Unit 4: Reproductive Endocrinology, Infertility & Related Topics

Educational Topic 44: Hirsutism and Virilization

Rationale: Androgen excess causes short and long-term morbidity, and may represent serious underlying disease.

Intended Learning Outcomes:

A student should be able to:

• Recognize normal variations and abnormalities in secondary sexual characteristics
• Define hirsutism and virilization
• Describe pathophysiology and identify etiologies of hirsutism
• Describe the steps in the evaluation and initial management options for hirsutism and virilization
• Describe how hirsutism and virilization are manifested in other medical disorders

TEACHING CASE

CASE: A 25 year-old G0 woman presents with increased hair growth on the face, particularly the upper lip, chin and neck. Her menses started about age 13, occur every 2-4 months and have never been regular. She noted the onset of facial hair around menarche, and it has gradually increased. She has been shaving twice a week and using electrolysis when she can afford it. She wonders about her fertility. She has no allergies and takes no medications. LMP was 2 months ago. Duration is 7-10 days with heavy flow for 3 days. She has been sexually active and is using condoms for contraception. No prior abnormal pap smears or STIs.

Social history is remarkable for occasional alcohol and no recreational drugs or smoking. She is a bus driver. Family history is remarkable for mother with irregular cycles, obesity, diabetes, hypertension and similar facial hair growth, and sister with obesity, irregular cycles, and similar facial hair growth.

On physical exam, her weight is 204 pounds, height is 5 feet, 3 inches, BP 120/80. She is noted to have terminal hair on the upper outer 1/3 of her lip, few sparse hairs in the sideburn area and chin, midline terminal hairs on the chest and in the periareolar area, and obese abdomen without striae. Terminal hair is noted in a vertical band below the umbilicus. Normal external genitalia are present. Uterus is anteflexed, antverted, midline and normal size. Adnexae are without palpable masses.
COMPETENCY-BASED DISCUSSION & KEY TEACHING POINTS:
Competencies addressed:
- Patient Care
- Medical Knowledge
- Systems-based Practice

1. What is the differential diagnosis for the patient’s hirsutism based on the history and physical examination alone, and what is the most likely diagnosis?
   - PCOS is the most likely diagnosis.
   - Other possible diagnoses include: hypothyroidism, late-onset congenital adrenal hyperplasia and Cushing’s syndrome.
   - Other less common diagnostic considerations include an ovarian or adrenal androgen-producing tumor.

2. What additional evaluation would you recommend?
   - Urine hCG: negative
   - Total Testosterone: 84 μg/dL (Normal range: 20-80)
   - DHEA-S: 247 μg/dL (Normal range: 62-615 μg/dL)
   - Prolactin: 15 ng/dL (Normal range <20)
   - TSH: 2.6 uIU/mL (Normal range: 0.4-4.0)
   - 17-hydroxyprogesterone: 120 ng/dL (Normal range <200)
     - This rules out congenital adrenal hyperplasia
   - Fasting glucose: 86 (Normal: 60-110). Some professional organizations recommend a formal 2-hour 75g GTT as a more sensitive means to diagnose impaired glucose tolerance (IGT) and DM
   - If Cushing’s syndrome were seriously considered, a dexamethasone suppression test or a 24-hour urine free cortisol test would be appropriate.
   - Lipid profile

3. For what short and long term health concerns is this patient at high risk?
   - Infertility
   - High cholesterol
   - Diabetes
   - Endometrial hyperplasia
   - Endometrial cancer
     - An endometrial biopsy may be warranted in these patients despite age <35-years. It is recommended when patients have prolonged periods of unopposed estrogen stimulation secondary to chronic anovulation.
     - Endometrial biopsy with Pipelle: Hyperplasia without atypia
     - Ultrasound of adnexae shows multiple small follicles bilaterally (>12 antral follicles on each ovary) and thickened endometrial stripe measuring 16mm.

4. What would you recommend to minimize these risks?
   - Weight loss
   - Induced withdrawal bleeding with either cyclic progestins or treat with combination hormonal contraceptives, levonorgestrel IUD, or oral/injectable progesterone
• Increasing the sex hormone binding globulin (thus decreasing free testosterone), reducing androgen production, blocking androgen receptors, or interfering with the 5-alpha reductase enzyme will improve hirsutism.
• Medical treatment with combined hormonal contraceptives or antiandrogens (spironolactone) are effective at slowing down hair growth. These treatments will not remove terminal hair already present.
• Cosmetic treatments for existing hair include depilatories, bleaching agents, shaving/plucking, waxing, electrolysis and laser once testosterone levels are normalized.

5. Outline a management plan for helping the patient achieve pregnancy.

• Weight loss (start with 5% of weight).
• 85% of women will ovulate on clomiphene citrate. Letrozole is not FDA approved but is also an excellent ovulation induction agent.
• Metformin or other insulin-sensitizing agents may also enhance her response to clomiphene citrate. However, metformin is not considered first line treatment, and as monotherapy is less effective than clomiphene citrate.
• If neither treatment is effective, she may need gonadotropin therapy and/or IVF.

6. What is virilization and how would the management change if virilization was present?

• Virilization findings include deepening of the voice, increased muscle mass and clitoromegaly along with hirsutism.
• The presence of virilization suggests exposure to higher levels of androgens than that typically seen with hirsutism (e.g. an androgen secreting tumor). Virilization is not usually seen in PCOS or Cushing Syndrome.
• If this patient had rapidly progressing hirsutism and virilization, an androgen-producing tumor would need to be ruled out. Total testosterone levels greater than 200 μg/dL and/or DHEA-S greater than 700-μg/dL would be suggestive of a tumor and would require imaging of the ovaries (ultrasound) and adrenal glands (CT scan recommended). In both cases these “cut-off” values are not particularly sensitive or specific for androgen secreting tumors.

REFERENCES


Polycystic ovary syndrome. ACOG Practice Bulletin No. 108.