

Reproductive Endocrinology

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Case 1

- A 24-year-old lady presents with increased hair and irregular menses
- **How would you approach?**

Case 1: history

- Increased hair and irregular menses for 6 years
- Increased hair mainly over the face (chin)
- Increased hair the same over last few years
- None on other areas (chest, arms, abdomen)
- Menses occur once every 3-4 months (always)
- Menarche at age 13
- Past history
- Medications
- Family history

Polycystic ovary syndrome (PCOS)

- One of the commonest causes of hirsutism and infertility

1) Diagnosis in adults:

- **Rotterdam criteria: (2 out of 3)**

- 1) Menstrual abnormality

- 2) Signs of hyperandrogenism (clinical or biochemical)

- 3) Ultrasound criteria

** Exclusion of other disorders that can result in menstrual irregularity and hyperandrogenism

Diagnosis of PCOS

- Menstrual abnormality:

- Oligomenorrhea: less than 9 periods in a year
- Amenorrhea: no periods for ≥ 3 consecutive months
- Anovulation: can occur with a normal period

(regular menses does not rule out PCOS)

- Hyperandrogenism:

- Clinically: hirsutism, acne, male-pattern hair loss
- Or biochemically: mildly high testosterone

Diagnosis of PCOS

- Ovarian ultrasound

- Transvaginal better than abdominal
- Not needed if oligomenorrhea + hyperandrogenism
- Obtain if normal menses + hirsutism
- Presence of ≥ 12 follicles in either ovary measuring 2 to 9 mm in diameter and/or increased ovarian volume (>10 mL) without a cyst or dominant follicle
(it does not depend on presence of cysts)

PCOS associations

- Obesity or overweight
- Metabolic syndrome
- Insulin resistance:
 - Prediabetes & type 2 diabetes
- Dyslipidemia
- Non-alcoholic fatty liver disease
- Sleep apnea
- Endometrial hyperplasia (& possibly cancer)
- Depression, anxiety

PCOS:

rule out other causes

- Thyroid disease (hypo- & hyperthyroidism)
- Hyperprolactinemia
- Nonclassic congenital adrenal hyperplasia [rare]
- Androgen-secreting tumors (adrenal or ovary)

Lab. evaluation

- In most patients, history & exam are clear
- Some will check:
 - Total Testosterone
 - TSH
 - Prolactin

Lab. evaluation

- **If history is short or not clear:**
 - 1) FSH (to rule out primary ovarian insufficiency)
 - **LH is not helpful** (LH:FSH ratio is not sensitive)
 - 2) 17-hydroxy progesterone (to rule out NCCAH)
 - At 8 AM
 - In follicular phase (at any time if no menses)
 - 3) Some do serum progesterone (to assess ovulation):
 - Day 21 if normal menses
 - If irregular, 7- 10 days before the next expected menses

Ordering tests

- Some medications can affect testosterone level:
 - Oral contraceptives
 - Metformin
 - Spironolactone
 - Stop medications for 4 weeks then do test

When to suspect androgen-secreting tumor?

- Severe hirsutism (virilization)
 - Frontal balding, severe acne, clitoromegaly, increased muscle mass, or deepening of the voice
- Rapidly progressive hirsutism
- Very high serum testosterone [>150 ng (5.2 nmol)]
- Order DHEAS (will be high)
- The tumor could be in the ovary or adrenal
- Pelvic ultrasound
 - If normal, do CT adrenals

Other tests for PCOS

- **Weight, BMI**
- **Blood pressure**
- **Glucose:**
 - Oral glucose tolerance test (OGTT) using 75 grams
 - If OGTT is not possible, do fasting glucose and A1c
 - If normal, monitor every 2 years
- **Lipids**

Treatment of PCOS

Is pregnancy desired?

YES

- Weight loss
- Clomiphene
- Letrozole
- Metformin
- Gonadotropins

NO

- Weight loss
- Combined OCP
- Antiandrogens
- Metformin
- Hair removal methods

Case 2

- A 37-year-old woman presents with fatigue, weight loss, decreased appetite, low mood for 2 years
- Irregular menses (once every 3-4 months) for 3 years
- Pregnancy attempts were not successful
- She has 2 children (youngest age 3)
- Hb 10.2, Cr normal, sodium 133, K 4.4
- **How would you approach?**

Causes of hypopituitarism

1) Sheehan' syndrome:

- Pituitary infarction due to postpartum hemorrhage
- May happen even with no hemorrhage

2) Tumors (pituitary or hypothalamus)

3) Surgery for pituitary tumors

4) Radiation therapy for brain/head tumors

5) Traumatic brain injury

6) Infections (meningitis, HIV)

Features of hypopituitarism

- Depends on affected hormone
- Pituitary hormones:
 - FSH, LH (gonadal function)
 - ACTH (adrenal function)
 - TSH (thyroid function)
 - Prolactin
 - Growth hormone
- Most affected initially:
 - Gonadal & GH
 - Then ACTH, TSH
 - But, not always

Features of hypopituitarism

- ↓ FSH, LH: hypogonadism
 - Irregular menses, amenorrhea, infertility, hot flashes, ↓ energy, ↓ libido
- ↓ ACTH: adrenal insufficiency
- ↓ TSH: hypothyroidism
- ↓ Prolactin:
 - Failure to lactate after delivery
- Growth hormone:
 - ↓ energy

Diagnosis of hypopituitarism

1) LH, FSH:

- If normal menses, no tests needed
- If symptoms, check LH, FSH, testosterone in men

2) ACTH:

- Low-normal ACTH
- AM cortisol. May need ACTH stimulation test

3) TSH:

- Check TSH & Free T4
- TSH may be low or normal but low Free T4

4) Prolactin: not useful

5) GH:

- Low IGF-1

Treatment of hypopituitarism

1) LH, FSH:

A) Women:

- If no pregnancy desired: estrogen/progestin
- If pregnancy desired: gonadotropins

B) Men:

- If no fertility desired: testosterone
- If fertility desired: gonadotropins

Treatment of hypopituitarism

2) ACTH:

- Glucocorticoids (see adrenal disorders talk)

3) TSH:

- Thyroxine
- Follow Free T4
- Keep Free T4 in upper half of normal

4) GH:

- Not generally treated

Case 3

- A 42-year-old man presents with:
 - Decreased sexual desire
 - Weak erections
- **How would you approach?**

Case 3: information

- Decreased sexual desire, weak erections for 6 months
- Also has fatigue
- No past medical history
- No medications
- Married with 2 children (youngest age 3)
- BMI 31.2. normal hair distribution
- No testicular masses. Size of testes are normal
- **Labs?**
- Hb 11.2, kidney and liver function, glucose normal
- Total testosterone 150 ng/dL (normal 300-1000)
- **How would you approach?**

Examination of the testes

- Are both descended?
- Size
- Masses
- Tenderness



Evaluation for male hypogonadism

- Check fasting total testosterone (8-10 in the morning)
- Free testosterone if suspecting abnormal SHBG (obesity, aging)
- If low testosterone, confirm by repeating
- If still low, check FSH, LH
- Primary (testicular): \uparrow FSH/LH
- Secondary (pituitary/hypothalamic): NL or \downarrow FSH/LH

Manifestations of male hypogonadism

- Low libido (sexual drive)
- Erectile dysfunction (weak erections)
- Low energy
- Loss of body hair
- Decreased muscle strength and mass
- Hot flushes
- Gynecomastia
- Infertility
- Low bone density

Causes of primary male hypogonadism

- Chromosomal abnormalities (Klinefelter syndrome)
- Cryptorchidism (undescended testes)
- Infections (mumps)
- Trauma
- Testicular torsion
- Autoimmune
- Chronic systemic disease (cirrhosis, CKD, AIDS)
- Idiopathic

Causes of secondary male hypogonadism

- Congenital
- Pituitary disorders (tumor, granuloma, infections, trauma)
- Hyperprolactinemia
- Opiates
- Glucocorticoids
- DM
- Chronic illness

Evaluation of male hypogonadism

- **Primary hypogonadism:**
 - Order karyotype
- **Secondary hypogonadism:**
 - Prolactin
 - Free T4, TSH
 - Iron, transferrin
 - AM cortisol
 - MRI pituitary & hypothalamus

Treatment of male hypogonadism

- If the patient desires **fertility**:
 - DO NOT give testosterone
 - Testosterone will suppress LH/FSH and impair spermatogenesis
 - Gonadotropin (hCG) therapy
 - Refer to a specialist

Testosterone for male hypogonadism

- If the patient **does not** desire fertility
- IM commonly used
 - Testosterone enanthate or cypionate 100 mg every week or 200 mg every 2 weeks (some do 300 mg q 3 weeks)
 - Testosterone undecanoate every 3 months
- Other forms (gel, transdermal, nasal)
- Do not use if prostate cancer, prostate nodule, ↑ PSA, ↑ hematocrit, severe obstructive sleep apnea, severe lower urinary tract symptoms, uncontrolled heart failure, myocardial infarction or stroke within 6 months, or thrombophilia

Monitoring testosterone therapy

- For patients on IM testosterone:
 - If on testosterone enanthate or cypionate:
 - Obtain serum testosterone mid-way between injections
 - Target for mid-normal [500 to 600 ng (17.3 to 20.8 nmol)]
- For patients on transdermal testosterone:
 - Serum testosterone can be measured at any time
- For patients on testosterone gel:
 - Serum testosterone levels vary
 - Obtain 2 levels at any time

For talks & educational materials:

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