PCOS and Female Hyperandrogenism:
Treatment goals and options

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No disclosures

Learning Objectives

- Recognize evidence of androgen excess in pre- and postmenopausal women
- Define the appropriate lab and radiologic evaluation of female hyperandrogenism
- Discuss the differential diagnosis and treatment options

Hyperandrogenic Anovulation in Premenopausal Woman

- Polycystic Ovarian Syndrome or hyperthecosis
- Congenital adrenal hyperplasia
- Ovarian or adrenal tumor
- Obesity-induced Hyperandrogenic Anovulation
- Other: exogenous androgen administration, Cushing's syndrome, prolactinoma
Hyperandrogenism in Postmenopausal Woman

- Polycystic Ovarian Syndrome or hyperthecosis
- Obesity-induced Hyperandrogenism
- Iatrogenic: exogenous androgen administration or exposure, other drugs
- Congenital adrenal hyperplasia
- Ovarian or adrenal tumor
- Other: Cushing's syndrome, prolactinoma

History

- Onset and pace of hirsutism
- Prior Menstrual history
- Stress, weight history ie timing wt gain
- Medications
- Family history of endocrine disorders
- Acne, balding, headaches, breast discharge

Physical Exam

- Visual field testing
- Evidence and pattern of acne and hirsutism, male pattern balding
- Evidence of acanthosis nigricans
- Thyroid exam
- Galactorrhea
- Pelvic exam for anatomy, clitoromegaly
Ferriman-Galloway Score for Hirsutism

Lab Evaluation in Female Hyperandrogenism
- Testosterone (total +/- freeT)
- Dehydroepiandosterone sulfate (DHEAS)
- Prolactin
- 17OHProgestrone 30min after Cosyntropin (250ug) stimulation
- Urinary free cortisol and creatinine or 1mg DEX suppression test if suspect adrenal source

Radiologic Evaluation
- Pelvic Ultrasound
- CT/MRI of adrenals
- MRI of Pituitary
Case 1: Too Much

- 40 yr old woman referred for virilization
- Menarche age 12, regular menses until age 48, weight gain over 30 months, 2-3 menses then amenorrhea
- She denies exogenous drugs
- Exam: BP: 160/90, BMI-32, anabolic appearing, low voice, full beard, breast atrophy, male hair pattern, clitoromegaly

Differential diagnosis of Female Hyperandrogenism
Case 1: Too Much

- Labs: LH-1.5, FSH- 2.2 mIU/ml, T-450 ng/dl (nl<40), DHEAS 240ng/ml (nl to 260), E 45 pg/ml, PRL 6, Hct 52, creatinine 1.4
- What is the cause of her virilization?
- What other diagnostic tests should be performed?

Hyperandrogenic Anovulation: Tumors

- Rapid onset of symptoms and signs in a woman with previously normal menses
- Location of hirsutism: upper back and chest and abdomen
- Virilization: temporal recession, anabolic phenotype, loss of breast tissue, clitoromegaly
- Procedure: Vaginal US, ? CT adrenals
Origins of Ovarian Tumors

- Hyperandrogenism: Tumors
  - **Ovarian** (T>200ng/dl), 10% of ovarian tumors
    - Sertoli-Leydig cell
    - Hilar cell tumor
    - Lipoid cell tumor
  - **Adrenal** (DHEAS>8-900ng/ml)
    - Adrenocortical adenoma or carcinoma
    - Virilizing T secreting tumor (rare)

**Treatment:** Surgery, GnRH agonists?

Case 2:

- 38 yr old female presented for a second opinion concerning progressive hirsutism, worsening over the last year
- Menarche age 10 and irregular menses, mild hirsutism and acne; on OCPs for contraception in college
- Pregnancies at 28, 32 with weight gain from 135 to 165 to 180
- Age 33-38 gradual wt gain to 205 with new sx of facial hair, acne
Case 2:

- Exam: Grade 2 acne, central obesity, thinning of hair, hair upper lip and chin, no clitoromegaly
- Labs: LH 8 and FSH 5 mIU/ml, T 85 ng/dl (<20), DHEAS 380 (<350), E2 45 pg/ml
- Ultrasound: cystic ovaries
- What is her dx and how would you treat?

IS THIS a case of:
- PCOS?
- Obesity induced hyperandrogenic anovulation?
- What do these look like during the perimenopausal transition?

PCOS: Definition

- Hyperandrogenism: clinical or biochemical**
- Chronic anovulation: oligo- or amenorrhea
- ** after exclusion of CAH, Cushing’s, hyperprolactinemia, androgen-secreting tumors
- Rotterdam conference: add criteria of ovarian cysts by ultrasound

NIH Consensus Conf. 1990, Rotterdam Conf. 2004
Acanthosis Nigricans

Polycystic Ovary

Disordered LH secretory profile in PCOS adolescents
PCOS: no pregnancy desired

- Insulin sensitizers (metformin)
  - 50% responders with regular menses by 6 mo
  - Overall 2/6 rather than 1/6 ovulations
  - No info yet on how to pick responders: Family hx of Type 2 DM, BMI, androgen levels, pace of weight gain?
  - If unmonitored what is risk of endometrial hyperplasia?
  - Modest effect on hirsutism

- WE NEED data on combination therapy: OCP with antiandrogen and insulin sensitizer

PCOS: Treatment Options

- Pregnancy desired
  - GnRH agonist and HMG or FSH
  - Progesterone and HMG or FSH
  - Clomiphene citrate alone or with an Insulin sensitizer: clomiphene>>> metformin
  - Stop spironolactone 3 mo before attempting conception (antiandrogen effects on fetus)
Steroidogenesis in the Postmenopausal Ovary
Havelock JC et al Hum Reprod 2006

Androgens and Age in Normal Women
Davison SL et al JCEM 2005

Testosterone Levels in PCOS
Winters S et al Fertil Steril 2000

No extensive data in PMP women with PCOS
Hyperthecosis

- Nests of luteinized stromal cells in the ovarian stroma
- Differentiation of ovarian interstitial cells into steroidogenically active luteinized stromal cells
- Scattered throughout the stroma of the ovary, rather than being confined to areas around cystic follicles as in PCOS
- Ovarian stromal cells produce androstenedione; peripheral estrogen production is increased, can predispose to endometrial carcinoma
- Can occur in postmenopausal women
- Severe hirsutism and virilization in postmenopausal women are more often due to ovarian hyperthecosis than virilizing ovarian tumors
- Often associated with insulin resistance and hyperinsulinemia

Obesity Induced Hyperandrogenism

- History of normal menarche, regular menses
- Progressive weight gain without problems then surpass “threshold weight” with onset of irregular menses, hirsuitism and acne
- Cysts on ovaries due to anovulation
- Successful weight loss reverses phenotype
- Caveat: PCOS patient’s lose gonadotropin abnormality with increasing BMI

Complications of Postmenopausal Hyperandrogenism

- Worsened Hypertension
- Worsened hyperlipidemia: inc LDL, decreased HDL, +/- effects on TG
- Worsened insulin resistance, metabolic syndrome
- ?impact on risk of diabetes
- ? Dose dependent effects of hyperandrogenism
PCOS/hyperthecosis: Treatment Options

- **Treat hirsutism**: spironolactone: 50-100mg /d (antiandrogen), local control: electrolysis
- **Treat metabolic issues**: diet lifestyle
  - Insulin sensitizer: ? Role in halting progressive weight gain, improving androgen levels and insulin resistance?
- **Hyperthecosis**: surgery, GnRH agonist
- *No outcome data in PMP women with PCOS or obesity induced hyperandrogenism*

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Case 3:

- 64 yr old WF presents with severe hirsuitism
- Hx of infertility and irregular menses in 30's
- Early menopause after treatment for breast cancer '94 ER+, chemo,xrt, SERMx5 yrs, recurrent '99 now on letrozole an aromatase inhibitor (block E production)

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Severe hirsuitism: temporal recession
Case 3:

**Labs:**
- E: 88 pg/ml (<20)
- T: 120 ng/dl (<20)
- DHEAS: 120 ng/ml (<240)
- **WHY?**

Case 3:

- Pelvic US: normal
- CT: bilateral adrenal hyperplasia and 1.5 cm nodule
- 1 mg DEX suppression: cortisol suppressed < 1
- Adrenal nodule: myolipoma by MRI
- **17-OHP**: 369 ng/dl: preMP (40-120 ng/dl EFP, up to 400 luteal), but PostMP: 10-60 ng/dl
- **Diagnosis**: untreated CAH in menopause on aromatase inhibitor

Drugs that cause Hirsutism

- Androgens alone or with estrogens
- Anabolic steroids
- Some OCPs with androgenic progestins
- Minoxidil
- Dilantin
- Diazoxide
- Cyclosporin
- **Aromatase inhibitors in the face of inc. prohormones**: ie CAH, PCOS?
**Congenital Adrenal Hyperplasia in PMP**

- Hx of early pubarche
- Family hx and ethnic predisposition
- Stimulated 17OHP 30min after Cosytropin greater than 1000ng/dL (preMP) but PMP have different criteria
- Treatment: historically steroids, now OCPs and antiandrogens premenopausal: No guidelines postMP
- Aromatase inhibitor: block production of all estrogens results in increase in prohormones and androgens
- Normally androgens not an issue in PMP unless preexisting CAH or PCOS/hyperthecosis
- RX: very low dose glucocorticoids: DEX 1.25mg biweekly: T:50ng/dl, 17OHP 50ng/ml, E<18pg/ml; symptoms resolving

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**Pre- and Post-menopausal Androgen Excess**

- Polycystic Ovarian Syndrome or hyperthecosis
- Obesity induced Hyperandrogenism
- Ovarian or adrenal tumor
- Congenital adrenal hyperplasia
- Other: DRUGS, exogenous androgens, prolactinoma, Cushing's syndrome