Amenorrhea; Primary & Secondary

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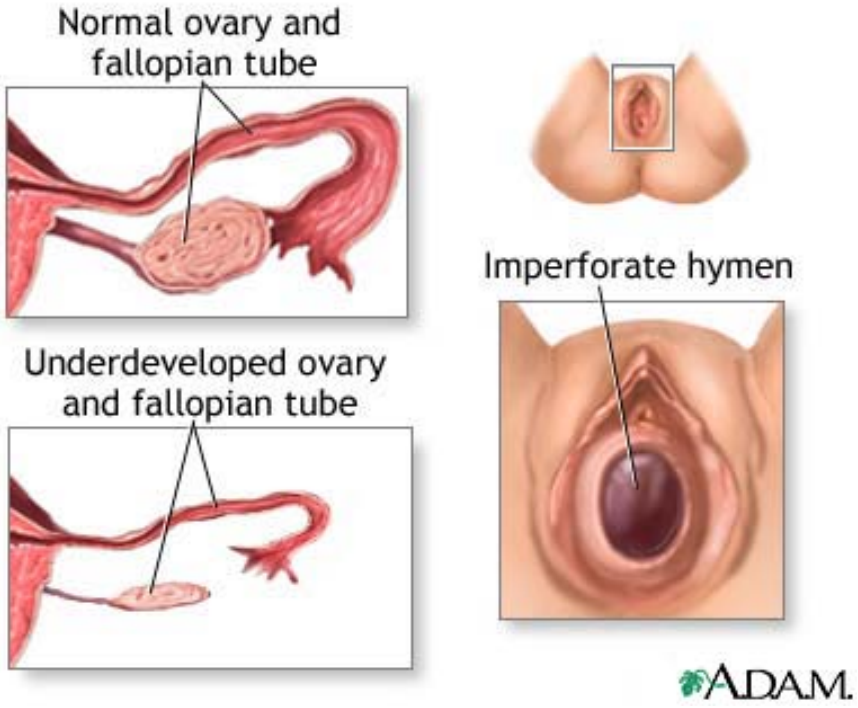


Amenorrhoea: Primary and Secondary

Primary Amenorrhoea

1. *No menstruation by the age of 14 years accompanied by failure to grow properly or develop secondary sexual characteristics. Menarche does not occur.*

2. *No menstruation by age of 16 when growth with secondary sexual characteristics' development being normal.*

Secondary Amenorrhoea

- *Secondary 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 Amenorrhoea should be investigated → 18 years is often suggested.

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

While those patient with Primary amenorrhoea and sexual infantilism should be investigated at about the age of 15 or 16 years (may be earlier).

***Cryptomenorrhoea**: a condition where menstrual products are prevented from exiting the body by a partial or complete obstruction (e.g. imperforate hymen).*

***Sexual infantilism**: failure to develop secondary sexual characteristics after the normal time of puberty.*

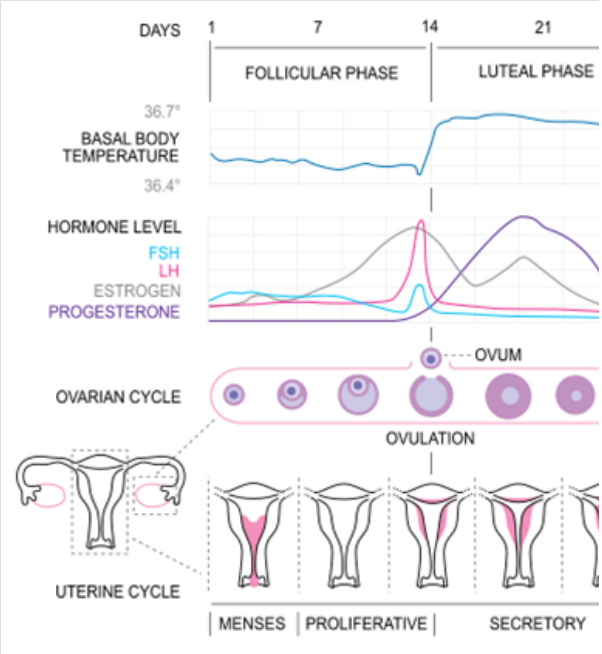
***From Hacker and Moore's:** The diagnosis of primary amenorrhea is made when no spontaneous uterine bleeding has occurred by the age of 16. The workup should be initiated earlier if there is no breast development (thelarche) by age 14 years or if the patient has failed to menstruate (menarche) spontaneously within 2 years of thelarche.*

- *Accurate, adequate history is essential to reach a firm diagnosis.*
- *Specific questioning is necessary to establish diagnosis of primary or secondary amenorrhoea.*
- *Is the amenorrhoea truly secondary? Ask if the previous menses were spontaneous or induced (e.g. previous menses may actually be steroid–induced).*
- *Careful physical examination aids in reaching a fairly firm provisional diagnosis.*
- *In a minority, there is a need to go beyond simple out-patient investigation.*

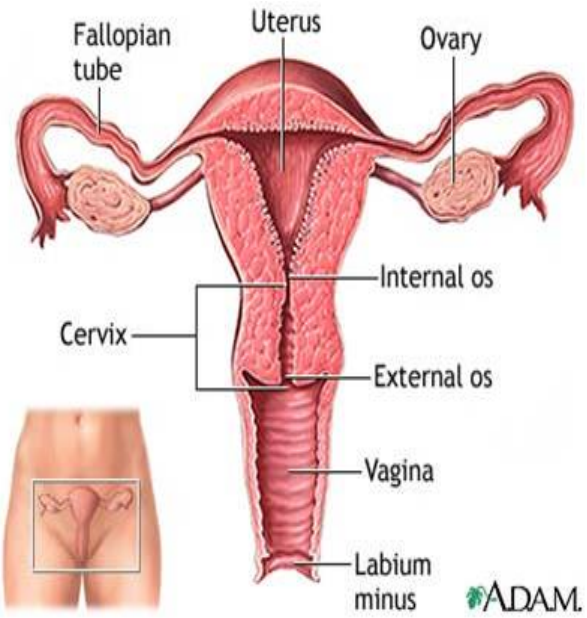
CAUSES OF AMENORRHOEA

1. *Disorders of outflow tract and/or uterus*
2. *Disorders of ovary*
3. *Disorders of anterior Pituitary*
4. *Disorders of hypothalamus*

Normal Menstrual Cycle



Normal Uterus



1. DISORDERS OF OUTFLOW TRACT AND/OR UTERUS

A. Cryptomenorrhoea

A condition where menstrual products are prevented from exiting the body by a partial or complete obstruction (Vaginal atresia or imperforate hymen).

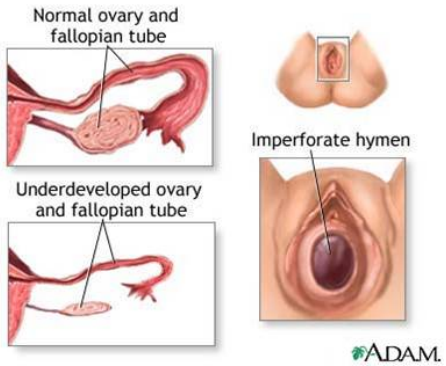
FEATURES:

Primary Amenorrhoea in a teenage girl with normal sexual development present complaining of:

1. *Intermittent lower abdominal pain.*
2. *Possible difficulty of micturition (Retained blood in the vagina → the vagina enlarges → pressure on the bladder → urinary retention and dysuria).*
3. *Palpable lower abdominal swelling (Haematometra).*
4. *Bulging, bluish membrane at lower end of vagina (Haematocolpos).*

***Haematometra**: collection of blood in the uterine cavity.*

***Haematocolpos:** accumulation of menstrual blood in the vagina.*



MANAGEMENT:

Incising the imperforate membrane (hymenotomy).

B. Absence Or Hypoplasia Of The Vagina

FEATURES:

1. *Growth, development, and ovarian function are usually normal.*
2. *Uterus may be normal or rudimentary.*
3. *Renal anomalies (in 30%) or skeletal defects (in 10%) may be present.*

MANAGEMENT:

Creating a functional vagina by surgery or dilators.

C. Androgen Insensitivity (Testicular Feminization)

failure of the normal masculinization of the external genitalia in chromosomally male individuals. This failure of virilization can be either complete androgen insensitivity syndrome (CAIS) or partial androgen insensitivity syndrome (PAIS), depending on the amount of residual receptor function.

- *Phenotype is female. Genotype is male (XY) → testes are present, but are undescended.*
- *Inherited by an X-linked recessive gene (familial).*
- *Resulting in absence of **cytosol androgen receptor**.*

From Hacker and Moore's: *Patients with **androgen insensitivity syndrome** –Pseudohermaphrodites- usually have mildly elevated FSH and LH levels because their testes are located within the abdominal wall or cavity. This location, with greater body heat, typically does not allow for normal male hormonal secretion. Breast development is caused by the testicular secretion of estrogens and by the conversion of circulating androgens to estrogens in the liver and elsewhere.*

FEATURES:

4. *Growth and development are normal (may be taller than average).*
5. *Breasts are large but with sparse glandular tissue and pale areola.*
6. *Inguinal hernia in 50% of cases.*
7. *Scanty, or no axillary and pubic hair.*
8. *Labia minora underdeveloped.*
9. *Blind vagina, absent uterus, rudimentary fallopian tubes. Due to the secretion of antimüllerian hormone during development.*
10. *Testes in abdomen or inguinal canal.*
11. *Normal levels of testosterone are produced. But no response to androgens (endogenous or exogenous).*
12. *No spermatogenesis.*
13. *There is ↑ incidence of testicular neoplasia (50%).*

CONSIDER THE DIAGNOSIS IN A FEMALE CHILD:

- With inguinal hernia.
- With primary amenorrhoea and absent uterus.
- When body hair is absent.

MANAGEMENT:

- These patients are females (phenotypically). Thus, the creation of a neovagina (a functional vagina) is part of the treatment.
- The gonads must be removed after puberty → then HRT (Hormone Replacement Therapy) must be started, to avoid neoplasia (i.e. gonadoblastoma and dysgerminoma).
- Rare cases of incomplete testicular feminization do occur → have variable degrees of masculinization.

D. Asherman's Syndrome:

Secondary amenorrhoea following destruction of the endometrium by overzealous curettage (during D & C)→ multiple synechiae show up on hysterography.

Patients with Asherman's syndrome should be evaluated by hysterosalpingography or sonohysterography.

Synechiae: Intrauterine scarring and adhesions.

Hysterography: Radiography of a uterine cavity filled with contrast medium.

MANAGEMENT:

Under general anesthesia→ intrauterine adhesions are excised by a hysteroscope→ an IUCD is inserted to prevent adhesion reformation→ hormone therapy with estradiol and progesterone (E_2 + P).

E. Infection

e.g. Tuberculosis. Schistosomiasis.

2. DISORDERS OF THE OVARIES

A. Chromosomal Abnormalities

Turner's syndrome (45 X0) → gonadal dysgenesis.

FEATURES:

- Amenorrhoea (1^0, rarely 2^0).
- Short stature.
- Failure of secondary sexual development.
- Webbing of the neck → increased carrying angle.
- Shield (broad) chest.
- Coarctation of aorta.
- Renal collecting system defects.

☛

- ***Streak ovaries present***.
- ***Gonadotrophins ↑↑***
- ***↓ Estrogens***

Mosaic Chromosome 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 (gonadoblastoma –a benign germ cell tumor- and eventually dysgerminoma –a malignant germ cell tumor-) makes gonadectomy advisable.

Mosaicism: *is a condition in which cells within the same person have a different genetic makeup. It is caused by an error in cell division very early in the development. Examples of mosaicism include:*

- *Mosaic Down Syndrome*
- *Mosaic Klinefelter Syndrome*
- *Mosaic Turner Syndrome*

From Hacker and Moore's: Most affected patients show no signs of secondary sexual characteristics , occasionally a person with Turner's syndrome will have sufficient ovarian follicular activity and secrete enough estrogen to cause breast development, menstruation, ovulation, and rarely even pregnancy.

B. Gonadal Agenesis

Failure of gonadal development → no other congenital abnormalities. FSH is elevated in these patients.

C. Resistant Ovary Syndrome

A rare condition that is characterized by amenorrhoea, endogenous hypergonadotrophinemia, and resistance to exogenous gonadotrophins. It is thought to be secondary to a receptor block on the surface of the ovary to FSH, antibodies to gonadotrophins (FSH and LH) or a post receptor defect, that prevents the ovary from responding.

- *Normal ovarian development and potential.*
- *Elevated FSH.*
- *It may resolve spontaneously.*
- *If associated with hot flushes → treated with estrogen.*

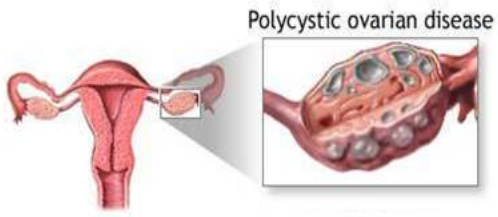
D. Premature Menopause

Premature Ovarian Failure (POF) due to:

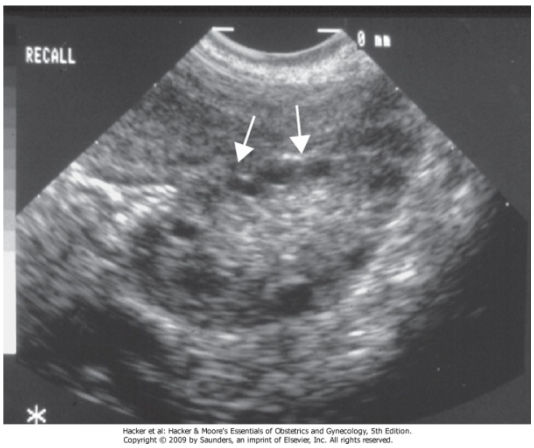
- *Auto-immune disease (associated with Addison's disease, Hashimoto's…).*
- *Viral infection (e.g. mumps).*
- *Cytotoxic drugs.*

E. PCOS

A chronic condition that has been defined as anovulation or oligo-ovulation with clinical or laboratory evidence hyperandrogenism.



Mostly present with classical Stein-Leventhal syndrome (oligomenorrhea, obesity, hirsutism, and infertility)



- *However a substantial group will have secondary amenorrhoea with no obesity or hirsutism.*
- *Diagnosis is made by detecting 2 of the 3 following findings:*
  - *Clinical/biochemical hyper-androgenism (hirsutism or any result from high androgen).*
  - *Cyclical or fertility problems (amenorrhea, irregular periods or infertility).*
  - *U.S evidence.*
- *One of the characteristics is a ↑ LH/FSH ratio*
- *Confirmation is made by laparoscopy.*
- *Ultrasound Scan (USS): multiple subcapsular follicular cysts with their "string of pearls" appearance. The cysts are inactive and arrested in mid-antral stage of development. The cysts are located peripherally in the cortex of the ovary.*

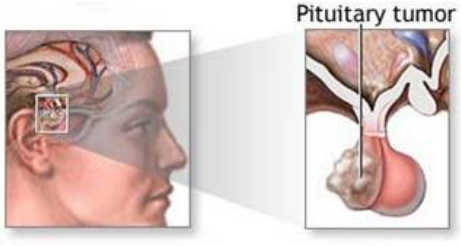
Sometimes, PCOS can present without cysts, and ultrasonographic findings are not necessary to establish the diagnosis.

The ovarian stroma is hyperplastic and usually contains nests of luteinized theca cells that produce androgens. Patients with PCOS exhibit increased levels of LH, which promotes androgen secretion from theca cells. Patients, also, have estrogen levels that are higher than normal due to the peripheral conversion of androgen to estrogen. Thus, they present with virilization –due to ↑ androgens- and they are at risk of developing endometrial hyperplasia and cancer –due to the unopposed estrogen release-.

3. DISORDERS OF PITUITARY

A. Pituitary Tumor causing "Hyperprolactinemia"

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



FEATURES

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

If any of the above features is present, CT scan or MRI + Assessment of visual fields (to detect hemianopia).

MANAGEMENT

1. ***Bromocriptine (Dopamine agonist):***

   - *Suppresses prolactin secretion.*
   - *Corrects estrogen deficiency.*
   - *Permits ovulation.*
   - *↓ Size of most prolactinomas.*

2. ***Surgical removal of tumor:***

If extracellar manifestations are present (e.g. pressure on optic chiasma), or if patient cannot tolerate or respond to medical treatment.

B. Other Causes Of Increased Prolactin Secretion

Drugs: e.g. phenothiazines, methyl-dopa, metoclopramide, anti-histamines, estrogens and morphine.

C. Craniopharyngioma

Intracranial tumor

D. Sheehan's Syndrome

Necrosis of the anterior pituitary due to severe PPH (Post-Partum bleeding) resulting in pan – or partial hypopituitarism. It is a rare problem today due to advanced obstetric care and adequate blood transfusion.

4. DISORDERS OF 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.*

OTHER TYPES OF AMENORRHEA

WEIGHT – LOSS ASSOCIATED AMENORRHEA

A loss of > 10 kilograms is frequently associated with amenorrhoea.

- *In young women and teenage girls who become obsessed with their body image and starve themselves.*
- ***Jogger's amenorrhoea:*** *This is seen frequently in women training for marathon racing, in ballet dancers and other athletes due to strenuous daily exercise.*
- ***Anorexia Nervosa:*** *Associated with secondary amenorrhoea. (anorexia is a misnomer → because it means: loss of appetite, and people with anorexia nervosa do not in fact, lose their appetites).*

Kallman's syndrome is thought to be caused by autosomal mutations that prevent the embryologic migration of GnRH neurons into the hypothalamus. These individuals may have other anomalies of midline structures of the head. One in 50,000 females is affected. It is characterized by low gonadotrophin levels with primary amenorrhea due to mutations of the GnRH receptor gene.

CAUSES

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

AMENORRHOEA AND ANOSMIA

- *Anosmia; a lack of functioning olfaction (inability to perceive odors)*
- *A rare cause of amenorrhoea of hypogonadotrophic hypogonadism. (Counterpart in males is Kallman's syndrome).*

POST-PILL AMENORRHOEA

- *There is no evidence that Estrogen-progesterone 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 Premature ovarian failure will be missed in 1:10 cases*
- *Once other causes are excluded, this type of amenorrhea responds well to ovulation induction with* ***Clomiphene citrate*** *if pregnancy is desired.*

INVESTIGATIONS OF AMENORRHOEA

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 (per vaginal) =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 pituitary gland is necessary, regardless of prolactin level and menstrual pattern.*
- *If PRL is significantly elevated (excluding stress) → Radiology exam of pituitary to exclude the presence tumor. Visual fields assessment should be performed if X-Ray abnormal.*
- *FSH & LH level, especially if there is no withdrawal bleeding following progesterone challenge.*

- *LH (<5 IU/ml) → hypogonadotrophic-hypogonadism.*
- *FSH (>40 IU/ml) on successive readings → ovarian failure.*

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

5. ***USS:*** *Of uterus and ovaries → can be useful to investigating and monitor treatment of these women.*

Investigations of secondary amenorrhea:

- *It's held according to the following:*
  1) *Pregnancy? → check for beta-hCG*
  2) *Anovulation? → do progesterone challenge test*
  3) *Estrogen deficiency (due to ovarian or HPO-axis failure) → do 'estrogen + progesteron'e challenge test*
  4) *Outflow tract lesion → hysterosalpingogram*

Anovulation investigation

A. *High GnRH → Ovaries problem*
B. *Low GnRH → Hypothalamus or pituitary problem*
C. *Normal GnRH → pregnancy, anovulation-other-causes or outflow tract lesion*