[Color index: Important | Notes | Extra]

Green=Primary amenorrhea **Orange=secondary amenorrhea**

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Amenorrhea

Objectives:

- Define primary and secondary amenorrhea
- Explain the pathophysiology of amenorrhea
- Identify the following types of **primary amenorrhoea:**

a. Amenorrhea with no breast development and sexual infantilism (gonadal dysgenesis or HP Axis failure).
b. Amenorrhea with breast development and mullerian anomalies (Mullerian agenesis).
c. Amenorrhea with breast development and normal mullerian structures (androgen insensitivity).

- Explain the pathophysiology and identify the etiology of **secondary amenorrhoea** including:
  - a. Pregnancy
  - b. Hypothalamic causes
  - c. Pituitary causes
  - d. Ovarian causes
  - e. Uterine causes
  - f. Hyperandrogenism
- Describe the symptoms and signs of amenorrhea
- Outline a plan for investigation and management of amenorrhoea.

References: 435 lecture and notes, Hacker and moore's, Kaplan, 433 team.

First Studying Embryology (intertextuality) and precocious puberty lectures is highly advisable, as some topics will be discussed further in these lectures.

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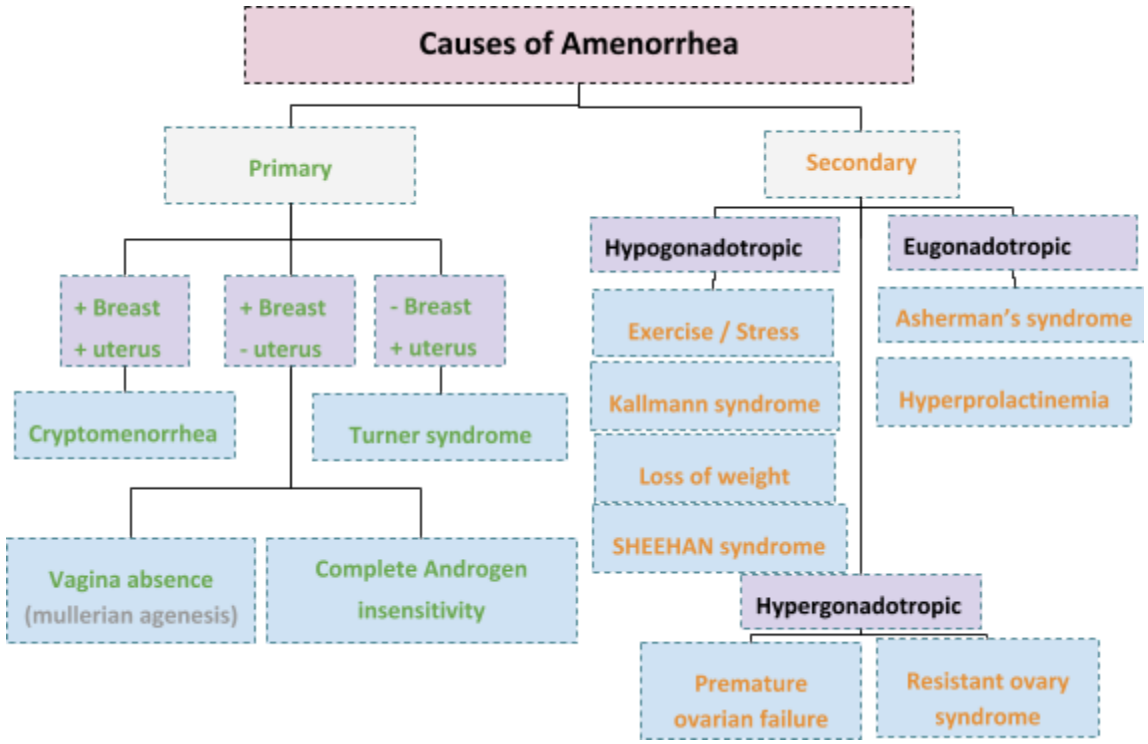
Amenorrhea

Primary Amenorrhea[1]	Secondary Amenorrhea
Absence of menstruation (never menstruated)**:** 1- by the age of 16 y.o If Normal growth and secondary sexual characteristics development is **present**[2] 2- by the age of 14 y.o If **Failing** to grow or to develop secondary sexual characteristics (sexual infantilism) ★ **Clinical approach:** ● Some wait until the age of 18 if you exclude cryptomenorrhea (obstruction of outflow tract).[3] ● Clinically some wait to investigate until age of 15 or even 16 y.o .	**In women who've menstruated before, secondary amenorrhea is absence of Menses for a period of:** ● when menses are irregular: 6 months ● when menses are regular: > 3 times previous cycle interval. **Exclude:** ● **Pregnancy**[4], lactation or hysterectomy ● Physiological Prepubertal and post-menopausal conditions ● Is the amenorrhoea truly secondary (e.g. previous menses were actually steroid – induced)

Clinical approach: 1- accurate history 2- physical examination 3- investigations if needed

Amenorrhea etiology:

1- Hypothalamus disorders (stress,loss of weight,athletic,with anosmia)
2-Anterior pituitary disorders (adenoma or drugs→ hyperprolactinemia,SHEEHAN's)
3-Ovary disorders (PCOS,premature failure,resistant,Turner,agenesis)
4-Uterus or outflow disorders (androgen insensitivity,Asherman,crypto,no vagina)



[1] When evaluating a patient with primary amenorrhea, note presence/absence of breasts and uterus.
[2] The presence of normal breast development confirms gonadal secretion of estrogen but not necessarily the presence of ovarian tissue.
[3] Always make sure to ask about history of late puberty in any family member (constitutionally delayed puberty)
[4] **Most common cause of amenorrhea.**

1- Hypothalamus disorders

can cause either primary or secondary

Commonest cause of hypogonadotropic Secondary Amenorrhea

1- Associated with stress and emotional shock.

2- Amenorrhea Anosmia (rare) (Kallmann syndrome is a genetic condition that results in hypogonadotropic hypogonadism caused by a defect in gonadotropin-releasing hormone (GnRH) production and release from the hypothalamus. Because the area in the hypothalamus where GnRH is produced is near the olfactory center, the sense of smell is usually affected, resulting in anosmia)

3- 10 Kg weight loss associated amenorrhea :

- Young woman obsessed with their body image they starve themselves.
- Jogger's amenorrhea (jog = Run = Athletics): because of
  - Redistribution between proportion of body fat mass and muscle mass
  - Exercise-related beta-endorphins.
- Anorexia Nervosa (misnomer= No loss of appetite)
  - BMI < 17 kg/m2 -> menstrual irregularity and amenorrhea.
  - Hypothalamic suppression.
  - Mean age onset (13-14 years)
  - Low estradiol -> risk of osteoporosis.

Diagnosis: Diagnosed by exclusion of pituitary disorders[5]

Treatment: Remember you don't treat those patient unless they desire to be pregnant > you can give them hormone therapy or ovulation induction[6].

Post-pill amenorrhea

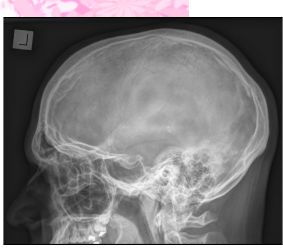
- There is no evidence that Est. prog. OCP predispose to amenorrhoea. If this assumption of amenorrhoea being merely an after-effect of pill taking, many cases of hyperprolactinemia (1:5) and Premature ovarian failure (1:10) will be missed .[7]
- Once other causes are excluded and pt wish to be pregnant manage by ovulation induction with **Clomiphene citrate**.

[5] Evaluation should also include MRI of the hypothalamus and pituitary gland to exclude neoplastic and other lesions if it is uncertain whether the patient has a functional disorder.

[6] combination estrogen and progestin therapy should be prescribed to reduce the risk of osteoporosis

[7] so basically this is not a real amenorrhea,if you consider it as one you will start missing cases of hyperprolactinemia and premature ovarian failure

2- Pituitary disorders Secondary amenorrhea



A. Hyperprolactinemia[8] Increased prolactin >Suppression of GnRH >suppression of FSH,LH>Impaired follicular development

either by:

- 40% of women with hyperprolactinemia will have a pituitary adenoma (Any prolactinemia suspect pituitary adenoma)
- drugs[9] (phenothiazines, methyl-dopa, metclopramide, anti-histamines, oestrogens,Tricyclic Antidepressants and morphine)
- Primary hypothyroidism (low T4 > lack of the (-ve) feedback on the hypothalamic–pituitary axis > high TRH > high TSH and prolactin).
- Others: CNS Lesions Affecting Prolactin (empty sella syndrome, Hypothalamic tumors), acute or chronic renal failure,...

CAUSES OF ELEVATED PROLACTIN
Pregnancy (10-fold increase from baseline)
Excessive exercise
Postprandial states
Stimulation of the chest wall or nipple
Medications
Metoclopramide
Phenothiazines
Butyrophenones
Risperidone
Monoamine oxidase inhibitors
Tricyclic antidepressants
Serotonin reuptake inhibitors
Verapamil
Reserpine
Methyldopa
Estrogens
Craniopharyngiomas
Granulomatous infiltration of the pituitary or hypothalamus
Acromegaly
Severe head trauma
Prolactinomas
Pituitary stalk compression
Primary hypothyroidism
Chronic renal failure
Marijuana or narcotic use

Investigations[10]:

The first thing you do is pituitary fossa x-ray:

➔ **features**: Erosion of clinoid process - Enlarge of pituitary fossa - Double flooring of fossa

If you find any of the above > do CT or MRI and assess visual field (since pituitary adenomas can compress optic chiasm)

Management:

➢ **Bromocriptine**[11] (Dopamine Agonist):

- Decrease size of most prolactinomas
- Suppress Prolactin secretion
- Increase estrogen
- Permit ovulation[12] (by stopping suppression of prolactin on GnRH)

➔ Start with small doses at bedtime then increase it slowly bc it has a high initial incidence of side effects.

➔ usually discontinued as soon as a pregnancy is confirmed.

➢ **Surgery** should be performed for patients with significant visual field defects or if patient cannot tolerate or respond to medical therapy.

➢ Patients with **primary hypothyroidism** should be given T4 replacement therapy

B. CRANIOPHARYNGIOMA: intracranial tumor

C. SHEEHAN'S SYNDROME: Postpartum hemorrhage→ Necrosis of anterior pituitary→ complete or partial hypopituitarism. It is rare problem today due to better obstetric care and adequate blood transfusion.

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[8] Hypersecretion of prolactin leads to gonadal dysfunction by interrupting the secretion of GnRH, which inhibits the release of LH and FSH and thereby impairs gonadal steroidogenesis.

[9] secondary to reduced hypothalamic secretion of dopamine, depriving the pituitary of a natural inhibitor of prolactin release.

[10] Serum prolactin should be measured in all cases of amenorrhea of unknown cause.

[11] Not indicated in women with normal estrogen level. The primary influence on prolactin secretion is tonic inhibition of dopamine input from the hypothalamus.

[12] It restores menses and fertility in over 90% of the cases but it takes time to be effective. Return of ovulation requires an average of 10 weeks without a tumor and 16 weeks with a microadenoma.

3- Ovary disorders

A. Chromosomal Abnormalities: (Turner's syndrome=gonadal dysgenesis = 45xo)

Features:

- Primary amenorrhea rarely secondary (in mosaic chrom pattern X0/XX)
- **No secondary sexual characteristics**
- short stature
- Webbing neck, increased carrying angle[13] and shield chest[14]
- Coarctation of aorta or renal collecting system defects

Investigations:

streak ovaries present (dysgenesis), increased gonadotropin (FSH & LH), decreased estrogen.

- Mosaic Chrom. Pattern (e.g. XO/XX) lead to various degrees of **gonadal dysgenesis** and **sec. amenorrhea** + **premature menopause**
- Y chromosome in genotype > there is risk for malignancy > advice for **gonadectomy**.

B. Gonadal agenesis with no other congenital abnormality (pure dysgenesis): very rare.

C. Resistant ovary syndrome ovaries receptors are not responding to hormones (savage syndrome):

Rare condition, Normal ovaries but unresponsive

Investigations:

- High FSH (no estrogen although follicles are present but temporary resistant)

Management:

- if you do biopsy you will find follicle that's why it may resolve spontaneously
- Deficiency of estrogen causes hot flushes so treat with estrogen simply

D. Premature menopause or Premature ovarian failure (Secondary amenorrhea):

Premature ovarian failure is defined as ovarian failure ***before*** the age of 40 years.

➔ Can be idiopathic or due to many things:

- Autoimmune (associated with addison's)
- Infections (e.g. Mumps)
- Ovarian injury as a result of Cytotoxic Drugs (Chemotherapy), Radiation, or surgery.
- carrier status of the fragile X syndrome.

E. PCOS: will be explained in details in a separate lecture

Mostly present as Stein-Leventhal syndrome (OO Hi/LH):

Oligomenorrhea[15],Obesity, Hirsutism and infertility

➔ Hirsutism and obesity are not necessarily present

Investigations:

- LH/FSH ratio increased LH increasing 2 or 3 times more compared to FSH.
- You may use U/S.
- You can make sure with laparoscopy.

F. granulosa cell tumor

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[13] "*carrying angle*" of the elbow allows forearms to clear hips when arms swing during walking.
[14] *Shield chest*: The chest appears to be broad with widely spaced nipples.
[15] *oligomenorrhea=infrequent menstruation

G. congenital adrenal hyperplasia

- Autosomal recessive trait ,21-hydroxylase deficiency.
- +ve Family history.
- Resembles PCOS.
- High 17-OH progesterone blood level.
- Presence of uterus and upper vagina.

Treatment:

Cortisol replacement + Corrective surgery.

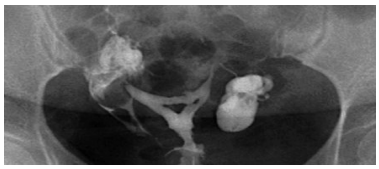
4- Uterus or outflow disorders:

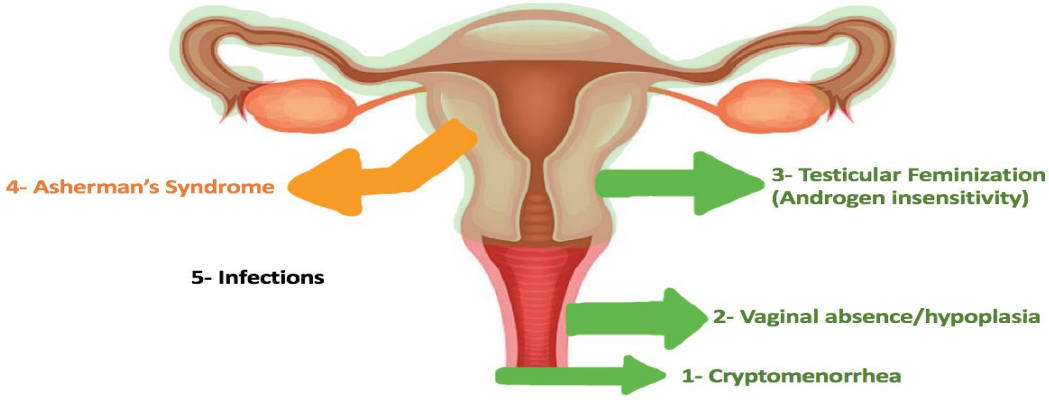
Condition	Overview	Features	Management
1-Cryptomenorrhea:	Vaginal atresia (absence of opening) or imperforate hymen [16]→ preventing menstrual loss from escaping. Pt are usually teenage girls with primary amenorrhea and Normal secondary sexual charac.	1- Intermittent (cyclic) lower abdominal **pain** 2- lower abdominal palpable **swelling** → Hematometra (collection of blood in uterus) 3-Bulging bluish membrane at lower end of vagina (Hematocolpos) 4-Possible difficulty of micturition	Simply incise membrane **(Hymenectomy)**
2-Vagina absence or hypoplasia	It is frequently associated with Mayer-Rokitansky-Küstner-Hauser (MRKH) syndrome (mullerian agenesis): absent uterus + deformed or missing vagina + normal ovaries + normal external genitalia,Karyotype 46XX.	1-Normal Ovaries 2-Uterus can be normal or rudimentary (immature) 3-Associated with Renal anomalies (30%) and skeletal anomalies(10%)	create functional vagina by surgery or dilator (so pt can have intercourse)
3-Testicular feminization or Androgen insensitivity	Familial X-linked recessive gene > Result in absence of cytosol Androgen receptors The baby Genotype is XY (Testis are present in the abdomin or inguinal canal) but the baby phenotype is female. Can have variable degrees of masculinization in case of **incomplete** androgen insensitivity. **CONSIDER THE DIAGNOSIS IN A FEMALE CHILD with:** - inguinal hernia - primary amenorrhoea and absent uterus - Absent body hair	1-Normal growth (maybe taller than average) 2-Secondary Sexual characteristics: - Large breasts with sparse glandular tissue and pale areola[17] - Scanty to No pubic or axillary hair - Underdeveloped Labia minora with blind vagina 3-No uterus and rudimentary fallopian tubes 4- 50% have inguinal hernia and testis at inguinal hernia or abdominal (This increase incidence of testicular neoplasia).[18] 5-No spermatogenesis 6-Normal testosterone but no response to any androgens (exogenous or endogenous)	1-Gonads removed after puberty "they are female"(why? Because we don't want to interfere with her growth and cause short stature) 2- Start Hormone replacement therapy

[16] KAPLAN: Imperforate Hymen: Primary amenorrhea , (+) breast and uterus, Normal height and weight.

[17] because androgen is converted peripherally to estrone

[18] There is a risk of developing gonadoblastoma (benign) and eventually dysgerminoma (malignant)

4-Asherman's Syndrome: Secondary amenorrhea	Destruction of endometrium by over curettage	if you do hysterography study (x-ray with contrast) you will find multiple **synechiae** (adhesions) 	under general anesthesia→ insert hysteroscope to break adhesions→ insert IUCD[19] to deter reformation of adhesions→ give hormone therapy (E2+ Progesterone).
5-Infections:	TB or uterine Schistosomiasis		



Amenorrhea Investigations:

* Exclude pregnancy by beta-HCG

1. **Serum Prolactin level** and **Thyroid function test** (for hypothyroidism)
   - ➔ If GALACTORRHOEA is present→ further evaluation of pit. gland is necessary regardless of level of PRL and menstrual pattern.
   - ➔ If PRL is significantly elevated (excluding stress) → radiology exam of pituitary to exclude tum.
     - ◆ **if X-Ray abnormal → Visual fields assessment** and CT/MRI
   - ➔ If Prolactin is normal + no galactorrhoea → no need for further investigation for pituitary tumor
2. **karyotyping** if chromosomal anomaly suspected: e.g. If women < 35 years with menopause check karyotype (if Y-Chrom = high risk of gonadal malignancy)
3. **Progesterone withdrawal test**[20] e.g. Provera (medroxy-prog).
   - ➔ if vaginal bleeding = reactive endometrium and patent outflow tract (Dx: anovulation).
   - ➔ if no withdrawal bleeding = check FSH & LH level:
     - ◆ Decrease LH (<5 IU/ml) → hypogonadotropic hypogonadism (hypothalamus / pituitary disorders)
     - ◆ Increase FSH (>40 IU/ml) on successive readings → ovarian failure
     - ◆ Normal = non-reactive endometrium or obstruction of uterine outflow tract[21]
4. **US of uterus and ovaries** → can be useful to investigating and monitor Rx.

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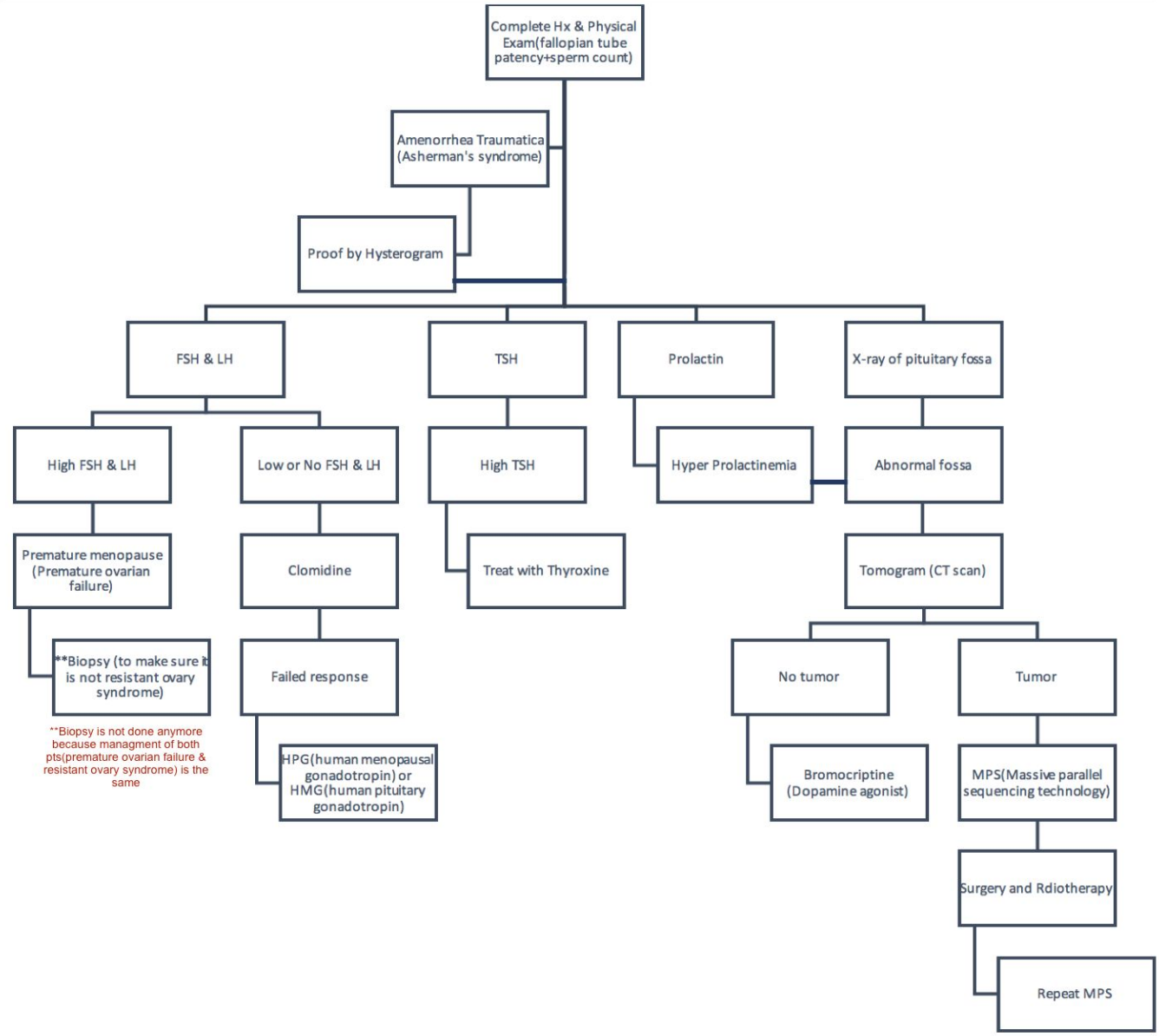
[19] IUCD: intra-uterine-contraceptive-device

[20] Progesterone challenge test (PHT): Anovulation > no corpus luteum > no progesterone > no progesterone withdrawal bleeding (amenorrhea) > unopposed estrogen stimulation of myometrium > bleeding

[21] In order to distinguish between **hypoestrogenism** or a **uterine outflow tract problem/nonreactive endometrium**, 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.

Flow chart for investigations & treatment of secondary amenorrhea



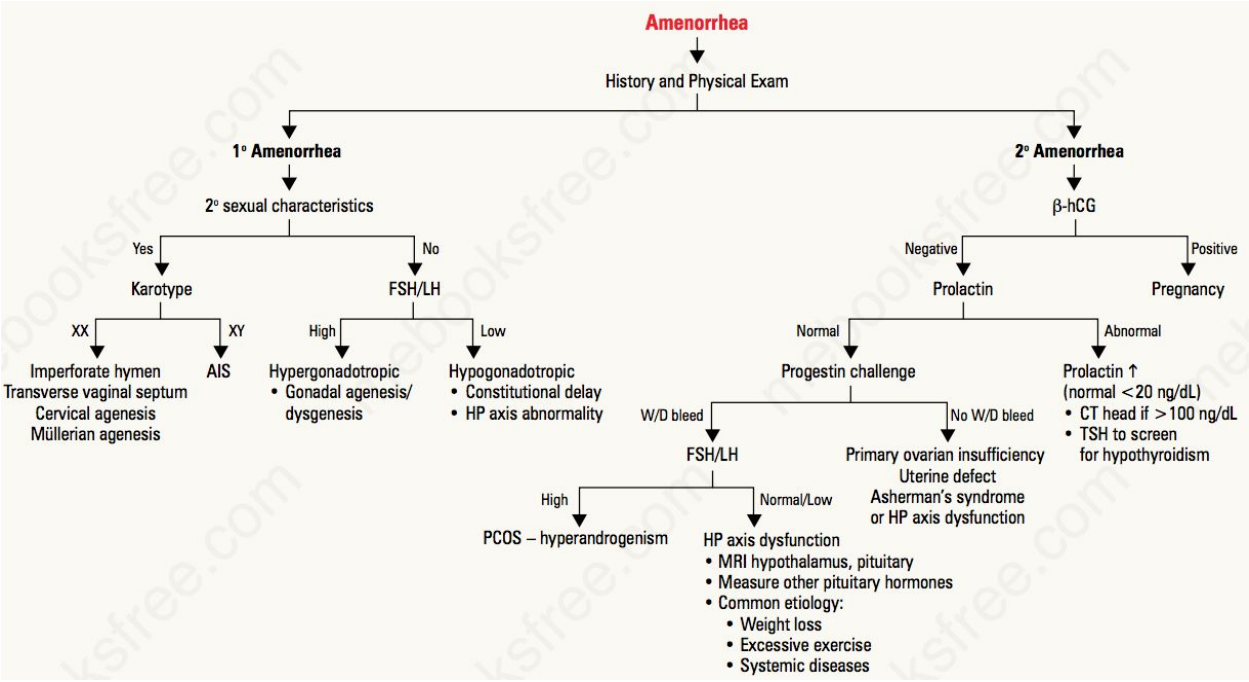
The table below from the textbook and it is in the objectives

You have to identify these types and explain pathophysiology

CLINICAL CLASSIFICATION OF MENSTRUAL DISORDERS

Disorder	Notable Diagnostic Findings	Examples	Notable Clinical Features
Primary Amenorrhea with Sexual Infantilism			
Hypogonadotropic hypogonadism	Low FSH and LH, low estrogen; screening for other pituitary hormones is indicated; MRI of the hypothalamic and/or pituitary area is recommended	Central nervous system or pituitary tumor, constitutionally delayed puberty, Kallmann syndrome; rarely presents as secondary amenorrhea with late onset	Exclude serious causes before diagnosing constitutional delay (diagnosis of exclusion); anosmia/hyposmia with Kallmann syndrome
Hypergonadotropic hypogonadism	Elevated FSH and LH, low estrogen, karyotype indicated to rule out Y chromosome	Gonadal agenesis and/or dysgenesis (most common cause of primary amenorrhea), including Turner syndrome (45,XO) and pure gonadal dysgenesis (46,XX) or (46,XY)	May rarely present as secondary amenorrhea; streak gonads, short stature, and webbing of the neck with Turner syndrome
17-Hydroxylase (P450c17) deficiency	Low sex steroids (estrogens and androgens); a rare genetic disorder	Primary amenorrhea usually in 46,XX and female external genitalia in 46,XY	Hypertension and hypokalemia caused by mineralocorticoid excess (see Figure 33-1)
Primary Amenorrhea with Breast Development and Müllerian Anomalies			
Androgen insensitivity (46,XY)	Male levels of androgens in serum (which distinguishes androgen insensitivity from other müllerian anomalies)	Androgen insensitivity syndrome (formerly called *testicular feminization syndrome*)	Internal testicles, vaginal dimple, no uterus, and near-normal breast development with smaller areolae and/or nipples
Normal female karyotype (46,XX)	Female levels of androgens in serum	Anatomic defects resulting in outflow obstruction	Surgical correction possible in many, but not all, types
Imperforate hymen	Hematocolpos on abdominal ultrasound		Bulge at introitus, cyclic pain with absent vaginal bleeding
Transverse vaginal septum	Obstruction visible on MRI scan		Cyclic lower abdominal pain without menses, hematometra, decreased fertility potential
Cervical agenesis	Cervix absent on MRI scan		Hysterectomy likely
Müllerian agenesis and/or dysgenesis	Intravenous pyelogram or other renal imaging indicated	Mayer-Rokitansky-Küster-Hauser syndrome	Vaginal dimple only, absent uterus on rectal
Secondary (Rarely Primary) Amenorrhea and/or Oligomenorrhea with Breast Development and Normal Müllerian Structures			
Pregnancy	Positive pregnancy test		Always rule out first
Uterine defects	Intrauterine scarring visible on hysterosalpingogram	Asherman syndrome	Fertility problems
Hypoestrogenism	Low serum estrogen levels	Various types listed below	
Hypothalamopituitary dysfunction	Low FSH, LH, and prolactin; other hormone deficiencies should be ruled out	Excessive exercise (runner's amenorrhea); anorexia nervosa	Lean body mass; anorexia nervosa is primarily a psychiatric disorder with significant mortality (about 7%)
Premature ovarian failure	Elevated serum FSH, low serum estrogen, karyotype indicated if age <30 yr	Autoimmune premature ovarian failure	Age <40 yr
Hyperprolactinemia (serum estrogen level can vary)	Elevated serum prolactin	Pituitary adenoma, empty sella syndrome, primary hypothyroidism, drugs (for others, see Box 33-2)	Galactorrhea
Normal estrogen and amenorrhea and/or oligomenorrhea	Normal hormone levels	Mild hypothalamic amenorrhea: exercise, nutrition, stress, hypothyroidism	
Hyperandrogenism	Elevated androgens (variable)	Congenital adrenal hyperplasia, polycystic ovarian syndrome, HAIR-AN syndrome (for others, see Box 33-2)	Hirsutism, acne, insulin resistance, virilization in some severe cases

With Secondary Sexual Development		Without Secondary Sexual Development	
Normal breast and pelvic development	**Normal breast, abnormal uterine development**	**High FSH (hypergonadotropic hypogonadism)**	**Low FSH (hypogonadotropic hypogonadism)**
Hypothyroidism Hyperprolactinemia PCOS Hypothalamic dysfunction	Androgen insensitivity Anatomic abnormalities Müllerian agenesis, uterovaginal septum, imperforate hymen	Gonadal dysgenesis Abnormal sex chromosome (Turner's XO) Normal sex chromosome (46XX, 46XY)	Constitutional delay (rare in girls) Congenital abnormalities Isolated GnRH deficiency Pituitary failure (Kallman syndrome, head injury, pituitary adenoma, etc.) Acquired Endocrine disorders (type 1 DM) Pituitary tumours Systemic disorders (IBD, JRA, chronic infections, etc.) Functional hypothalamic amenorrhea



Breasts Present/Uterus Absent	Müllerian Agenesis (46,XX)	Androgen Insensitivity (46,XY)
Uterus absent?	Idiopathic	MIF
Estrogen from?	Ovaries	Testes
Pubic hair?	Present	Absent
Testosterone level?	Female	Male
Treatment	No hormones Create vagina IVF—surrogate	Estrogen Create vagina Remove testes

Definition of abbreviations: MIF, Müllerian inhibitory factor.

★ **Q1: A 22-year-old lady, married, came to your clinic complaining of 2 months secondary amenorrhea. What's the initial test you want to run?**

A. Beta-HCG.
B. Estrogen.
C. Progesterone.
D. Prolactin.

The Answer is: A

★ **Q2: A 16 years old girl presents with primary amenorrhea. Although she has cyclical pain and well developed secondary sexual characteristics, she is worried that her menstruation has not commenced yet. Which one of the following is responsible for her problem?**

A. Bicornuate uterus.
B. Imperforate hymen.
C. Polycystic ovarian syndrome.
D. Sheehan's syndrome.

The answer is: B (cyclical pain) (A->will have problem if she gets pregnant,C-> a syndrome with either high androgen levels or US finding and it causes anovulation but not primary amenorrhea, D-> always secondary amenorrhea after postpartum hemorrhage

★ **Q3: A 26-year-old female patient presented with secondary amenorrhea her lab results showed high FSH and LH, what is the most likely diagnosis?**

A. Premature ovarian failure.
B. Pregnancy.
C. PCOS.
D. Sheehan's syndrome

The Answer is: A (if it specified LH double or triple FSH then it is more toward PCOS)
**You will probably never find Premature ovarian failure and resistant ovary syndrome as 2 individual choices for the same question and if you do then go check again if the question mentioned any Biopsy? Yes then the answer is definitely one of them .No biopsy mentioned>> then you can cross them out and think about the other choices!