AMENORRHEA

DONE BY: WASEEM AL HALAWANEE
• **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 (i.e., Turner syndrome)
2. normal sex chromosomes (46,XX or 46,XY)
CAUSES OF PRIMARY AMENORRHEA

• Hypogonadotropic 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
CLINICAL APPROACH
PRELIMINARY EVALUATION

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.
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 donar
1. Short Stature
2. Webbing Of The Neck
3. Short Fourth Metacarpal
4. Cubitus Valgus
5. Cardiac Abnormality
6. Renal Abnormalities
7. Hypothyroidism
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>
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<tr>
<th>Breasts Absent/Uterus Present</th>
<th>Gonadal Dysgenesis (45,X)</th>
<th>HP Axis Failure (46,XX)</th>
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<tr>
<td>FSH</td>
<td>↑</td>
<td>↓</td>
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<tr>
<td>Why No estrogen?</td>
<td>No ovarian follicles</td>
<td>Follicles not stimulated</td>
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<td>Ovaries?</td>
<td>“Streak”</td>
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<td>Treatment pregnancy</td>
<td>E + P</td>
<td>E + P</td>
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<td></td>
<td>Egg donor</td>
<td>Induce ovulation (HMG)</td>
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<td>Diagnostic test?</td>
<td>—</td>
<td>CNS imaging</td>
</tr>
</tbody>
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**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 (TESTICULAR FEMINIZATION): 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
Integration of knowledge:

**ANDROGEN INSENSITIVITY (TESTICULAR FEMINIZATION): 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
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<th><strong>ANDROGEN RESISTANCE</strong></th>
<th><strong>MÜLLERIAN AGENESIS</strong></th>
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<tr>
<td><strong>Karyotype</strong></td>
<td>XY</td>
<td>XX</td>
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<tr>
<td><strong>Breast</strong></td>
<td>Present</td>
<td>Present</td>
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<tr>
<td><strong>Uterus</strong></td>
<td>Absent</td>
<td>Absent</td>
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<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>
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<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
BREASTS ABSENT,
UTERUS ABSENT
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.
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
STEP 1: HISTORY

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) Was neonatal and childhood health normal?
   • Neonatal crisis suggests congenital adrenal hyperplasia.
   • Poor health may be a manifestation of hypothalamic-pituitary disease.
4) 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.

5) Lately, has there been stress, change in weight, diet, or exercise habits, or illness?
   • might result in hypothalamic amenorrhea.
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
3) 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

4) Examination of the skin for:
   - hirsutism
   - acne
   - striae
   - increased pigmentation
STEP 3: BASIC INVESTIGATION

- whether there are any anatomic abnormalities of the vagina, cervix, or uterus by **physical examination** or **ultrasonography**
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)
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 (eg. kallmann syndrome)

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 (e.g., 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.