Amenorrhea, Hirsutism

N. Shirazian MD
Internist, Endocrinologist
Amenorrhea

- **primary** (absence of menarche by age 15 years) irrespective of the presence or absence of secondary sexual characteristics

- **secondary** (absence of menses for more than 3 cycles or 6 months in women who previously had periodic menses).
However, women who do not fulfill these criteria should be evaluated if

- (1) the patient and/or her family are greatly concerned,
- (2) no breast development has occurred by age 13,
- (3) any sexual ambiguity or virilization is present.
Type of amenorrhea

- Primary: gonadal dysgenesis
- Secondary: pco
classification based on the underlying physiologic derangements:

1. anatomic defects,
2. ovarian failure,
3. chronic anovulation with or without estrogen present.
1. ANATOMIC DEFECTS

- Congenital defects of the vagina,
- imperforate hymen,
- transverse vaginal septae
- müllerian agenesis (the Mayer-Rokitansky-Küster-Hauser syndrome),
- Asherman's syndrome
2. OVARIAN FAILURE

- gonadal dysgenesis (TURNER SYN)
- pure gonadal dysgenesis 46XY
- chemotherapy or radiation therapy
- chemotherapy or radiation therapy
- POF (seases of menstruation before 40)
3. Chronic Anovulation

- CHRONIC ANOVULATION WITH ESTROGEN PRESENT
- CHRONIC ANOVULATION WITH ESTROGEN ABSENT
primary amenorrhea

- whether müllerian structures are present or absent (by physical examination or ultrasonography)

- **Uterus absent**; karyotype

  measurement of serum testosterone

  - abnormal müllerian development (46,XX karyotype with normal female serum testosterone concentrations)
  - androgen insensitivity syndrome (46,XY karyotype & normal male serum testosterone concentrations).
  - 5-alpha-reductase deficiency 46,XY karyotype & normal male serum testosterone concentrations but, in contrast to the androgen insensitivity syndrome, which is associated with a female phenotype, these patients undergo striking virilization at the time of puberty (normal development of secondary sexual hair, muscle mass, & deepening of the voice).
primary amenorrhea, Uterus present —

- beta HCG to exclude pregnancy
- FSH,
- high serum FSH is indicative of primary ovarian failure.
- low or normal serum FSH concentration suggests disorders of hypothalamic-pituitary axis.
- If there are signs or symptoms of hyperandrogenism, serum testosterone & dehydroepiandrosterone sulfate (DHEA-S)
- Among women who are also hypertensive, blood tests should be drawn for evaluation for CYP17 deficiency. The characteristic findings are elevations in serum progesterone (>3 ng/mL [9.5 nmol/L]) & deoxycorticosterone & low values for serum 17-alpha-hydroxyprogesterone (<0.2 ng/mL [0.6 nmol/L]).
Secondary Amenorrhea

- **I**: FSH elevated
  - primary ovarian failure
- **II**: FSH Not elevated
secondary amenorrhea

- serum hCG to rule out pregnancy,

- serum prolactin, FSH, & TSH

- If there is clinical evidence of hyperandrogenism, serum total testosterone should be measured.

- In patients with evidence for hyperandrogenism, some clinicians also measure 17-hydroxyprogesterone (R/O nonclassic 21-hydroxylase deficiency), & dehydroepiandrosterone sulfate (DHEA-S) (R/O an adrenal source of androgens.)
secondary amenorrhea

- Assessment of estrogen status — help with interpreting the FSH values,

Estrogen status can be assessed with:
1. a progestin withdrawal test,
2. measurement of endometrial thickness on ultrasound,
3. serum estradiol.

- There are no data to suggest the best approach.
Continue: **How to check for the Estrogen status?**

- Serum Estradiol level..... Variable
- Progesterone challenge test
- Endometrial thickness....
- Transvaginal US scan < 5mm hypo.  >6 mm Normal
secondary amenorrhea

- High FSH — premature ovarian failure (primary ovarian insufficiency).

- Normal or low FSH — indicates secondary hypogonadotrophic hypogonadism.

- MRI of the sella region is indicated in all women without a clear explanation for hypogonadotrophic hypogonadism.

- Other specific tests; high serum transferrin saturation may indicate hemochromatosis, high serum angiotensin-converting enzyme values sarcoidosis, and high fasting blood glucose or hemoglobin A1c values diabetes mellitus.
Premature ovarian failure:

- **Causes:**
  - Chromosomal abnormalities. Amenorrhoea < 35 years of age
  - 47 XXY ..... High risk of malignancy... gonadectomy
  - Turner’s syndrome mosaic (XX/XO)
  - Resistant ovarian syndrome. May be due to auto antibodies against ovaries or gonadotropin receptors. Could be part of disease involving thyroid, adrenal and acid receptors in stomach

If present in younger age <35 years check auto antibodies

- **Premature menopause.** < 45 mainly familial

- High FSH & LH, Low Estradiol, chromosomal analysis / ovarian biopsy
secondary amenorrhea

- Normal labs and history of uterine instrumentation — Evaluation for Asherman's syndrome (intrauterine adhesions)

- High serum androgen concentrations — Depending upon the clinical picture, a high serum androgen value may be consistent with the diagnosis of PCOS or may raise the question of an androgen-secreting tumor of the ovary or adrenal gland. Tumors are typically associated with the rapid onset of virilizing symptoms and, in some cases, with glucocorticoid excess.

- Most clinicians initiate evaluation for a tumor if the serum concentration of testosterone is greater than 150 - 200 ng/mL (5.2 to 6.9 nmol/L) or that of DHEA-S is greater than 700 mcg/dL (13.6 µmol/L).
FIGURE 326-6 Flow diagram for the evaluation of women with amenorrhea. The most common diagnosis for each category is shown in parentheses. The dotted lines indicate that in some instances a correct diagnosis can be reached on the basis of history and physical examination alone. PCOS, polycystic ovarian syndrome.
Hypothalamic-pituitary dysfunction:

- Eating disorders e.g., Anorexia nervosa, extensive dieting or exercise. A loss of >10 kg … a’hoea… estrogen lllow …osteoporosis
- Hypothalamic lesions
- Nonsecreting pituitary adenomas
- Other CNS system neoplasms

Sheehan’s syndrome

Combined care with endocrinologist, psychotherapist,… Etc is usually needed
Diagnosis & D.D:

- The diagnosis is usually based on a combination of clinical, USS and biochemical criteria.
THE CLINICAL PROBLEM

- Physicians' impressions about hirsutism range from considering it simply a cosmetic problem to assuming it is the fact that evidence of excess androgen. The truth lies somewhere in between.
Introduction

- Hirsutism is the development of androgen-dependent terminal body hair in places in which terminal hair is normally not found.
- Hirsutism affects between 5-10% of women of reproductive age.
Hirsutism may be the initial and possibly only sign of an underlying androgen disorder, the cutaneous manifestations of which may also include acne and male-pattern balding (androgenic alopecia).

Virilization refers to the state in which androgen levels are sufficiently high to cause not only hirsutism but additional signs and symptoms such as deepening of the voice, breast atrophy, increased muscle bulk, clitororomegaly, and increased libido.
Hirsutism is caused by either increased androgen production by the ovaries or adrenal glands or rarely increased target organ production of androgen.

Several different androgens may be secreted in excess:
- **Testosterone** excess is usually of ovarian origin,
- **DHEAS** excess is of adrenal origin,
- **Androstendione** excess can be of either adrenal or ovarian origin.
Total testosterone

SHBG

Free Testosterone
Although **DHEA** and **DHEAS** are general markers of adrenal androgen production, they have little if any intrinsic androgenic activity.

Small amounts are converted to androstendione and then to testosterone (and to estrogen) in both the adrenal glands and peripheral tissues, including hair follicles and external genitalia.
Thus the hirsutism and virilization that may be seen with adrenal hyperandrogenism are caused by androstendione and testosterone.
Causes of hirsutism in women

- **Common:** idiopathic hirsutism, polycystic ovary syndrome
- **Uncommon:** Drugs (danazol, oral contraceptives containing androgenic progestins)
- **CAH** (most often 21-hydroxylase deficiency)
- Hyperthecosis
- **Ovarian tumors:** (serotile-leydig cell tumors, granulosa-theca cell tumors, hilus-cell tumors)
- Adrenal tumors
- Severe insulin resistance syndromes
- Hyperprolactinemia
Basic approach

- The basic approach to the differential diagnosis should be:

  Documentation of the degree of androgen excess

  Exclusion of the serious but rare causes of hirsutism such as ovarian and adrenal androgen-secreting tumors
Moderately elevated (or higher) serum androgen levels, eg:

- Serum testosterone above 150 ng/dl (5.2 nmol/l),
- Serum free testosterone values above 2 ng/dl (0.07 nmol/l) and
- Serum DHEAS above 700 mcg/dl (13.6 micro/mol/l)

In young women raise the possibility of an androgen-secreting tumor.
Figure 1. The Ferriman–Gallwey Scoring System for Hirsutism.
Each of the nine body areas most sensitive to androgen is assigned a score, from 0 (no hair) to 4 (frankly virile),
Ferriman-Gallwey scale

- This scoring system has **limitations**, particularly because of the **subjective** nature of the assessment, which is specially problematic in evaluating women who have blond hair or have had cosmetic treatment.
- The scale also **does not include** the sideburn, perineal, buttocks areas.
- Moreover, substantial hirsutism may exist in one or two areas without yielding a high score.
Laboratory testing

- The serum testosterone concentration provides the best overall estimate of androgen production in hirsute women, and therefore is the single best test for evaluating them.

- Values below 150ng/dl (5.2nmol/l) exclude ovarian or adrenal tumors also tend to exclude ovarian hyperthecosis.

- Serum DHEA-s should also be drawn, concentrations > 700mcg/dl raise suspicion for an adrenal tumor.

- Serum prolactin, serum LH,
Adrenal androgens

- Serum DHEA concentrations exhibit a circadian rhythm that reflects the secretion of corticotropin (ACTH), while serum DHEA sulfate concentrations do not exhibit a circadian rhythm because the plasma half-life of DHEA sulfate is much longer.

- As a result, serum DHEA sulfate reflects integrated production and is usually a better marker of production.

- Measurements of serum testosterone are of little value in assessing adrenal function in men because the testes produce nearly all of it.

- In women, however, two-thirds of the testosterone in serum is derived from the adrenal cortex, mostly via peripheral conversion of DHEA and androstenedione.
17-OHprogesterone: late onset CAH should be considered in women with an early onset of hirsutism, (including those with premature adrenarche) hyperkalemia, a family history of CAH or a strong desire to know a specific etiologic diagnosis.

A morning value greater than 200 ng/dl in the early follicular phase strongly suggests the diagnosis, which may be confirmed by an ACTH stimulation test, the response to ACTH is exaggerated, and most patients have values exceeding 1500 ng/dl after ACTH stimulation.
Imaging studies

- We suggest an adrenal CT scan to look for an adrenal androgen-secreting tumor if serum DHEA-s concentrations are >700 mcg/dl.
- We suggest a transvaginal ultrasound if total testosterone concentration is >150 nmol/l.
- Radiologic testing is otherwise not indicated and may be misleading, because nonfunctioning adrenal masses are common.