M08: Evaluation and Management of Hirsutism

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Section of Endocrinology, Diabetes, and Metabolism
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Chicago, IL
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<td><strong>Modified Ferriman-Gallwey Score</strong></td>
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<td>Unwanted sexual hair growth of any degree that causes sufficient distress for women to seek additional treatment.</td>
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Evaluation and Treatment of Hirsutism

From: Role of Hormones in Pilosebaceous Unit Development
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Modified Ferriman – Gallwey Hirsutism Scoring System

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Evaluation
Hypertrichosis?
Treated Hirsutism?
Non-classic congenital adrenal hyperplasia (21-hydroxylase)

Polycystic ovary syndrome
Hirsutism, Acne, and Androgenic Alopecia
Ovarian Neoplasm
Hirsutism with Folliculitis Barbae
Androgen Production in Women

- **OVARY**
  - Androstenedione (50%) → Testosterone (25%)
  - DHEAS (30%) → DHEA (20%)

- **ADRENAL**
  - Androstenedione (50%) → Testosterone (25%)
  - DHEAS (30%) → DHEA (100%)
  - DHEA (50%) → Androstenedione (50%)
<table>
<thead>
<tr>
<th>Condition</th>
<th>Hyperandrogenic</th>
<th>Irreg Menses</th>
<th>Clinical</th>
<th>Hormonal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonclassic 21-hydroxylaseCAH</td>
<td>Yes</td>
<td>Not typically</td>
<td>+FHx infertility, hirsutism; Eastern Europe Jewish (Ashkenazi)</td>
<td>High basal or ACTH stimulated 17-OHProg</td>
</tr>
<tr>
<td>Cushing’s Syndrome</td>
<td>Yes</td>
<td>Yes</td>
<td>HTN, striae, easy bruising</td>
<td>Incr. 24hr urinary free cortisol</td>
</tr>
<tr>
<td>↑ Prolactin</td>
<td>No/Mild</td>
<td>Yes</td>
<td>Galactorrhea</td>
<td>Elevated prolactin level</td>
</tr>
<tr>
<td>Primary Hypothyroidism</td>
<td>No/Mild</td>
<td>May be present</td>
<td>Goiter, etc.</td>
<td>Elevated TSH, low T₄/FT₄</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>No/Mild</td>
<td>Often</td>
<td>Acral enlargement, coarse features, prognathism</td>
<td>Increased IGF1</td>
</tr>
<tr>
<td>Primary Ovarian Insufficiency</td>
<td>No</td>
<td>Yes</td>
<td>Other autoimmune disorder, recurrent miscarriage</td>
<td>Increased FSH Low E₂ Low AMH</td>
</tr>
<tr>
<td>Simple Obesity</td>
<td>Often</td>
<td>Variable</td>
<td>Dx of Exclusion</td>
<td>None</td>
</tr>
<tr>
<td>Virilizing Neoplasms</td>
<td>Yes, extreme</td>
<td>Yes</td>
<td>Clitoromegaly, extreme hirsutism, pattern alopecia</td>
<td>Extreme elevation of androgen levels</td>
</tr>
<tr>
<td>Medications</td>
<td>Variable</td>
<td>Variable</td>
<td>History</td>
<td>Variable</td>
</tr>
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</table>
METABOLIC REPRODUCTION SYNDROME (PCOS)

Insulin

Testosterone

SHBG

CHOLESTEROL

PREGNENOLONE

PROGESTERONE

17-OH-PROGESTERONE

ANDROSTENEDIONE

TESTOSTERONE

DEHYDROTESTOSTERONE

ESTRONE

ESTRADIOL

Granulosa Cell

Theca Cell

LH

FSH

GnRH

Normal

progestrone

PCOS
## Metabolic Reproductive Syndrome (PCOS): Diagnostic Criteria

<table>
<thead>
<tr>
<th>NIH consensus criteria (all required)</th>
<th>Rotterdam criteria (two out of three required)</th>
<th>Androgen Excess PCOS Society criteria (all required)</th>
</tr>
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<tbody>
<tr>
<td>Oligo- or anovulation (&lt;6-8 menses/yr)</td>
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<td>Clinical and/or biochemical signs of hyperandrogenism</td>
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<td>Clinical and/or biochemical signs of hyperandrogenism</td>
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<td>Ovarian dysfunction – oligo/anovulation (&lt;6-8 menses/yr) and/or polycystic ovaries on ultrasound</td>
</tr>
<tr>
<td>Exclusion of other disorders: NCCAH, androgen-secreting tumors, etc.</td>
<td>Polycystic ovaries (by ultrasound)</td>
<td>Exclusion of other androgen excess or ovulatory disorders</td>
</tr>
</tbody>
</table>
Initial evaluation of hirsutism

- Isolated, local terminal hair growth
  - Trial of dermatologic therapy
    - Course stable or improving
      - Normal Variant

- Abnormal F-G score or local sexual hair growth with clinical evidence of hyperandrogenic disorder*
  - Total testosterone blood level by specialty assay
    - Hair growth progresses
    - Testosterone normal
    - Testosterone elevated

- Medication use
  - Discontinue if possible
Androgen excess

Laboratory Work-Up

Hirsutism mod-severe ± evidence of other hyper-androgenic disorder

Re-evaluate if hirsutism progresses

Free T elevated

Androgen excess Laboratory Work-Up

Testosterone elevated

Initial evaluation of hirsutism

Testosterone normal

Hirsutism mild & isolated

Dermatologic Rx or OCP

Stable/Improved Progression

Idiopathic Hirsutism

Free T calculated By Total T & SHBG or Equilibrium Dialysis

Free T normal Free T elevated

Re-evaluate if hirsutism progresses

Hirsutism mild & isolated

Idiopathic Hirsutism

Dermatologic Rx or OCP

Stable/Improved Progression

Testosterone normal

Initial evaluation of hirsutism
Treatment
### Pharmacologic Therapy of PCOS (Hirsutism)

<table>
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<tr>
<th>Agent</th>
<th>Mechanism(s)</th>
<th>Examples</th>
<th>Use(s)</th>
</tr>
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</table>
| Combination estrogen-progestin | Increase SHBG; suppress LH and FSH; suppress ovarian androgen production | • Ethinyl Estradiol  
• Mestranol  
• Progestin            |                             |
| Antiandrogens           | Inhibit androgens from binding to the androgen receptor                     | • Cyproterone acetate  
• Spironolactone  
• Flutamide            |                             |
## Pharmacologic Therapy of PCOS (Hirsutism)

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<th>Examples</th>
<th>Use(s)</th>
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<tr>
<td>Biguanides (Metformin)</td>
<td>Reduce hepatic glucose production with 2º lowering of insulin levels; ?Direct effects on ovarian steroidogenesis</td>
<td>•Metformin (Glucophage, Glucophage XR)</td>
<td></td>
</tr>
</tbody>
</table>

- **Hirsutism/Acne**: little evidence to support
- **Oligo/amenorrhea**: modestly effective
- **Ovulation induction**: modestly effective
- **Insulin lowering**: effective
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<th>Mechanism(s)</th>
<th>Examples</th>
<th>Use(s)</th>
</tr>
</thead>
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<tr>
<td>Glucocorticoids</td>
<td>Suppress ACTH and adrenal androgen production</td>
<td>• Prednisone</td>
<td>Hirsutism ± Acne</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dexamethasone</td>
<td></td>
</tr>
<tr>
<td>5α-reductase inhibitors</td>
<td>Inhibition of 5α-reductase</td>
<td>• Finasteride (5α-type2)</td>
<td>Hirsutism ± Acne</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dutasteride (5α-types 1 &amp; 2)</td>
<td>Alopecia</td>
</tr>
<tr>
<td>Ornithine decarboxylase inhibitors</td>
<td>Inhibition of ornithine decarboxylase</td>
<td>• Vaniqa (topical)</td>
<td></td>
</tr>
<tr>
<td>Minoxidil</td>
<td>?antiandrogenic; vaso-dilatory, antiinflammatory</td>
<td>• Minoxidil</td>
<td>Alopecia</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Inhibits steroidogenesis; Decr. DHT in hair follicle</td>
<td>• Ketoconazole</td>
<td>Alopecia</td>
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Conversion of Testosterone to Dihydrotestosterone (DHT) by 5α-reductase

Type 1: predominantly expressed in skin and annexes (sebaceous glands, sweat glands, and hair follicles).

Type 2: expressed in the epididymis, seminal vesicles, prostate, and genital fibroblasts.

Type 3: expressed both in benign and neoplastic prostate tissue, but overexpressed and more broadly distributed in advanced prostate cancer.
<table>
<thead>
<tr>
<th>Highest Androgenic Activity</th>
<th>Moderate Androgenic Activity</th>
<th>Lowest Androgenic Activity</th>
</tr>
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<tbody>
<tr>
<td>Levonorgesterel</td>
<td>Desogestrel</td>
<td>Ethynodiol Diacetate</td>
</tr>
<tr>
<td>Norgesterel</td>
<td>Norethindrone Acetate Acetate</td>
<td>Dienogest</td>
</tr>
<tr>
<td></td>
<td>Norgestimate</td>
<td>Drosperinone</td>
</tr>
</tbody>
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Table 2. Oral Contraceptives and Associated Venous Thromboembolism Risks

<table>
<thead>
<tr>
<th>Progestin Generation</th>
<th>Progestin Relative Androgenicity</th>
<th>Progestin Relative VTE Risk&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Progestin Absolute VTE Risk&lt;sup&gt;b,c&lt;/sup&gt;</th>
<th>Progestin/Dose</th>
<th>EE Dose (mcg)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Medium</td>
<td>2.6</td>
<td>7</td>
<td>Norethindrone 0.5–1.0 mg</td>
<td>20, 35</td>
</tr>
<tr>
<td>2</td>
<td>High</td>
<td>2.4</td>
<td>6</td>
<td>Levonorgestrel 0.15 mg</td>
<td>20, 30</td>
</tr>
<tr>
<td>2–3</td>
<td>Low</td>
<td>2.5</td>
<td>6</td>
<td>Norgestimate 0.25 mg</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>Low</td>
<td>3.6</td>
<td>11</td>
<td>Gestodene 0.075 mg</td>
<td>20, 30</td>
</tr>
<tr>
<td>3</td>
<td>Low</td>
<td>4.3</td>
<td>14</td>
<td>Desogestrel 0.15 mg</td>
<td>20, 30</td>
</tr>
<tr>
<td>4</td>
<td>Antiandrogen</td>
<td>4.1</td>
<td>13</td>
<td>DSP 3 mg</td>
<td>20, 30</td>
</tr>
<tr>
<td>—</td>
<td>Antiandrogen</td>
<td>4.3</td>
<td>14</td>
<td>CPA 2 mg&lt;sup&gt;d&lt;/sup&gt;</td>
<td>35</td>
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<sup>a</sup>Relative risk compared with no OC use.

<sup>b</sup>Vinogradova *et al.* (72); Stegeman *et al.* (56).

<sup>c</sup>Extra cases VTE per 10,000 women treated with OCs per year.

<sup>d</sup>OCs containing CPA are not available in the United States.
Cases
Evaluation and Treatment of Hirsutism: Case 1

• An 18 yr old woman is concerned about increased hair growth on her face and lower abdomen. Menarche at age 11yr. For the first year post-menarche she had approximately 4 menstrual periods. Between 11 and 14yr, cycles remained unpredictable; approximately 6 - 7 menses/yr.

• At age 16 yr, developed acne on her face and upper back. A dermatologist recommended topical Clindamycin, then isotretinoin. She is now 17 yr old.

• Non-smoker. EtOH – social. Her father has T2DM; mother had a DVT with a pulmonary embolism.
Evaluation and Treatment of Hirsutism: Case 1

• Never used any form of contraception, but now sexually active; inquires about oral contraceptives.

• Physical exam: is 5’5” (1.65 m) in height, her weight is 211 lb (95.9 kg); BMI is 35.3 kg/m²; moderate pustular acne on chin and upper back. BP 138/94 mmHg. HR is 104 bpm. She has centripetal obesity; no other signs of Cushing syndrome or lipodystrophy. Acanthosis nigricans on her neck. Her Ferriman-Gallwey score is 7. There is some thinning of her scalp hair but no alopecia.

• A transvaginal ultrasound showed a 2 cm cyst in the right ovary but no clear evidence of multiple follicles. The ovaries were of normal size.
Evaluation and Treatment of Hirsutism: Case 1

1. Does this patient have PCOS?
   a. Yes
   b. No
   c. Not sure, but does it matter?
Evaluation and Treatment of Hirsutism: Case 1

2. Are additional blood tests required before recommending treatment?
   a. Yes
   b. No
   c. Optional
Evaluation and Treatment of Hirsutism: Case 1

3. In addition to lifestyle intervention, what treatment(s) would you recommend for her hirsutism and oligomenorrhea?
   a. An oral contraceptive
   b. Metformin
   c. A progestin (levonorgestrel) containing IUD
   d. Spironolactone alone
   e. An oral contraceptive together with spironolactone
   f. Finasteride
   g. Photoepilation
Evaluation and Treatment of Hirsutism: Case 1

4. How will you monitor response to treatment?
   a. Measure serum testosterone level in 3 months
   b. Measure serum dihydrotestosterone level in 3 months
   c. Measure LH and FSH
   d. Use a patient-provided self-assessment
Evaluation and Treatment of Hirsutism: Case 2

- A 32 year old woman with a hx. of PCOS is referred for management. Menarche was at 10 yr. At age 19 yr, she was diagnosed with PCOS based upon her history of 9 years of oligomenorrhea together with a total serum testosterone that was 2.5X the upper limit of normal in the assay used.

- OCPs were taken intermittently but stopped after “migraine” headaches developed. A progestin releasing IUD was placed. She has persistent headaches, at times with vision disturbances. She is G0P0. She had photoepilation of her facial hairgrowth, but is not satisfied with the result. She describes persistent fatigue and a recent weight gain of 12 lb (5.5 kg) over the last 6 – 8 mo.
Evaluation and Treatment of Hirsutism: Case 2

- Her BMI is 37.3 kg/m^2, BP 162/94 mmHg. Fasting labs: total cholesterol 258 mg/dl, HDL cholesterol 33 mg/dl, triglycerides 194 mg/dl, and LDL cholesterol (calculated) 187 mg/dl; HbA1c is 6.2%. The patient is taking atorvastatin 10 mg/day and amlodipine 10 mg/day. On exam, she has centripetal obesity with a Ferriman-Gallwey score of 16 (nl < 8).
Evaluation and Treatment of Hirsutism: Case 2

1. Which, if any, of the following tests are appropriate at this time?
   a. Polysomnography to exclude obstructive sleep apnea
   b. Factor V Leiden assay
   c. Prolactin level
   d. MRI of the brain
   e. A, B, C, and D
   f. None of the above
Evaluation and Treatment of Hirsutism: Case 2

2. What is your treatment recommendation now?

a. Removal of her IUD
b. Start metformin with the aim of reaching 2000 mg/d

Start an oral contraceptive with close monitoring
d. Start spironolactone 100mg BID
e. Start dutasteride 0.5mg/d
f. A and D only
g. A, B, C, and D
Thank you!

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The University of Chicago
Chicago, IL
Evaluation and Treatment of Hirsutism

Causes of Hirsutism

Gonadal hyperandrogenism
- Ovarian hyperandrogenism
- Polycystic ovary syndrome
- Ovarian steroidogenic blocks
- Syndromes of extreme insulin resistance (e.g., lipodystrophy)
- Ovarian neoplasms
- Hyperthecosis

Adrenal hyperandrogenism
- Premature adrenarche
- Functional adrenal hyperandrogenism
- Congenital adrenal hyperplasia (nonclassic and classic)
- Abnormal cortisol action/metabolism
- Adrenal neoplasms
Evaluation and Treatment of Hirsutism

Causes of Hirsutism

Other endocrine disorders
- Cushing’s syndrome
- Hyperprolactinemia
- Acromegaly

Peripheral androgen overproduction
- Obesity
- Idiopathic

Pregnancy-related hyperandrogenism
- Hyperreactio luteinalis
- Thecoma of pregnancy

Medications
- Androgens
- Oral contraceptives containing androgenic progestins
- Minoxidil
- Phenytoin
- Diazoxide
- Cyclosporine
- Valproic Acid
Evaluation and Treatment of Hirsutism

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