hydroxylase and desmolase
  • Lessens androgen effect on target tissues
    • Competitive inhibitor of the androgen receptor blocking the androgen action in the hair follicle
• Arrests hair loss progression
Spironolactone - Evidence

• No randomized controlled trials evaluating efficacy in FPHL
• Case study of four patients -> 200 mg daily
  • Reduced hair loss by 50%–62.9%
  • Increased the total number of anagen hairs
• Open-label study of 80 women with biopsy-proven FPHL who either received spironolactone (200 mg daily) or cyproterone acetate for at least 12 months
  • 44% of patients experienced visible hair growth
  • 12% had reduced hair density

Spironolactone - Dosing

• Optimal: 100-200 mg daily
  • Lower doses may stabilize hair loss
• Start 25-50mg daily, titrate up as tolerated
• > 100 mg, more side effects
Spironolactone - Side Effects

• Dose dependent
• Primarily due to aldosterone effects on the renal system:
  • Hypotension, hyperkalemia, fatigue, headache, weight loss, increased urinary frequency, and dry skin
• Antiandrogenic effects:
  • Menstrual irregularities
  • Breast tenderness
• Teratogen - pregnancy category D
• To minimize side effects:
  • Hypotension, fatigue, headache: increase fluid intake
  • Menstrual irregularity and pregnancy prevention: combination birth control pill
Spironolactone

The rate of hyperkalemia in healthy young women taking spironolactone for acne is equivalent to the baseline rate of hyperkalemia in this population. **Routine potassium monitoring is unnecessary for healthy women taking spironolactone for acne**.
Reductase Inhibitors

• Finasteride and Dutasteride
Finasteride

• Competitive and specific inhibitor of type II 5α-reductase – the isotype most common in the hair follicles
• Blocks the intracellular conversion of testosterone to DHT
  • Integral role in the process of hair miniaturization
• No affinity for the androgen receptor and has no androgenic, antiandrogenic, estrogenic, antiestrogenic, or progestational effects
Finasteride - Evidence

• Conflicting reports of the effectiveness in FPHL
• Multicenter, randomized placebo-controlled trial:
  • 137 postmenopausal women with FPHL
  • Finasteride 1 mg daily or placebo
  • 1-year follow-up period
  • **No significant change in the hair count**
• Authors concluded that finasteride provided no benefit in increasing hair growth in women with FPHL over a 1-year period

Finasteride - Evidence

• 36 patients with elevated androgens and alopecia
  • 250 mg daily flutamide vs cyproterone vs 5 mg finsteride ->
    • Flutamide benefit - 21% reduction in Ludwig score
  • finasteride and cyproterone -> no change

Finasteride - Evidence

- Case reports of 5 mg finasteride use in patients with androgen excess
  - Improvement in hair density and thickness
  - 6 months to 2.5 years to see effects
Dutasteride

• More potent reductase inhibitor than finasteride
• Inhibits both types I and II 5α-reductase

• ½ life very long – 5 years

• Teratogen – use with great caution in pre-menopausal women
Dutasteride - Evidence

• One report of successful treatment with dutasteride for FPHL:
  • 46-year-old patient who had failed both minoxidil and finasteride treatment
  • No observed side effects
• Mesotherapy
• Topical preparation being studied

Low Level Light Devices

• Laser Combs/Caps/Wands/Bands
• Red or near infra-red light
  • 500-1100 nm with power density 3-90 mw/cm²
  • 650-900 nm & 5 mw effective for aga
• FDA clearance
  • Increase terminal hair density & improve hair regrowth
  • Decrease inflammation
• 3 times per week for 90 sec to 20 minutes
  • Device specific
• 3-4 months to see results
Fig. 3 Male and female pattern hair loss before and after lasercomb treatment. Global photographs of a female subject, at baseline (a) and after 26 weeks (b) of the 12-beam lasercomb treatment. Macrophotographs of a male subject, at baseline (c) and after 26 weeks (d) of the 9-beam lasercomb treatment. Increased hair count through conversion of vellus or intermediate follicles to active follicles producing terminal hair (ovals) or resting telogen to active anagen follicles (rectangles) is highlighted.
KETOCONAZOLE SHAMPOO (1 or 2%)

- Antifungal
- Anti-inflammatory
- Anti-androgen
  - Decrease Testosterone
  - Increase Hair growth
- Oral ketoconazole
  - Anti-androgen
  - Monitor liver function
Ketoconazole - Evidence

• 2% shampoo in men with AGA vs non-medicated shampoo +/- minoxidil
  • Increased hair density
  • Increased size and proportion of anagen follicles
  • Results similar +/- minoxidil

• Anti-androgen effect?

• Anti-inflammatory effect?

• 2% shampoo added to regimen

Zinc Pyrithione shampoo

- 6 months, 200 males (18-49 years) Norwood III vertex or IV
- 9 week study

- Hair counts $P < 0.05$ net increase in total visible hair counts - maintained 26 weeks

- 50% less than minoxidil

- Conclusion: hair counts had modest & sustained improvement with daily use for 26 weeks/study

Prostaglandins

• Brimatoprost and lanatoprost
• Eyelash hypertrichosis

• Mechanism:
  • Prolong anagen
  • Push more hair into anagen

• Risks:
  • Hyperpigmentation –
  • Lashline and iris
Prostaglandins - Evidence

• latanoprost on scalp hair growth in macaque model of AGA
• Well-controlled study (8 monkeys, 4 treated and 4 controls)
• Results:
  • 50 mcg/ml latanoprost daily over 5 months -> minimal hair growth
  • 500 mcg/ml daily over 3 months -> moderate-to-marked hair regrowth.

Oral Prostaglandin

• On-going Phase 2 clinical trial in male pattern alopecia

• Safe, non-hormonal treatment for hair loss
Nutritional Supplements

- Biotin
- B complex vitamins
- Zinc
- Copper
- Iron
- Vitamin C
- Vitamin E
- Coenzyme Q10
- Vitamin A
- Saw palmetto
- Green tea extract
- Methylsulfonylmethane (MSM)
- Beta-sitosterol
- Rosemary
- Lavender
- Thyme
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Minoxidil + Spironolactone

- Open-label, uncontrolled study
- Compounded oral pill
  - Low-dose minoxidil (0.25 mg) and spironolactone (25 mg)
- 3 months – significant drop in hair shedding
- 6 months – improved density
- Well-tolerated - 8 of 100 patients experiencing side effects
  - Eg: urticaria, hypertrichosis, and postural hypotension
- Transient increased shedding in first 3 to 12 weeks in 22 patients

Platelet Rich Plasma
Double-Blind, Placebo-Controlled Pilot Study on the Use of Platelet-Rich Plasma in Women With Female Androgenetic Alopecia

Carlos J. Puig, DO,* Robert Reese, DO,† and Michelle Peters, EdD*†


Platelet-rich plasma for androgenetic alopecia: Does it work? Evidence from meta analysis.

Giordano S,^1,2 Romeo M,^3 Lankinen P^4.

LETTERS AND COMMUNICATIONS

Platelet-Rich Plasma for the Treatment of Female Pattern Hair Loss: A Patient Survey

Platelet-Rich Plasma for Androgenetic Alopecia: A Pilot Study

Giovanni Schiavone, MD,* Desanka Raskovic, MD,† Joseph Greco, PhD, PA/C,‡ and Damiano Abeni, MD, MPH^8
What is Platelet Rich Plasma (PRP)?

• Autologous high concentration of platelets in small volume of plasma

• **1,000,000 platelets/µL** or **4-7 times concentration of whole blood**

• Contains >20 Growth factors, fibrin, fibronectin, vitronectin
  • Fibroblast activation
  • Collagen synthesis
  • ECM stimulation
  • Overexpression endogenous growth factors
Platelets

• **ALPHA GRANULES** Secrete protein growth factors
  - **Platelet derived growth factor (PDGF):** Cell growth, generation & repair of blood vessels, collagen production
  - **Transforming growth factor (TGF):** Cellular transformation
  - **Vascular endothelial growth factor (VEGF):** Growth & generation of vascular endothelial cells
  - **Epidermal growth factor (EGF):** Promotion of epithelial cell growth, angiogenesis, promotion of wound healing
  - **Fibroblast growth factor (FGF):** Tissue repair, cell growth, collagen production
  - **Insulin-like growth factor (igf):** Induces & prolongs Anagen phase of hair cycle
# Alpha Granules Are Important In Hair Loss

<table>
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<tr>
<th>Granule Type</th>
<th>Examples of Mediator</th>
<th>Role</th>
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<tr>
<td><strong>Alpha</strong></td>
<td></td>
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<tr>
<td>Adhesion Molecules</td>
<td>Fibrinogen</td>
<td>Leukocyte Adhesion</td>
</tr>
<tr>
<td>Chemokines</td>
<td>CXCL-1, 4, 5, 7, 8 CCL-2, 3, 5</td>
<td>WBC Recruitment</td>
</tr>
<tr>
<td>Cytokines</td>
<td>IL-1β</td>
<td>Ag Presentation</td>
</tr>
<tr>
<td>Growth Factors</td>
<td>PDGF, TGG-β</td>
<td>Wound Healing, Immune Modulation</td>
</tr>
<tr>
<td>Microbicidal Proteins</td>
<td>Kinocidins, Defensins Thrombocidins</td>
<td>Antimicrobial Peptides</td>
</tr>
</tbody>
</table>
Platelets

• **Dense GRANULES** contain bioactive factors that increase membrane permeability & modulate inflammation
  - Serotonin
  - Histamine
  - Dopamine
  - Calcium
  - adenosine
History of PRP

• 2006 PRP improved elbow epicondylitis, reduced healing time

• Accelerate tissue repair & reduce postoperative pain in surgical wounds

• Growth factors, chemokines, cytokines → tissue healing in hard & soft tissue

PRP preparation: 10-15 min process

- Venipuncture
- Centrifugation
- Removal of PPP
- Collect PRP
PRP FDA Status

• FDA cleared 510(k) Class II medical device to produce PRP
• PRP for Hair Growth & skin rejuvenation (off-label)

**FDA cleared 510(k) Class II medical device.**
PRP is intended for the safe and rapid preparation of autologous platelet-rich plasma (PRP) from a small sample of blood at the patient point of care. The PRP is mixed with autograft or allograft bone prior to application to a bony defect for improving handling characteristics.
PRP – Who?

• Acute TE, actively shedding after full work up and triggers addressed
• AGA – especially when combined with other treatments
Microneedling
Microneedling

- Percutaneous collagen induction therapy (PCI)
- Superficial controlled puncturing of skin with fine needles
- Microinjuries release growth factors
- Neovascularization & neocollagenesis initiated by migration & growth of fibroblasts

- **Epidermis:** heals by transepidermal migration
- **Dermis:** heals with collagen remodeling
Microneedling: The science

• Needle penetrate skin → localized damage superficial collagen bundles & blood vessels → induction of new collagen & elastin through wound healing cascade & release of platelet growth factors
  • Stage 1: inflammation
  • Stage 2: proliferation
  • Stage 3: remodeling

• Continues for 6 months post treatment
Microneedling MOA

• Release of PDGF & epidermal growth factors increased through platelet activation
• Stimulation & Activation of stem cells in hair bulge area
• Targets multiple pathogenic factors of aga
• Overexpression of hair growth related genes
  • Vascular endothelial growth factor
  • B catenin
  • Wnt3a
  • wnt10b

Transdermal Drug Delivery: Microneedling

- Hair Restoration
  - PRP
  - minoxidil

- Skin Rejuvenation
  - Hyaluronic acid
  - Vitamin C or a Serum

- Melasma/Periorbital Melanosis
  - tranexamic +/- kojic acid
  - “depigmentation serum” rucinol & sophora-alpha
Microneedling: Adverse Events

• **Contact dermatitis** after microneedling when various topical agents applied post treatment (arnica)
  • provide written post procedure care for first 24 hours

• Only products made for **intradermal use** should be applied after skin barrier has been altered
  • Damaged skin barrier → direct cell toxicity

• **Foreign body granulomatous reaction** with systemic symptoms
  • Confirmed with patch testing
  • Treated with topical steroids and doxycycline
Microneedling with PRP

Treatment for alopecia

- Split scalp study (prp vs saline)
- 3 monthly sessions (P-prp)
- Increased mean hair diameter
- Increase hair growth & counts
- Increase root strength
- Less shedding (negative pull test)

Microneedling with minoxidil

- 2 groups: 5% minoxidil vs weekly microneedling + 5% minoxidil
- Baseline hair count at 12 weeks, patient & investigator assessment
- Hair counts: marked $1\text{cm}^2$ targeted fixed area
- Significant increase in mean hair count in microneedling group (91.4) vs minoxidil group (22.2)
Microneedling for AGA

- Regrowth in men who failed oral finasteride + topical minoxidil x 12 months
- 15 monthly microneedling sessions
  - 4 weekly sessions then 11 biweekly sessions
- Increased thickness after 4 weeks
- Average 75% improvement in hair density
- 18 month follow up → sustained improvement

Hair Transplantation

- More ‘permanent’
- In women hair loss more diffuse limiting donor hair

- Procedure: time consuming, uncomfortable, and expensive
- May not give an ultimate cure even after multiple treatments

- Must set realistic goal -> improved density rather than complete reversal

- Will need to continue all other therapies post-transplant
Summary

• You can help many patients regrow hair!

• Always consider androgen excess in hair loss patients
  • And consider other diagnoses/triggers in rapid onset

• Check labs – you may be the only chance for early diagnosis

• Consider co-morbidities and refer as appropriate

• Use a multi-prong approach to therapy for optimal results
Thank You

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