Hirsutism: Diagnosis and Treatment

Roger A. Lobo M.D.
Columbia University
Signs of hyperandrogenism

- Acne, Hirsutism, Alopecia
- All explained by increased androgen production and/or increased sensitivity at the PSU (mainly enhanced 5α-reductase activity)
- Virilization (defeminizing and masculinizing signs eg. Clitoromegalie) – signifies tumor
Sources of androgen secretion in women

• Ovary
• Adrenal
• Peripheral tissues (skin – pilo-sebaceous unit)
BASAL LEVELS
CONTROLS vs HYPERANDROGENIC

units/ml

Controls  Hyper

DHEA  ng
DHEAS  mcg
A  ng
tT 10 ng
uT pg

*p<.05
3α-diol G distinguishes between Hirsute and non Hirsute women with PCOS who have similar androgen levels

Lobo R. J Clin Endocrinol Metab 1983; 57: 393-97
Carmina E, Lobo RA, et al:
Evaluation and treatment of Hirsutism

- Endocrine Society Clinical Practice Guideline (JCEM 93: 1105-20, 2008/2016)
- Guidelines from AEPCOS (Human Reprod Update 2012)
Ferriman-Gallwey hirsutism scoring system

AEPCOS guideline review – Hirsutism grading varies by ethnicity

<table>
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<tr>
<th>Author, year</th>
<th>Year</th>
<th>Country</th>
<th>Race</th>
<th>Ethnicity</th>
<th>Sample size</th>
<th>Suggested mFG cut-off*</th>
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<td>291</td>
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</table>

Escobar Morreale H. Human Reprod Update 2012; 18: 146-170
Prevalence of Hirsutism in different populations

- 2-3% in Asian populations
- 4-5% in African Americans
- 7-30% in Caucasian/Mediterranean groups

Survey of studies in
Escobar Morreale H. Human Reprod Update 2012; 18:146-70
What is Hirsutism – who should be evaluated?

- Clinical exam – Hirsutism versus hypertrichosis
  Central distribution – androgen dependent pattern

- Severity of Hirsutism – the Endocrine Society guideline stratifies evaluation based on severity of Hirsutism – is this valid?

No correlation between severity and an endocrine disturbance; expression of androgenicity varies by ethnicity and genetics
Initial Evaluation for Complaint of Hirsutism

- Local hair growth
  - Trial of dermatologic therapy
    - Course stable or improving without clinical evidence of endocrine disorder
      - Normal variant
    - Hair growth progresses or clinical evidence of endocrine disorder
      - Abnormal hirsutism score
        - Evaluate for clinical evidence of endocrine disorder and work-up accordingly
          - Total testosterone blood level by specialty assay
            - Testosterone normal
            - Testosterone elevated
              - Hyperandrogenemia
                - Androgen excess laboratory work-up
                  - * Major hyperandrogenic endocrine disorders to consider:
                    - Polycystic ovary syndrome
                    - Nonclassic congenital adrenal hyperplasia
                    - Hyperprolactinemia
                    - Cushing’s syndrome
                    - Virilizing neoplasm

- Drug or medication use
  - Discontinue if possible

- Trial of dermatologic or oral contraceptive therapy
  - Course stable or improving
    - Idiopathic hirsutism
  - Hair growth progresses
    - Free testosterone blood level (calculated from total testosterone by specialty assay and SHBG)
      - Free testosterone normal
      - Free testosterone elevated
        - Re-evaluate if hirsutism progresses
What should be measured in the evaluation of hirsutism?

- Endocrine Society: **Testosterone (early am)** – note commentary on imprecision and lack of reliability of clinical assays in US (Task Force in place)

- Option: Different subspecialists may include pregnancy test, ultrasound, PRL, DHEAS, 17OHP; R/O Cushing’s, thyroid, acromegaly if other features are present
What to measure? (continued)

- **“Free” testosterone** – is this necessary? Do we need a test to prove clinical hirsutism is androgen related? Clinical assays are not accurate; FAI (with SHBG) is a good substitute but is dependent on a good Testosterone assay.

- **DHEAS** – does this help? Adrenal tumor?
  - $11\beta$ 0H androstenedione – research?

- **3α androstanediol glucuronide (3α diol G)** – a good peripheral marker but has been misinterpreted – but is it necessary?
Is there a need to measure “free” testosterone in Hirsutism? Excellent correlation between T and AFT in all ranges.
Serum Levels of 11β-A in Normal and Hyperandrogenic Women

Adrenal markers $11\beta$ OH-A and DHEAS do not correlate
Androgen action in Skin

Diagram showing the conversion of testosterone to dihydrotestosterone (DHT) in skin, with further conversion to 3α diol and 3α diol G.
Role of 3α-diol G

- Non glandular/extraslanchnic origin
- Reflection of peripheral action of 5α reductase activity
- An androgen disposal mechanism
- Excellent correlation with clinical state
- Data on clinical use have been misinterpreted, but its measurement is not an absolute requirement
Increased 5α-reductase activity in Hirsutism

Increased 5α reductase activity in Hirsutism

Correlation of skin 5α-reductase activity and serum 3α-diol G
Interpretation of serum 3α diol G is dependent on knowledge of substrate.
Serum markers of 5α reductase activity in the hair and sebaceous components of the PSU
Markers of peripheral androgen action

- Specific 5α-reductase metabolites
- Interpretation is substrate dependent
- Best markers:
  - **Hirsutism** – 3α-androstanediol glucuronide
  - **Acne** – Androsterone glucuronide
  - **Alopecia** – 3α sulfate: 3α glucuronide ratio
Differential diagnosis of Androgen Excess

- R/O Drug exposure; intersex disorders
- Diagnoses based on Compartment

- **Peripheral**  
  "Idiopathic"  
  Hirsutism

- **Ovary**  
  PCOS  
  Hyperthecosis

- **Adrenal**  
  Adult CAH  
  Cushings  
  Tumors

- "Idiopathic" Hyperandrogenism - combined
Prevalence of various etiologies among women presenting with Hirsutism

- PCOS (71%)
- Idiopathic Hyperandrogenism (15%)
- Idiopathic Hirsutism (10%)
- Non classical CAH (3%)
- Tumors (0.3%)
- Miscellaneous (0.7%)

Escobar-Morreale H. AEPCOS consensus 2012
The measurement of 17 OHP should be determined by ethnicity/gene frequency.
ACTH stimulation testing for a functional diagnosis
Various combinations of the 21 OH-B gene mutations are possible giving rise to the spectrum

<table>
<thead>
<tr>
<th>Form of 21-Hydroxylase Deficiency</th>
<th>Clinical Phenotype</th>
<th>Hormonal Phenotype (in Response to ACTH)</th>
<th>Genotype</th>
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<tbody>
<tr>
<td>Classic (CAH)</td>
<td>Prenatal virilization, fully symptomatic</td>
<td>Marked elevation of precursors (serum 17-hydroxyprogesterone and Δ-androstenedione)</td>
<td>21-OH-de&lt;sup&gt;severe&lt;/sup&gt;</td>
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<tr>
<td>Nonclassic (LOHD)</td>
<td>Symptomatic: later development of virilization; milder symptoms</td>
<td>Moderate elevation of precursors</td>
<td>21-OH-de&lt;sup&gt;mild&lt;/sup&gt;</td>
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<tr>
<td>Carrier</td>
<td>Asymptomatic: no virilization or other symptoms</td>
<td>Precursor level greater than normal</td>
<td>21-OH-de&lt;sup&gt;severe&lt;/sup&gt;</td>
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<tr>
<td>Normal</td>
<td>Asymptomatic</td>
<td>Lowest levels—some overlap seen with carriers</td>
<td>21-OHase (normal)</td>
</tr>
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</table>
Treatment of Androgen Excess/Hirsutism in CAH

- Not necessary to use corticosteroids
- Many women evolve into a PCOS-like disorder
- Treatment is similar to that for women with PCOS – usually with an OCP ± an anti-androgen
Suspicion of Androgen secreting tumor

- **History:**
  rapidity of onset and progression

- **Signs:**
  Virilization in addition to hirsutism – defeminizing signs (body contour, decrease in breast size) and masculinization (muscle mass, balding, clitoromegalie)

- **Androgen level**
Androgen secreting tumors: reason for assessing blood levels

- Testosterone – know the lab (2½ times upper normal range); DHEAS > 8µg/ml in premenopausal women
- With confirmation - Imaging: Ultrasound (with/without color) best for ovary; CT, MRI, special scans best for adrenal or ectopic sources
Very small ovarian tumors may only be picked up by increased blood flow.
Screening for an androgen secreting tumor in a postmenopausal woman is different

- Abnormal bleeding is an important sign, even without virilization
- Abnormal androgen levels are lower:
  - Testosterone > 100 ng/dl
  - Androstenedione > 2 ng/ml
  - DHEAS > 4µg/ml

Other diagnostic strategies

- Particularly if the Ovary seems normal and there are signs of virilization, the adrenal needs to be imaged: CT, MRI, Iodo-cholesterol, PET, and PET/CT

- Occasionally selective catheterization is necessary – a dying art
What should be measured from a practical standpoint?

- Testosterone (good clinical assay)
- DHEAS
- 17OHP in high risk populations (>2-3 ng/ml)
- Other caveats: If a specific diagnosis is not necessary, US is not needed; 11βOH-A and 3α-diol G for research only
Treatment of Hirsutism

- Directed at cause – majority of women will have PCOS or an “idiopathic” cause
- Main therapy is androgen suppression – OCP with/without antiandrogens
- Differences between Endocrine Society and AEPCOS Society: Even mild hirsutism deserves workup and suppression (AEPCOS); greater tendency to use OCPs with antiandrogens (AEPCOS)
Endocrine Society Guidelines - Treatment

- Stresses “monotherapy”
- OCPs if significant – or antiandrogens if no concerns of pregnancy
- **Recommend against:**
  - Flutamide
  - Topical antiandrogens
  - Insulin sensitizing drugs
  - Glucocorticoids (even in CAH unless unresponsive to other therapies)
  - GnRH agonists
- Treat for at least 6 months to see change
AEPCOS algorithm for treatment

Escobar Morreale HC. Human Reproduction Update 2012; 18: 146-70
TREATMENT OF HIRSUTISM

LH Suppression

Combination Birth Control Pill

↑ SHBG

↑ Testosterone Binding Capacity

↓ LH

↓ Testosterone Production

↓ Free Testosterone
Guiding principals of therapy for Hirsutism

- Peripheral targeting – data consistent with skin receptor blockade and/or 5α reductase inhibition is most efficacious
- Time-related – anagen cycle
- Objective criteria most useful
Hair growth cycle: The length of hair is determined by the time spent in anagen; treatment takes time because of this hair programming.
# Hirsutism is Largely a "Peripheral" Disorder

<table>
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<tr>
<th>Specific agents</th>
<th>5α R</th>
<th>AR</th>
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<td>Cyproterone acetate</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Spironolactone</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Flutamide</td>
<td></td>
<td>X</td>
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<tr>
<td>Finasteride</td>
<td>X(II)</td>
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Peripheral androgen blockade versus glandular suppression for the treatment of Hirsutism

Spironolactone

- 100 – 200 mg per day
- Some decrease in T, none in DHEAS
- Strong anti-androgen effect – androgen receptor (competitive inhibition) and decrease in 5 α-reductase activity
- Overall response rate of ~ 70%
- Occasional side effects – unpredictable menses common without OCPs
- Rarely hyperkalemia
ANAGEN HAIR SHAFT DIAMETERS

% decrease

S200

S100

FERRIMAN GALLWEY SCORE

Before and After 3 months of Finasteride

* p < 0.001

Equivalence of spironolactone 100mg to Finasteride 5 mg in a RCT

Hirsutism and 5α-reductase

- Two isoenzymes – types 1 and 2
- Studies have been carried out with finasteride – inhibits type 2 (genital form) – used for prostate disorders
- Hirsutism is a combination of type 1 and 2
- Dutasteride inhibits both type 1 and 2 and is used for prostate disorders – no studies in hirsutism
Use of “anti androgens” in OCPs for Hirsutism

- Use of less “androgenic” OCPs is logical but unproven – no efficacy benefit in RCTs
- “Anti androgenic” progestogens are not quite as claimed: Drosperinone 3 mg ~ 10 mg spironolactone; CPA 2 mg ~ 50 mg spironolactone (Muhn P, 1995; Elger W, 2003)
- Endocrine Society Guidelines 2016 discuss increased VTE risk of less androgenic OCPs
Use of “pure” anti-androgens

- Concerns with hepatic toxicity – dose dependent
- ? Safer with Bicalutamide (Casodex)
- Endocrine Society – stronger statement in 2016, that IT SHOULD NOT BE USED
Second line agents – with occasional indications

- Glucocorticoids
- GnRH agonists
- Ketoconazole
Localized therapies

- **Eflornithine (13.9%)** – Vaniqa – inhibition of ornithine decarboxylase, common to all hair follicles; only facial - efficacious and reasonable for mild cases or as adjunct (Wolf JE. Int J Dermatol 2007; 46: 94-8)

- Electrolysis

- Laser – alexandrite and diode lasers seem to be best (Sanchez LA. Hum Reprod Update 2002; 8: 169-81)

- Other depilatories

- Local hormonal therapies – ie canrenone are not recommended (Martin K, 2016)
Hair removal techniques: Endocrine Society guidelines 2016

- 2.2.1 Photoepilation techniques for women with darker hair and electrolysis for blond hair
- 2.2.2 Photoepilation: long wave length/long pulse duration – Nd:YAG or diode laser (some paradoxical effects can occur on face in Mediterranean/Mid-Eastern women)
- 2.2.3 When more rapid effects are wanted: use topical eflornithine cream
- 2.2.4 Pharmacological therapy in women with known hyperandrogenism
General principals of treatment and longer term follow up

- Make the correct diagnosis
- Treatment takes time
- Removing excess hair after adequate suppression
- Objective measures are difficult to come by – photography
- Overall success rates in the range of 70% may be expected
- Tapering for long term treatment is possible
Hair Growth Cycle

- Anagen (Growth)
- Telogen (Quiescent)
- Catagen (Rapid Involution)
Frequency of the various etiologies of Hirsutism based on an analysis of 2601 hirsute women

<table>
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<tr>
<th>Author, year</th>
<th>Sample size (n)</th>
<th>PCOS (n)</th>
<th>Idiopathic hyperandrogenism (n)</th>
<th>Idiopathic hirsutism (n)</th>
<th>NCCAH (n)</th>
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<td>Total no. (%)</td>
<td>2601 (100)</td>
<td>1835 (71)</td>
<td>385 (15)</td>
<td>277 (10)</td>
<td>79 (3)</td>
<td>8 (0.3)</td>
<td>17 (0.7)</td>
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</table>

71% 15% 10% 3% 0.3%

Escobar Morreale H. Human Reprod Update 2012; 18: 146-70