433 Teams

OBSTETRICS & GYNECOLOGY

Primary and secondary Amenorrhea

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OBJECTIVES

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

DEFINITIONS

Primary Amenorrhea

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 are normal.**

Always make sure to ask about history of late puberty in any family member (constitutionally delayed puberty)

Secondary Amenorrhea

- ✶ **Absence of menses for six months (or greater than 3 times the previous cycle interval) in a women who has menstruated before.**
- ✶ **Pregnancy, lactation or hysterectomy must be excluded.**
- ✶ **Pre-pubertal and post-menopausal conditions are also to be excluded as physiological causes.**

CLINICAL APPROACH

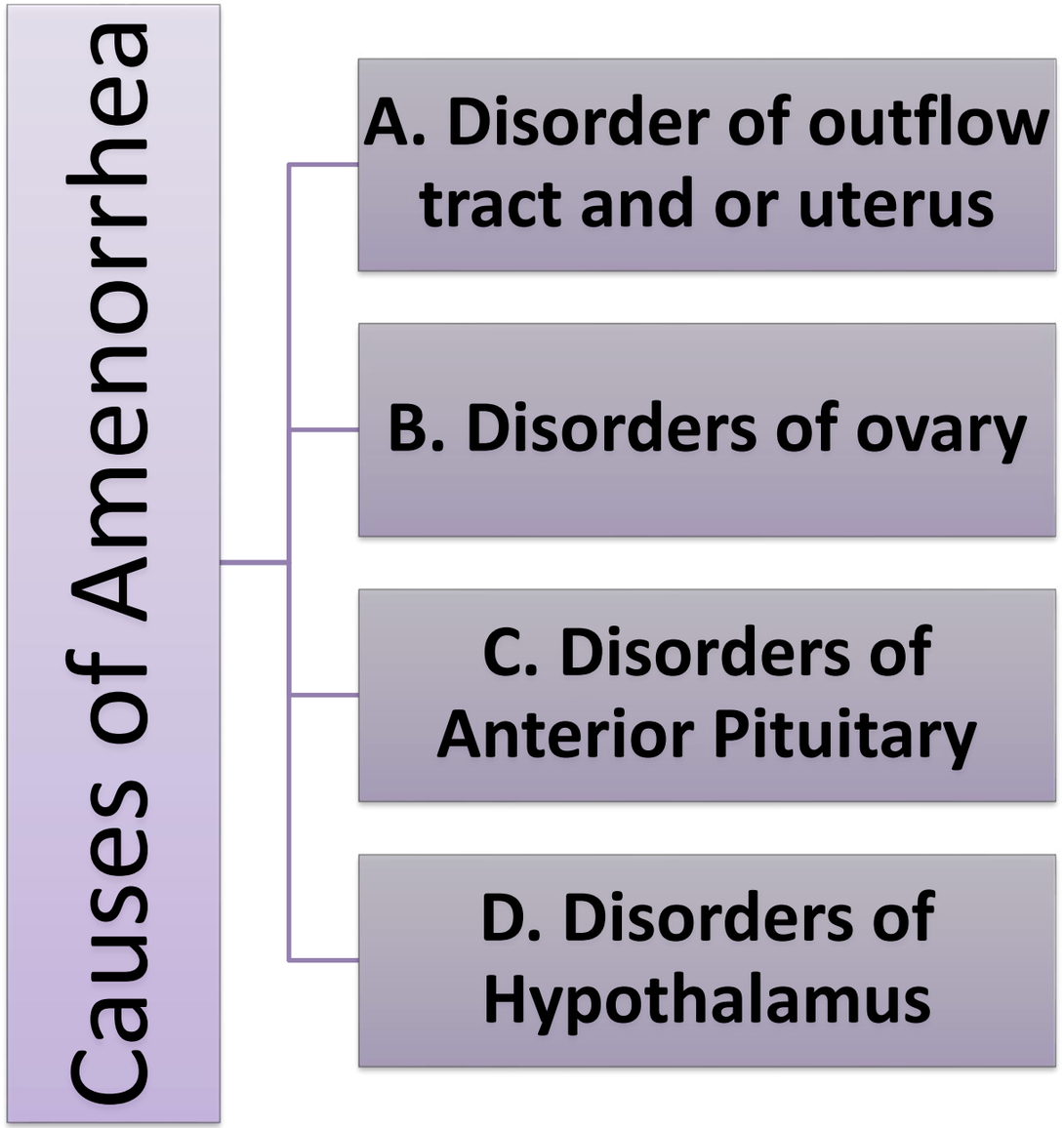
There is a difference of opinion about the age at which Primary Amenorrhea should be investigated
→ 18 yrs. often suggested**.**

Provided the patient has developed normal secondary sexual Characteristics and cryptomenorrhea has been excluded.

While those patient with Primary amenorrhea and sexual infantilism should be investigated at age of 15 years or 16 years (maybe earlier).

- **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 is truly secondary? (e.g. previous menses were actually steroid – induced)**
- **Careful physical examination aids in reaching a fairly firm provisional diagnosis.**
- **In minority, there is a need to go beyond simple out-patient investigation..**

CAUSES OF AMENORRHEA



DISORDERS OF OUTFLOW TRACT AND/OR UTERUS

1. CRYPTOMENORRHOEA

Vaginal atresia or imperforated hymen→ prevent menstrual loss from escaping.

- **An imperforated hymen should be suspected in adolescents who report monthly dysmenorrhea with the absence of vaginal bleeding.**

FEATURES:

✶Primary Amenorrhea in a teenage girl with normal sexual development present

Complaining of:

I. **Intermittent lower abdominal pain.**
II. **Possible difficulty of micturition.**
III. **Palpable lower abdominal swelling (Hematometra)**
IV. **Bulging, bluish membrane at lower end of vagina (Hematocolpus).**

MANAGEMENT: INCISE MEMBRANE (Hymenectomy)

2. ABSENCE OR HYPOPLASIA OF VAGINA:

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

DISORDERS OF OUTFLOW TRACT AND/OR UTERUS

3. TESTICULAR FEMINIZATION (Androgen Insensitivity syndrome):

- **Phenotype is woman. Genotype is man (xy) → testes are present.**
- **Inherited by an X-linked recessive gene (familial)**
- **Absence of cytosol androgen receptor.**

FEATURES:

i. **Growth and develop are normal (may be taller than average).**
ii. **Breasts are large but with sparse glandular tissue and pale areola.**
iii. **Inguinal hernia in 50% of cases.**
iv. **Scanty, or no axillary and pubic hair.**
v. **Labia minora underdeveloped.**
vi. **Blind vagina, absent uterus, rudimentary fallopian tubes.**
vii. **Testes→ in the abdomin or inguinal canal**
viii. **Normal levels of testosterone are produced BUT no response to androgens (endog. or exogen)**
ix. **No spermatogenesis**
x. **There is incidence of testicular neoplasia (50%)**
There is a risk of developing gonadoblastoma (benign) and eventually dysgerminoma (malignant)

Consider the diagnosis in a female child:

1) With inguinal hernia
2) With 1^0 amenorrhoea and absent uterus
3) When body hair is absent

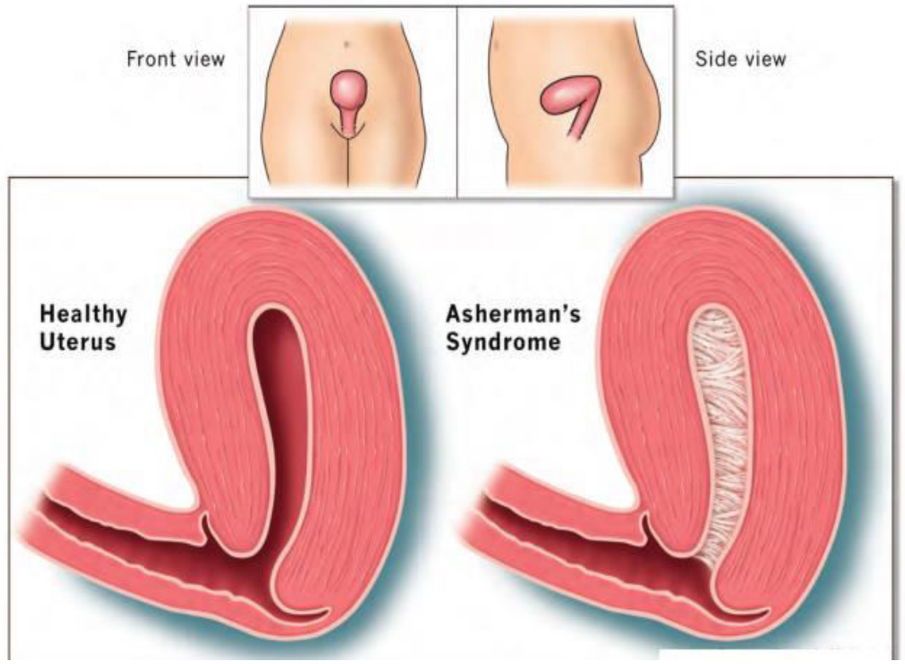
MANAGEMENT:

- **These patients are females.**
- **The gonads must be removed after puberty → then HRT started**

DISORDERS OF OUTFLOW TRACT AND/OR UTERUS

4. ASHERMAN'S SYNDROME:

Secondary amenorrhea following destruction of the endometrium by overzealous curettage→ multiple Synechiae show up on "Hysterography".



MANAGEMENT:

Under G.A. →breakdown intrauterine Adhesions through hysteroscope → insert an IUCD to deter reformation → hormone therapy (E_2 + P)

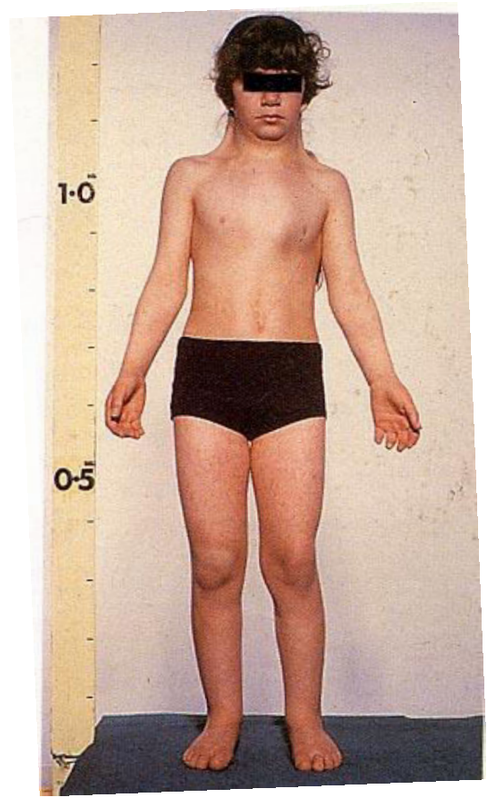
5. INFECTION

e.g. Tuberculosis. Ut. Schistosomiasis

DISORDERS OF THE OVARIES

1. CHROMOSOMAL ABNORMALITIES

Turner's syndrome (45 x 0) → gonadal dysgenesis



FEATURES:

I. Amenorrhoea (1^0, rarely 2^0)
II. Short stature
III. Failure of sec. sex. Develop
IV. Webbing of the neck→
V. Carrying angle
VI. Shield chest
VII. Coartution of aorta
VIII. Renal collecting system Defects
IX. Streak ovaries present
X. Gonadotrophins ↑↑
XI. Estrgoens

→ **Mosaic Chromosomal Pattern**
(e.g. XO/XX)→ lead to various degrees of gonadal dysgenesis and secondary amenorrhea + premature menopause

→ If Y-Chromosome is present in the genotype→ risk of gonadal malignancy makes gonadectomy advisable.

DISORDERS OF THE OVARIES

2. GONADAL AGENESIS:

(Failure of gonadal develop):→ no other congenital abnormalities.

3. RESISTANT OVARY SYNDROME

- **A rare condition**
- **Normal ovarian develop and potential**
- **FSH ↑↑**
- **It may resolve spontaneously**
- **If hot flushes → Rx. With estrogen**

4. PREMATURE MENOPAUSE:

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

Ovarian failure due to

i. Auto-immune diseases (associated with Addison's disease. ??)

ii. Viral infection (e.g. mumps)

iii. Cytotoxic drugs

Other causes of premature ovarian failure include: Ovarian injury from surgery, radiation, or chemotherapy, galactosemia, and carrier status of the fragile X syndrome.

5. PCOs:

- **Mostly present with classical Stein-Leventhal syndrome (of oligomenorrhoea, obesity, hirsuitism, and infertility)**
- **However a substantial group will have secondary amenorrhoea with no obesity or hirsuitism**
- **Diagnosis is made by finding LH/FSH ratio**
- **Confirmation is made by laparoscopy.**
- **USS +**

DISORDERS OF THE PITUITARY

1. Pituitary Tumor causing "Hyperprolactinemia"

40% of women with hyperprolactinemia will have a pituitary adenoma

Pit. Fossa XR is necessary in all cases of amenorrhea – particularly 2^0.

FEATURES: In coned view:

- ✶ **Erosion of clinoid process**
- ✶ **Enlargement of pituitary fossa**
- ✶ **Double flooring of fossa**

If any of above features seen → CT san or MRI + Assessment of visual fields

MANAGEMENT:

- ✶ **Bromocriptine (Dopamine agonist)**
  - **Suppress prolactin secretion**
  - **Correct estrogen deficiency**
  - **Permits ovulation**
  - **Size of most prolactinomas**

- ✶ **Surgical removal of tumor → extra-cellar manifestation (e.g. pressure on optic chiasma) or if patient cannot tolerate or respond to medical Rx.**

DISORDERS OF THE PITUITARY

2. OTHER CAUSE OF PROLACT.

- ♣ **Drugs: e.g. phenothiazines, methyl-dopa, metclopramide, anti-histamines, oestrogens and morphine.**

3. CRANIOPHARYNGIOMA

- ♣ **Other intracranial tumor**

4. SHEEHAN'S SYNDROME

- ♣ **Necrosis of ant. pituitary due to severe post partum hemorrhage → Pan – or partial hypopituitarism**
- ♣ **It is rare problem today due to better obstetric care and adequate blood transfusion**

More about Sheehan's Syndrome: https://www.khanacademy.org/science/health-and-medicine/human-anatomy-and-physiology/pregnancy/v/sheehan-syndrome

DISORDERS OF THE HYPOTHALAMUS

- **Commonest reason for hypogonadotrophic secondary amenorrhoea**
- **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 patient wishes to become pregnant**

DISORDERS OF THE HYPOTHALAMUS

1. WEIGHT – LOSS ASSOCIATED AMENORRHOEA

A loss of > 10 kg is frequently associated with amenorrhea

i. In young women and teen ages girls become obsessed with their body image and starve themselves.

ii. Jogger's amenorrhea: This is seen frequently in women training for marathon racing, in ballet dancers and other form of athletes.

CAUSES:

- **redistribution between proportion of body fat mass and body muscle mass.**
- **May be also mediated by exercise related changes in endorphins**

iii. ANOREXIA NERVOSA: Associated with sec. amenorrhoea (misnomer→ no loss of appetite

2. AMENORRHOEA AND ANOSMIA: rare cause of amenorrhoea of hypogonadotrophic – hypogonadism (Counterpart in males is Kallman's syndrome)

POST-PILL AMENORRHOEA:

- **There is no evidence that Est. prog. Contraceptive pills predispose to amenorrhoea once pill taking is ceased.**
- **An irregular menstrual cycle frequently precedes pill taking**
- **If this assumption of amenorrhoea being merely an after-effect of pill taking → many cases of hyperprolactinemia will be missed (1:5)**
- **And Premat. ovarian failure will be missed in 1:10 cases**
- **Once other causes are excluded, this type of ameno. Responds well to ovulation induction with Clomiphene citrate if preg. is desired.)**

INVESTIGATION OF AMENORRHEA

1. **Serum Prolactin level and TFT (Thyroid function test)**

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 PRL is normal + no galactorrhea → no need for further investigation for pituitary tumor.**
- **If galactorrhea 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 tumors.**
- **Visual fields assessment – if X-Ray abnormal**
- **FSH & LH level… especially if no withdrawal bleeding following progestrone challenge.**
- **↓ LH (<5 IU/ml)→ hypogonafotrophic- hypogonadism**
- **↑ FSH (>40 IU/ml) on successive readings → ovarian failure**

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

4. **USS: Of uterus and ovaries → can be useful to investigating and monitor Rx. Of these women**

SUMMARY

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

FLOW CHART FOR INVESTIGATING OF SEC. AMENORRHOEA

Complete History
Full Ph. exam.,tubal patency + sperm count

Amen. Traumatica
↓
Proof by Hysterogram

FSH, LH, TSH, P RL, X-RAY of Pit. Fossa

↑FSH, LH
↓
? Premat Menopause
↓
Biopsy Failed ?"Resist. Ovary

Low or N LH, FSH
↓
Clomid
↓
Response
↓
HPG or HMG

Hyperprolac.

Abn.Fossa

Tomograms

TSH ↑
↓
Thyroxin

Tumor
↓
Srug. & OR ext. radioth.
↓
Repeat MPS

No Tum

MPS

Bromocriptine

Best of luck!

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