Hirsutism

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Nothing to disclose

Evaluation and Treatment of Hirsutism in Premenopausal Women: An Endocrine Society Clinical Practice Guideline

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Objectives

At the conclusion of this activity, participants will be able to:

- Convey common definitions regarding excess hair growth to patients and other providers
- Choose appropriate tests for patients with hirsutism
- Select / Recommend appropriate treatment options based on various clinical indicators while recognizing limitations and benefits of individual options
Definitions
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirsutism</td>
<td>Hirsutism is excessive terminal hair that appears in a male pattern (excessive hair in androgen-dependent areas; i.e., sexual hair) in women.</td>
</tr>
<tr>
<td>Ferriman–Gallwey score</td>
<td>The modified Ferriman–Gallwey score is the gold standard for evaluating hirsutism. Nine body areas most sensitive to androgen are assigned a score from 0 (no hair) to 4 (frankly virile), and these separate scores are summed to provide a hormonal hirsutism score (Fig. 1).</td>
</tr>
<tr>
<td>Local hair growth</td>
<td>This is unwanted localized hair growth in the absence of an abnormal hirsutism score.</td>
</tr>
<tr>
<td>Patient-important hirsutism</td>
<td>Unwanted sexual hair growth of any degree that causes sufficient distress for women to seek additional treatment.</td>
</tr>
<tr>
<td>Hyperandrogenism</td>
<td>Hyperandrogenism (for the purposes of this guideline) is defined as clinical features that result from increased androgen production and/or action.</td>
</tr>
<tr>
<td>Idiopathic hirsutism</td>
<td>This is hirsutism without hyperandrogenemia or other signs or symptoms indicative of a hyperandrogenic endocrine disorder.</td>
</tr>
</tbody>
</table>
Cercis canadensis
Diagnosis of Hirsutism
Figure 1. Ferriman–Gallwey hirsutism scoring system (4). Each of the nine body areas most sensitive to androgen is assigned a score from 0 (no hair) to 4 (frankly virile). These separate scores are summed to provide a total hormonal hirsutism score. Generalized hirsutism (score ≥8) is abnormal in the general US population, whereas locally excessive hair growth (score <8) is a common normal variant. The normal score is lower in some Asian populations and higher in Mediterranean populations (see text). Reproduced from Hatch et al. (5).
Diagnosis

• If abnormal hirsutism score:
  • Random androgen testing

• If Normal random T + mod/severe or mild sexual hair growth + clinical endocrine abnormality such as menstrual disturbance or worsening w/ treatment
  • Early morning T/Free T

Norms are standardized for early morning, when levels are the highest, and for days 4 to 10 of the menstrual cycle
Diagnosis

• If Elevated T or free T check either
  • early morning, follicular phase 17-OHP

Or

• Random 17-OHP if amenorrhea/rare menses (P4 can verify this was truly in a non-post-ov phase)
Diagnosis - NCCAH

• “High risk of NCCAH” due to 21-hydroxylase deficiency + hirsutism
  • Includes FH + or higher risk population
  • Test 17OHP even if normal T values
  • Prevalence worldwide NCCAH is 4.2%
    • 1% to 2% among US Whites and Hispanics, < AA
    • 3% to 6% in Spain, France, Italy, and Canada
    • 5% to 10% in the Middle East
    • Particularly high risk Ashkenazi Jews 37-fold greater than in the general Caucasian population
Diagnosis - NCCAH

• 17OHP = 170 to 200 ng/dL
  • 95% sensitive and 90% specific for NCCAH

• Definitive diagnosis 17OHP requires >= 1000 to 1500 ng/dL either basally or in response to cosyntropin stimulation testing

• Confirmation by molecular genetic analysis of the CYP21A2 gene if btwn 1000-1500 ng/dL
Diagnosis – Adrenal tumor

• DHEAS is increased in 17% of hirsute women with normal total and free testosterone levels
  • Mildly elevated DHEAS level in the setting of normal free testosterone is unlikely to affect management.

• The magnitude of the androgen level is of poor predictive value for tumors although a very high testosterone (adult male range) or DHEAS level (>700 mg/dL) is suggestive

• Consider in acute onset patients or with virilization

• Androgen secreting tumor ~ 0.2% (adrenal + ovarian) and >½ are malignant
Initial evaluation of complaint of hirsutism

- Local hair growth, isolated
  - Trial of dermatologic therapy
    - Hair growth progresses
      - Hair growth progresses
        - Re-evaluate if hirsutism progresses
      - Testosterone normal
        - Hyperandrogenemia
          - Free testosterone blood level (calculated from total testosterone and SHBG or equilibrium dialysis)
            - Free testosterone normal
              - Trial of dermatologic or oral contraceptive therapy
                - Course stable or improving
                  - Idiopathic hirsutism
            - Free testosterone elevated
              - Hirsutism moderate-severe and/or other clinical evidence of hyperandrogenic endocrine disorder*
                - Hyperandrogenemia
                  - Androgen excess laboratory work-up*
          - Drug or medication use
            - Discontinue if possible
          - Testosterone elevated
            - Hirsutism mild and isolated
              - Trial of dermatologic therapy
                - Course stable or improving
      - Testosterone normal
        - Total testosterone blood level by specialty assay
          - Drug or medication use
            - Discontinue if possible
          - Abnormal hirsutism score or local sexual hair growth with clinical evidence of hyperandrogenic endocrine disorder*
            - Hyperandrogenemia
              - Androgen excess laboratory work-up*
          - Normal variant
            - Total testosterone blood level by specialty assay
              - Drug or medication use
                - Discontinue if possible
          - Abnormal hirsutism score or local sexual hair growth with clinical evidence of hyperandrogenic endocrine disorder*
            - Hyperandrogenemia
              - Androgen excess laboratory work-up*

*Major hyperandrogenic endocrine disorders to consider:
- Polycystic ovary syndrome
- Nonclassic congenital adrenal hyperplasia
- Cushing's syndrome
- Virilizing tumor
- Hyperprolactinemia


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A Diagnostic Don’t

• Do not order androgens:

  • Focal unwanted hair (normal score) + eumenorrheic
Hirsutism Management
Treatment in pre-menopausal women of patient-important hirsutism beyond basic cosmetic mgmt

• Endocrine disorder associated
  • Pharmacologic therapy – 1st
  • Non-pharmacologic options – 2nd

• Non-endocrine disorder related
  • Either pharmacologic or non-pharmacologic

*If obesity is present lifestyle changes are also recommended
Basic Cosmetic Management
Depilation: removal of the hair shaft from the skin surface

- Mechanical
  - Shaving
    - no change in hair growth, hair diameter, or hair color
    - sharply cut hair tip feels coarse (illusion of thicker hair)
  - Plucking, waxing, or mechanical devices
  - All have r/o discomfort, scarring, folliculitis, and hyperpigmentation
- Chemical depilatory agents dissolve the hair
  - Most are thioglycolates: disrupt disulfide bonds
  - Side effects: sulfurous odor and irritant dermatitis, hyperpigmentation

Bleaching:
- hydrogen peroxide and sulfates masking pigmented hair
- Side effects include irritation, pruritus, and possible skin discoloration
Pharmacologic Management
Pharmacologic Treatment

• Not seeking fertility
  • 1st line:
    • OCPs (any combo E/P)
    • Antiandrogens if using LARC, sterilization, not sexually active

• Recommend wait 6 mo to add/change
OCP Treatment: Higher thromboembolic risk patients

- Over age 39, Obese
  - Consider 20mcg ethinyl estradiol OCP and “low risk” progestin*

*19-nortestosterone derivatives

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### Table 2. OCs and Associated VTE Risks

<table>
<thead>
<tr>
<th>Progestin Generation</th>
<th>Progestin Relative Androgenicity</th>
<th>Progestin Relative VTE Risk</th>
<th>Progestin Relative Absolute VTE Risk</th>
<th>Progestin/Dose</th>
<th>EE Dose (mcg)</th>
</tr>
</thead>
<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</td>
<td>35</td>
</tr>
</tbody>
</table>

*Relative risk compared with no OC use.

**Vinogradova et al. (73); Stegeman et al. (57).**

*Extra cases VTE per 10,000 women treated with OCs per year.

**OCs containing CPA are not available in the United States.**
OCP Treatment:
Higher thromboembolic risk patients

>39 : OCs confer 4-fold risk (100 vs 25/100,000 women years)

Obese women : OCs confer 2- to 10-fold higher risk

Benefits outweigh the risks based on obesity alone when using OCs for contraception

*Low risk users - thromboembolic risk > w/ pregnancy
OCP Treatment:
What about the “Special” OCP?

3 mg DSP (the dose used in OCs) ~ 9 to 10 mg spironolactone

2 mg CPA ~ 50mg spironolactone

100 to 200 mg spironolactone is the therapeutic dose

DSP OCP d/t mild mineralocorticoid effect so avoid K+-sparing diuretic
OCP Treatment:
Mechanisms of Action

- Suppression of LH secretion
  - ovarian androgen secretion
- Stimulation of hepatic production SHBG
  - androgen binding in serum
  - serum free androgen concentrations
- Slight reduction in both adrenal androgen secretion and binding of androgens to their receptor
  - testosterone production
- Androgenic progestins also increase the metabolic clearance of testosterone
- Direct inhibition of 5α-reductase activity in the pilosebaceous unit
Antiandrogen Pharmacologic Treatment

- Antiandrogens
  - 1st line: (if using LARC, sterilization, not sexually active)
    - Any except flutamide
      - d/t risk of hepatotoxicity
  - 2nd line if sexually active/potentially become sexually active:
    - after 6 mo monotherapy
    - Combination antiandrogen + OCP
      - Prior failure monotherapy
      - Severe emotional distress
  - Considerations: efficacy, side effects & costs
# Antiandrogen Pharmacologic Treatment

<table>
<thead>
<tr>
<th>Antiandrogens</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>50–100 mg/d on menstrual cycle days 5–15, with EE 20–35 mg on days 5–25</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>100–200 mg/d [given in divided doses (twice daily)]</td>
</tr>
<tr>
<td>Finasteride</td>
<td>2.5–5 mg/d</td>
</tr>
</tbody>
</table>
| Flutamide<sup>b</sup> | 250–500 mg/d (high dose)  
                      | 62.5 to ≤250 mg/d (low dose)                                           |

<sup>a</sup>Not available in the United States; also prescribed as an OC (2 mg CPA + 35 mcg EE).

<sup>b</sup>Flutamide not recommended because of hepatotoxicity.
Antiandrogen Pharmacologic Treatment

Spironolactone is an aldosterone antagonist
- dose-dependent competitive inhibition of androgen receptors
- inhibition of 5α reductase activity
- avoid w/ renal impairment
- May cause menstrual irregularity (off OCPs)
- Rarely results in hyperkalemia
- May cause diuresis, postural hypotension, dizziness early on

D/C all antiandrogens pre-pregnancy d/t the exquisite sensitivity of the fetal genitalia to exposure to maternal synthetic sex hormone ingestion
Antiandrogen Pharmacologic Treatment

CPA inhibits the androgen receptor and somewhat inhibits 5α-reductase activity and suppresses serum gonadotropin and androgen levels.

Finasteride inhibits type 2 (but not type 1) 5α-reductase activity

Flutamide is a “pure” antiandrogen: inhibition of the androgen receptor **advised against now even at lower doses**
Glucocorticoid Pharmacologic Treatment

- Utilized for treatment of NCCAH itself
- Limited efficacy for hirsutism other than this tx can result in remission of the condition after withdrawal of long-term therapy
- OCPs + antiandrogen is more efficacious despite hydrocortisone treated women being the ones with normal androgen levels
- prednisone 4 to 6 mg daily or dexamethasone 0.25 mg/d

prednisone 5 mg daily for ovulation induction then incr to 7.5mg daily prn
Avoid dexamethasone because it is not inactivated by placental 11b-hydroxysteroid dehydrogenase type 2 (i.e., fetal exposure occurs)
Glucocorticoid Pharmacologic Treatment

Risks:
adrenal atrophy
increased blood pressure
weight gain
Cushingoid striae (particularly with dexamethasone)
dehased bone mineral density
“Other” Pharmacologic Treatment

Suggest against using insulin-lowering drugs for the sole indication of treating hirsutism

Suggest against using GnRH agonists except in women with severe forms of hyperandrogenemia (such as ovarian hyperthecosis) who have a suboptimal response to OCs and antiandrogens.

Suggest against the use of topical antiandrogen therapy for hirsutism
Direct Hair Removal
Direct Hair Removal

Photoepilation

• If unwanted hair is auburn, brown, or black
• POC - long-wavelength, long pulse-duration light source such as Nd: YAG or diode laser delivered with appropriate skin cooling
  • Clinicians should warn Mediterranean and Middle Eastern women with facial hirsutism about the increased risk of developing PH (Paradoxical hypertrichosis)
    • consider topical or photoepilation
• eflornithine topical cream → quicker results
  • irreversibly inhibiting ornithine decarboxylase
  • catalyzes the rate-limiting step for follicular polyamine synthesis
Direct Hair Removal

Electrolysis
• white or blonde hair

For women with known hyperandrogenemia who choose hair removal therapy, recommend pharmacologic therapy to minimize hair regrowth.
Thank You

Here’s a link to the guideline:

https://academic.oup.com/jcem/article/103/4/1233/4924418