

Amenorrhoea - Primary & Secondary

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Objectives:

1. Define primary and secondary amenorrhea
2. Explain the pathophysiology amenorrhoea and identify the
3. following types of primary amenorrhoea.
 - Amenorrhea with no breast development and sexual infantilism
 - Amenorrhea with breast Development and mullerian anomalies
 - Amenorrhea With breast development and normal mullerian structures
4. Explain the pathophysiology and identify the etiologies of
5. secondary amenorrhea including:
 - Pregnancy
 - Hypothalamic causes
 - Pituitary causes
 - Ovarian causes
 - Uterine causes
 - Hyperandrogenism
6. Describe the symptoms and signs of amenorrhea
7. Outline a plan for investigation and management of amenorrhoea

Primary Amenorrhea	Secondary Amenorrhea
<ol style="list-style-type: none"> 1. No menstruation by the age of 14 years accompanied by failure to grow properly or develop secondary sexual characteristics. 2. No menstruation by age of 16 when growth and sexual development (characteristics) are normal. 	<ol style="list-style-type: none"> 1. Secondary absence of menses for six months (or greater than 3 times the previous cycle interval) in a woman who has menstruated before. 6 months if irregular period, 3 if regular 2. Pregnancy, lactation or hysterectomy must be Excluded 3. Prepubertal and post-menopausal conditions are also to be excluded as physiological causes
Clinical approach	

- There is a difference of opinion about the age at which Primary Amenorrhea should be investigated at 18 yrs. often suggested.
- Provided the patient has developed normal sec. sex. Characteristics and cryptomenorrhea (imperforate hymen) has been excluded. Why? because it could be normal and harmless, especially if it runs in the family.
- While those patients with Primary amenorrhea and sexual infantilism should be investigated
- at the age of 15 years or 16 years (may be earlier (14)).
- **Accurate, adequate history is essential to reach a firm diagnosis**
- Specific questioning is necessary to establish diagnosis of Primary or Secondary amenorrhea
- Is the amenorrhea truly secondary (e.g. prev. menses were actually steroid –induced) here it's considered primary.
- Careful physical examination aids in reaching a fairly firm provisional diagnosis
- In the minority, there is a need to go beyond simple out-patient investigation. Like in turner's syndrome we need laparoscopy to look for the uterus.

Causes of amenorrhea

- A. Disorder of outflow tract and or uterus
- B. Disorders of ovary
- C. Disorders of Ant. Pituitary
- D. Disorders of Hypothalamus

How does menses happen?

- 1- Communicating and normal genital tract.
- 2- Developed endometrial lining.
- 3- Functioning endometrium and adequate progesterone and estrogen from the ovaries.
- 4- FSH and LH with normal pituitary and hypothalamus

Abnormalities could be caused by:

1- Anatomical

- Uterus and Vagina.
Primary: imperforate hymen, absence of Uterus, androgen insensitivity.
Secondary: Asherman's Syndrome and Infections.
- Ovary.
Primary: Turner's syndrome
Secondary: PCOS
- Pituitary or Hypothalamic disorder.

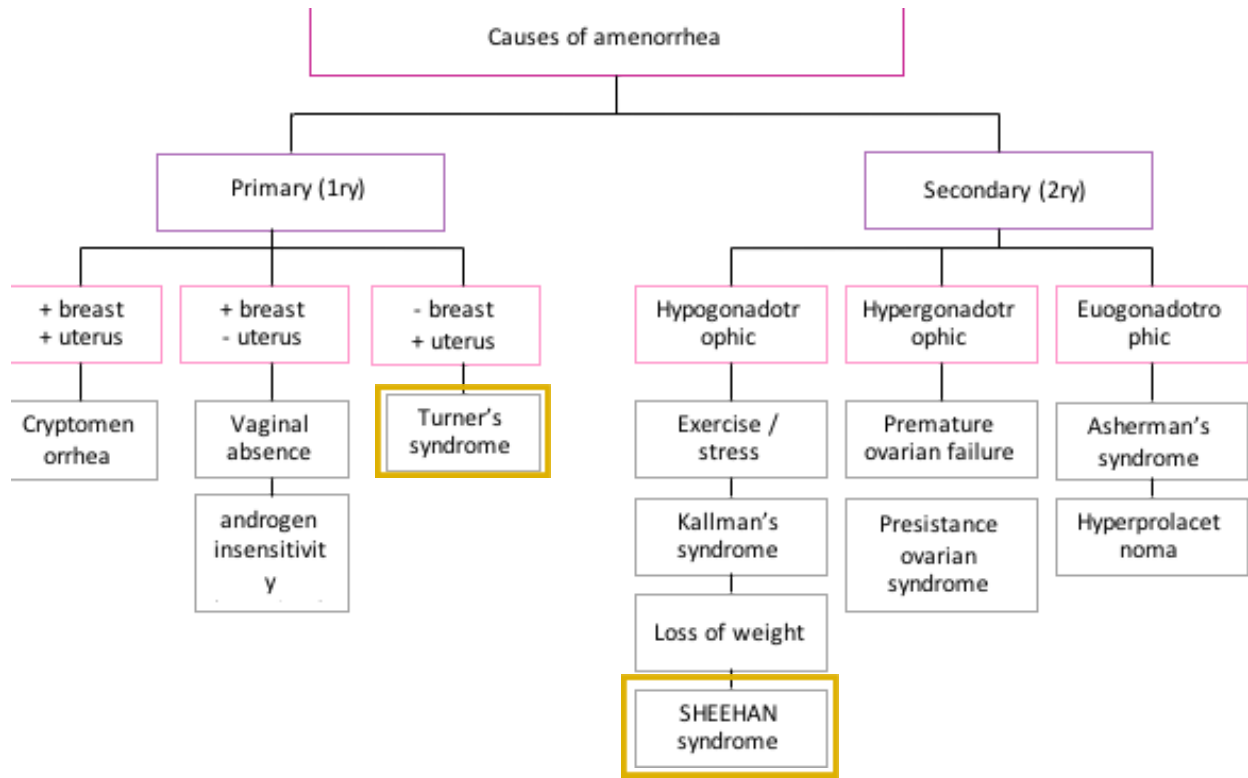
2- Hormonal

GnRH.

- high: Ovarian disease.
- normal: Anovulation (PCOS) (high LH).
- low: Hypothalamic/ pituitary disease (low LH and FSH).

3- Presence of breast and uterus

- +Uterus (-breast): Turner's syndrome and müllerian syndrome.
- + Breast (-uterus): Androgen Sensitivity.



Primary amenorrhea

- **Clinical Approach—Preliminary Evaluation**
 - **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.
 - **Is a uterus present or absent?** An ultrasound of the pelvis should be performed to assess presence of a normal uterus.
- **Clinical Approach—Based on Findings Regarding Breasts and Uterus**
 - **Breasts present, uterus present.** Differential diagnosis includes an imperforate hymen, vaginal septum, anorexia nervosa, excessive exercise, and possible pregnancy before first menses. History and physical examination will identify the majority of specific diagnoses. Otherwise the workup should proceed as if for secondary amenorrhea.
 - **Breasts present, uterus absent.** Differential diagnosis is Müllerian agenesis (Mayer-Rokitansky-Kuster-Hauser syndrome) and complete androgen insensitivity (testicular feminization). Testosterone levels and karyotype help make the diagnosis.

Secondary amenorrhea

There are multiple etiologies for **secondary amenorrhea, which can be classified by alterations in FSH and LH levels**. They include hypogonadotropic (suggesting hypothalamic or pituitary dysfunction), hypergonadotropic (suggesting ovarian follicular failure), and eugonadotropic (suggesting pregnancy, anovulation, or uterine or outflow tract pathology).

Specific etiology:

- **Pregnancy.** The first step is a β -hCG to diagnose pregnancy. This is the most common cause of secondary amenorrhea.
- **Anovulation.** If no corpus luteum is present to produce progesterone, there can be no progesterone-withdrawal bleeding. Therefore, anovulation is associated with unopposed estrogen stimulation of the endometrium. Initially the anovulatory patient will demonstrate amenorrhea, but as endometrial hyperplasia develops, irregular, unpredictable bleeding will occur. The causes of anovulation are multiple, including PCOS, hypothyroidism, pituitary adenoma, elevated prolactin, and medications (e.g., antidepressants).
- **Estrogen Deficiency.** Without adequate estrogen priming the endometrium will be atrophic with no proliferative changes taking place. The causes of hypoestrogenic states are multiple, including absence of functional ovarian follicles or hypothalamic–pituitary insufficiency.
- **Outflow Tract Obstruction.** Even with adequate estrogen stimulation and progesterone withdrawal, menstrual flow will not occur if the endometrial cavity is obliterated or stenosis of the lower reproductive tract is present.

Disorders of outflow tract or uterus

1. Cryptomenorrhea (common topic in MCQs)

- Vaginal atresia (septum) or imperforate hymen → prevent menstrual loss from escaping.
- everything is fine, she is XX and has ovaries. The problem only is obstructed outflow.

Features

- Primary Amenorrhea in a teenage girl with normal sexual development present to the ER
Complaining of:
 - Intermittent lower abdomen pain
 - Possible difficulty of micturition (urine retention)
 - Palpable lower abdominal swelling (Hematomata)
 - Bulging, bluish membrane at lower end of vagina (hymen) (Haematocolpus).

Management

Incise membrane. cruciate incision (diamond shaped) and give Antibiotics.

2. Absence or hypoplasia of vagina (Müllerian agenesis)

Features

- Growth, develop, and ovarian function are usually normal.
- Uterus may be normal or rudimentary
- Renal anomalies (in 30%) or skeletal defects (in 10%) may be present.

Management

Create a functional vagina by surgery or dilators. We do skin graft. She can get pregnant because she still has ovaries but needs a different woman to carry the embryo.

3. Testicular feminization (androgen insensitivity)

- Phenotype is woman. Genotype is man (xy) → testes are present.
- Inherited by an X-linked recessive gene... (familial)
- Resulting in absence of cytosol androgen receptor
- gonad (males) different from genitalia (female)

Features

- Growth and development are normal (may be taller than average).
- Breasts are large but with sparse glandular tissue and pale areola
- Inguinal hernia in 50% of cases
- Scanty, or no axillary and pubic hair no receptor for androgen
- Labia minora underdeveloped

- **Blind vagina**, absent uterus, rudimentary fallopian tubes **due to presence of inhibitory mullerian factor.**
- **Testes** in abdomen or inguinal canal
- Normal levels of testosterone are produced.. But no response to androgens (endogenous or exogenous)
- No spermatogenesis (**azoospermia**)
- There is an increase in incidence of testicular neoplasia (50%) **that's why it needs to be removed.**

Consider the diagnosis in a female child **they usually are very attractive**

1. With inguinal hernia (**bilateral**)
2. With 10 amenorrhea and absent uterus
3. When body hair is absent

Management

- These patients are female.
- The gonads must be removed after puberty **or immediately** → then HRT (hormonal replacement therapy) started **for bone and breast development**
- Rare cases of incomplete test. Feminization do occur → have variable degrees of masculinization

4. Asherman's syndrome

Secondary amenorrhea following destruction of the endometrium By overzealous curettage → multiple Synechiae show up on "Hysterography". She always has thin endometrium. **due to aggressive curettage caused adhesions**

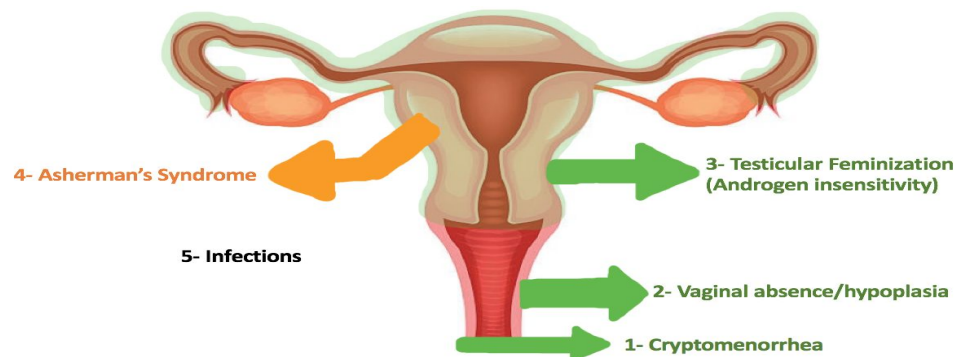
Diagnosis: hysteroscopy

Management

Under general anesthesia → breakdown intrauterine **Adhesions** through hysteroscopy insert → an IUCD to deter reformation → hormone therapy (E2 + P) (estrogen progesterone for three months at least to allow her to refunction again).

5. Infection

e.g. Tuberculosis. Utrine Schistosomiasis (**Any post-op Infection like cesarean can cause adhesions**)



Disorder of The Ovaries

1. Chromosomal abnormalities

Turner's syndrome (45 x 0) → gonadal dysgenesis 30% turner's syndrome present amenorrhea

Features

- Amenorrhea (1⁰ primary if 45 XO, rarely 2⁰ secondary if XX) 30% of all primary amenorrhea.
- Short stature
- Failure of secondary sexual Develop (no breast, axillary or pubic hair)
- Webbing of the neck
- Increase carrying angle
- Shield chest
- Coartution of aorta
- Renal collecting system Defects in 30%

Investigation

- do US and find small ovaries then do laparoscopy streak ovaries present but no follicles
- Streak ovaries present
- Gonadotrophins ↑ ↑ FSH , LH
- ↓ Estrogens
- Mosaic Chromosomal Pattern (e.g. XO/XX) → lead to various degrees of
- gonadal dysgenesis and sec. amen. + premature menopause/ ovarian failure.
- If Y-Chromosome is present in the genotype → risk of gonadal malignancy Makes gonadectomy advisable

2. Gonadal agenesis imp

(Failure of gonadal develop): no other congenital Abnormalities they have normal chromosomes not like turners.

3. Resistant ovary syndrome imp

- A rare condition (they have follicle but no receptor for FSH, they can get pregnant)
- Normal ovarian develop and potential
- FSH ↑ ↑
- It may resolve spontaneously
- If hot flushes → Rx. With estrogen

4. Premature menopause¹

❖ Ovarian failure² due to:

- Auto-immune dis. (associated with Addison's disease and thyroid)
- Viral infection (e.g. mumps)
- Cytotoxic drugs

How to differentiate between Resistant and premature?

Resistances have low amounts of follicles and it can be resolved (meaning there's a chance they get pregnant), while premature can't be resolved because there's no follicles.

5. PCOS

- Resistant ovaries with no ovulation.
- Follicles produce ↑ estrogen causing thickened endometrium.
- Mostly present with classical Stein-Leventhal syndrome (of oligomenorrhoea, obesity, hirsutism, and infertility)
- However, a substantial group will have secondary amenorrhea with no obesity or hirsutism
- Diagnosis is made by finding ↑ LH/FSH ratio 2:1, while normally it's 1:1
- Confirmation is made by laparoscopy.
- USS ± pearl follicles
- It can be treated.

¹ إيش فرقها عن الريبستانس؟ الفوليكل

² Which means that resistance ovary patient can get pregnant if they have spontaneous ovulation.

Disorder of pituitary

1. Pituitary tumor causing Hyperprolactinemia

- 40% of women with hyperprolactinemia will have a pituitary adenoma
- Pituitary Fossa X-Ray is necessary in all cases of amenorrhea – particular secondary

Feature

- In coned view (X-ray):
 - Erosion of clinoid process
 - Enlarge of pituitary fossa
 - Double flooring of fossa
- If any of above features seen, then do CT scan or MRI + Assessment of visual fields **send ophthalmologist**

management

- Bromocriptine (Dopamine agonist)
 - Suppress prolactin sec.
 - Correct estrogen deficiency **to induce ovulation**
 - Permits ovulation
 - ↓ Size of most prolactinomas
- Surgical removal of tumor
 - if extracellular manifestation (e.g. pressure on optic chiasma) or if the patient cannot tolerate or no response to medical Rx.

2. Other cause of ↑ prolactin

Drugs: e.g. phenothiazines, methyl-dopa, metoclopramide, anti-histamines, oestrogens and morphine. **psychiatric disorders , HTN med**

3. Craniopharyngioma

Other intracranial tumor **nasal pharyngioma**

4. Sheehan's syndrome

- Necrosis of ant. pituitary due to severe PPH **postpartum hemorrhage (Pan – or partial hypopituitarism)³**
- It is rare problem today due to better obstetric care and adequate blood transfusion

³ Bc of panpituitarism the prolactin may not secreted → unable to breastfeed

Disorder of hypothalamus

- Commonest reason for **hypogonadotropic secondary amenorrhea**
- Often associated with **stress** e.g. in migrants, young women when leave home, university students
- Diagnosis by exclusion of pituitary lesions.
- Hormone therapy or ovulation induction is not indicated unless the patient wishes to become pregnant. **We give them estrogen and progesterone to have a period, if they want pregnancy give her clomiphene and gonadotropin.**

1. Weight- loss associated amenorrhoea

A loss of > 10 kg is frequently associated with amenorrhea

- **Young women and teenages girls** become obsessed with their body image and starve themselves.
- **Jogger's amenorrhea:** This is seen frequently in women training for marathon racing, in ballet dancers and other forms of athletes

Causes

+ redistribution between proportion of body fat mass and body muscle mass. **fat < muscle**

May be also mediated by exercise related changes in **β**-endorphins

- **ANOREXIA NERVOSA:** Associated with secondary amenorrhea (misnomer → no loss of appetite)

2. Amenorrhea and anosmia

rare cause of amenorrhea of hypogonadotropic–hypogonadism. (Counterpart in males is Kallman's syndrome⁴)

investigation

- FSH will be low
- CNS image will roll out a brain tumor

Management

Treatment: GnRH analogue

Estrogen and progesterone replacement for development of the secondary sexual characteristics.

⁴ The inability of the hypothalamus to produce GnRH and also anosmia. The defect in the area of the brain that produce GnRH, but it's also close to the olfactory center

3. Post-pill amenorrhea

- There is no evidence that Estrogen Progesterone Contraceptive pills predispose to amenorrhea once pill taking is ceased.
- An irregular menstrual cycle frequently precedes pill taking
- If this assumption of amenorrhea being merely an after-effect of pill taking many cases of hyperprolactinemia will be missed (1:5)
- And Premature ovarian failure will be missed in 1:10 cases **they do not respond to ovulation induction**
- Once other causes are excluded, this type of amenorrhea Responds well to ovulation induction with Clomiphene citrate if pregnancy is desired.

Investigation of amenorrhea

1. S. Prolactin level and TFT

2. Karyotyping

- if chromosomal anomaly is suspected on clinical grounds

3. Progesterone withdrawal test

- To check endogenous Estrogen. e.g. Provera (medroxy-prog) if bleeding PV=reactive endometrium and patent outflow tract. **if negative> adhesions or obstructed outflow.**
 - If **PRL is normal** + no galactorrhea → no need for further investigation for pituitary tumor
 - If **GALACTOR is present** → further evaluation of pituitary gland is necessary regardless of level of PRL and menstrual pattern
 - If **PRL is significant**. elevated (excluding stress) Radiology exam **(X-ray and MRI)** of pituitary to exclude tumor
 - Visual fields assessment if X-Ray abnormal
 - **FSH & LH level...** especially if no withdrawal bleeding following progesterone Challenge.
 - ↓ LH (<5 IU/ml) hypogonadotrophic-hypogonadism
 - ↑ FSH (>40 IU/ml) on successive readings → ovarian failure
 - **Thyroid**
 - **GnRH.**
 - **high: Ovarian disease.**
 - **normal: Anovulation (PCOS) (high LH).**

- o low: Hypothalamic/ pituitary disease (low LH and FSH).

- If women < 35 years = premature ovarian failure (menopause) → check karyotype. (if Y-Chromosome + → high risk of gonadal malignancy)

4. USS

- o Of uterus and ovaries → can be useful to investigate and monitor Rx. Of these women

Uterus:

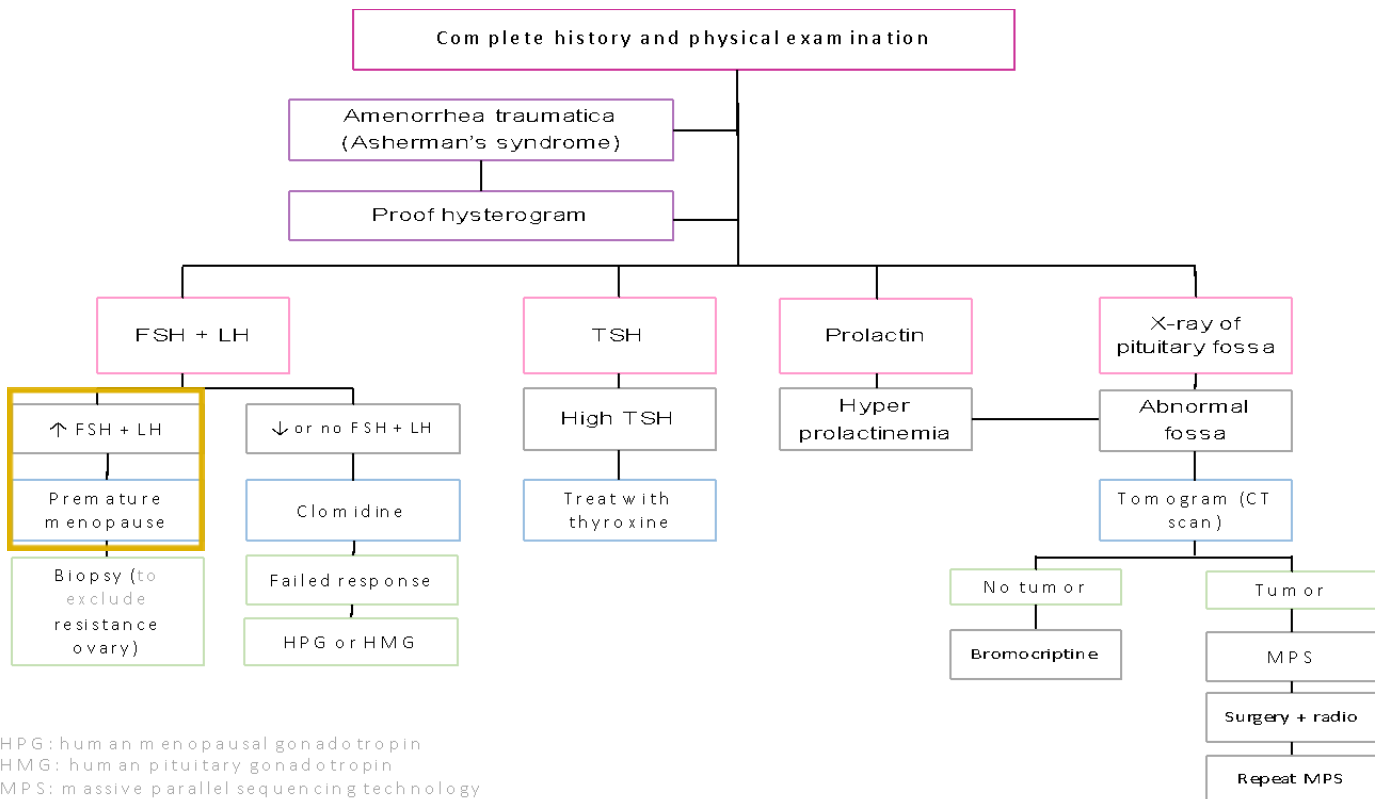
Thin lining: not working

Thick lining: high estrogen

Ovaries:

Multiple follicles: PCOS

Flowchart for investigating of Secondary Amenorrhea



Management (from Kaplan)

- **Pregnancy Test.** The first step in management of secondary amenorrhea is to obtain a qualitative β -hCG test to rule out pregnancy.
- **Thyrotropin (TSH) Level.** If the β -hCG test is negative, hypothyroidism should be ruled out (TSH level). The elevated thyrotropin-releasing hormone (TRH) in primary hypothyroidism can lead to an elevated prolactin. If hypothyroidism is found, treatment is thyroid replacement with rapid restoration of menstruation.
- **Prolactin Level.**
- **Progesterone Challenge Test (PCT).** If the β -hCG is negative, and TSH and prolactin levels are normal, administer either a single IM dose of progesterone or seven days of oral medroxyprogesterone acetate (MPA).
 - **Positive PCT.** Any degree of withdrawal bleeding is **diagnostic of anovulation**. Cyclic MPA is required to prevent endometrial hyperplasia. Clomiphene ovulation induction will be required if pregnancy is desired.
 - **Negative PCT.** Absence of withdrawal bleeding is caused by either inadequate estrogen priming of the endometrium or outflow tract obstruction.
- **Estrogen–Progesterone Challenge Test (EPCT).** If the PCT is negative, administer 21 days of oral estrogen followed by 7 days of MPA.
 - **Positive EPCT.** Any degree of withdrawal bleeding is diagnostic of inadequate estrogen. An FSH level will help identify the etiology
 - **Elevated FSH suggests ovarian failure.** If this occurs age <25, the cause could be Y chromosome mosaicism associated with malignancy, so order a karyotype. **Savage syndrome** or resistant ovary syndrome is a condition in which follicles are seen in the ovary by sonogram, though they do not respond to gonadotropins. **Other cause is ovarian failure (premature menopause)**
 - **Low FSH suggests hypothalamic–pituitary insufficiency.** Order a CNS imaging study to rule out a brain tumor. Whatever the result, women with a positive EPCT will need estrogen-replacement therapy to prevent osteoporosis and estrogen-deficiency morbidity. Cyclic progestins are also required to prevent endometrial hyperplasia.
 - **Negative EPCT.** Absence of withdrawal bleeding is diagnostic of either an outflow tract obstruction or endometrial scarring (e.g., **Asherman syndrome**). A hysterosalpingogram (HSG) will identify where the lesion is. Asherman is the result of extensive uterine curettage and infection- produced adhesions. It is treated by hysteroscopic adhesion lysis followed by estrogen stimulation of the endometrium. An inflatable stent is then placed into the uterine cavity to prevent re-adhesion of the uterine walls.

Summary

Causes of Amenorrhea			
Classification	Features	Management	
Disorder of outflow tract and or uterus	Cryptomenorrhea	<p>Primary amenorrhea in teenage w/ normal sexual development.</p> <ul style="list-style-type: none"> • Intermittent lower abd pain • Difficulty of micturition • Hematometra, Hematocolpus 	Incise membrane
	Absence or hypoplasia of vagina	<ul style="list-style-type: none"> • Growth + development + ovarian function normal • Uterus: normal or rudimentary 	Create functional vagina by surgery or dilators
	Testicular feminization	<ul style="list-style-type: none"> • Growth + development normal • Large breast + pale areola • Inguinal hernia (50%) • Scant axillary and pubic hair • Blind vagina, absent uterus. 	Gonads must be removed after puberty (↑ incidence of testicular neoplasm) then HRT started
	Asherman's syndrome	Secondary amenorrhea following overzealous curettage.	Breakdown adhesions + insert IUCD + HRT
	Infection	Ex: tuberculosis, schistosomiasis	
Disorders of ovary	Chromosomal abnormalities: Turners (45X0)	<ul style="list-style-type: none"> • Amenorrhea • Short stature + Webbing of neck • Failure of 2° sexual development 	
	Gonadal agenesis	Failure of gonadal development → no other congenital abnormalities	
	Resistant ovary syndrome	Normal ovarian development ↑ ↑ FSH	May resolve spontaneous If hot flushes → estrogen.
	Premature menopause	Due to: autoimmune disease, viral infection, or cytotoxic drugs.	



	PCOS	May present with: <ul style="list-style-type: none"> Stein-leventhal syndrome 2° amenorrhea, no obesity, hirsutism 	Decrease weight +/- metformin
Disorders of the Anterior Pituitary	Pituitary tumor "prolactinoma"	Hyperprolactinemia → most commonly due to adenoma	<ul style="list-style-type: none"> Bromocriptine Surgical removal
	Other causes	<ul style="list-style-type: none"> Drugs: phenothiazines, methyl-dopa, metoclopramid, anti-histamines, estrogen and morphine Craniopharyngioma Sheehan syndrome 	
Disorders of Hypothalamus	Stress	Most common cause	Hormone therapy or ovulation induction indicated if pt wants to be pregnant
	Weight-loss associated	> 10 kg loss. Seen in: <ul style="list-style-type: none"> Teens conscious about their body Joggers Anorexia nervosa 	
	Amenorrhea +anosmia	Hypogonadotropic –hypogonadism	

MCQs

1- A 17 year old presented to your clinic with amenorrhea. She has normal development. Which of the following supports diagnosis of cryptomenorrhea?

- A- Inguinal hernia
- B- Cyclic abdominal pain
- C- Webbing of neck
- D- Short stature

2- A 15 year old girl presented with inguinal hernia. Past medical history revealed amenorrhea. Physical examination shows scant pubic hair and blind vagina. What is the underlying mechanism for this presentation?

- A- Chromosomal abnormalities
- B- Drug induced
- C- Testicular feminization
- D- Hypo-pituitarism

3- Which of the following drugs can cause amenorrhea?

- A- Phenothiazines
- B- Misoprostol
- C- Warfarin
- D- Gentamycin

4- A 24 year old complains of amenorrhea and galactorrhea. She is not married. What investigation will you order?

- A- FSH
- B- LH
- C- TSH
- D- PL

5- In the previous question, how will you manage the patient?

- A- Medically with bromocriptine
- B- Weight loss + metformin
- C- Surgical removal of lesion
- D- HRT+ovulation induction

Answers: 1- B. 2- C. 3- A. 4- D. 5- A.