


# Amenorrhea

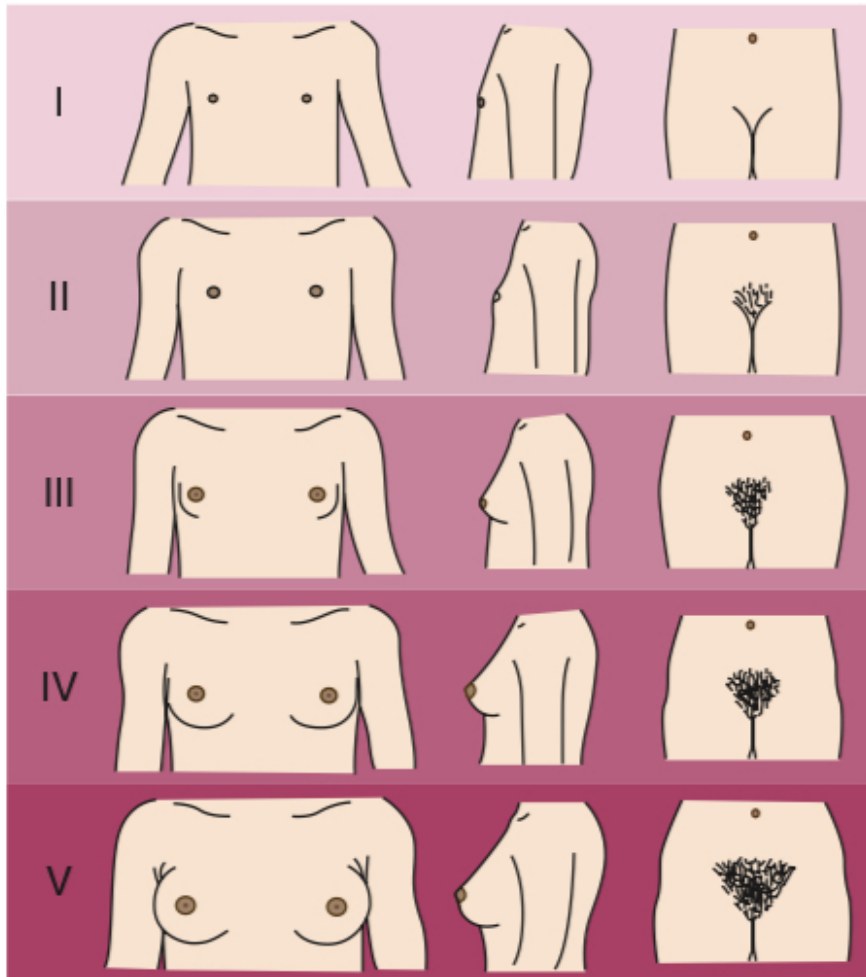
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- **Amenorrhea is the absence of menstruation in a woman of childbearing age.**
  - It is divided into two types: **primary and secondary.**
  - **Primary amenorrhoea:**
    - Failure to establish menstruation by **15 years of age** in girls **with 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

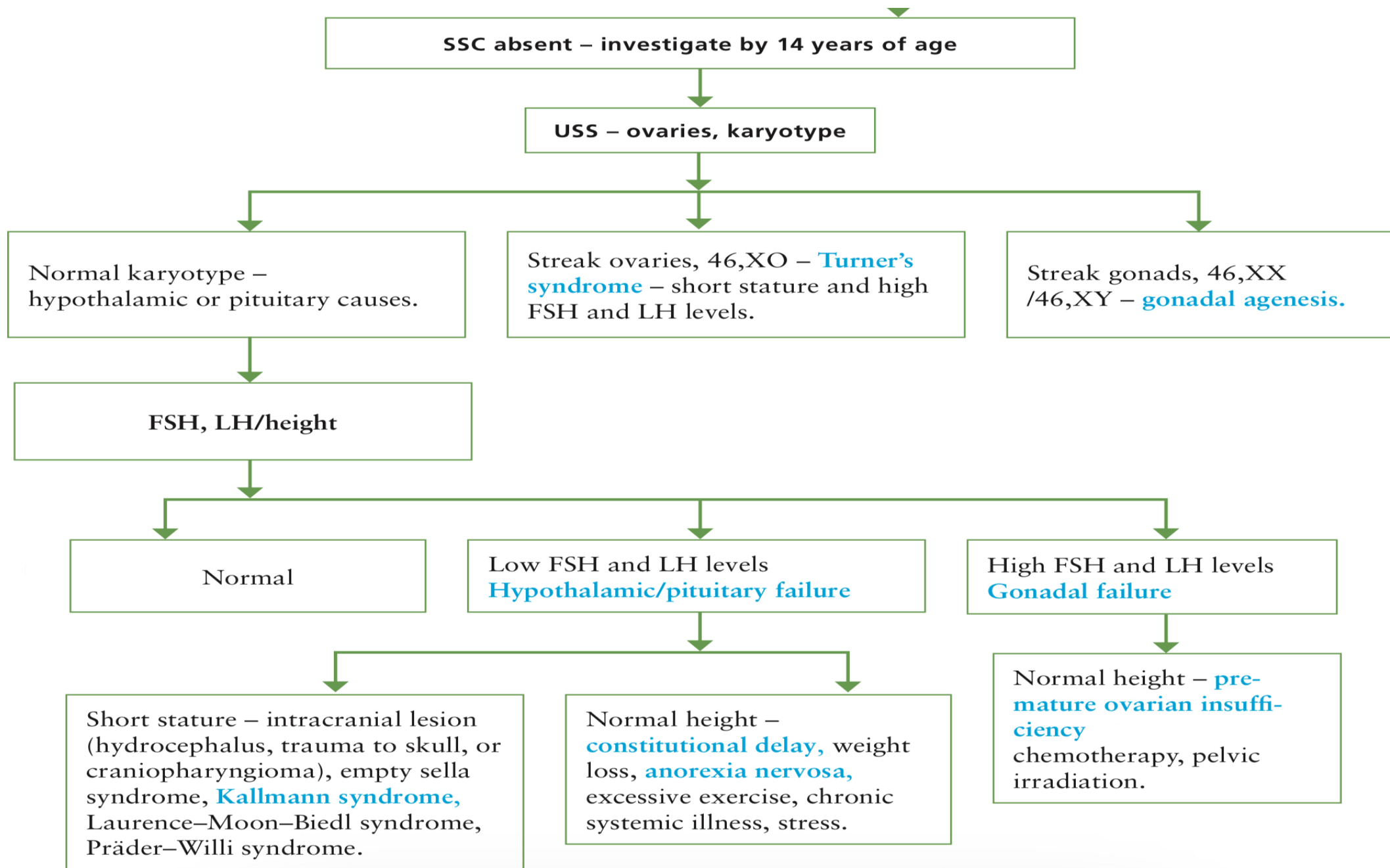
- The **hypothalamus** produces gonadotrophin releasing hormone (**GnRH**) which acts on the **pituitary** to release (follicle-stimulating hormone) **FSH** and (leutenising hormone) **LH**, These gonadotrophins then stimulate the release of **estrogens** and **progesterones** from the **ovary**, which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

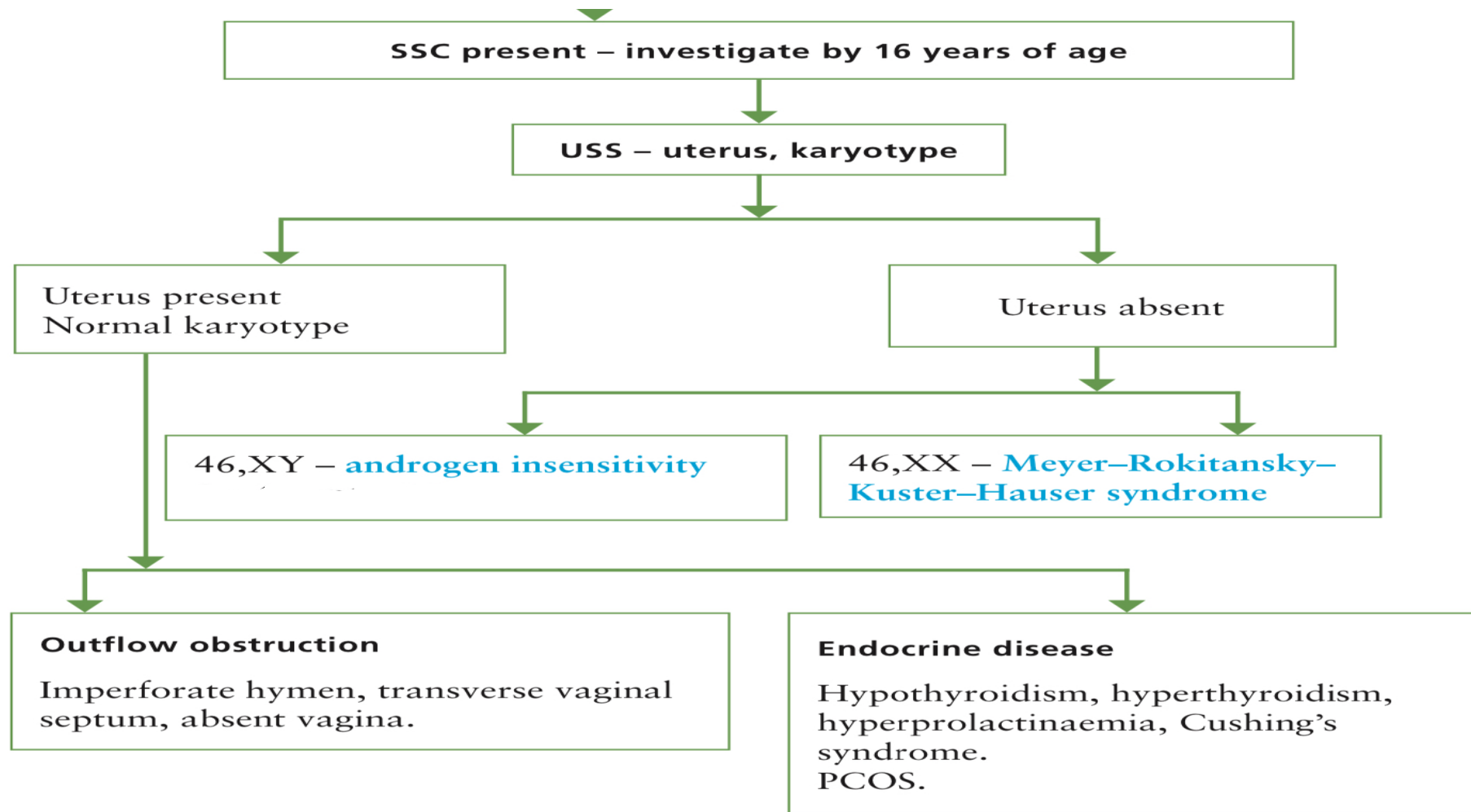


How can the causes of amenorrhea be categorized?

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








**Total testosterone level**

**High** ( $\geq 5.0$  nmol/L) – **late-onset congenital adrenal hyperplasia**, Cushing's syndrome, or androgen-secreting tumour,  $5\alpha$ -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

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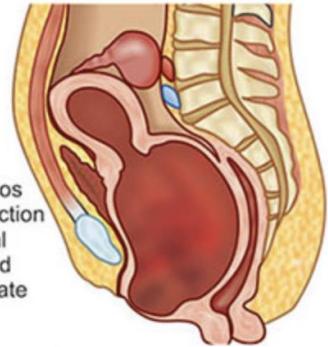
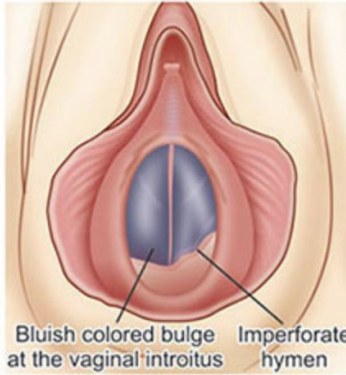
- **External genitalia , clitoromegaly**
- Pelvic examination – inappropriate in young girls who are not sexually active, **examination can be effectively undertaken under anesthesia**
- **Speculum examination or vaginoscop .**
- Atrophic appearance of the external genitalia and loss of rugosity of the 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.
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# Outflow tract obstruction

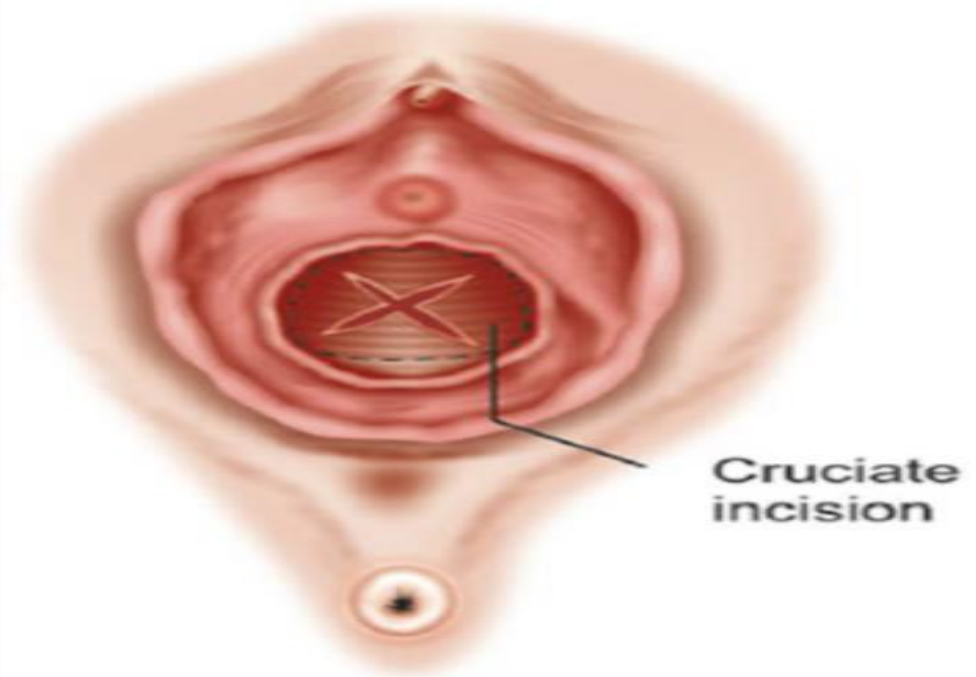
- **Imperforate hymen:**
  - Normal SSC.
  - Cyclical lower abdominal pain.
  - Visible haematocolpos with a bulging purple/blue, stretching thin hymen at introitus.
- **USS** may show haematometra.
- **Treatment** – surgery – simple cruciate incision on the hymen.



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

Ultrasound





**Cruciate  
incision**

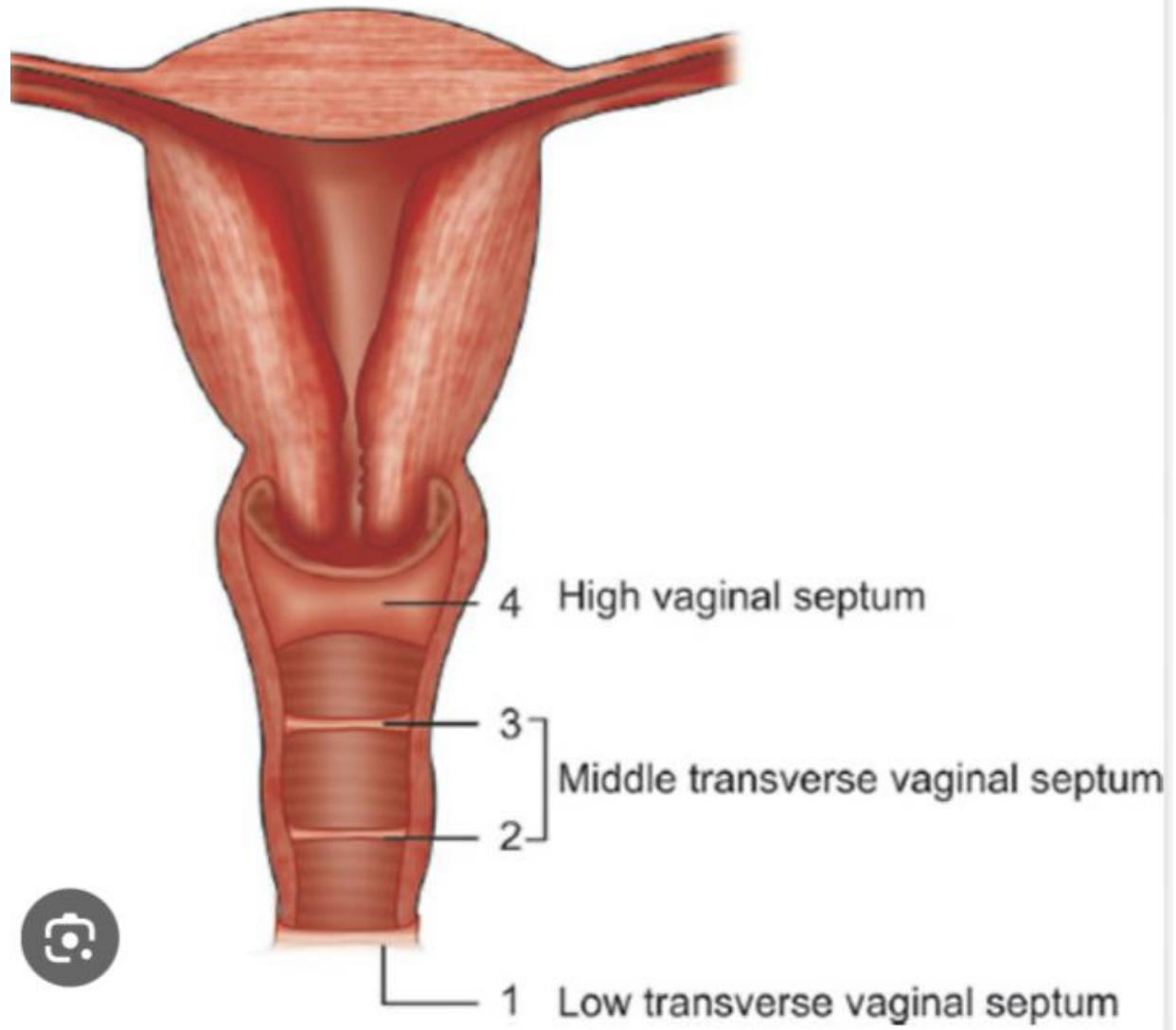


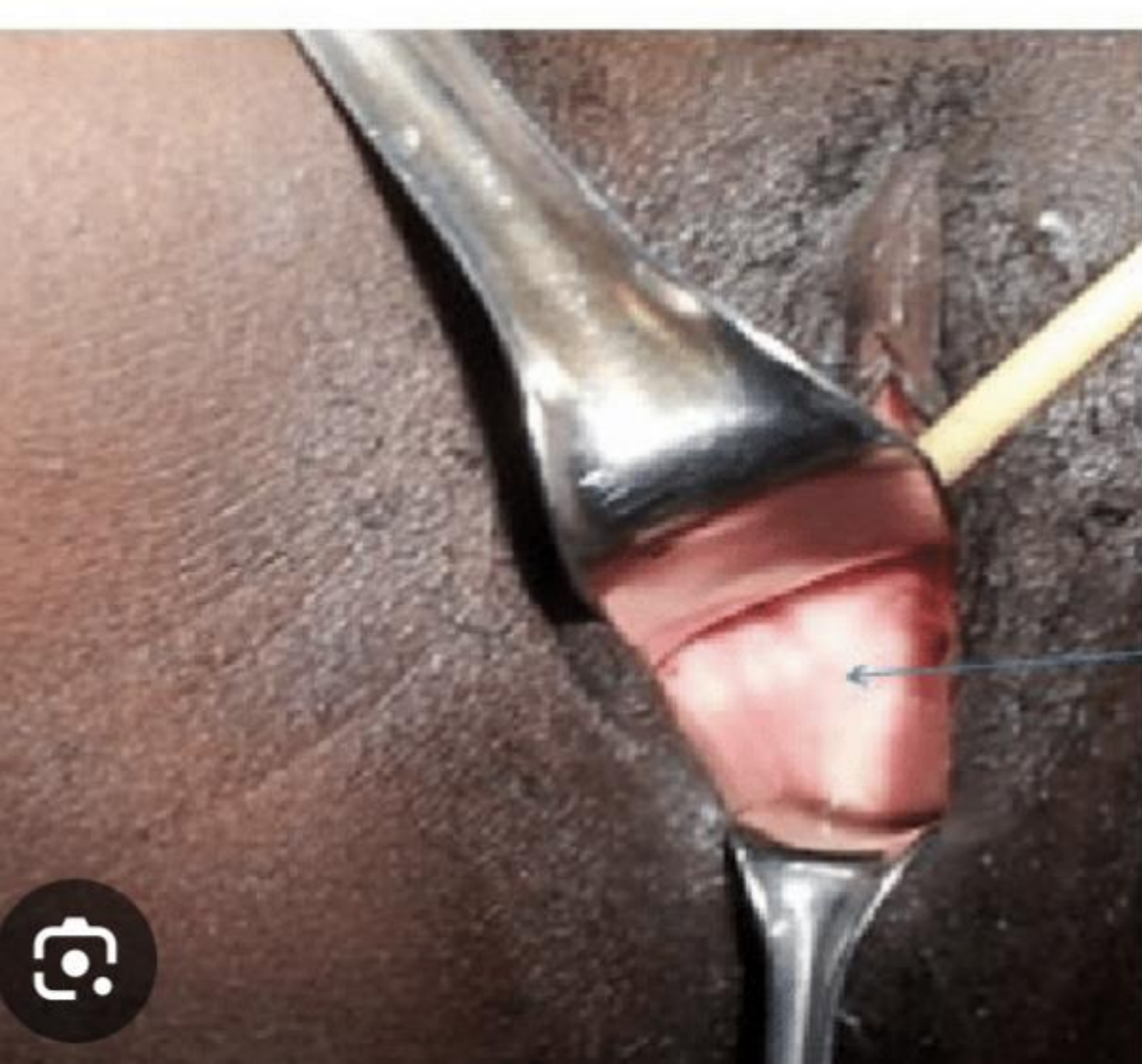
**Sutured  
mucosa  
margin**



# 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





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 uridylyltransferase (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

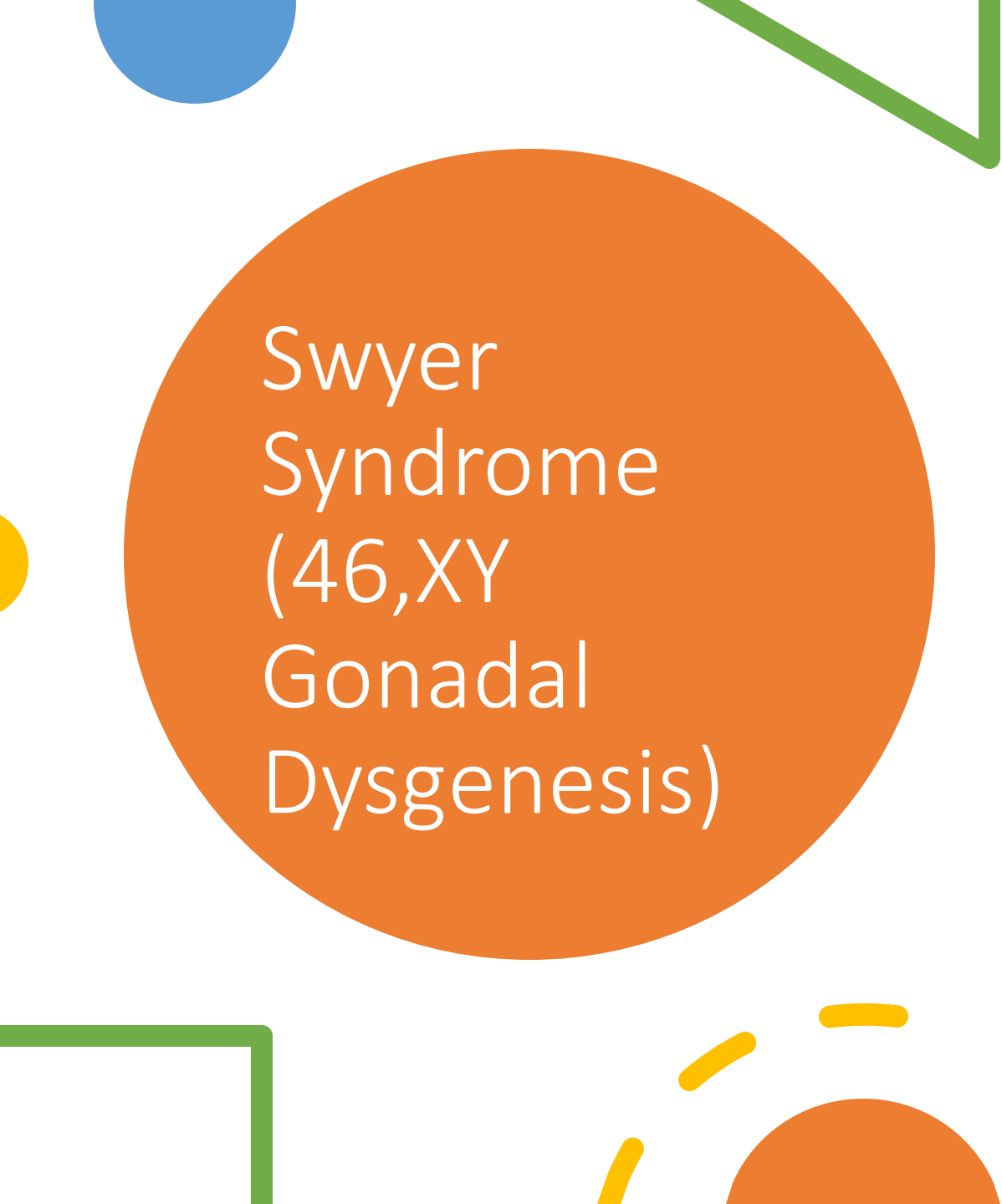
- The **management** of patients with complete AIS has two major components:
  1. One focusing on **creation of a functional vagina** to allow attainment and optimization of potential for sexual relations
  2. Another relating to the **risk for developing malignancy** in the cryptorchid testes
- **Gonadectomy** 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**.
- 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)

- The **presence of pubic hair reflects a normal adrenarche and hence rules out complete AIS as a possible diagnosis.**
- **Gonadectomy** is indicated soon after diagnosis is made due to the significant risk for malignant transformation in occult testicular elements (20–30%).



# Turner's syndrome

- **Most common cause of gonadal dysgenesis.**
- **45,XO. Classical features** – short stature, webbing of the neck, coitus 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.


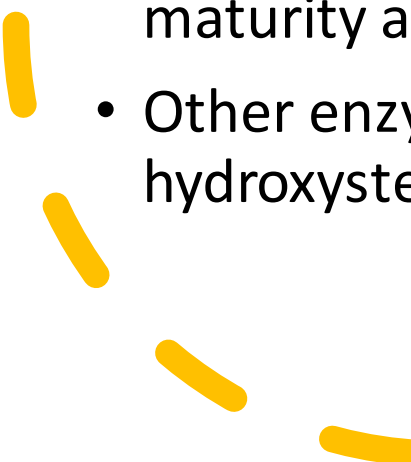


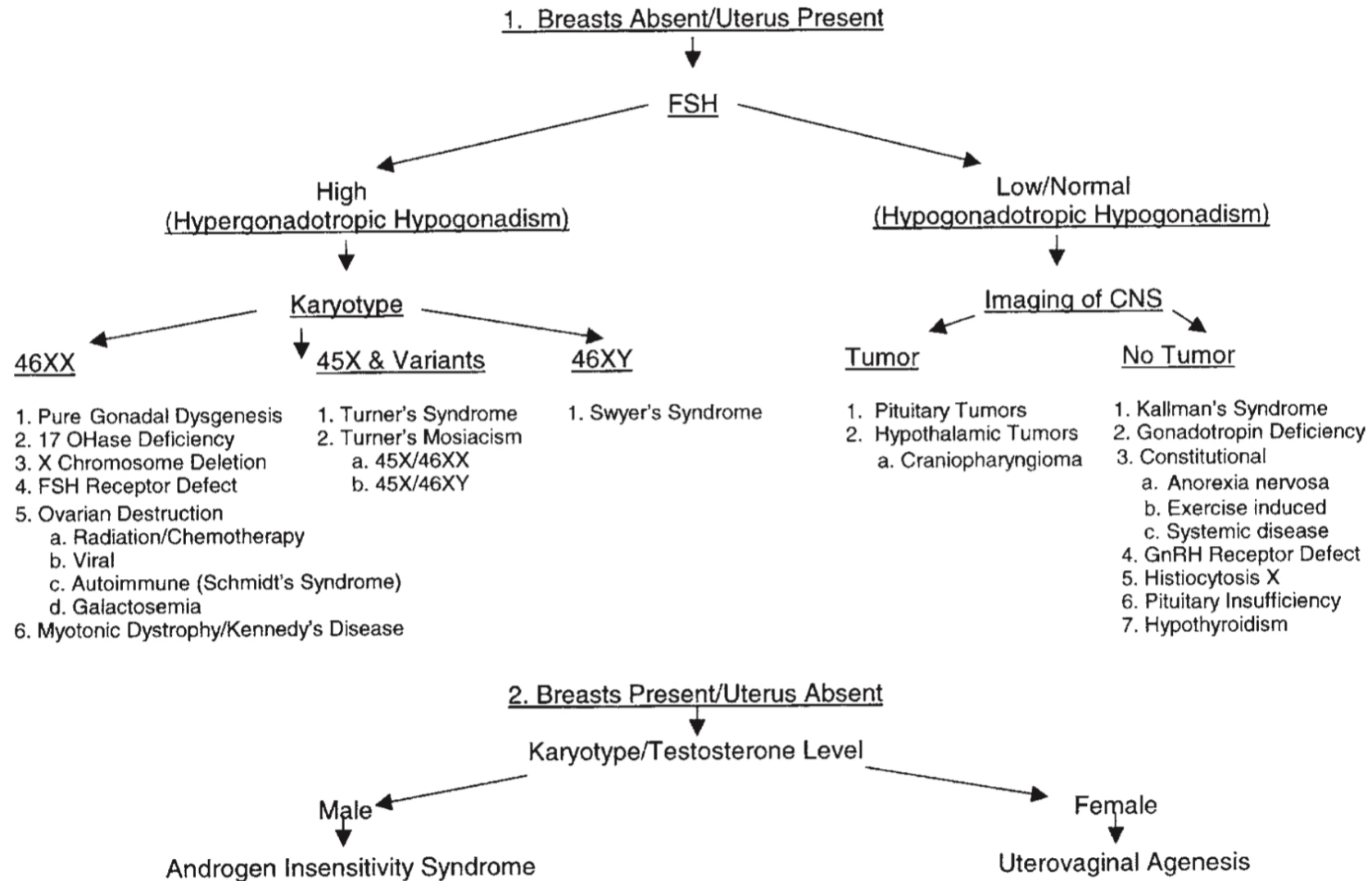
# Kallman's syndrome

- **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 (hyponatremia 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.

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- 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.
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**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 in origin.**
  - **35% hypothalamic in origin.**
  - **5% uterine in origin.**



DDx **FSH, LH, TSH, prolactin, testosterone** Rx

FSH, LH

TSH high/low – thyroid disorder

Prolactin high

Testosterone  $\geq 5.0$  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**

**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.

Intra-uterine adhesions.  
History of excessive curettage, infection, hysterosonogram, hysteroscopy.  
Treatment – hysteroscopic resection, IUD, and oestrogen.

# History

- History of infertility, contraceptive use.
- 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
- Pregnant 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.
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# 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.

# KEY POINTS: SECONDARY AMENORRHEA

- The **most common cause** of secondary amenorrhea is **pregnancy**.
- Hypothalamic and pituitary causes of secondary amenorrhea include idiopathic conditions, eating disorders or excessive exercise, infection, and neoplasms (most commonly prolactinoma).
- POI is usually idiopathic but can also result from Turner syndrome, fragile X syndrome, metabolic and autoimmune disorders, or chemotherapy or radiation therapy.
- medications that stimulate prolactin secretion include antipsychotic, antidepressants, gastrointestinal medications, antihypertensives, and hormones.
- Nonclassic CAH caused by 21-hydroxylase deficiency can cause secondary amenorrhea and hirsutism. 17-Hydroxyprogesterone is elevated in these patients.

# What are the **hypothalamic** causes of amenorrhea?

- **Dysfunctional** gonadotropin-releasing hormone (**GnRH**) **secretion**:
  - polycystic ovarian syndrome.
  - 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 adrenocorticotrophic hormone, with resulting Cushing syndrome.

# 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 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 hypogonadotropic 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*

