AMENORRHEA

DONE BY: THA’ER AHMAD ALAJOU
DEFINITION

• **Amenorrhea**: absence of menstrual bleeding.

• There are some **physiological** situations where the woman is amenorrhoeic:
  • Pregnancy
  • Lactation
  • Prior to the onset of puberty

• **Otherwise**: we are talking about abnormal cessation of menses, which could be:
  • Primary
  • Secondary
DEFINITION

- **Primary amenorrhea**: when the female has never had menses before.  
  absence of menses at age 16 in the presence of *normal growth* and *secondary sexual characteristics OR absence of secondary sexual characteristic by age of 14.*
**Secondary amenorrhea:**
when the female was having menses in the past but now she is not.

absence of menses for $>3$ cycle intervals if *previously regular* menses OR 6 months if *previously irregular* menses.
CAUSES OF PRIMARY AMENORRHEA

• Hypergonadotrophic Hypogonadism (48.5%):

1. abnormal sex chromosomes (ie, Turner syndrome)
2. normal sex chromosomes (46,XX or 46,XY)
CAUSES OF PRIMARY AMENORRHEA

• Hypogonadotrophic Hypogonadism (27.8%):
  • Congenital abnormalities
    • Isolate GnRH deficiency
    • Forms of hypopituitarism
    • Congenital CNS defects
    • Constitutional delay

• Endocrine disorders
  • Congenital adrenal hyperplasia
  • Cushing syndrome
  • Pseudohypoparathyroidism
  • Hyperprolactinemia

• Tumor
  • Pituitary adenoma
  • Craniopharyngioma
    • Unclassified malignant tumor

• Systemic illness
• Eating disorder
CAUSES OF PRIMARY AMENORRHEA

• Eugonadism:
  • anatomic abnormalities
    • congenital absence of the uterus and vagina (CAUV)
  • cervical atresia
  • intersex disorders
    • androgen insensitivity
  • 17-ketoreductase deficiency
  • inappropriate feedback
CLINICAL APPROACH
1- Are **Breasts** Present Or Absent?

A physical examination will evaluate *Secondary Sexual Characteristics* (breast development, axillary and pubic hair, growth).

- **Breasts are an endogenous assay of estrogen.**

Presence of breasts indicates adequate estrogen production. Absence of breasts indicates inadequate estrogen exposure.

2- is a **Uterus** Present Or Absent?

An ultrasound of the pelvis should be performed to assess presence of a normal uterus
BREASTS ABSENT, UTERUS PRESENT

BREASTS PRESENT, UTERUS ABSENT

BREASTS ABSENT, UTERUS ABSENT

BREASTS PRESENT, UTERUS PRESENT
BREASTS ABSENT, UTERUS PRESENT
BREAST (-)  UTERUS (+)

- Patients without breasts and with a uterus have **No Ovarian Estrogen**
- Mostly The external female genitalia are normal
  1. Gonadal Dysgenesis
  2. Hypothalamic-Pituitary disorders
GONADAL DYSGENESIS

- **Normal sex development**
- During embryogenesis, without any external influences for or against, the human reproductive system is intrinsically conditioned to give rise to a female reproductive organization.
- As a result, if a gonad cannot express its sexual identity via its hormones—as in Gonadal Dysgenesis—then the affected person, *no matter whether genetically male or female, will develop external female genitalia.*
- Internal female genitalia, primarily the uterus, may or may not be present depending on the etiology of the disorder.
GONADAL DYSGENESIS

• Failure of gonadal development resulting in the absence of ovarian follicles and Oocytes

• Most common cause of primary amenorrhea.

• Most commonly due to chromosomal deletion or disorder.

• Gonadal Streak: gonad is replaced by a streak of fibers

• Breast development does not occur due to Low levels of Estrogen

• FSH and LH levels are markedly elevated due to decrease negative feedback.
1. Turner syndrome: and its variations (i.e. Mosaicism)
2. XX gonadal dysgenesis, pure gonadal dysgenesis, 46XX
3. XY gonadal dysgenesis (Swyer syndrome), pure gonadal dysgenesis, 46XY
TURNER'S SYNDROME
45 XO

- Primary amenorrhea and absent breasts
- Somatic abnormalities:
  - Short stature (most prevalent), webbing of the neck, short fourth metacarpal, and cubitus valgus, cardiac abnormality, renal abnormalities, and hypothyroidism
  - **At puberty**, the patient is given **Estrogen** and **Progesterone** to allow for secondary sexual characteristics. Patients also receive **Growth Hormone**.
- **Fertility**: egg donor
1. Short Stature
2. Webbing Of The Neck
3. Short Fourth Metacarpal
4. Cubitus Valgus
5. Cardiac Abnormality
6. Renal Abnormalities
7. Hypothyroidism
GONADAL DYSGENESIS (46,XY)

- **Swyer syndrome**: a type of hypogonadism in which no functional gonads are present to induce puberty in an XY female
- **Externally female with streak gonads**
- **Remove gonads** (risk of cancer) and give **Hormonal Replacement Therapy**
HYPOTHALAMIC-PITUITARY DISORDERS

• Low levels of estrogen are due to low gonadotropin release so follicles not stimulated.
• Normal ovaries.
• FSH levels are low.

Causes:
1. Stress, excessive exercise, anxiety, anorexia nervosa
2. Anatomic lesions of the hypothalamus or pituitary

Ex. Kallmann syndrome: inability of hypothalamus to produce GnRH due to defect in brain close to the olfactory system so lead to anosmia
• All patients with hypothalamic-pituitary dysfunction should be evaluated for the status of the other pituitary hormones.

• Evaluation should also include MRI of the hypothalamus and pituitary gland to exclude neoplastic and other lesions.

• When hypothalamic-pituitary dysfunction cannot be resolved by identifying a modifiable underlying cause (e.g., excessive exercise), combination estrogen and progestin therapy, usually in the form of a combined oral contraceptive pill or E2 skin patches with oral progestins, should be prescribed to reduce the risk of osteoporosis.
### Table II-11-2. Gonadal Dysgenesis Versus HP Axis Failure

<table>
<thead>
<tr>
<th>Breasts Absent/Uterus Present</th>
<th>Gonadal Dysgenesis (45,X)</th>
<th>HP Axis Failure (46,XX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Why No estrogen?</td>
<td>No ovarian follicles</td>
<td>Follicles not stimulated</td>
</tr>
<tr>
<td>Ovaries?</td>
<td>&quot;Streak&quot;</td>
<td>Normal</td>
</tr>
<tr>
<td>Treatment pregnancy</td>
<td>E + P</td>
<td>E + P</td>
</tr>
<tr>
<td></td>
<td>Egg donor</td>
<td>Induce ovulation (HMG)</td>
</tr>
<tr>
<td>Diagnostic test?</td>
<td>—</td>
<td>CNS imaging</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:** CNS, central nervous system; E + P, estrogen and progestin; HMG, human menopausal gonadotropin.
BREASTS PRESENT, UTERUS ABSENT
ANDROGEN INSENSITIVITY (TESTICULAR FEMINIZATION): XY

- XY karyotype
- absence of androgen receptors or lack of responsiveness to androgen stimulus
- Have functioning male gonads that produce normal male levels of testosterone and dihydrotestosterone
ANDROGEN INSENSITIVITY (TESTICULARFEMINIZATION): XY

46

- Mullerian ducts regress due to the presence of antimullerian hormone
- No testosterone → Wolffian ducts do not develop

So:
- No male or female internal genitalia
- Have normal female external genitalia
- A short or absent vagina
- These patients have normal breasts and scant or absent axillary and pubic hair.
ANDROGEN INSENSITIVITY (TESTICULARFEMINIZATION): XY 46

Management

• The gonads should be removed after puberty because there’s a risk of malignancy
• Estrogen replacement
• Need for psychological counseling
• Raised as females.
MULLERIAN AGENESIS

Mayer-Rokitansky-Kuster-Hauser syndrome
MULLERIAN AGENESIS (IDIOPATHEIC)

- no uterus and have a shortened vagina
- normally ovulating ovaries, normal breast development, and normal axillary and pubic hair.
- Associated with renal and skeletal abnormalities and should be screened with an ultrasound or MRI.
- No need for supplemental hormones
- Surgical reconstruction of the vagina or use of dilators
- Fertility: IVF-surrogate
### Table 17-1: Comparison of Androgen Insensitivity and Müllerian Agenesis

<table>
<thead>
<tr>
<th></th>
<th>Androgen Resistance</th>
<th>Müllerian Agenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Karyotype</strong></td>
<td>XY</td>
<td>XX</td>
</tr>
<tr>
<td><strong>Breast</strong></td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td><strong>Uterus</strong></td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Pubic/axillary hair</strong></td>
<td>Absent</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Testosterone</strong></td>
<td>Normal male levels</td>
<td>Female levels</td>
</tr>
<tr>
<td><strong>Further evaluation</strong></td>
<td>Need gonadectomy</td>
<td>Renal/skeletal abnormalities</td>
</tr>
</tbody>
</table>
BREASTS PRESENT,
UTERUS PRESENT
IMPERFORATE HYMEN; TRANSVERSE VAGINAL SEPTUM

- Presentation:
  - Cyclic pelvic pain due to menstrual blood not having an egress.
  - Hematocolpos

- Physical exam:
  - Septa or hymen.
  - Perirectal or abdominal mass

- Treatment: Excision

- Other possible causes include: AN, excessive exercise or possible pregnancy before first menes

- Otherwise: The workup should proceed as for secondary amenorrhea
BREASTS ABSENT,
UTERUS ABSENT
• 17α-hydroxylase deficiency:
  • These patients are XY, have testes, but lack the enzyme needed to synthesize sex steroids. They have female external genitalia.
  • Antimullerian hormone causes the regression of the mullerian ducts.
  • Low testosterone levels do not allow the development of internal male genitalia.
  • There is insufficient estrogen to allow breast development.
DIAGNOSIS OF AMENORRHEA
Diagnostic steps help with the precise identification of a cause of primary amenorrhea:

- Step 1: History
- Step 2: Physical examination
- Step 3: Basic laboratory testing
Although there are several unique causes of primary amenorrhea, all causes of secondary amenorrhea can also cause primary disease. Thus, the following questions should be asked of a woman with primary amenorrhea:

1) Has she completed other stages of puberty, including a growth spurt, development of axillary and pubic hair, apocrine sweat glands, and breast development?
   - Lack of pubertal development suggests ovarian or pituitary failure, or a chromosomal abnormality.
2) Is there a family history of delayed or absent puberty?
   • suggests a possible **familial disorder**

3) What is the woman's height relative to family members?
   • **Short stature** may indicate **Turner syndrome** or **hypothalamic-pituitary disease**

4) Was neonatal and childhood health normal?
   • Neonatal crisis suggests **congenital adrenal hyperplasia**.
   • Poor health may be a manifestation of **hypothalamic-pituitary disease**.
5) Are there any symptoms of virilization?
   • The presence of virilization suggests:
     1. Polycystic ovary syndrome.
     2. Androgen-secreting ovarian or adrenal tumor.
     3. Presence of Y chromosome material.

6) Lately, has there been stress, change in weight, diet, or exercise habits, or illness?
   • might result in hypothalamic amenorrhea.
7) Is she taking any drugs that might cause or be associated with amenorrhea?
   • Medication for a systemic illness (e.g. medication for Sarcoidosis).
   • heroin and methadone can alter hypothalamic gonadotropin secretion.

8) Is there galactorrhea (suggestive of excess prolactin)?
   • Some drugs cause amenorrhea by increasing serum prolactin concentrations, including metoclopramide and antipsychotic drugs.

9) Are there symptoms of other hypothalamic-pituitary disease including headaches, visual field defects, fatigue, or polyuria and polydipsia?
STEP 2: PHYSICAL EXAMINATION

1) Evaluation of pubertal development, including:
   • **Current height, weight, and arm span** (normal arm span for adults is within 5 cm of height).
   • Evaluation of the **woman's growth chart**.

2) An assessment of breast development:
   • eg: by **Tanner staging**
4) A careful genital examination should be performed for:
   • Clitoral size
   • pubertal hair development
   • intactness of the hymen
   • depth of the vagina
   • presence of a cervix, uterus, and ovaries

5) Examination of the skin for:
   ➢ hirsutism
   ➢ acne
   ➢ striae
   ➢ increased pigmentation
   ➢ vitiligo
6) Evaluation for the classic physical features of Turner syndrome such as:
   • low hair line
   • web neck
   • shield chest
   • widely spaced nipples should be noted.

   ▸ Note: the **blood pressure** should be measured in **both arms** if Turner syndrome is suspected, because it is associated with an increased incidence of coarctation of the aorta.
STEP 3: BASIC INVESTIGATION

- whether there are any anatomic abnormalities of the vagina, cervix, or uterus by physical examination or ultrasonography

- If a normal vagina or uterus is not obviously present on physical examination, pelvic ultrasonography should be performed to confirm the presence or absence of ovaries, uterus, and cervix
In case of:

1) **Uterus absent**: do karyotype and measurement of serum testosterone

- **Abnormal müllerian development** (46,XX karyotype with normal female serum testosterone concentrations)

- **Androgen insensitivity syndrome** (46,XY karyotype and normal male serum testosterone concentrations)

- **5-alpha-reductase deficiency**, they also have a 46,XY karyotype and 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, and deepening of the voice)
2) **Uterus present:**

normal müllerian structures, no evidence of an imperforate hymen, vaginal septum, or congenital absence of the vagina, an endocrine evaluation should be performed:

- Measurement of **Serum Beta Human Chorionic Gonadotropin** to exclude pregnancy
- Serum **FSH**
Results of serum FSH can help as follows:

- A high serum FSH concentration indicates **primary ovarian failure**.
- A low or normal serum FSH concentration suggests:
  - functional hypothalamic amenorrhea
  - congenital GnRH deficiency (e.g., Kallmann syndrome)
  - Other disorders of the hypothalamic-pituitary axis.

Other important endocrine values include:

- Serum **prolactin** and **thyrotropin** should be measured if FSH is low or normal, especially if galactorrhea is present.
- If there are signs or symptoms of hyperandrogenism, serum **testosterone** and **dehydroepiandrosterone sulfate (DHEA-S)** should be measured to assess for an androgen-secreting tumor.
TREATMENT

Includes 3 aspects:

1. Correcting the underlying pathology (if possible)

2. Helping the woman to achieve fertility (if desired)

3. Prevention of complications of the disease process (eg: estrogen replacement to prevent osteoporosis)
A brief summary for methods of treatment may include:

1. **Psychological counseling** is particularly important in patients with **absent müllerian structures** or a **Y chromosome**.

2. **Surgery** may be required in patients with either congenital anatomic lesions or **Y chromosome material**.
   
   As an example, surgical correction of a vaginal outlet obstruction is necessary a.s.a.p.

3. **Symptomatic treatment** as in women with PCOS, treatment of hyperandrogenism is directed toward achieving the woman's goal (eg, relief of hirsutism, resumption of menses, fertility) and preventing the long-term consequences of PCOS.
4) **Functional hypothalamic amenorrhea** can be reversed by:
   - Weight gain
   - Reduction in the intensity of exercise
   - Resolution of illness or emotional stress.

- For women who want to continue to exercise, **estrogen-progestin replacement** therapy should be given to those not seeking fertility to prevent osteoporosis and heart disease.

- Women who want to become pregnant can be treated with **exogenous gonadotropins** or **pulsatile GnRH**, but increased caloric intake is simpler and clearly preferable.
5) Advances in assisted reproductive technologies now make it possible for many women with primary amenorrhea to participate in reproduction:

- For women with gonadal dysgenesis, the use of donor oocytes and their partners' sperm with IVF allow the women to carry a pregnancy in their own uterus.

- For women with an absent uterus, use of their own oocytes in IVF and transfer of their embryos to a gestational carrier can allow these women to have genetically related children.
SECONDARY AMENORRHEA
often caused by hormonal disturbances from the hypothalamus and the pituitary gland, from premature menopause or intrauterine scar formation

1- hypogonadotrophic (suggesting hypothalamic or pituitary dysfunction)
2- hypergonadotrophic (suggesting ovarian follicular failure)
3-eugonadotrophic (suggesting pregnancy, anovulation, or uterine or outflow tract pathology)
ETIOLOGY

- Pregnancy most common
- Ovarian (40%)
  - Polycystic ovary syndrome (40%)
  - anovulation
  - Ovarian failure
  - Autoimmune oophoritis
- Hypothalamic (35%)
  - Functional GnRH deficiency (same reasons as under 1o amenorrhea)
  - Infiltrative
  - eating disorders and weight loss (obesity, anorexia nervosa, or bulimia)
- Pituitary (20%)
  - Hyperprolactinemia (90%) > decreased GnRH
  - Sheehans
- Uterine (5%)
  - Asherman’s (>90%).
- Others (1%) e.g. cervical & endocrine
  - hypothyroidism, hyperthyroidism, arrhenoblastoma
ETIOLOGIES
ACCORDING
TO CLINICAL
IMPORTANCE

• Pregnancy (MC)
• Anovulation: (polycystic ovary syndrome, hypothyroidism, pituitary adenoma, elevated prolactin, and medications (e.g., antipsychotics, antidepressants)) → first patient present with amenorrhea then irregular bleeding.
• Estrogen Deficiency (absence of functional ovarian follicles or hypothalamic-pituitary insufficiency).
• Outflow Tract Obstruction (Asherman's syndrome)
HYPOTHALAMIC CAUSES

- **Functional hypothalamic amenorrhea**: ↓ GnRH secretion, without other causes.

- **Weight loss/anorexia nervosa**: malnourishment will ↓ reproductive ability. Tx: Weight gain.

- **Stress and exercise**: E.g. athletes.

- **Drugs**: OCPs act at the level of the hypothalamus and pituitary. Postpill amenorrhea can occur up to 6 months after stopping the pill.

- **Lesions**: Craniopharyngiomas, granulomatous disease, encephalitis sequelae.
Neoplasms: e.g. Prolactinomas, nonprolactin-secreting pituitary tumors.

Lesions: caused by anoxia, thrombosis, or hemorrhage.
Sheehan syndrome:

Postpartum hypopituitarism or postpartum pituitary necrosis caused by ischemic necrosis due to blood loss and hypovolemic shock during and after childbirth.

Rare complication, the presence of DIC (amniotic fluid embolism or HELLP syndrome) appears to be a factor in its development.

Symptoms: Most common initial symptoms of Sheehan's syndrome are agalactorrhea or difficulties with lactation, others like amenorrhea or oligomenorrhea after delivery, features of hypopituitarism, may be asymptomatic.

Treatment includes replacement of pituitary hormones.

Simmonds disease:

Pituitary damage unrelated to pregnancy.
Premature ovarian failure (POF):
• Aka Primary ovarian insufficiency, premature menopause
• the loss of function of the ovaries before age 40
• It leads to estrogen deficiency, endometrial atrophy, and cessation of menstruation.
• triad for the diagnosis is amenorrhea, hypergonadotropinism, and hypoestrogenism
• Causes: autoimmune ovarian destruction, Radiation therapy, chemotherapy, genetic or infection

Polycystic ovaries.
- **Anovulation:**
  - no corpus luteum → no progesterone → no progesterone withdrawal bleeding.
  - Cause endometrial hyperplasia (unopposed estrogen stimulation of endometrium)
  - Causes include: PCOS, hypothyroidism, hyperprolactenemia, drugs (antipsychotics and antidepressants)

- **Surgical:** Bilateral salpingo-oophorectomy.
Asherman syndrome:

- Intrauterine adhesions can obliterate the endometrial cavity and cause amenorrhea.
- Most frequent cause is endometrial curettage associated with pregnancy.
- Adhesions may form after myomectomy, metroplasty, or cesarean delivery.
- Confirm the diagnosis with hysterosalpingogram (HSG) or hysteroscopy.
- Treat via hysteroscopic resection of adhesions. Estrogens administered to stimulate regrowth of endometrium.
➢ **Endometrial ablation:** This procedure may have been performed for menorrhagia.

➢ **Infection:** Endometritis or tuberculosis.

**Cervical:** Stenosis due to loop electrosurgical excision procedure (LEEP) or cold-knife cone. Treat with cervical dilation.

**Endocrine disease:** can cause secondary amenorrhea.

• Hyper/hypothyroidism.
• Diabetes mellitus.
• Hyperandrogenism (neoplasm, exogenous androgens).
Once pregnancy and Asherman's syndrome have been excluded, all of the remaining causes of amenorrhea are associated with anovulation due to hypothalamic, pituitary, or ovarian disorders.

Step 1: Confirm the case By Hx and P/E
Step 2: Rule out pregnancy.
Step 3: Hormonal assay (TSH, Prolactin, FSH/LH, Androgens).
Step 4: Progestin challenge
Step 5: Depend on progestin challenge Test result
Questions 6-9 of the primary amenorrhea history + the following: (refer to previous slides)

- Are there any symptoms of estrogen deficiency?
  - hot flashes
  - vaginal dryness
  - poor sleep
  - decreased libido

These symptoms may be prominent in the **early stages of ovarian insufficiency**. In contrast, women with **hypothalamic amenorrhea** do **not** usually have these symptoms.
Is there a history of obstetrical catastrophe?

- severe bleeding
- dilatation and curettage
- endometritis or other infection that might have caused scarring of the endometrial lining (Asherman's syndrome)
1. Measurements of height and weight.

- A body mass index greater than \(30 \text{ kg/m}^2\) is observed in approximately 50 percent of women with PCOS.

- Women with a BMI less than \(18.5 \text{ kg/m}^2\) may have functional hypothalamic amenorrhea due to an eating disorder, strenuous exercise, or a systemic illness associated with weight loss.
2. The patient should be examined for hirsutism, acne, striae, acanthosis nigricans, vitiligo, and easy bruisability.

3. Breasts should be examined for evidence of galactorrhea.

4. Vulvovaginal exam should look for signs of estrogen deficiency.
Patient with SECONDARY AMENORRHEA

Pregnancy test

- Negative
  - Thyroid-stimulating hormone level
    - Abnormal
      - Thyroid disease
    - Normal
      - Prolactin level
        - Normal
          - Progestin Challenge
        - Hyperprolactinemia
          - Head MRI
            - Tumor
              - Dopamine Agonist or Radiation Therapy or NEUROSURGERY
            - No tumor
              - Observe Consider: Trial of bromocriptine
STEP 2: RULE OUT PREGNANCY

A pregnancy test is recommended as a first step. Measurement of serum beta subunit of hCG is the most sensitive test.
STEP 3: HORMONAL ASSAY

Minimal laboratory testing should include:

1. Serum prolactin.

2. FSH, LH.

3. TSH.

4. Serum Androgens (testosterone, DHEA).
Progestin Challenge

- Withdrawal bleeding
  - Anovulation
  - Consider: Polycystic ovarian disease, Adrenal hyperplasia or tumor, ovarian tumor (p 152), Cushing’s syndrome (p 154)
- No withdrawal bleeding
  - Estrogen and Progestin Challenge
    - Withdrawal bleeding
      - LH, FSH
      - Low or normal
        - Head MRI
        - Normal
          - Hypothalamic amenorrhea
          - Consider: Anorexia nervosa, Stress, Exercise related
        - Abnormal
          - Consider: Pituitary tumor (p 158), Craniopharyngioma, Meningioma, Nonneoplastic process
    - No withdrawal bleeding
      - End-organ problem
      - High
        - Ovarian failure
        - Consider autoimmune disease
      - Low or normal
        - Head MRI
        - Normal
          - Hypothalamic amenorrhea
          - Consider: Anorexia nervosa, Stress, Exercise related
        - Abnormal
          - Consider: Pituitary tumor (p 158), Craniopharyngioma, Meningioma, Nonneoplastic process
      - End-organ problem
        - Hormonal Replacement Therapy
Progestin challenge, or progesterone withdrawal test

The test is performed by administering progesterone orally in the form of medroxyprogesterone acetate (Provera), or intramuscularly.

- If the patient has sufficient serum estradiol (greater than 50 pg/mL) then withdrawal bleeding should occur 2-7 days after the progestin is finished, indicating that the patient's amenorrhea is due to anovulation.
if no bleeding occurs after progesterone withdrawal, then the patient's amenorrhea is likely to be due to either:

a) Low serum estradiol.

b) A problem with the uterine outflow tract, such as cervical stenosis or uterine synechiae (Asherman's syndrome).

In order to distinguish between hypoestrogenism or a uterine outflow tract problem, estrogen may be administered followed by a course of progestin in order to induce withdrawal bleeding. If the patient experiences withdrawal bleeding with the combined estrogen/progestin therapy, then the amenorrhea is likely due to low estrogen.
1. **Assessment of estrogen status:**
   - in some cases to help with interpreting the FSH values, and in others to help guide therapy.

2. **High serum prolactin concentration:**
   - Prolactin secretion can be transiently increased by stress or eating.
   - Women should be screened for thyroid disease because hypothyroidism can cause hyperprolactinemia.
3. **High serum FSH concentration**
   - A high serum FSH concentration indicates primary ovarian insufficiency (premature ovarian failure)

4. **Normal or low serum FSH concentrations**
   - A serum FSH concentration that is low or "normal" is inappropriately low in the presence of a low serum estradiol concentration and indicates secondary (hypogonadotrophic) hypogonadism
5. **Normal labs and history of uterine instrumentation:**
   - Evaluation for Asherman's syndrome (intrauterine adhesions) should be performed

6. **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.
Approach to Secondary Amenorrhea

- **Rule out pregnancy**
  - $\beta$-HCG
- **Physical exam**
  - R/O Asherman’s
- **Prolactin level**
  - If very high, CT or MRI of pituitary
- **TSH**
  - If very high = hypothyroidism
- **FSH and LH**
  - If very high = ovarian failure, if < 30 → karyotype
  - If low = stress?, low BW?, pit failure?
- **DHEA-S and testosterone**
  - Only if virilized, looking for PCOS
- **17OH-progesterone**
  - Looking for congenital adrenal hyperplasia
TREATMENT

Treat the cause

- **Hypothalamic amenorrhea:**
  - **Lifestyle changes:** For many athletic women, simply explaining the need for adequate caloric intake to match energy loss results in increased caloric intake or reduced exercise, followed by resumption of menses
  
  - **Cognitive behavioral therapy:** may be effective for restoring ovulatory cycles in some women

- **Leptin administration:** women with hypothalamic amenorrhea (HA) have relative leptin deficiency.
Hyperprolactinemia:

The management of women with amenorrhea due to hyperprolactinemia depends upon the cause of the hyperprolactinemia and the patient’s goals (eg, pursuing fertility or not).

Primary ovarian insufficiency (premature ovarian failure):

Women with primary ovarian insufficiency should receive estrogen therapy for prevention of bone loss. This can be either an oral contraceptive, or replacement doses of estrogen and progestin.
Polycystic ovary syndrome:

Treatment of hyperandrogenism is directed toward achieving the woman's goal (eg, relief of hirsutism, resumption of menses, fertility) and preventing the long-term consequences of PCOS.

Intrauterine adhesions:

Therapy of Asherman's syndrome consists of hysteroscopic lysis of adhesions followed by long-term estrogen administration to stimulate regrowth of endometrial tissue.
THE END

ANY QUESTION ?