# AMENORRHEA

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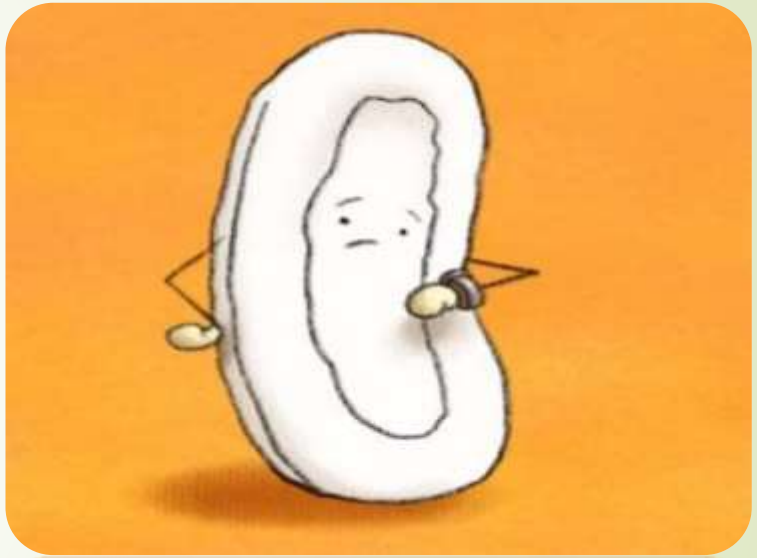
# What does Amenorrhea mean?

**The Origin** → Greek

- **A** = without ;
- **Meno**= Relating to Menstruation ;
- **rrhea** = discharge/flow An absence of menstruation



➢ ***"Amenorrhea Is A Symptom ; Not a Disease"***

✓ *The Final Diagnosis should be a Pathological Diagnosis..*

# *Definition:

***Amenorrhea*** **is the absence of menstruation.**

- **Primary Amenorrhea-**

– Absence of menses by age of 15 **regardless** of secondary sexual characteristics.

**OR**

– Absence of menses by age of 13 **without** development of secondary sexual characteristics

# Events of puberty

- *** Thelarche** (breast development)

**→ Requires estrogen**

- *** Pubarche** (pubic hair development)

**→ Requires androgens**

- *** Menarche** (the first mense)

**→ Requires**:

1– GnRH from the hypothalamus

2– FSH and LH from the pituitary

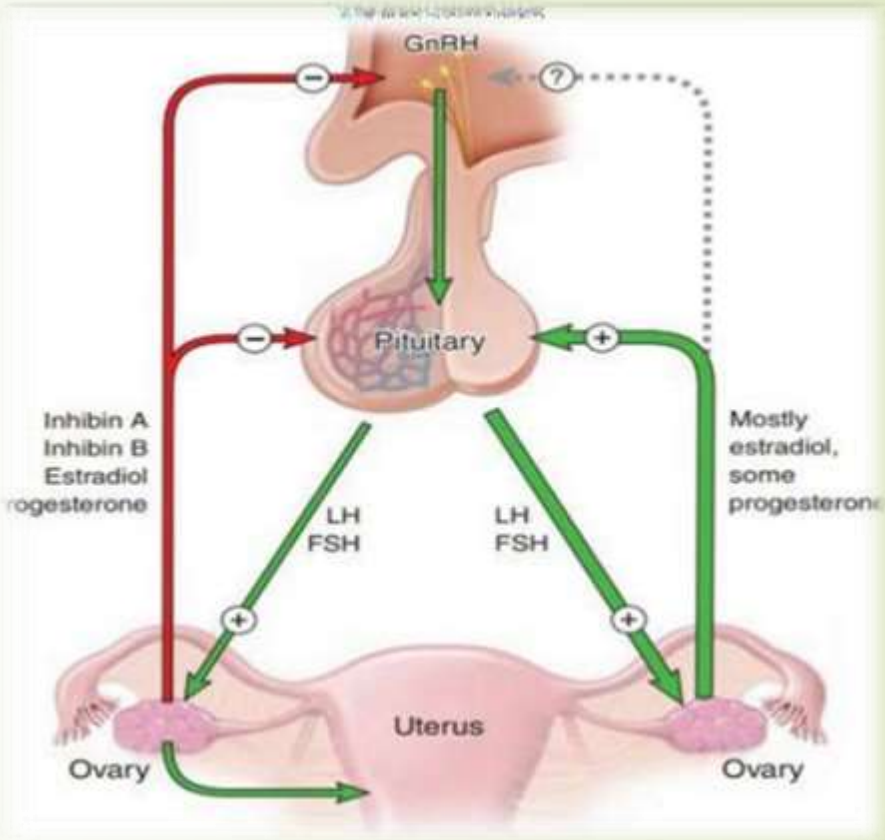
3– Estrogen and progesterone from the ovaries

4-- Normal outflow tract

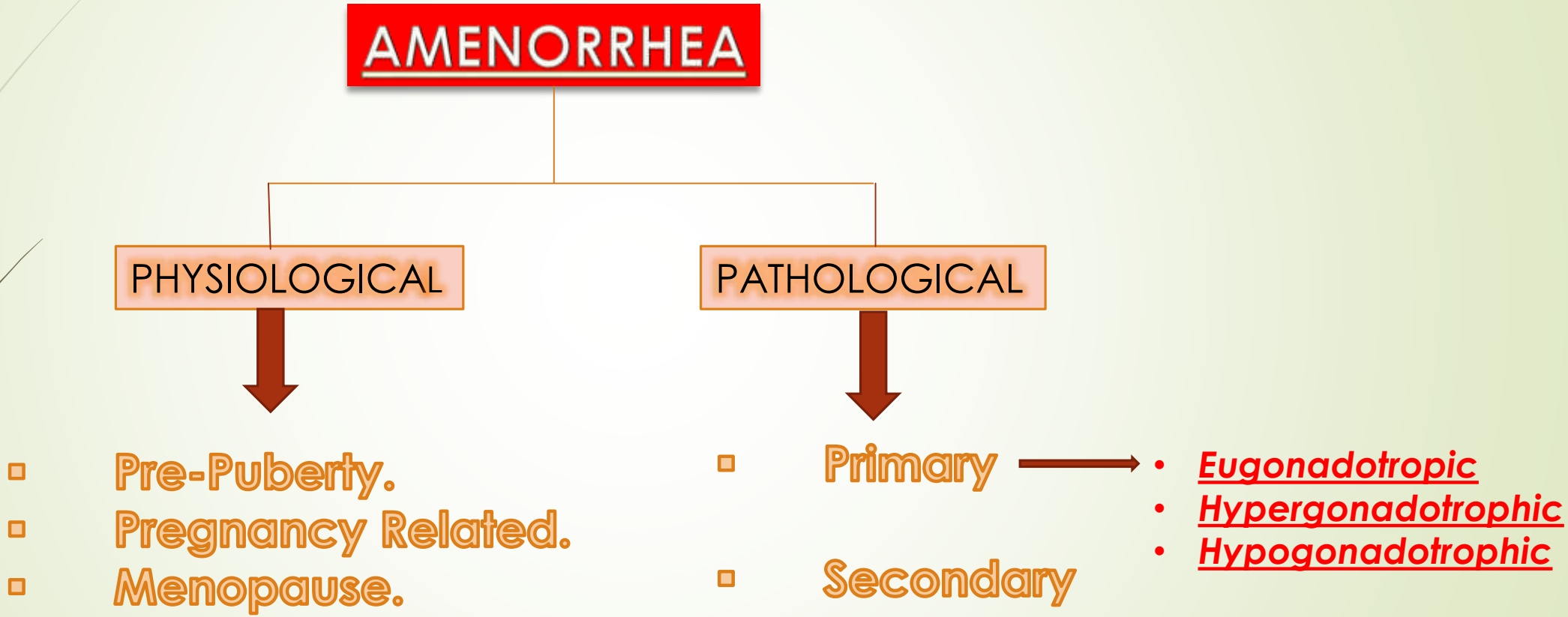
# *H-P-O-U Axis*

❖ **Menarche : → Requires:**

- **GnRH** from **the Hypothalamus.**
- **FSH and LH** from **the Pituitary.**
- **Estrogen and Progesterone** from **the Ovaries.**
- **Normal Uterus** & **Outflow tract**.



# CLASSIFICATION OF AMENORRHEA



# PRIMARY AMENORRHOEA

## ➨ EUGONADOTROPIC

**Anatomic /genital outflow tract**

** Müllerian dysgenesis (Mayer -Rokitansky–Küster–Hauser syndrome)

***1.Complete androgen insensitivity syndrome***

***(testicular feminisation synd.)***

❖ Distal genital tract obstruction-

Imperforate hymen, Transverse vaginal septum, cervical atresia, Vaginal atresia

❖ **Others**

PCOD, constitutional delay

# HYPERGONADOTROPIC (follicle–stimulating hormone>40 mIU/mL) hypogonadism (gonadal "failure"):

- 1. Gonadal dysgenesis with stigmata of Turner syndrome45.OX, mosaics.
- 2. Pure gonadal dysgenesis.

*a. 46,XX*

*b. 46,XY-swyer*

- 3. Early gonadal "failure" with apparent normal ovarian development.
- 4. Gonadotropin resistant ovary syndrome, savage syndrome.
- 5. Galactosemia.
- 6. Enzyme deficiency:17 alpa hydroxylase deficiency.5 alpha reductase deficiency.

# HYPOGONADOTROPIC:

- **1. Isolated gonadotropin deficiency:**
  - Associated with midline defects (Kallmann ).
  - Independent of associated disorders.
  - Prader–Labhart–Willi syndrome.
  - Laurence–Moon–Bardet–Biedl syndrome.
  - Many other rare syndromes (Frohlich syndrome).
- **2. Associated with multiple hormone deficiencies.**
- **3. Neoplasms of the hypothalamic–pituitary area:**
  - Craniopharyngiomas.
  - Pituitary adenomas.
  - Empty sella turcica.

- • Infiltrative processes *(Langerhans cell–type histiocytosis)*.
- • After irradiation of the central nervous system.
- • *Severe chronic illnesses* with malnutrition.
- • Anorexia nervosa and related disorders.
- • Anti-dopaminergic and gonadotropin–releasing hormone–inhibiting drugs **(especially psychotropic agents, opiates)**.
- • Primary hypothyroidism.
- • Cushing syndrome.
- • Use of chemotherapeutic **(especially alkylating)** agents.

# IMPERFORATE-HYMEN:

* May be discovered at birth because of presence of suprapubic mass **"mucocolpos or hydrocolpos".**

* More commonly however it remains undetected until puberty **(hematocolpos).**

* Patient presents with c/o cyclic perineal, pelvic or abd pressure or pain resulting from accumulation of obstructed menstrual blood or urinary retention.

*Genital ex.reveals ***no obvious vaginal orifice and a thin often bulging, blue perineal membrane***.

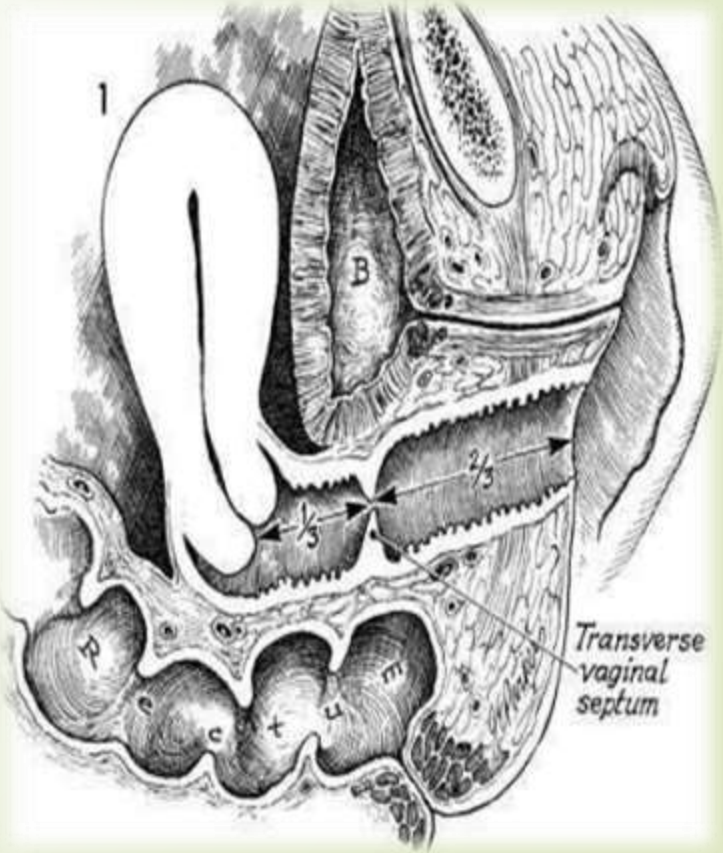
# CRYPTOMENORPHEA

- Menstruation occurs but **there is obstruction To the outflow of blood.**

- ***CAUSES*** ⟶ ***Congenital:*** imperforate hymen.
  ⟶ ***Acquired:*** Vaginal atresia, cervical stenois.

# TRANSVERSE VAGINAL SEPTUM

- • Failure of vertical fusion SEPTUM **(complete cavitation of the vaginal plate between the sinovaginal bulbs and uterovaginal canal)**.
- • More common ***in the upper portion***, that is, at the junction between the sinovaginal plate and the caudal end of the fused müllerian ducts.
- • The septum may ***be obstructive***, with accumulation of mucus or menstrual blood, or may be non obstructive, allowing for egress of mucus and blood.



# Clinical Manifestations:

- **• Obstructive Manifestations transverse vaginal septum:-**

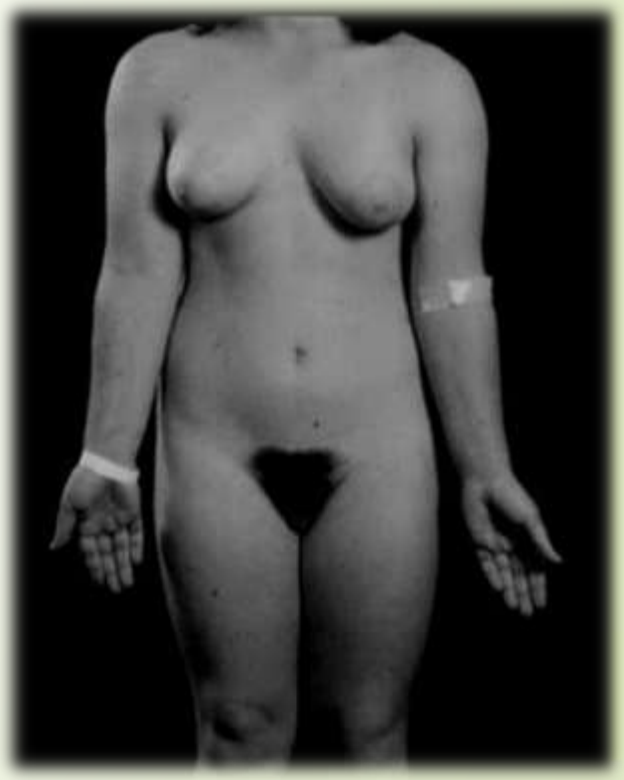
-- usually present during adolescence with cyclic lower abdominal pain, amenorrhea, and gradual development of a central pelvic mass.

- **• Nonobstructive or incomplete transverse vaginal septum:-**

-- complain of abnormal menstrual flow, pain with intercourse, difficulty in placing or removing tampons, or obstructed labor.

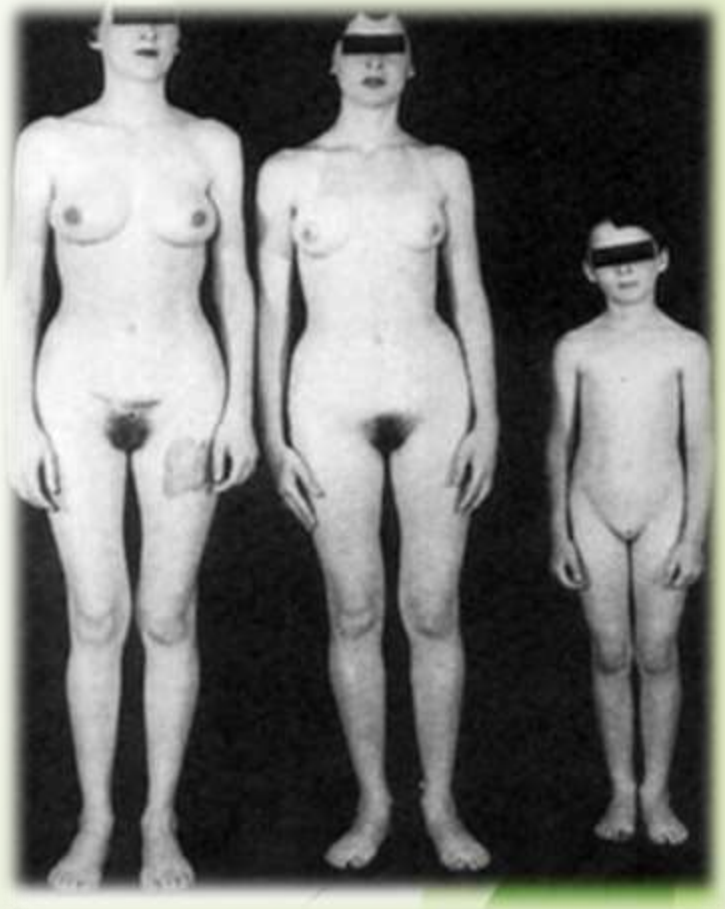
# Mayer-Rokitansky-Kuster Hauser (MRKH) Syndrome :Utero-Vaginal agenesis

- **15%** of primary amenorrhea **(2nd M/C Cause)**
- Normal secondary development & external female genitalia.
- Normal female range testosterone level Absent uterus and **upper vagina & normal ovaries.**
- Karyotype 46;XX .
- **15-30%** renal, skeletal and middle ear anomalies.



# Androgen Insensitivity Syndrome (AIS):

- **Normal breasts** but sparse/absent sexual hair.
- **Normal looking female external genitalia.**
- **Absent** uterus and upper vagina.
- **Karyotype 46;XY.**
- *Male range testosterone level*.
- Genotype-Male; Phenotype-Female.
- M/C Cause of **Male-Intersex.**



# Gonadal Dysgenesis

❖ **** PURE GONADAL DYSGENESIS:**

**E.g. Swyer's Syndrome**

- **46;XY + Defect in SRY Gene**
- Bilateral Streak Gonads
- Geno-Male ; PhenoFemale
- Infantile uterus present
- Height-Normal/Tall
- ***1°Amenorrhea***

❖ **** MIXED GONADAL DYSGENESIS:**

- Mosaics ( 46;XY + 45;XO).
- Testis Present.

**Streak Ovary( 1°amenorrhea)**

- Ambiguous Genitalia

# GONADAL DYSGENESIS: 46XX

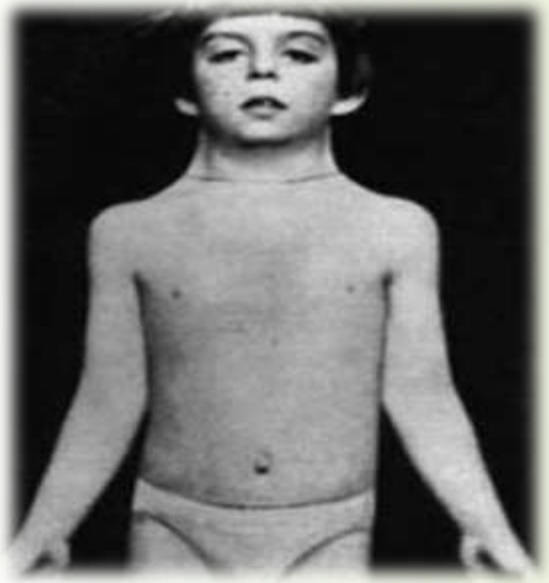
- •Refers to a number of conditions in which abnormal development leads to streak gonads
- •Incidence: <1/10,000 in women less than 30
- •Familial inheritance 7-30%.
- •Premutations in the FMR1 gene (Fragile X Syndrome).
- •15% of carriers have POF.
- •Associated with :

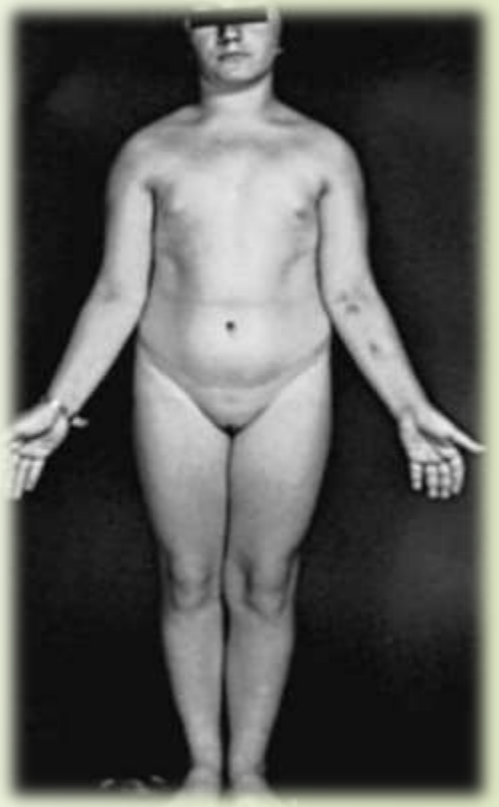
•autoimmune diseases (18-30%) like Hashimoto's Thyroiditis,Addison's disease, hypoparathyroidism, vitiligo.

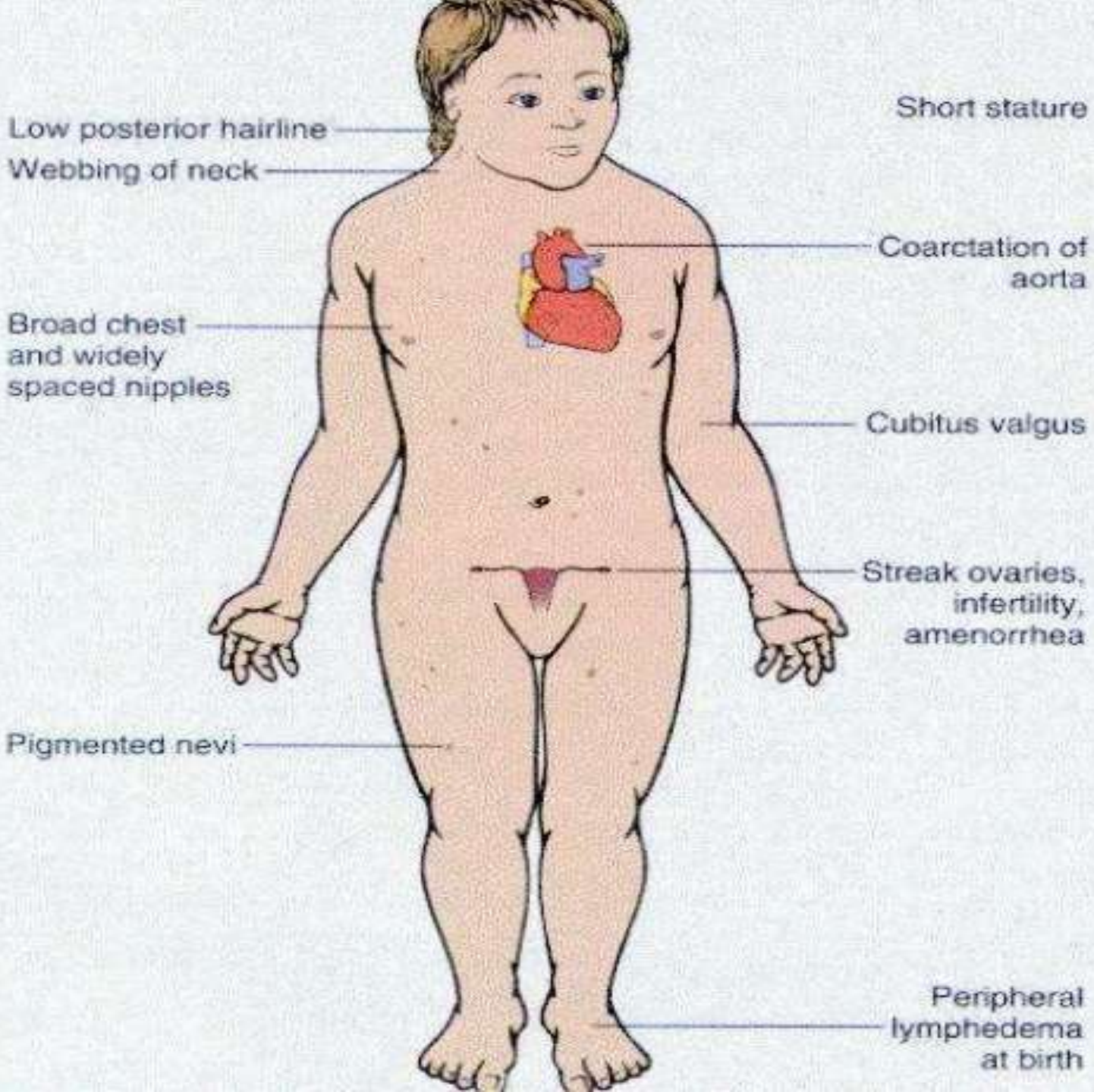
•Acquired: Radiation, chemotherapy, Environmental, Childhood viruses.

# Turner Syndrome (M/C Cause ):

- Karyotype 45;XO
- Generally grow slowly so shorter inheight
- Lymphadema at birth
- Webbed neck & Short MetacarpalIV
- Pigmented spots on the wholebody
- Shield Chest with widely spaced Nipples
- DM ; Thyroid disorder
- Streak gonads/ovaries (Amenorrhea)
- Do not develop breast at puberty
- CVS ( Bicuspid aortic valve> Coarctation of aorta) ; Horseshoe Kidney
- Cubitus Valgus



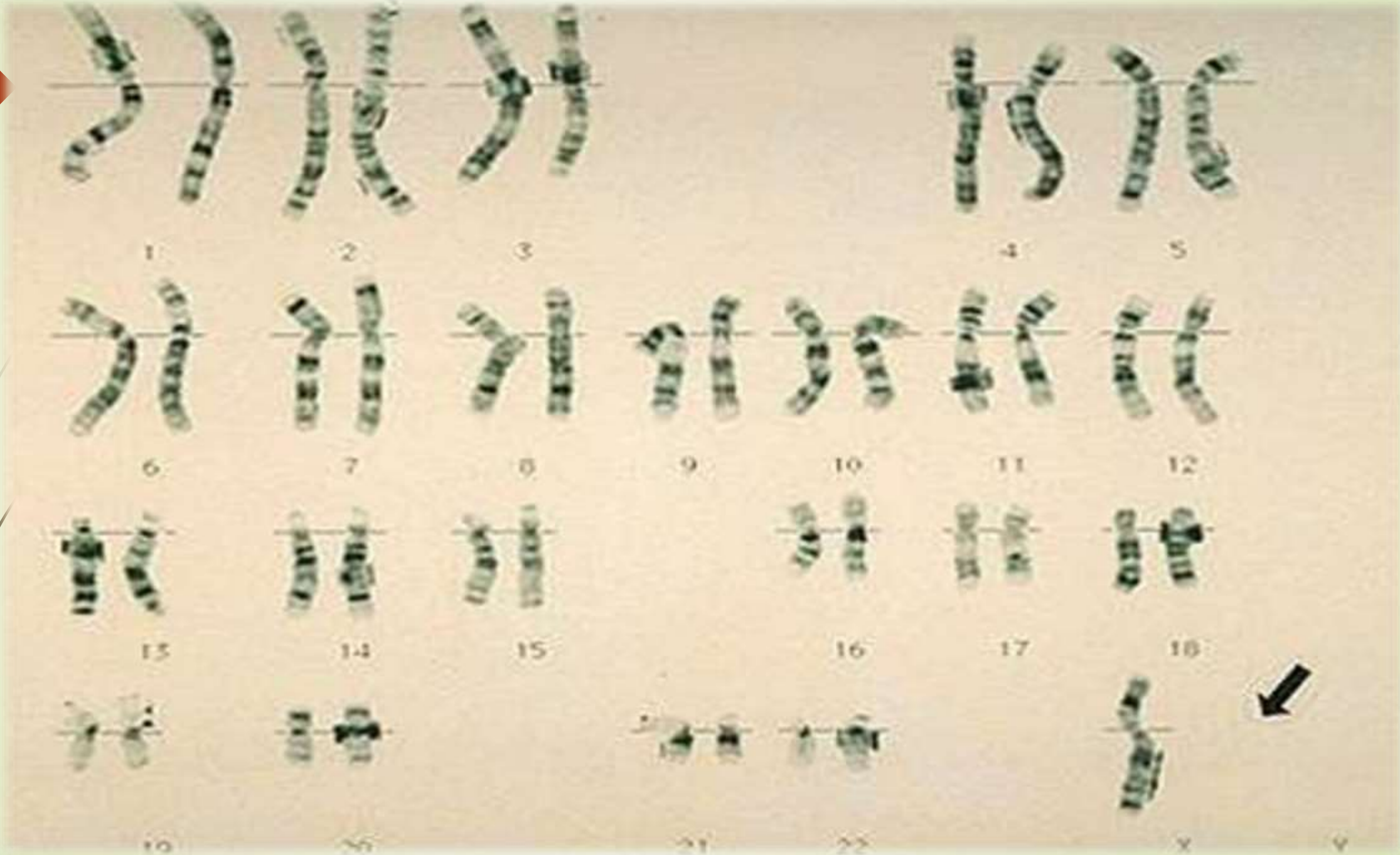





## TURNER SYNDROME

Incidence: 1 in 3000 female births

| | |
|---|---|
| Karyotypes: | |
| Classic: | 45,X |
| Defective second X chromosome: | 46,X,i(Xq)<br>46,XXq–<br>46,XXp–<br>46,X, r(X) |
| Mosaic type: | 45,X/46,XX |



# 46 XY Swyer Syndrome:

- **Cause: Associated with mutations in the SRY gene.**
  - Streak gonads present; **No testesformation**
  - Anti-Mullerian hormone and testosterone ***not produced***
  - **Normal** uterus and fallopian tubes, female external genitalia
  - Estrogen also ***not produced*** from streak gonads therefore breast development does not occur
  - ***Elevated FSH/LH***
  - Streak Gonads need removal as increased **risk for (25%)**
- **germ cell tumors: most common gonadoblastoma**

# Kallmann Syndrome

- Congenital GnRH Deficiency.
- Anosmia + Amenorrhea + Colour Blindness.
- Poorly developed secondary sexual characters.
- *Cleft* lip/ palate.

# RESISTANT OVARY SYNDROME OR SAVAGE SYNDROME:

- • **Absence or malfunction** of FSH receptor in ovarian follicle.
- • ↑ **(increase)** gonadotrophin.
- • ***Apparently normal*** ovarian tissue.
- • Some degree of sec. sexual character.
- • ***Rare*** cause of primary amenorrhea.
- • May resolve spontaneously.
- • If hot flushes-Rx with **estrogen**.

# Frohlich Syndrome (Adiposo Genital Dystrophy):

- • Broad spectrum of hypothalamic lesions.
- • Hyperphagia, obesity, and central hypogonadism.
- • *Decreased* GnRH production results in attenuated pituitary FSH and LH synthesis and release.
- • Deficiencies of leptin, or its receptor, cause these clinical features.

# Heterosexual development:

- ✓ • Congenital adrenal hyperplasia –21 hydroxylase ***deficiency*** (commonest), 17∞ Hydroxylase *deficiency*17, 20-desmolase *deficiency*.
- ✓ • Androgen secreting tumor –Arrhenoblastoma.
- ✓ • 5 ∞-Reductase *deficiency*.

***XY, testis, virilization at puberty,***

***no mullerian structure,***

***non development of breast,***

***normal male internal genitalia but non development of external.***

# Congenital Adrenal Hyperplasia- CAH

- Autosomal Recessive Inheritance.
- Deficiency of ***21-Alpha-Hydroxylase enzyme*** in **>90%cases.**
- Decreased synthesis of both ***Cortisol and Aldosterone.***
- ***Decrease Cortisol production*** leads ***to increased ACTH*** and hence **adrenal cortical hyperplasia.**
- Accumulated **17-ALPHA-HYDROXYPROGESTERONE** is diverted to **Androgen** production and Signs of **Androgen excess appears**.
- Aldosterone deficiency leads to ***Salt wasting.***
- Most common cause of **Ambiguous Genitalia** in females (Female Intersex).
- Vagina and uterus **are present**.
- Ovaries are usually polycystic in appearance and anovulatory **(Amenorrhea).**

# Weight-related Amenorrhoea:

## →*Anorexia Nervosa*

- • **1 ° or 2 °** Amenorrhea is often first sign (commonest cause of amenorrhea **among teenagers**)
- • A body mass index (BMI) ***<17 kg/m² menstrual irregularity and amenorrhea.***
- • Hypothalamic suppression ,hypogonadotropic state.
- • ***Abnormal*** body image***, intense fear of weight gain***, often strenuous exercise
- • O/E-hypotension, bradycardia ,hypothermia,dry skin and lanugo hairs.
- • Mean age onset **13-14 yrs** (range 10-21 yrs).
- • Low estradiol → risk of osteoporosis , osteopenia
- **• Bulemics less commonly have amenorrhea** due to fluctuations in body wt, but any disordered eating pattern (crash diets) can cause menstrual irregularity.

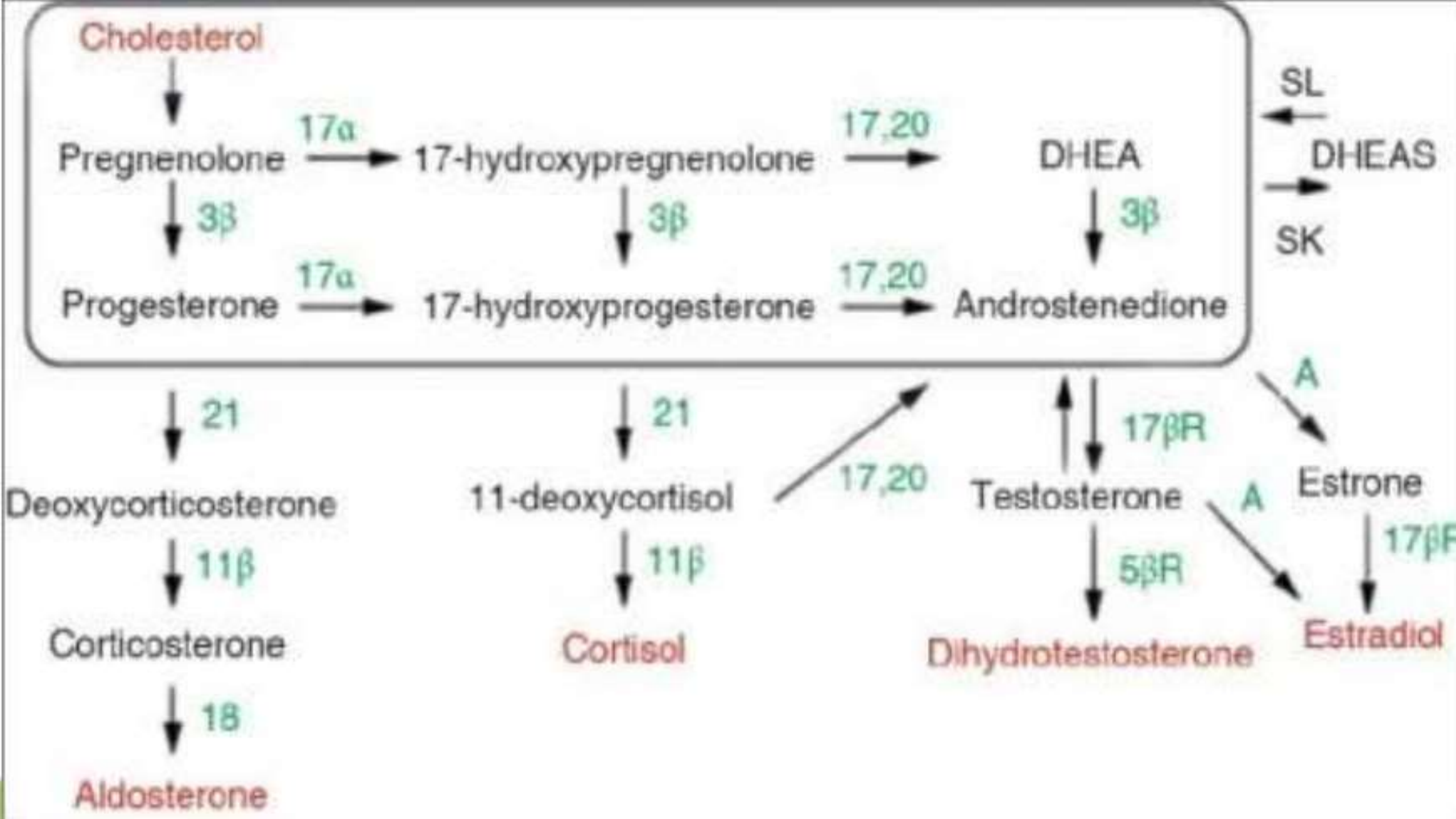
# Constitutional Delay:

- ***•Puberty occurs at a time greater than 2.5 standard deviations from the mean.***
- ***•Family history of delayed puberty.***

- ***•Characteristics:***

I. Significantly shorter.
II. Bone age lags behind age matched controls.
III. Often present at early Tanner stage 2.
IV. Low gonadotropin levels.

- ***•Diagnosis of exclusion—exclude other reproductive disorders.***


Cholesterol
Pregnenolone
17α
17-hydroxypregnenolone
17,20
DHEA
SL
DHEAS
SK
3β
3β
3β
Progesterone
17α
17-hydroxyprogesterone
17,20
Androstenedione
21
21
17βR
A
Deoxycorticosterone
11-deoxycortisol
17,20
Testosterone
A
Estrone
11β
11β
5βR
17βR
Corticosterone
Cortisol
Dihydrotestosterone
Estradiol
18
Aldosterone

# OBJECTIVES OF EVALUATION:

- *1.) Understand the causes of primary amenorrhea .*
- *2.) How to elicit a pertinent history and perform a focused physical exam to evaluate primary amenorrhea.*
- *3.) Understand how to perform and interpret selected diagnostic tests and imaging to evaluate primary amenorrhea.*

## Compartment I

- Imperforate Hymen
- Transverse Vaginal Septum
- Mullerian Agenesis
- Androgen Insenstivity Syndrome
- Asherman's syndrome 7 %

## Compartment II

- Gonadal Dysgenesis XX, XY
- Turners Syndrome
- Premature Ovarian Faliure
- Radiation / Chemotherapy
- Galactosemia

## Compartment III

- Pituitary Adenomas
- Prolactin tumors 7.5 %
- Empty Sella
- Sheehan's Syndrome

## Compartment IV

- Hypothalamic suppression 10 %
- Eating Disorders
- Exercise
- Cogenital GnRH deficiency

# APPROACH TO A CASE OF PRIMARY AMENORRHOEA:

- • **CAREFUL MEDICAL HISTORY** DM, TB, f/h of pcod ,delayed puberty, testicular feminization.
- • ***PHYSICAL EXAMINATION:***
  → Height, weight, BMI, Skin, Acne, Hirsutism, thyroid.
- • **Breast:** Indicator of estrogen production or exposure to exogenous estrogen
- • Abdominal Examination-mass
- • External Genitalia and pubic hair, axillary hair PV ex. /PS ex. /PR ex

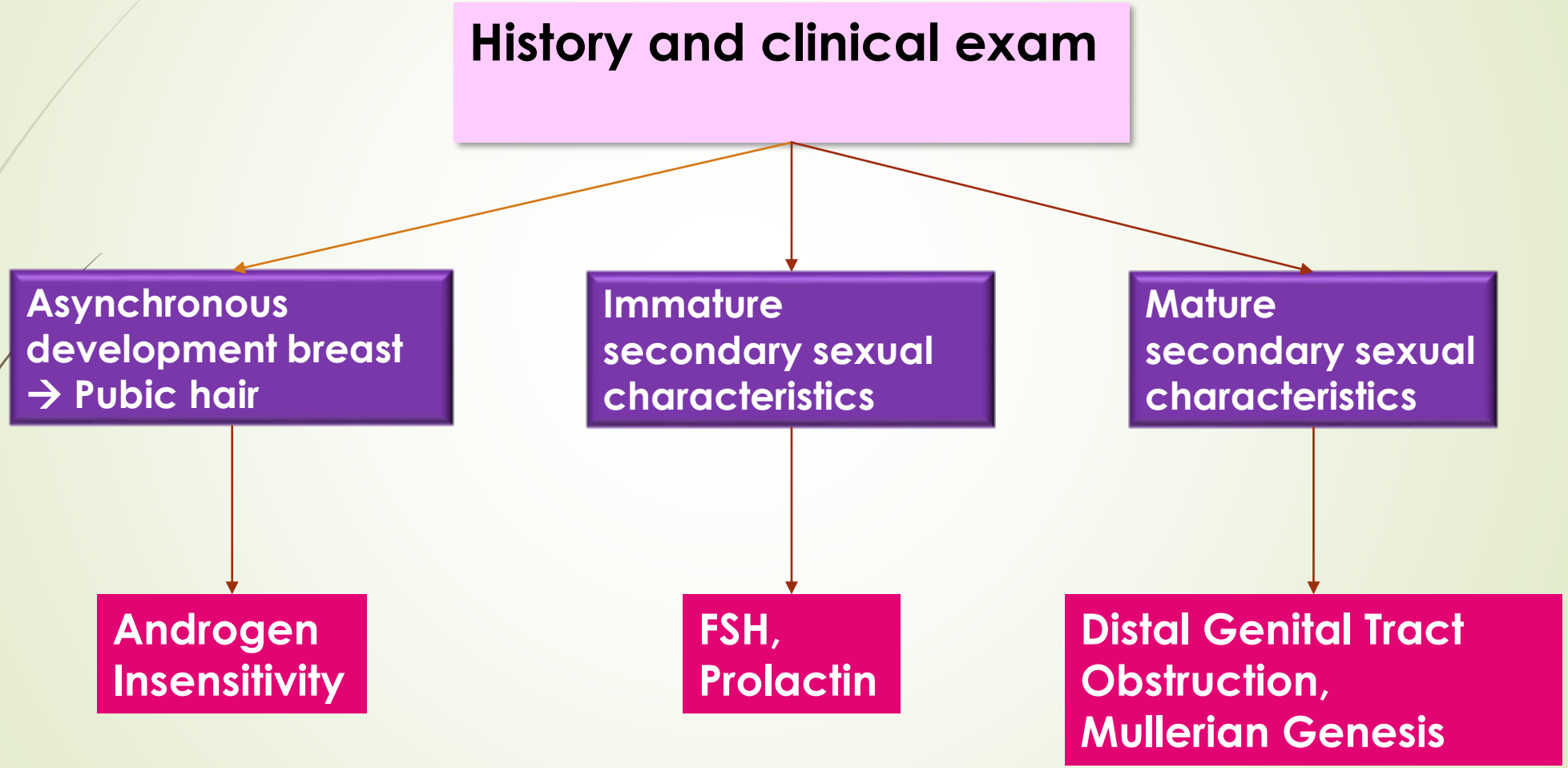
# INVESTIGATION:

- ✓ **HORMONAL PROFILE** →

*(beta-HCG,FSH,LH,TSH,PROLACTIN, sex hormones).*

- ✓ **USG/MRI.**
- ✓ **Karyotyping.**
- ✓ **Laparoscopy.**
- ✓ **Miscellaneous.**

# *Approach to a case of primary AMENORRHOEA:*



- ****WHO divides patients into groups based on endogenous oestrogen production, folliclestimulating hormone (FSH) levels, prolactin levels, and hypothalamic-pituitary dysfunction.**

→ ***This classification is a guide that eliminates several diagnoses based on initial information.***

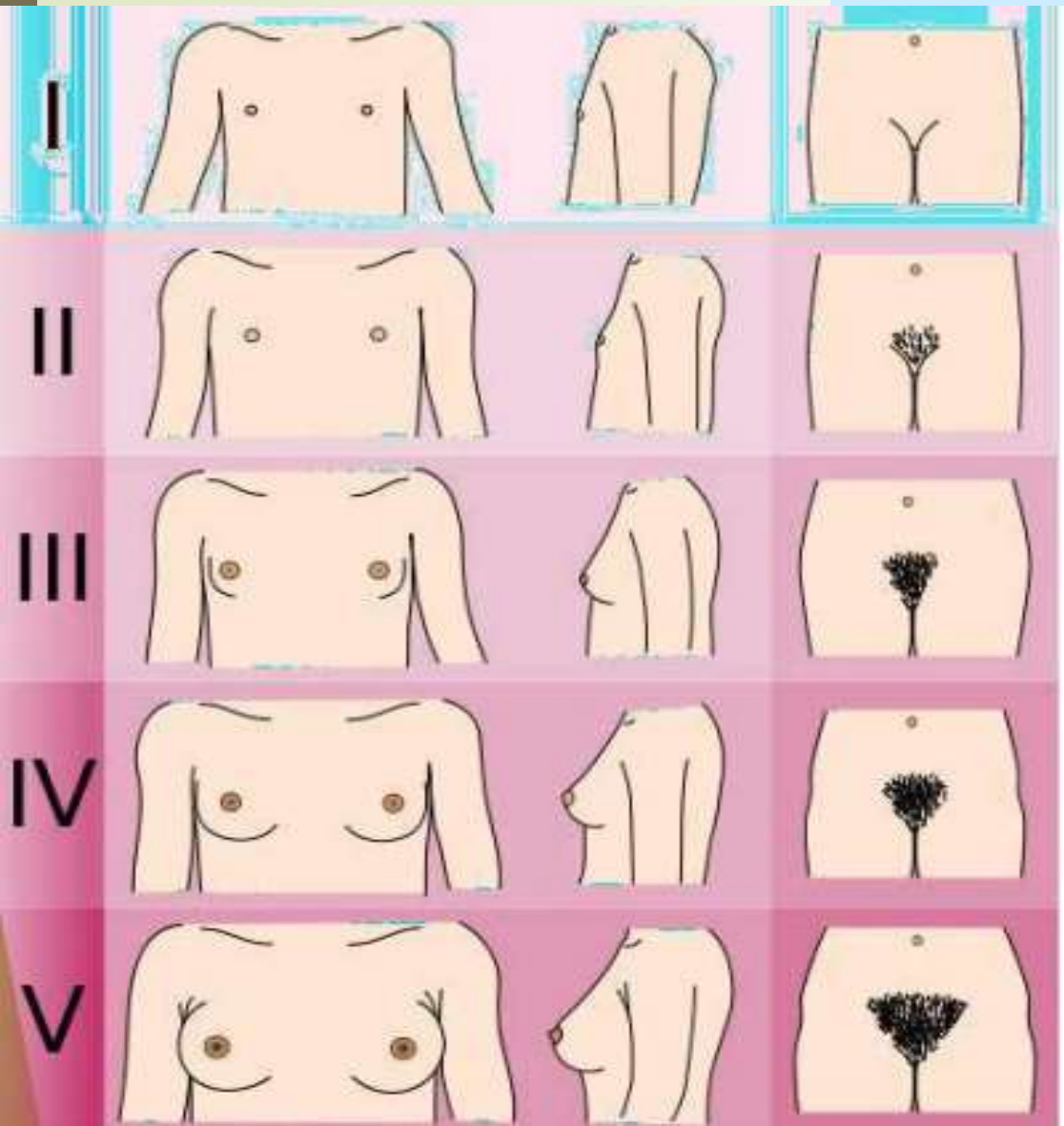
→ ***However, further work-up is still required.***

- • ***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.

**TABLE 23.2 Clinical approach to primary amenorrhoea**

| Clinical Features | Presumptions | Distinguishing Tests |
|---|---|---|
| **Breasts absent**<br>**Uterus present** | Lack of breasts indicates lack of oestrogen production from gonads (causes—HPO failure, lack of ovarian follicles, lack of two active X chromosomes, Turner's syndrome)<br>Presence of uterus indicates that the Y chromosome is absent | **FSH level** identifies cause of oestrogen lack. High FSH (ovarian failure), Low FSH indicates hypothalamic-pituitary failure. GnRH distinguishes hypothalamus (LH ↑) from pituitary cause (no LH response) |
| **Breasts present**<br>**Uterus absent** | Presence of breasts indicates presence of gonadal oestrogen. Absent uterus indicates Müllerian agenesis, or presence of Y-chromosome or testicular feminizing syndrome. | S. Testosterone levels high in androgen insensitivity (Y chromosome), but normal in 46 XX with Müllerian agenesis. Karyotyping confirms genetic sex. Gonadectomy advised s.o.s., Müllerian |
| **Breasts absent**<br>**Uterus absent** | Absent breast suggests lack of oestrogen. Because of gonadal agenesis, absence of gonads, gonadal enzyme defects. Absent uterus indicates presence of Y-chromosome with testes that suppresses Müllerian development. Presence of normal female external genitals indicates absence of testes, hence no testosterone present when external genitals were developing | Karyotyping - 46 XY, high FSH and testosterone – normal female range suggests gonadal agenesis/absence. Gonadal biopsy to detect enzyme deficiency. |
| **Breasts present**<br>**Uterus present** | Presence of breasts indicate oestrogen present. Uterus present indicates Y chromosome is absent | Investigations include: progesterone challenge test, S. prolactin and thyroid profile, tests to exclude genital TB. Urine test for presence of β-hCG and USG are essential to rule out pregnancy. |

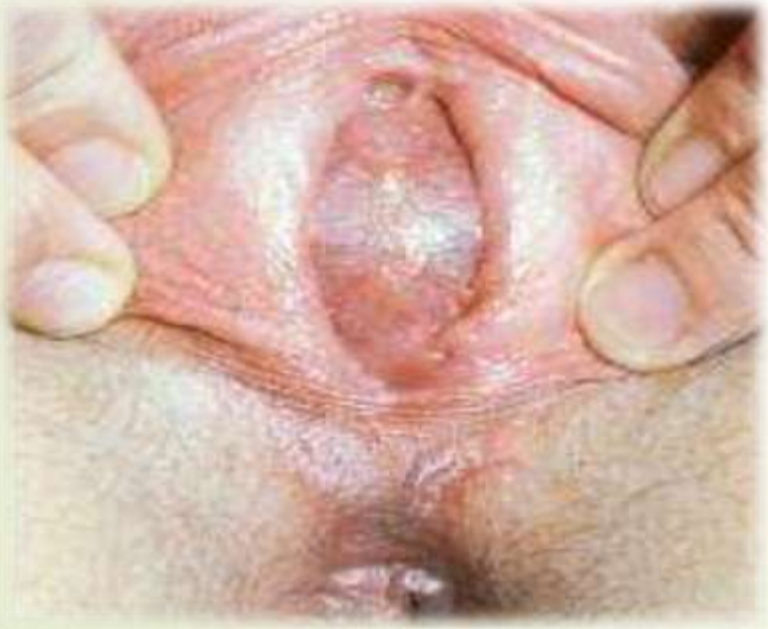
# Tanner Staging:

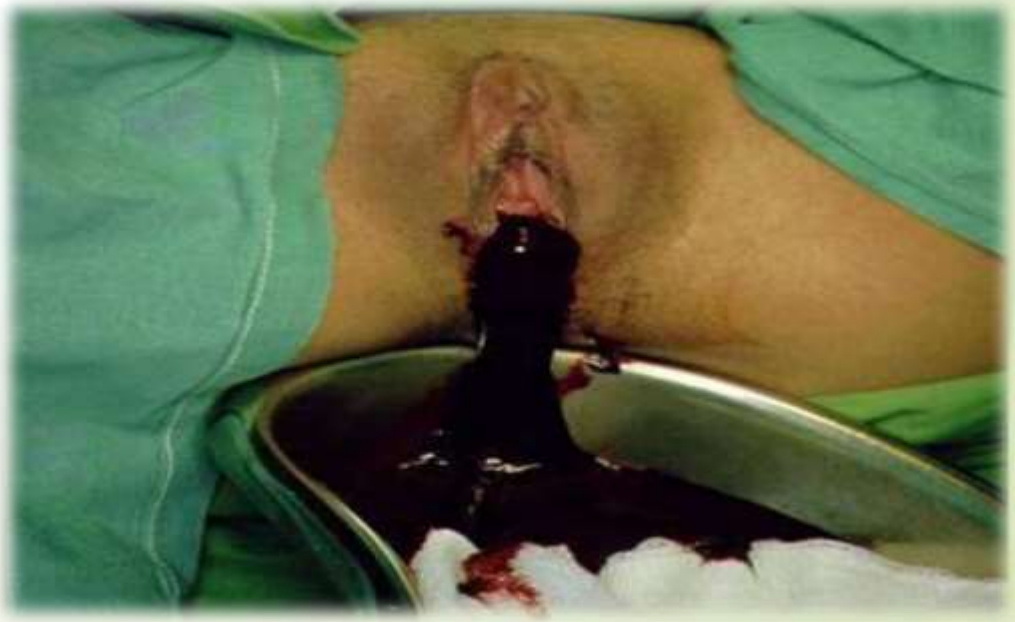



| | | |
|---|---|---|
| **Prepubertal (Stage 1)** | **Elevation of the papilla only** | **No pubic hair** |
| Stage 2 | Elevation of the breast and papilla as a small mound, areola diameter enlarged | Sparse, long, pigmented hair chiefly along labia majora |
| Stage 3 | Further enlargement without separation of the breast and areola | Dark, coarse, curled hair sparsely spread over mons |
| Stage 4 | Secondary mound of areola and papilla above the breast | Adult-type hair, abundant but limited to mons |
| Stage 5 | Recession of areola to contour of breast | Adult-type spread in quantity and distribution |

# ***TREATMENT OF IMPERFORATE HYMEN:***

- -Relief of symptoms.
- -Definitive surgery **as soon as possible**
- -a simple cruciate incision in the hymen and **to allow drainage of altered menstrual fluid** or **a sterile puncture of the distended membrane and enlarged to allow insetion of a 16F Foley's cathter which is placed for 2 weeks.**





# Diagnosis :

**On physical ex-normal vaginal orifice, shortened vagina of varying length, no visible cervix and *a palpable hematocolpos* in the proximal vaginal segment or a pelvic mass from *hematometra and hematosalpinges*.

**Valsalva maneuver distinguishes it from imperforate hymen-in case of imperforate hymen there is distention at the introitus, blue convex vs pink concave.

- **Pelvic ultrasonography**-reveal extent and level.

Abdominal/pelvic MRI defines clearly the length of the atritic segment and septal thickness.

- **Avoid diagnosis** by inserting a needle which may convert a hematocolpos into a pyocolpos.

# Mayor Rokatinski Kauser Hauser Syndrome :

❖ **MRKH TWO TYPES:**

→ ***type A*** *(Symmetric rudiment uteri ,normal FT)*

→ ***type B*** (Asymmetric rudiment ut. and absent / hypoplastic FT)

❖ **ASSOCIATED ANOMALIES:**

- Urologic anomalies **(15-40%)** -u/l renal agenesis, horse-shoe kidney, duplication of the collecting system.
- Skeletal malformation-vertebra, ribs ,pelvis**. (10-15%).**
- hemivertebra, Cardiac anomalies .

❖ **DIAGNOSIS:**

- medical h/o, physical ex, karyotype,
- renal usg , spinal x-ray, MRI .
- laparoscopy.

# TREATMENT


➡ *Surgery is indicated*

♣ with symptoms of Hematometra, endometriosis or a hernia into the inguinal canal.

♣ ***Primary goal:*** creation of a functional vagina *by progressive. dilatation* **(non-surgical)** or **surgical creation** of Neovagina.

❖ *(Dilators Frank & Ingnam ):*

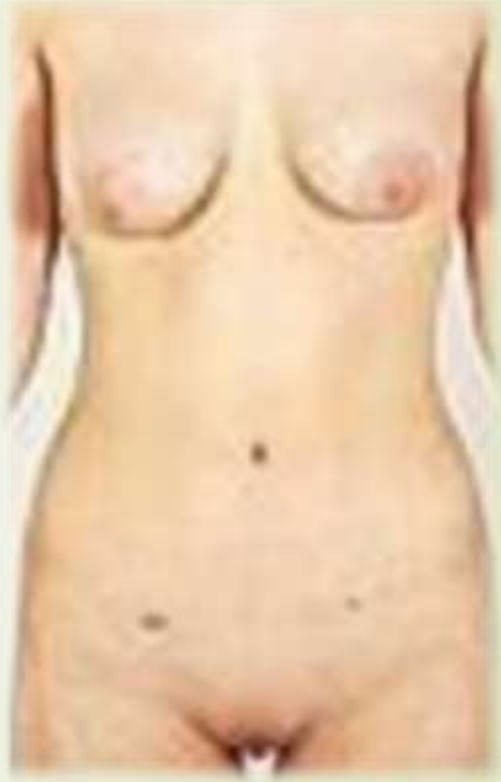
•Dilate at a **15 degree angle** by applying pressure daily for 20 minutes.

•Progressively work up to larger dilators

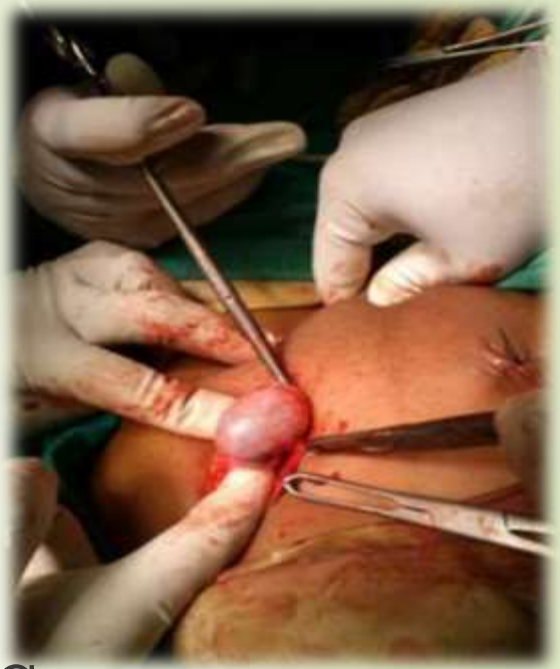
•Success defined as non-painful intercourse or vaginal length of **7cm.**

# Androgen Insensitivity Syndrome :

- • **Enzymatic failure** of testis to produce androgen (incomplete)
- • Absence of **androgen receptor or failure of function** (inactivating Mutation in gene encoding androgen receptor)



# Androgen Insensitivity Syndrome:



- **Normal** breast development.
- **Normal** vulva with short blind vagina.
- Uterus and tubes **absent**, Testes in abdomen/groin.
- Male range testosterone, Sr. LH also elevated reflecting androgen insensitivity at **hypothalmo-** pituitary level.

- **Treatment:**
  - gonadectomy after puberty + HRT(Malignant potential of gonad

**(5-10%)–** removal after puberty (to smoothen pubertal development and as it is very rare)

  - Vaginoplasty-**16 TO 18 YRS**
  - Psychological counselling

# Turner Syndrome:

- Turner **vs** mosaic.
- Karyotype-45/xo **vs** 45/xo or 46/xx.
- Height-short **vs** normal.
- Ovarian streaks-no follicle **vs** some follicle.
- Menstruation n preg-absent **vs** present.
- Classical features-present **vs** absent.

# Treatment

- • GH therapy **0.375mg/kg** weekly for about *7 yrs* starting at as early ***as 2-8 yrs*** for Height

- • To promote sexual maturation – exogenous estrogen such as **0.025 mg/day** transdermal estradiol or **0.3-0.625mg** CEE orally daily **25 days** at about ***12-13 yrs of age.***

- • ***5-10 mg*** MPA added to prevent endometrial hyperplasia after first experience of bleeding or after 6 months of E therapy for last ***10 days***.

# Kallman Syndrome:

***congenital GnRH deficiency with anosmia/hyposmia.***

- • **cyclic estrogen and progestin** (to induce sec. sexual character and to prevent osteoporosis).
- • Repetitive GnRH administration restores normal ovulation.
- • Fertility portable infusion pump to deliver subcutaneous, **pulsatile GnRH**

# Empty sella turcica

**characterized by herniation of subarachnoid membrane into the pituitary sella turcica and may exist with pineal gland tumour as prolactin adenoma.**

- In all such women, cyclic administration of ***oestrogen and progestogen*** to maintain femininity and prevent osteoporosis is essential.
- In case the woman desires to conceive, induction of **ovulation with gonadotropins** is warranted.
- In women with neoplasms, appropriate neurological consultation followed by treatment with **bromocriptine** for prolactinomas or surgery should be planned.

# Congenital Adrenal Hyperplasia :

- • Enzyme defect leading **to excessive androgen production.**
- • Autosomal recessive trait.
- • Milder form of disease diagnosed later in life(late onset) and **resembles PCOS.**
- • May present with primary amenorrhea but even more classical: hirsutism, virilization, anovulation.
- • Abnormal looking female external genitalia **(ambiguous)**
- • *Presence* of uterus and upper vagina.
- • Diagnosis: Fasting 17-OHP-

**Levels >1000 ng/dL are indicative of late-onset CAH.**

- ***INVESTIGATIONS:***

• • *USG internal genitalia shows presence of uterus, fallopian tubes, and vagina.*

- The gonads are ovaries. Sex chromatin study reveals positive Barr body.
- Karyotype is 46, XX.
- • *17 hydroxy-progesterone (17 OHP)*
- "salt loosing syndrome" (sodium and chloride— low, potassium raised ↑)
- Urinary excretion of pregnanetriol and 17 Ketosteroids are markedly elevated.

- ***TREATMENT:*** *Hydrocortisone **10–20 mg/m2 body** surface area per day is given to suppress the excess ACTH secretion.*

**Mineralocorticoid (fluorocortisone) is also given in cases with 21-hydroxylase deficiency and Corrective surgery **(reduction clitoroplasty & vaginoplasty).**

# Anorexia Nervosa :

- Management.
- Psychological .
- Psychotherapy .
- Nutritional .
- GnRH to initiate H-P-O axis.
- **Hormonal therapy:** *To initiate or complete H-P-A axis.*
- Seventy per cent improve with treatment.


Thank
You!
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