Amenorrhea

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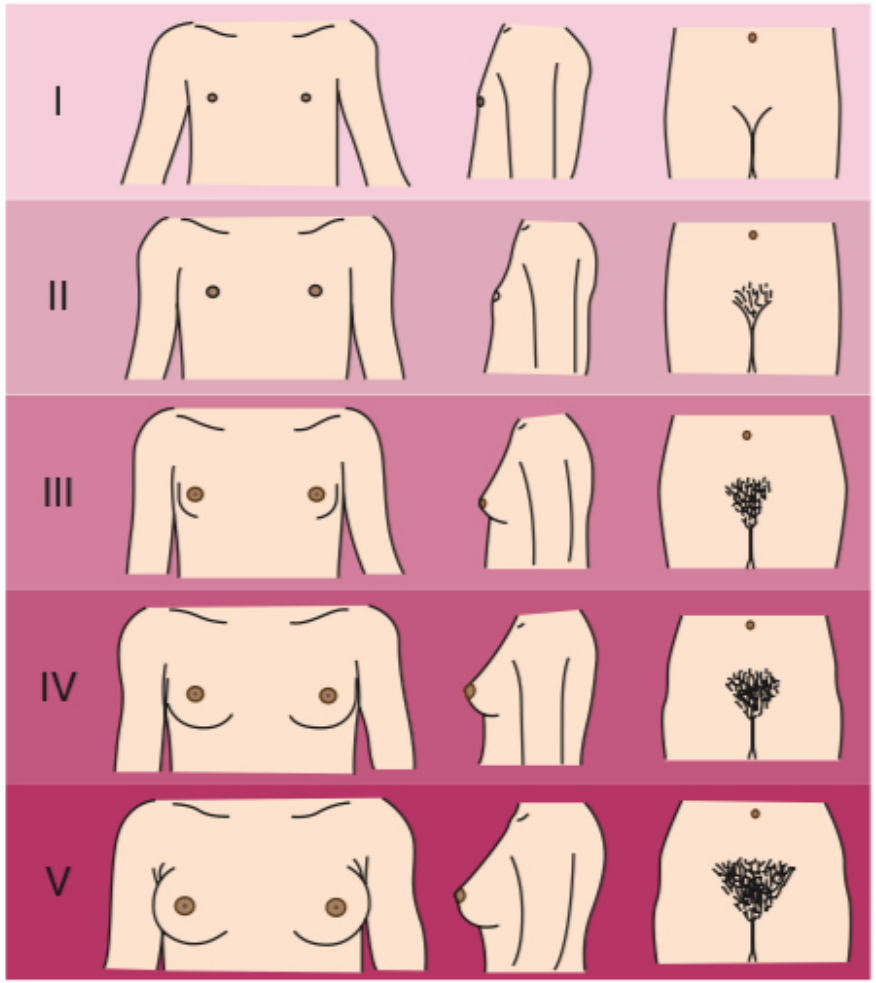
- **Amenorrhea is the absence of menstruation in a woman of childbearing age.**
- It is divided into two types: **primary and secondary.**
- **Primary amenorrhoea:**

➢Failure to establish menstruation by **15 years of** age in girls **with normal** secondary sexual characteristics (**SSC**)and **By 13 years of age** in girls with **no secondary sexual characteristics.**

- **Secondary amenorrhea:**

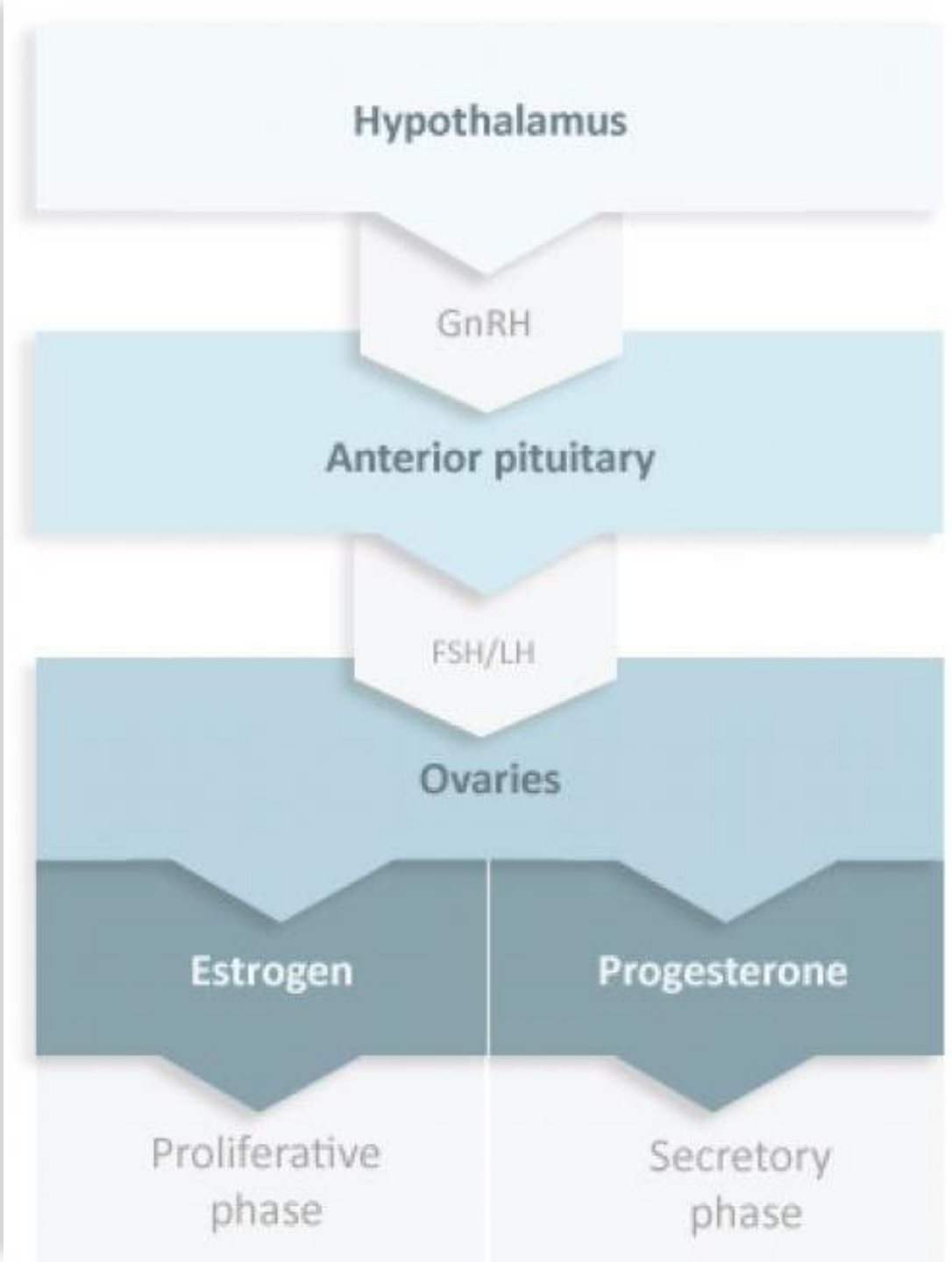
➢Absence of menstruation for **at least 6 consecutive** months in women with previously normal and regular menses **or for 12 months in women with prior oligomenorrhoea.**



Tanner stages	Breast development	Pubic hair growth
Stage I	Prepubertal.	Prepubertal.
Stage II	Breast buds form.	Few long, downy hairs at the labia majora.
Stage III	Breast buds larger.	Pubic hair growth continues, but mainly central.
Stage IV	Breasts in a 'mound' form.	Pubic hair in the triangular adult shape, but smaller.
Stage V	Breasts fully formed.	Pubic hair adult in shape, quantity, and type, and spread to the inner thighs.

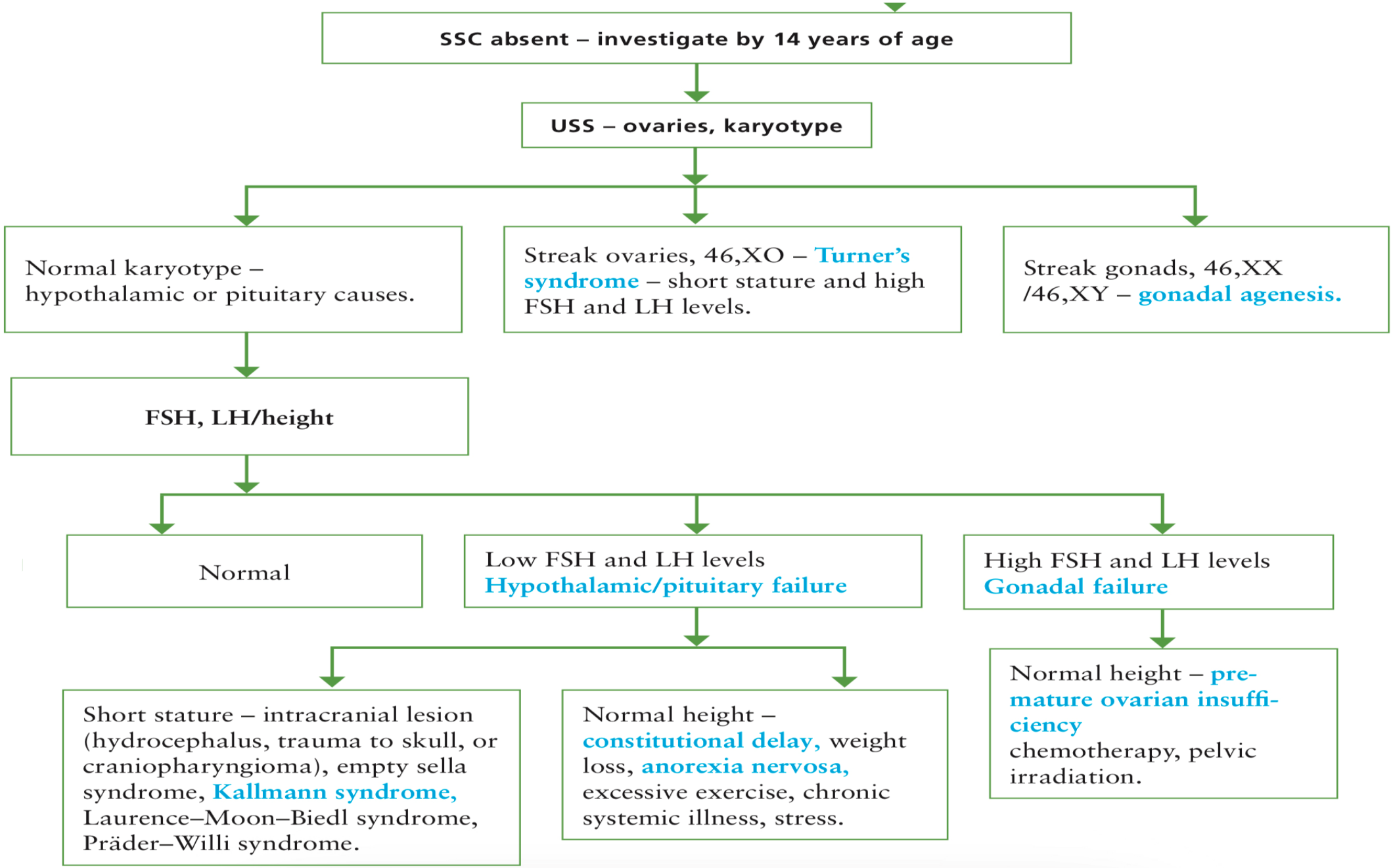
Role of hormones in amenorrhoea

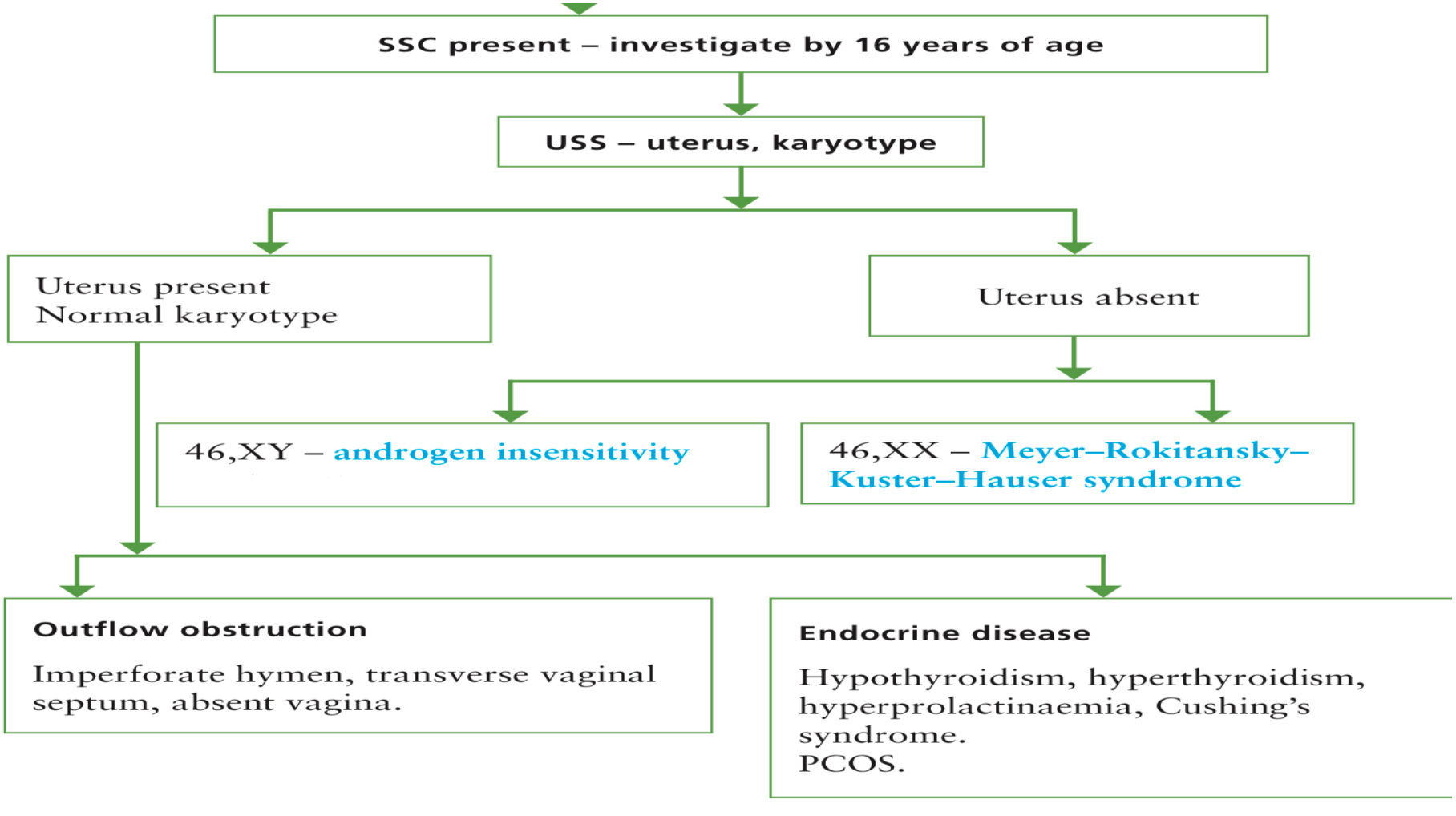
- The **hypothalamus** produces gonadotrophin releasing hormone (**GnRH**) which acts on the **pituitary** to release (follicle-stimulating hormone) **FSH** and (leutenising hormone) **LH**, These gonadotrophins then stimulate the release of **estrogens** and **progesterones** from the **ovary**, which are then responsible for the formation and breakdown of the **endometrium**.
- **Interruption** of this axis results in amenorrhoea.



How can the causes of amenorrhea be categorized?

- Uterus or outflow tract.
- Ovary.
- Pituitary.
- Hypothalamus or central nervous system.
- Endocrine system


SSC absent – investigate by 14 years of age
USS – ovaries, karyotype
Normal karyotype – hypothalamic or pituitary causes.
Streak ovaries, 46,XO – Turner's syndrome – short stature and high FSH and LH levels.
Streak gonads, 46,XX /46,XY – gonadal agenesis.
FSH, LH/height
Normal
Low FSH and LH levels Hypothalamic/pituitary failure
High FSH and LH levels Gonadal failure
Short stature – intracranial lesion (hydrocephalus, trauma to skull, or craniopharyngioma), empty sella syndrome, Kallmann syndrome, Laurence–Moon–Biedl syndrome, Präder–Willi syndrome.
Normal height – constitutional delay, weight loss, anorexia nervosa, excessive exercise, chronic systemic illness, stress.
Normal height – premature ovarian insufficiency chemotherapy, pelvic irradiation.



Total testosterone level

High (≥ 5.0 nmol/L) – late-onset congenital adrenal hyperplasia, Cushing's syndrome, or androgen-secreting tumour, 5α-reductase deficiency

Moderately increased (2.5–5.0 nmol/L) may be seen in PCOS

What are the most common causes of primary amenorrhea?

- The **most common** cause of primary amenorrhea is **gonadal dysgenesis,** such as in **Turner** syndrome this accounts for more than 40% of cases.
- Müllerian agenesis (**Mayer-Rokitansky-Küster-Hauser Syndrome)** is the **second most common** cause, accounting for 15% of patients with primary amenorrhea.

History in primary amenorrhea

- Sexual history, **exclude pregnancy.**
- **Cyclical lower abdominal pain,** haematocolpos (genital tract malformation).
- **Stress, depression, weight loss, disturbance of perception of weight or shape, level of exercise, and chronic systemic illness (hypothalamic dysfunction.)**
- **Headache, visual disturbance, or galactorrhoea** (Prolactinoma)
- **Family history of late menarche** . (constitutional delay)
- **Family history of autoimmune disorders, premature menopause.**
- **Medication** (such as antipsychotic), previous chemotherapy or radiotherapy, and illicit drug use (opiates and cocaine).

Examination

- Height and weight (**BMI**).
- Blood pressure.
- **Secondary sexual characteristics** (Tanner staging).
- **Breast** development , **pubic or axillary hair.**
- **Features of chromosomal abnormality** i.e Turner's syndrome.
- **Hirsutism, virilization, galactorrhoea.**
- Signs of **thyroid** and **other endocrine disease.**
- Abdominal examination rarely may reveal a suprapubic **mass.**

Examination …

- **External genitalia , clitoromegaly**
- Pelvic examination – inappropriate in young girls who are not sexually active, **examination can be effectively undertaken under anesthesia**
- **Speculum examination or vaginoscop .**
- Atrophic appearance of the external genitalia and loss of rugosity of the vaginal epithelium are features that would suggest a diagnosis of POI.

Investigations

- Trans-abdominal USS to assess pelvic anatomy – uterus, ovaries.
- Karyotype.
- Hormonal profile – FSH, LH, prolactin, TSH, testosterone.
- Other hormones or enzymes.
- Examination under anaesthesia.
- Bone mineral density.
- CT/MRI of head.

Outflow tract obstruction

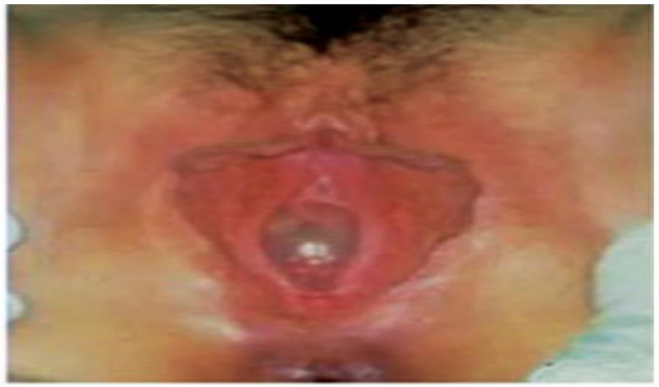
- **Imperforate hymen:**

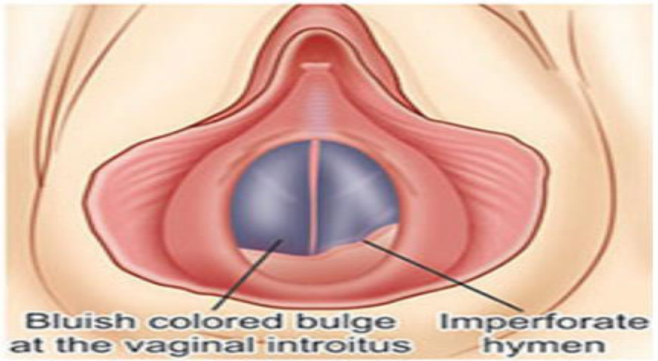
➢Normal SSC.

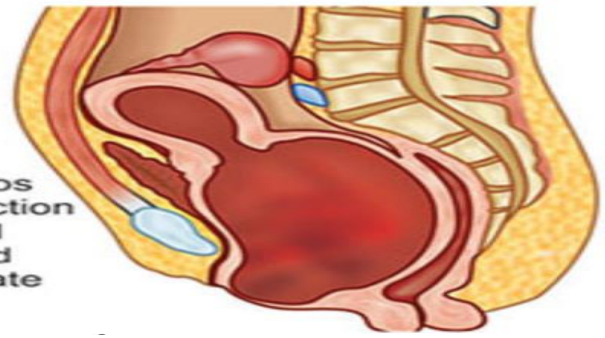
➢Cyclical lower abdominal pain.

➢Visible haematocolpos with a bulging purple/blue, stretching thin hymen at introitus.

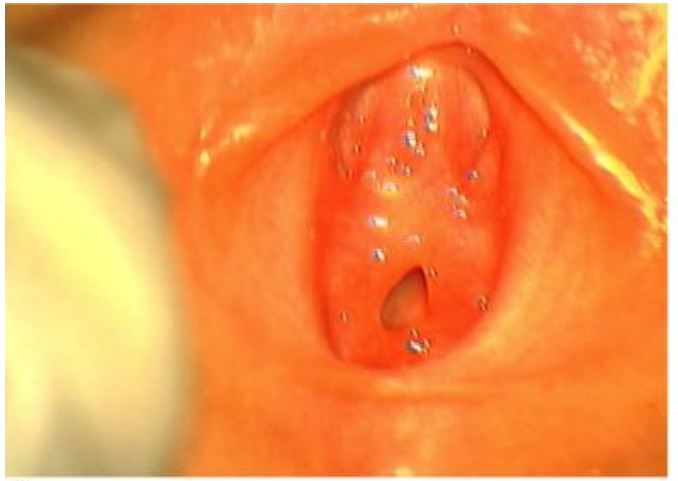
- **USS** may show haematometra.
- **Treatment** – surgery – simple cruciate incision on the hymen.







Secondary hematocolpos due to collection of menstrual blood behind an imperforate hymen



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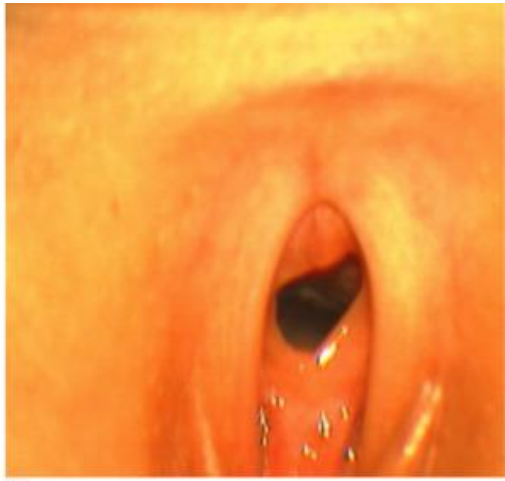

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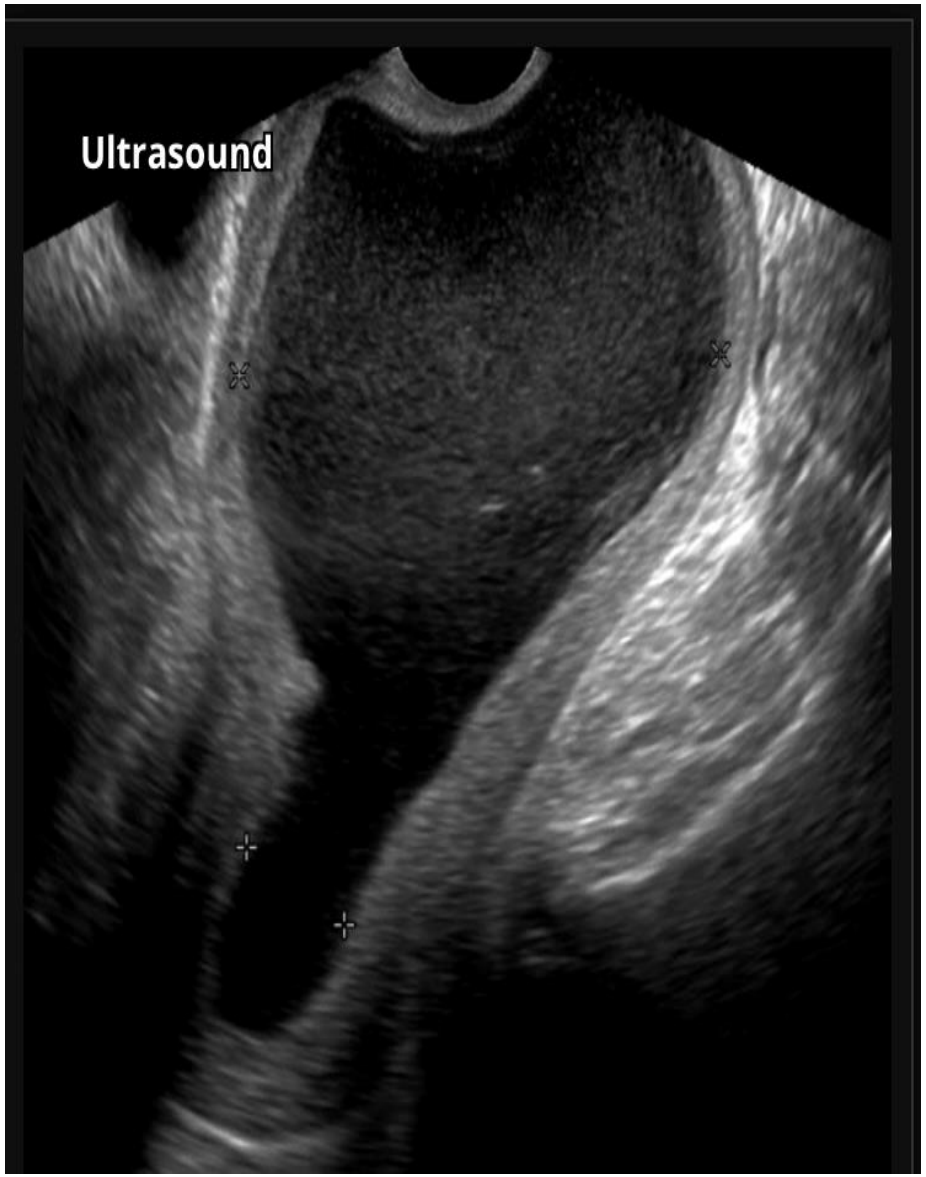
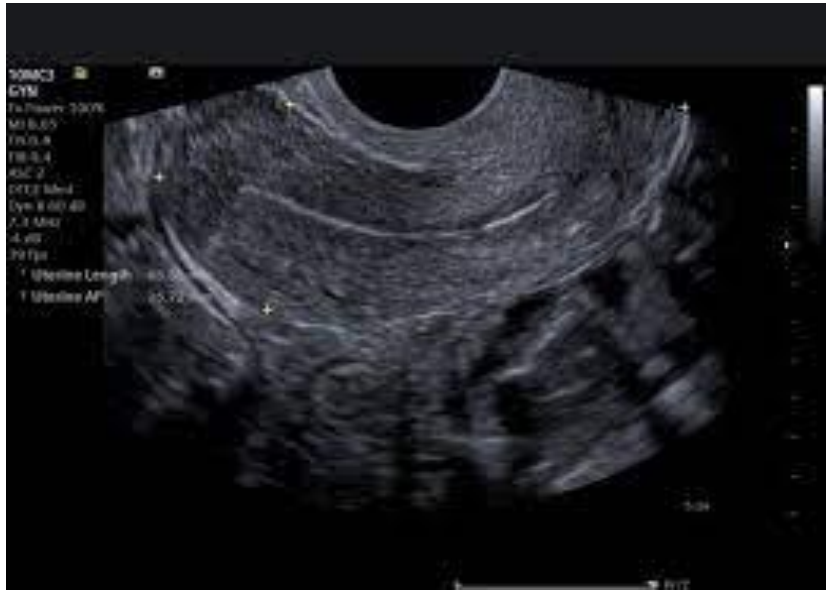
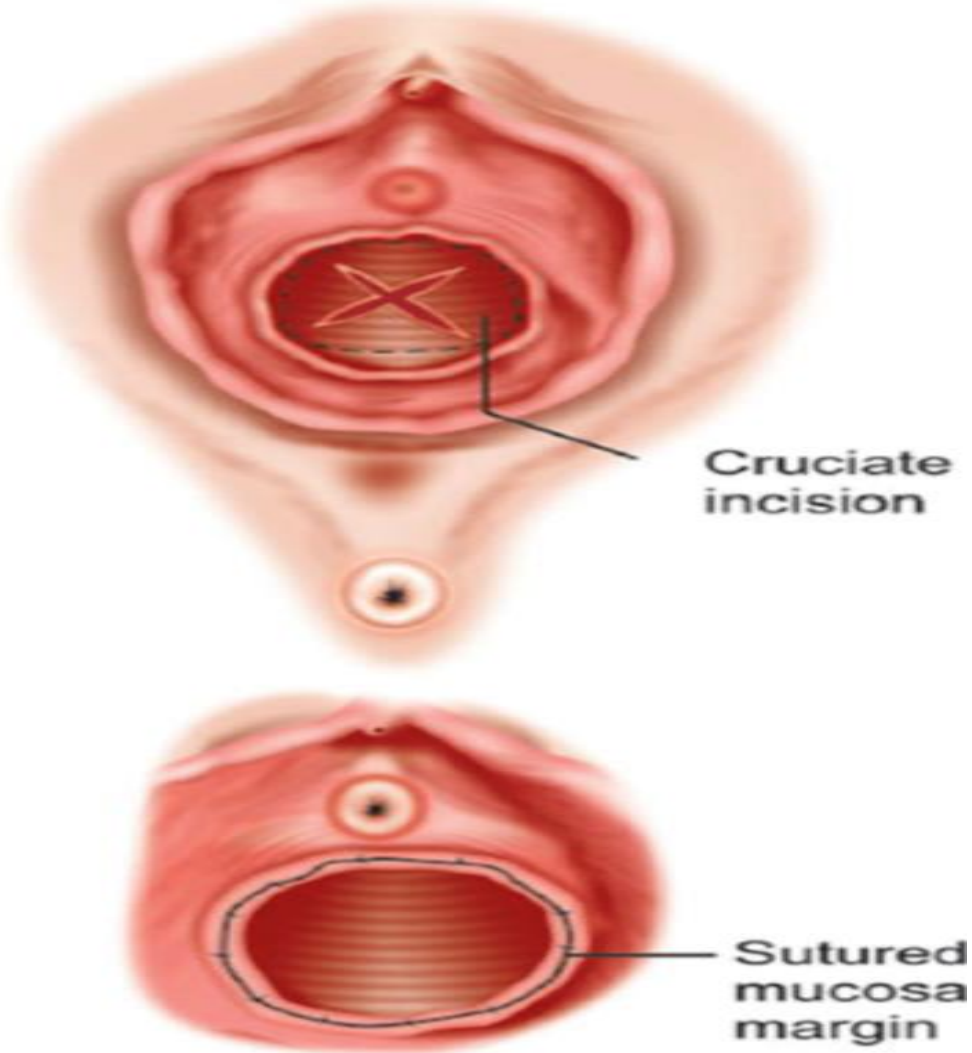

Ultrasound




Cruciate
incision
Sutured
mucosa
margin

Outflow tract obstruction

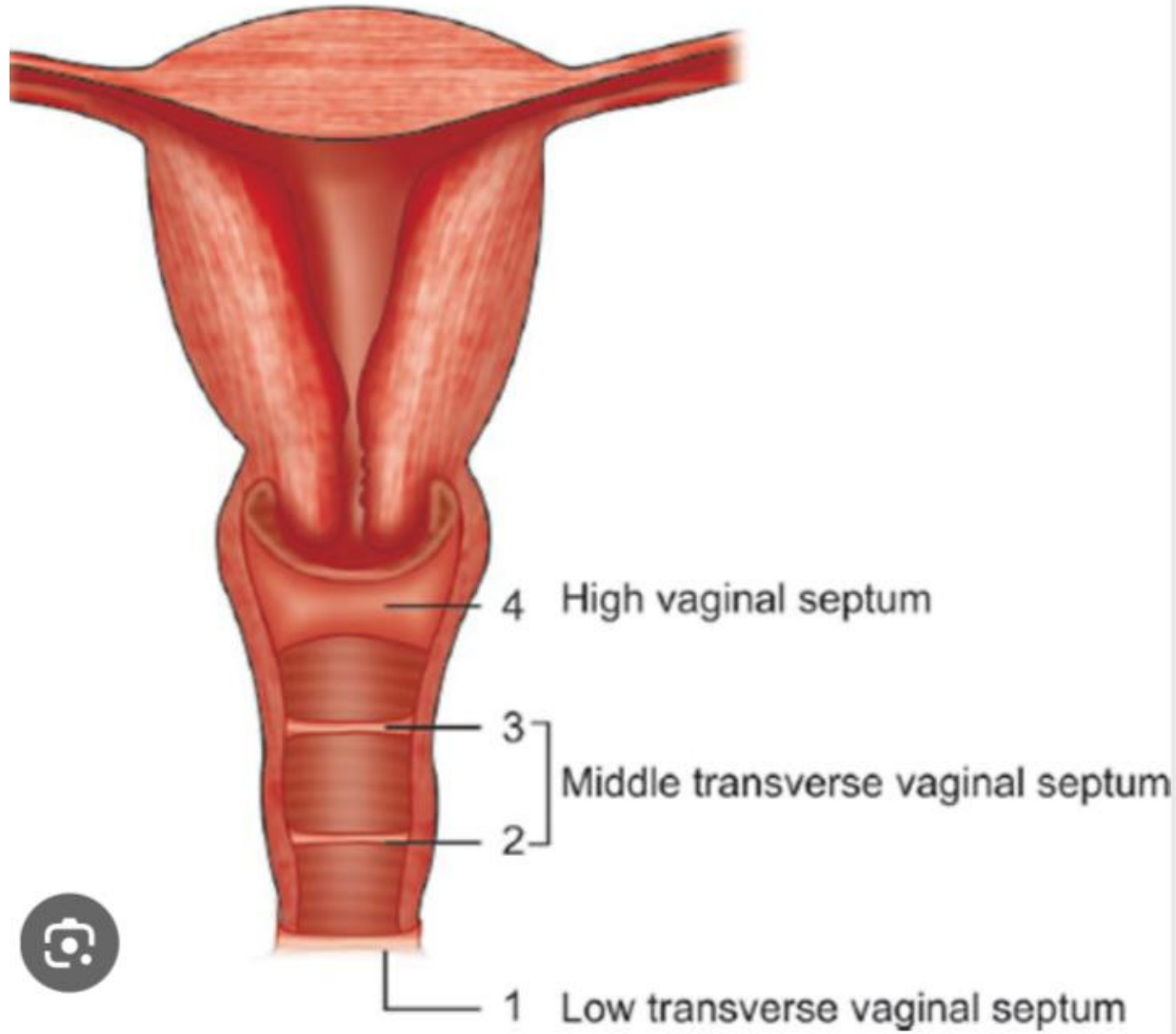
- **Transverse vaginal septum:**
- Owing to failure of fusion or canalization between the Müllerian tubercle and sinovaginal bulb.

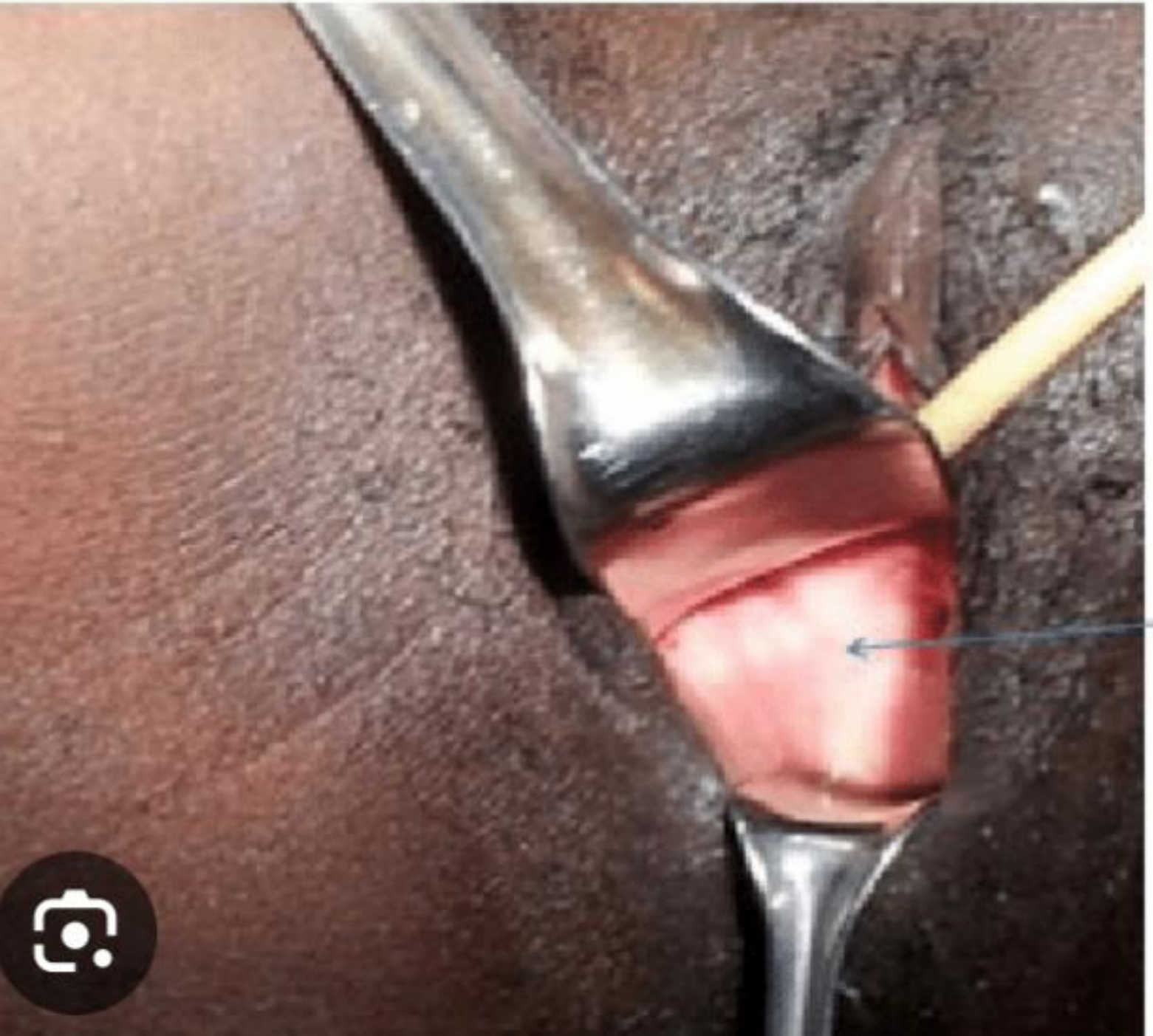
➢Normal SSC.

➢Cyclical lower abdominal pain.

➢Pink bulge at introitus as the septum is thicker than the hymen.

- Treatment – surgery


4 High vaginal septum
3
Middle transverse vaginal septum
2
1 Low transverse vaginal septum



Mayer–Rokitansky–Kuster–Hauser syndrome

- **It's the** müllerian **agenesis**
- **46,XX, normal female phenotype.**
- Incidence 1/5000 female births.
- **mutation** in the galactose-1-phosphate uridyltransferase (GALT) **gene** Although the **exact mechanisms remain unknown.**
- Ovarian tissue functions normally, normal hormones therefore **normal SSC.**
- **Müllerian ducts fail to fuse.**
- **Uterine** development is **rudimentary or absent**
- Vaginal agenesis with **short and blind ending vagina.**
- **External genitalia has normal appearance.**

Mayer–Rokitansky–Kuster–Hauser syndrome

- May be **associated with renal tract** (15–40%) and **skeletal anomalies** (10–20%).
- **Investigations**:
  - Karyotyping.
  - Pelvic ultrasonography
  - MRI is more accurate
  - Laparoscopy
- The **primary goal of treatment** in women with müllerian agenesis—**creation of a functional vagina** when the time is appropriate (Sexual function).
  - progressive vaginal dilation
  - Surgery to create neovagina
- **Fertility – oocytes retrieval and surrogacy.**
- **Uterine transplant**

Androgen Insensitivity Syndrome (AIS)

- **Complete AIS** (testicular feminization) is a form of male pseudohermaphroditism, the term referring to the **gonadal sex (male)** and the contrasting **phenotype female**
- the **third most common cause of primary amenorrhea**, after gonadal dysgenesis and müllerian agenesis.
- Patients with AIS have:
  - **normal male karyotype(46,XY)**
  - **testes as gonads that produce both testosterone and AMH.**
- an inactivating **mutation** in the **gene** encoding the intracellular androgen receptor (AR) (located on the long arm of the X chromosome, Xq) results in an **end-organ insensitivity to androgen** actions that prevents normal masculinization of the internal and external genitalia during embryonic development

AIS

- In the **absence of androgen action**, differentiation of the **external genitalia follows the "default" female pattern of development**
- **AMH signaling is intact in AIS, the internal genitalia follow the male** pattern of differentiation with regression of the müllerian structures.

- The **vagina is short and ends blindly** (derived only from the urogenital sinus).
- Patients with complete AIS appear as normal females at birth.
- **Growth and development during childhood also are generally normal**, although **overall height usually is above average.**
- At **puberty**, the **breasts develop**, driven by estrogen derived from the peripheral conversion of high circulating testosterone levels.

AIS

- **Pubic and axillary hair do not develop**, due to the absence of androgen action.
- The **gonads are testes**, and their location may be **intra-abdominal**, but often are partially descended into the **inguinal canal.**
- After puberty, the testes contain immature seminiferous tubules lined by immature germ cells and Sertoli cells, **with no evidence of spermatogenesis.**

AIS

- **Patients with complete AIS most commonly present** after the age of puberty in late adolescence or as young adults with primary amenorrhea.
- **Uncommonly,** AIS may be recognized at birth or in childhood during workup for an inguinal mass or hernia, particularly when the disorder is reasonably suspected because other family members such as a sister or maternal aunt are affected.

AIS

- The **management** of patients with complete AIS has two major components:

1. One focusing on **creation of a functional vagina** to allow attainment and optimization of potential for sexual relations
2. Another relating to the **risk for developing malignancy** in the cryptorchid testes

- **Gonadectomy** is indicated because the incidence of neoplasia in cryptorchid testes is relatively high.

AIS

- **Gonadectomy is recommended at the time of diagnosis** in other intersex states such as XY gonadal dysgenesis (**Swyer syndrome**),but it **is better delayed in those with AIS, for two reasons:**

1. The smooth pubertal development that results from **endogenous gonadal hormone production** is difficult to achieve with exogenous hormone treatment,
2. Gonadal tumors develop less often in patients with AIS and rarely before puberty.

- **Gonadectomy and hormone therapy (physiologic estrogen treatment)** generally are best postponed until after pubertal development is complete, by approximately age 16–18.
- **Complete AIS is the only exception to the rule** that gonads with a Y chromosome should be removed as soon as the diagnosis is made.

Swyer Syndrome (46,XY Gonadal Dysgenesis)

- **less common** form of gonadal dysgenesis that is characterized by a **46,XY karyotype.**
- Despite the **presence of a Y chromosome**, the phenotype is female because the dysgenetic (streak) gonads produce **neither AMH nor androgens.**
- Consequently, the **vagina, cervix, uterus, and fallopian tubes develop normally and the internal and external genitalia fail to masculinize.**
- **Undeveloped or Poorly developed secondary sexual characteristics.**
- 10– 15% of the affected individuals, a **mutation** of the SRY (Sex-determining Region **of the Y** chromosome) **gene** that is located on the short arm of the Y chromosome
- In the remainder, **no cause can be determined.**

Swyer Syndrome (46,XY Gonadal Dysgenesis)

- **Gonadectomy** is indicated soon after diagnosis is made due to the significant risk for malignant transformation in occult testicular elements (20–30%).
- Hormonal replacement therapy .

Turner's syndrome

- **Most common cause of gonadal dysgenesis.**
- **45,XO. Classical features** – short stature, webbing of the neck, cubitus valgus, widely spaced nipples, cardiac and renal abnormality, autoimmune hypothyroidism.
- **Mosaicism – spontaneous menstruation may occur, but leads to POF.**
- Streak gonads.
- **Treatment – low-dose oestrogen to promote breast development without affecting linear growth. Cyclical oestrogen and progesterone treatment for maintenance.**
- Fertility – egg donation.

Anorexia nervosa

- **Weight 10–12% less than ideal body weight.**
- **Growth spurt usually occurs, but SSC are absent.**
- **Associated features** – constipation, hypothermia, cold intolerance, bradycardia, hypotension, lanugo-type hair.
- **Low LH, FSH, E2;** anaemia; ECG abnormality in 52%, abnormal GTT in 37% of cases.
- **Management**:

➢Dietary therapy, psychotherapy, antidepressants.

➢Oestrogen replacement.

What causes athletic amenorrhea, and should it be treated?

- In athletes, amenorrhea can result from **high physiologic stress levels, energy deficit, or abnormal eating habits.**
- Physiologic stress can **increase catechol estrogens and endorphins** and cause the hypothalamus to **decrease the pulse frequency of GnRH release.**
- Over time, the **hypogonadotropic hypogonadism** that ensues can lead to osteoporosis and stress fractures.
- The combination of disordered eating, amenorrhea, and osteoporosis is referred to as the female athlete triad.
- Athletic amenorrhea **should be treated**; patients should be encouraged to improve their diet, decrease stress levels, and decrease the amount of strenuous exercise if possible.
- Estrogen and progesterone should be replaced (oral contraceptives are a good option) if lifestyle changes are not effective.

Kallman's syndrome

- **Congenital gonadotrophin deficiency** characterized by **anosmia** or hyposmia and other cranial anomalies.
- The **classical** X-linked form of the disorder is caused by a variety of **genetic mutations** in the KAL gene (located on the short arm of the X chromosome, Xp22.3) encoding anosmin-1, a neural adhesion molecule that promotes migration of GnRH neurons, and olfactory neurons, from the olfactory placode into the hypothalamus during embryonic development

What are enzyme defects can cause amenorrhea?

- **Congenital adrenal hyperplasia (CAH)** is an **autosomal recessive** disorder that can be caused by a variety of enzyme defects involved in steroidogenesis.
- Symptoms result from excessive or deficient production of mineralocorticoids, androgens, and estrogens.
- The **most common** enzyme deficiency in CAH is that of **21-hydroxylase**.
- Girls with **classic CAH** caused by 21-hydroxylase deficiency have **ambiguous genitalia** at **birth** as a result of exposure to androgens in utero, as well as salt wasting (hypona- tremia and hypovolemia) from decreased mineralocorticoids.
- The **nonclassic** form of 21-hydroxylase deficiency, however, may manifest in adolescents or young adults with **oligomenorrhea or amenorrhea and hirsutism.**
- **17-Hydroxyprogesterone** is elevated in patients with 21-hydroxylase deficiency.

- Another enzyme deficiency in CAH is that of **17 alpha hydroxylase,** which causes a lack of sex steroid and cortisol production and elevated mineralocorticoids.
- **Girls with this defect have normally developed external genitalia but experience delayed puberty and primary amenorrhea because of a lack of estrogen production.**
- Excess mineralocorticoids can also lead to hypertension, hypernatremia, and hypokalemia.
- These patients require exogenous estrogen and progesterone to attain sexual maturity and prevent osteoporosis.
- Other enzyme defects include defects of 11beta -hydroxylase and 3 beta hydroxysteroid dehydrogenase.

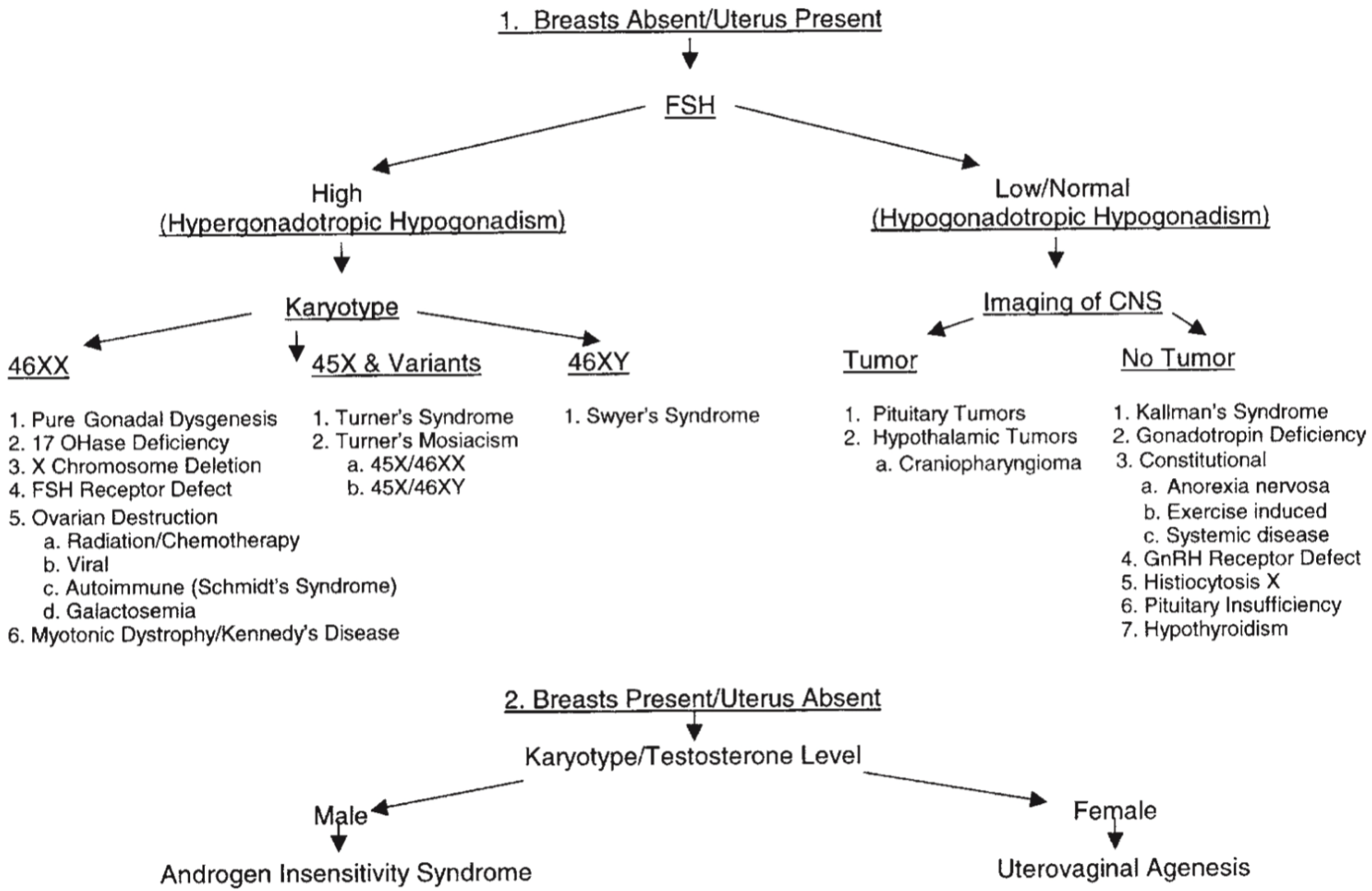
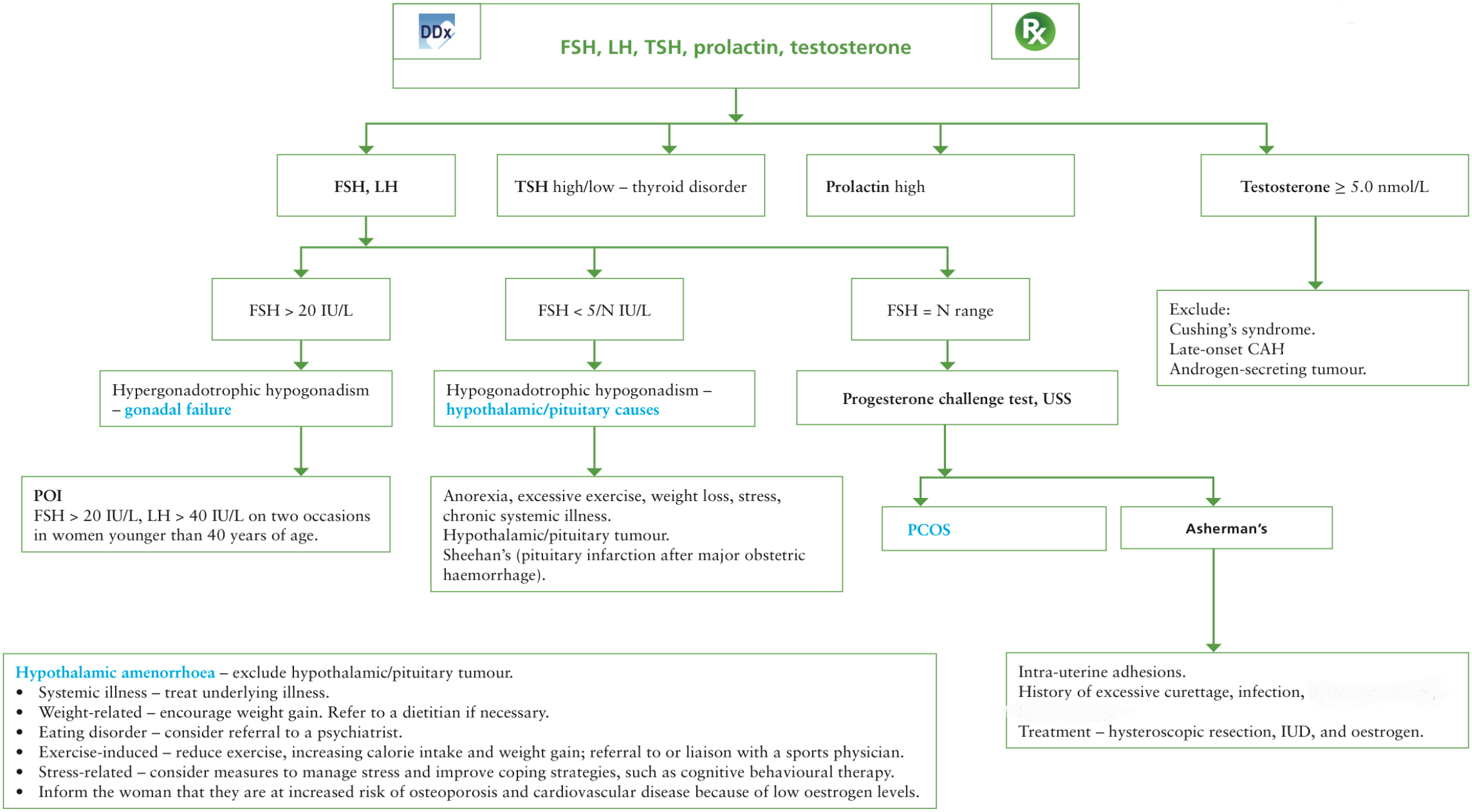


Figure 22-1. Workup of primary amenorrhea. *CNS,* Central nervous system; *FSH,* follicle-stimulating hormone.

Secondary amenorrhoea

- Absence of menstruation for
- ➢ **at least 6 consecutive** months in women with previously normal and regular menses
- ➢ **for 12 months in women with prior oligomenorrhoea.**
- ➢ **40% of the causes of secondary amenorrhoea are ovarian .**
- ➢ **35% hypothalamic- pituitary.**
- ➢ **5% uterine.**


DDx
FSH, LH, TSH, prolactin, testosterone
Rx
FSH, LH
TSH high/low – thyroid disorder
Prolactin high
Testosterone ≥ 5.0 nmol/L
FSH > 20 IU/L
FSH < 5/N IU/L
FSH = N range
Exclude:
Cushing's syndrome.
Late-onset CAH
Androgen-secreting tumour.
Hypergonadotrophic hypogonadism – gonadal failure
Hypogonadotrophic hypogonadism – hypothalamic/pituitary causes
Progesterone challenge test, USS
POI
FSH > 20 IU/L, LH > 40 IU/L on two occasions in women younger than 40 years of age.
Anorexia, excessive exercise, weight loss, stress, chronic systemic illness.
Hypothalamic/pituitary tumour.
Sheehan's (pituitary infarction after major obstetric haemorrhage).
PCOS
Asherman's
Intra-uterine adhesions.
History of excessive curettage, infection,
Treatment – hysteroscopic resection, IUD, and oestrogen.
Hypothalamic amenorrhoea – exclude hypothalamic/pituitary tumour.
• Systemic illness – treat underlying illness.
• Weight-related – encourage weight gain. Refer to a dietitian if necessary.
• Eating disorder – consider referral to a psychiatrist.
• Exercise-induced – reduce exercise, increasing calorie intake and weight gain; referral to or liaison with a sports physician.
• Stress-related – consider measures to manage stress and improve coping strategies, such as cognitive behavioural therapy.
• Inform the woman that they are at increased risk of osteoporosis and cardiovascular disease because of low oestrogen levels.

History

- History of infertility.
- Headache, visual disturbances, or galactorrhoea – pituitary tumour.
- Acne and hirsutism – PCOS.
- Weight loss or gain – eating disorders.
- Stress or depression – stress-related hypothalamic amenorrhoea.
- Exercise level – exercise-associated hypothalamic amenorrhoea.
- Symptoms of thyroid and other endocrine disease.

History

- Menstrual, obstetric, and surgical history such as endometrial curettage – intrauterine adhesions (Asherman's syndrome).
- Hot flushes and vaginal dryness – POI.
- Medical history, including chemotherapy, pelvic radiotherapy – POI.
- Diabetes – associated with PCOS
- Autoimmune disorders – associated with POI.
- Cranial radiotherapy, head injury, or major obstetric haemorrhage – hypopituitarism.
- Medication (such as antipsychotics) and illicit drug use (cocaine and opiates).
- Family history of cessation of menses before 40 years of age – POI.

Examinations

- Measure height and body weight, and calculate **BMI**.
- Examine for **galactorrhoea**, if appropriate.
- Signs of **excess androgens** (hirsutism, acne) or **virilization** (hirsutism, acne, deep voice, temporal balding, increase in muscle bulk, breast atrophy, and clitoromegaly).
- **Acanthosis nigricans** (associated with PCOS).
- Signs of **thyroid disease.**
- Signs of **Cushing's syndrome** (striae, buffalo hump, significant central obesity, easy bruising, hypertension, and proximal muscle weakness).
- Fundoscopy to assess **visual fields if a pituitary tumour** is suspected.
- Exclude pregnancy.

Investigations

- FSH, LH, prolactin, TSH.
- Total testosterone and sex hormone-binding globulin.
- Ultrasonography
- Images
- Pregnancy test.

Asherman Syndrome (Intrauterine Adhesions)

- results from **intrauterine adhesions** that obstruct or obliterate the uterine cavity, **because of trauma**.
- Disruption of the full thickness of the endometrium including the zona basalis, commonly resulting from **instrumentation** of the uterine cavity, is the most common mechanism for intrauterine scarring.
- **amenorrhea, dysmenorrhea,** hypomenorrhea, infertility, or recurrent pregnancy loss.
- **Diagnosed by** :

1. Transvaginal or transabdominal ultrasonograph ultrasound evidence of a thin, hyperechoic, and often irregular endometrial echo.
2. Saline infusion sonogram (SIS) or hysterosalpingography (HSG)
3. Hysteroscopy provides a definitive diagnosis and treatment through hysteroscop to remove the adhesions.

Sheehan Syndrome

- **Acute infarction** and ischemic necrosis of the **pituitary gland** resulting **from postpartum hemorrhage** and consequent hypovolemic hypotension
- Remains one of the most common causes of hypopituitarism in the underdeveloped or developing countries.
- **Failed lactation after delivery is the classical and earliest presenting symptom.**
- **clinical picture varies** with the severity of the pituitary insult, ranging from severe hypopituitarism soon after delivery, manifesting as lethargy, anorexia, and weight loss, **to secondary amenorrhea,** loss of sexual hair, and less severe symptoms of fatigue that emerge weeks and months later.
- Deficiencies in GH, prolactin, and gonadotropins are most common, although the majority also exhibit ACTH and TSH deficiencies.

What are the causes of primary ovarian insufficiency (POI)?

- POI is defined as **ovarian failure before the age of 40 years.**
- It is also referred to as premature ovarian failure.
- It has **several causes:**
- **Genetic defects**, including Turner syndrome and fragile X syndrome.
- **Toxins** can include chemotherapy, radiation, and certain viruses.
- **Autoimmune disease:** This can also cause thyroiditis, diabetes, and primary adrenal insufficiency(Addison disease).
- **Metabolic disorders:** These disorders include galactosemia.
- Up to **80%** of the time, POI is **idiopathic**.

What are the hypothalamic causes of amenorrhea?

- **Dysfunctional** gonadotropin-releasing hormone (**GnRH) secretion**:
  - **Excessive exercise.**
  - **Eating disorders.**
  - **Malnutrition.**
- **Isolated gonadotropin deficiency**:
  - **Kallmann** syndrome (lack of GnRH neurons associated with **anosmia**) .
  - **Idiopathic**.
- **Infection**: tuberculosis, encephalitis or meningitis, syphilis, or sarcoidosis.
- **Neoplasms**: craniopharyngioma, Langerhans cell histiocytosis, other tumors

What are pituitary causes of amenorrhea?

- **Cell damage** leading to **deficient LH and FSH secretion**:

➢**Autoimmune disease.**

➢**Thrombosis.**

➢**Hemorrhage (Sheehan syndrome.)**

- **Neoplasms**: most commonly **prolactinoma**, but also inactive adenomas or other hormone-secreting pituitary tumors including growth hormone leading to acromegaly and adrenocorticotropic hormone, with resulting Cushing syndrome.

What medications can cause amenorrhea?

- **Medications that stimulate prolactin secretion**

➢Prolactin has an inhibitory effect on GnRH secretion.

- **Dopamine antagonists:** Dopamine is a negative feedback inhibitor of prolactin release, so these medications **lead to increased prolactin secretion.**
- **Antidepressants**, (e.g., tricyclics)
- **Antipsychotics** (e.g., risperidone and haloperidol)
- **Some antiemetics** (e.g., metoclopramide)
- Selective serotonin reuptake inhibitors (**SSRIs**) and monoamine oxidase inhibitors (**MAOIs**) can induce amenorrhea through hyperprolactinemia.
- Other medications with this property include histamine receptor antagonists (**H2-blockers**), reserpine, methyldopa, opiates, benzodiazepines, barbiturates, estrogens, and antiandrogens.

- Based on the hormonal profile a classification system by the WHO divides patients into groups based on endogenous oestrogen production, follicle-stimulating hormone (FSH) levels, prolactin levels and hypothalamic-pituitary dysfunction .
- Group I: low oestrogen, low FSH, and no hypothalamic-pituitary pathology, leading to a diagnosis of hypogonadotrophic hypogonadism.
- Group II: normal oestrogen, normal FSH, and normal prolactin, leading to a diagnosis of polycystic ovary syndrome.
- Group III: low oestrogen and high FSH, leading to a diagnosis of gonadal failure.

Thank you