HORMONAL THERAPIES IN DERMATOLOGY

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Consultant*/ Speaker+/ Researcher#
(Updated as of 6-10-16)
Objectives of the Presentation

- Provide an overview of the role of hormonal therapies in the management of common dermatologic disorders
- Review specific therapies used to treat common disorders such as acne vulgaris and alopecia in men and women
  - FINASTERIDE / DUTASTERIDE
  - ORAL CONTRACEPTIVES
  - SPIRONOLACTONE
- Outline the use of each agent regarding dosing, monitoring of clinical response and potential adverse effects, and adjustments in therapy based on individual response
Acknowledgements

Oral 5-alpha Reductase Inhibitors (5ARIs)
Management of Androgenetic Alopecia (AgA)

- Androgenetic alopecia (AgA)\(^1,2\)
  - Affects >75% of males and ~50% of females by end of the 7\(^{th}\) decade
  - Pattern differences based on gender

- Finasteride / Dutasteride \(^2-4\)
  - Oral 5-alpha reductase inhibitors (5ARIs) → Reduce testosterone formation
    - Finasteride inhibits Type 2 5AR receptors
    - Dutasteride inhibits Type 1 and Type 2 5AR receptors (greater potency)
  - Finasteride FDA-approved for treatment of AgA in men
  - Use of 5AR inhibitors increasing in women in selected cases
  - Used to prevent progression of hair loss and promote hair regrowth

Oral 5-alpha Reductase Inhibitors
Emerging Concerns About Adverse Events: Fact or Fiction

- **Does Use of Finasteride Increase Risk of Prostate Cancer?**¹⁻³
  - Finasteride and dutasteride used to treat benign prostatic hypertrophy
  - Association of androgen dependency and prostate cancer ??
  - AAD Task force to address concern with position statement

- **Prostate Cancer Prevention Trial (PCPT)**²⁻⁴
  - 2003: 18,800 subjects ~ Finasteride vs Placebo – followed x 7 years
    - 25% relative risk increase of Prostate Cancer in Placebo arm
    - 27% greater risk of high grade prostate cancer in Finasteride arm
  - 2013: Initial PCPT group at 18 years follow-up
    - Prostate Cancer in 10.5% in Finasteride arm vs 14.9% in Placebo arm
    - High Grade Prostate Cancer in 3.5% Finasteride arm vs 3.0% in Placebo arm

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Oral 5-alpha Reductase Inhibitors (5ARIs)  
Emerging Concerns About Adverse Events: Fact or Fiction

- Does Use of Oral 5ARIs Increase Risk of Prostate Cancer?\(^1,2\)
  - Controversial Topic ~ Some Opposing Data Findings in Literature
  - Reports showing no statistical difference in prostate cancer grade with use of finasteride
  - Dutasteride vs Placebo trail (N=6729 males); potential suggestion of risk?
- Theories On Potential Increase in Higher Prostate Cancer Grade\(^3-7\)
  - Direct Induction Theory
  - Detection Bias Theory

- Summary → (1) No increased incidence (2) Possible increased risk of higher grade (3) No negative impact on overall survival rate

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Oral 5-alpha Reductase Inhibitors
Emerging Concerns About Adverse Events: Fact or Fiction

- Does Finasteride Cause Depression/Psychiatric Side Effects?¹-³
  - Depression not initially listed in approved product labeling with Finasteride for AgA (1 mg daily) or for BPH (5 mg daily)
    - Anecdotal and published reports of depression → subsequently added to product labeling for AgA product (1 mg daily)
  - Collection of studies correlating depressive symptoms with use of finasteride in some patients
    - Potential increase in depressive symptoms in past users of finasteride – possible association with concurrent sexual dysfunction
  - Summary → No definitive direct link with depression / Depressive symptoms may occur in some treated with 5ARIs / More data on reversibility of mood-related changes are needed

Oral 5-alpha Reductase Inhibitors
Emerging Concerns About Adverse Events: Fact or Fiction

Does Use of Oral Finasteride Cause Sexual Side Effects (SSEs)?

- Reported to occur in 0.9% - 38% ~ most common adverse effects\(^1-4\)
  - ERECTILE DYSFUNCTION: Finasteride – 3.4% - 15.8% vs Placebo 1.7% - 6.3%
  - EJACULATORY DISTURBANCE: Finasteride – 0.9% - 5.7% vs Placebo 0.5% - 1.7%
  - LOSS OF LIBIDO: Finasteride – 2.36% - 10.0% vs Placebo 1.2% - 6.3%
  - Incidence of SSEs increased vs placebo and not dose-dependent (1 mg = 5 mg)
  - Rates similar with dutasteride

Spontaneous Improvement/Resolution vs Persistence\(^5-6\)

- PLESS* reported 22% initial rate → Improved over 2-4 months → Baseline
- Averages: Start after 1.8 years + Last 5.4 months after stopping use

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*Proscar Long Term Efficacy and Safety Study
Oral 5-alpha Reductase Inhibitors
Use in Androgenetic Alopecia (AgA) in Women

- Major concern is exposure of male fetus in pregnant women\(^1-5\)
  - Abnormal development of male genitalia
  - Contraindicated in pregnancy ~ consider exclusion pre-treatment
  - Limited data on side effects ~ small studies and case reports
    - Decreased libido, breast tenderness, menstrual changes, and cephalgia reported
    - Some case reports and small series show lack of side effects
    - Long term data very limited
      - 137 women (age range 41-60 yrs) ~ Side Effects → Finasteride 1 mg = Placebo

Combination Oral Contraceptives (COCs) General Overview

- Combination of ethinyl estradiol (EE) and a progestin
  - EE dose range: 10 ug – 50 ug ~ variation is estrogenic potency
    - Marked variability among progestins used in different COCs
  - First and second generation progestins ~ derived from testosterone
    - May interact with progesterone, estrogen, and androgen receptors
    - NORETHINDRONE, NORETHINDRONE ACETATE, LEVONORGESTREL
  - Third generation progestins ~ derived from testosterone
    - Modified to induce LESS androgenic activity
    - NORGESTIMATE, DESOGESTREL, GESTODENE
  - Fourth generation progestins
    - Bind only to progesterone receptor → NO angrogenic effects
    - DROSPERINONE ~ derivative of 17-alpha spironolactone

Combination Oral Contraceptives (COCs) Use for Treatment of Acne Vulgaris (AV)\(^1-4\)

**Modes of action for Acne Vulgaris (AV)**
- Suppress ovarian production of androgens and ovulation
- EE increases hepatic synthesis of SHBG $\rightarrow$ decreases free testosterone
- Inhibition of 5-AR by some progestins

**Efficacy for treatment of AV**
- Most COCs not FDA-approved for AV
- Can be used with or without hyperandrogenism (clinical and/or lab)
- Multiple studies showing efficacy for facial AV $\sim$ allow 3 cycles for onset
- Data showing efficacy for moderate truncal AV $\sim$ 24 week study
- Comparative data limited among COCs for AV

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Combination Oral Contraceptives (COCs) Use for Treatment of Acne Vulgaris (AV)\textsuperscript{1-5}

- **“Bonus” Noncontraceptive Benefits of COCs**
  - Normalize menstrual cycle, reduce anemia
  - Reduce risks of endometrial, ovarian, and colorectal cancer
  - Decrease symptoms of premenstrual dysmorphic disorder

- **When to use COCs for treatment of AV**
  - Consideration in women with AV and no contraindications to COCs
    - Important to review potential risks and contraindications
  - Useful especially in women who also desire contraception

\textsuperscript{1} Harper JC. The Use of Oral Contraceptives for Management of Acne Vulgaris. Dermatol Clin. 2016;34:159-165
Combination Oral Contraceptives (COCs)
Potential Risks and Contraindications

CARDIOVASCULAR RISKS
- Increased risk of Venous Thromboembolism (VTE)
- Affected by dose of EE and progestin use
- Risk may be increased with drospirenone
- Overall 3-9 vs 1-5 events/10,000 woman years in COC users vs non-users/not pregnant
- Increased risk >age 35; phlebitis history; postpartum, immobilization, some GI diseases, others

CANCER RISKS
- Possible slight increase in breast cancer but not if at 10+ years after stopping COC use
- Cervical cancer increase correlated with duration of COC use - 2-fold higher after 5 years of use + no increased risk if at 10+ years after stopping COC use

BONE RISKS
- Risk of inadequate bone mass if EE <30ug especially if started within 3 years of menarche + used >2 years

Spironolactone

Approach to Monitoring of Serum Potassium Levels

  - 974 healthy adult women with acne
  - 1165 young healthy women on or off spironolactone
  - 13 ABNORMAL K+ VALUES / 1802 MEASUREMENTS
    - 6/13 normalized with repeat testing
- The rate of hyperkalemia in healthy young women taking spironolactone (0.72%) for acne is equivalent to the baseline rate of hyperkalemia in this population (0.76%).
- Routine potassium monitoring is unnecessary for healthy women taking spironolactone for acne.

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The rate of hyperkalemia in healthy young women taking spironolactone (0.72%) for acne is equivalent to the baseline rate of hyperkalemia in this population (0.76%).

Routine potassium monitoring MAY BE unnecessary for healthy women taking spironolactone for acne.
Approach to Monitoring of Serum Potassium Levels

POPULATION-BASED DATA
Spironolactone

Approach to Monitoring of Serum Potassium Levels

NOT LIKELY TO MATTER TO THIRD PARTY PAYOR

VERY LIKELY TO MATTER TO THE DOCTOR AND PATIENT