Hirsutism And Intersexes

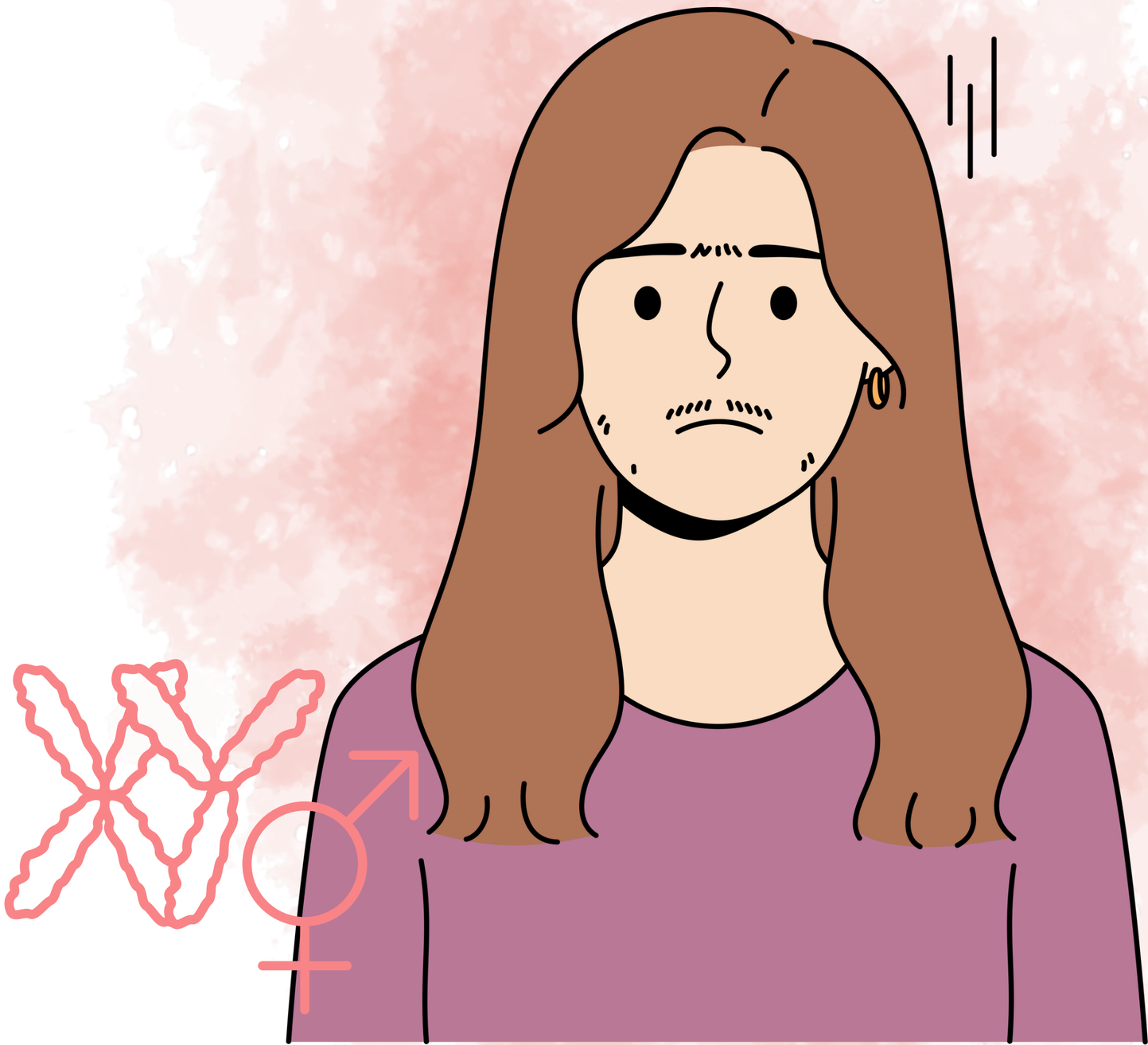
By:

Taqi Alawneh

Sadeen Al-Sarayreh

Mohammad Takhaineh

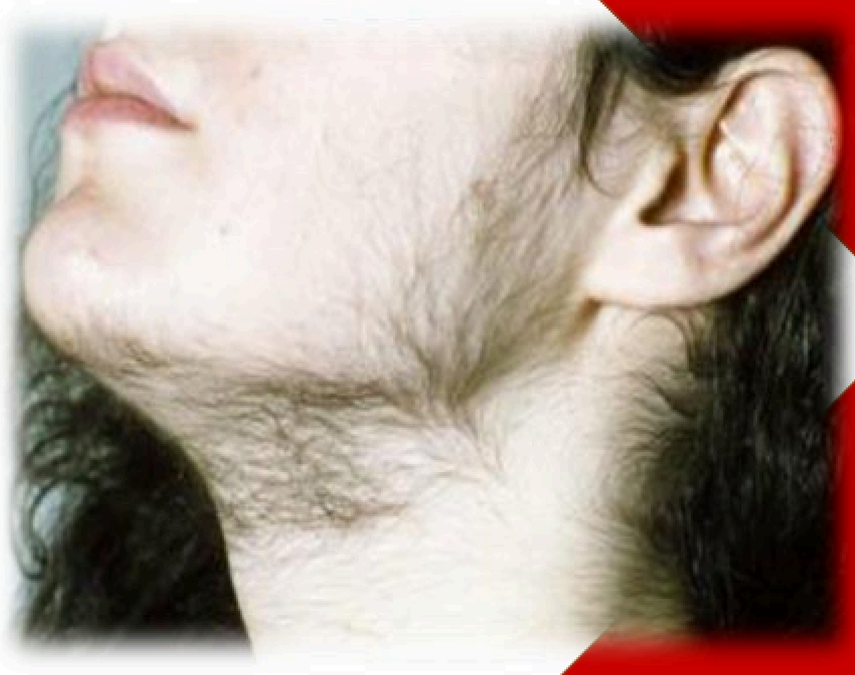
Salma Alnobani



WHAT IS HIRSUTISM ?

a condition in women that results inexcessive growth of coarse terminal hair in amale-like pattern.

- (face, chest and back)

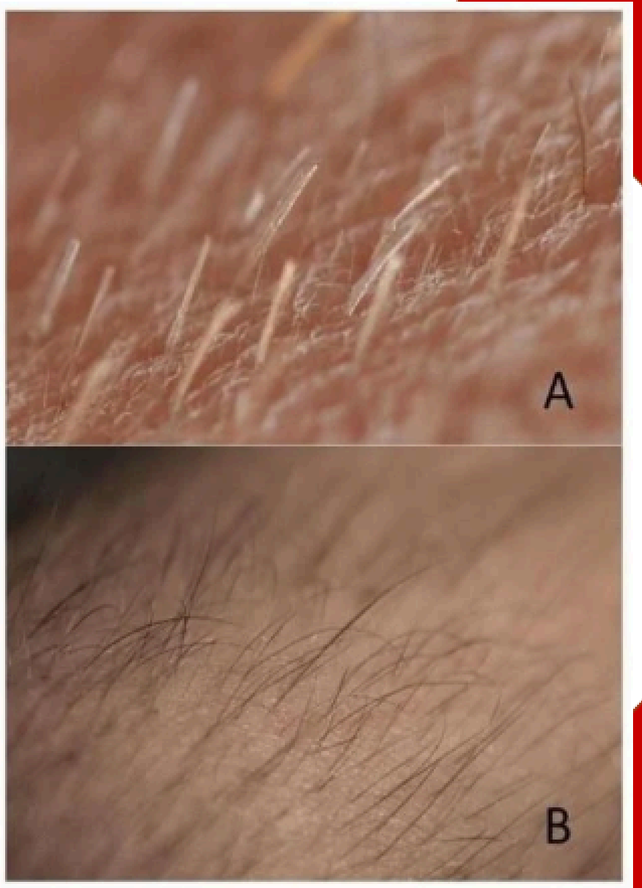


Vellus hair: Soft fine NOT PIGMENTED (colorless) and usually short Grow give the impression of (hairless) skin. on the face, chest, and backand

Terminal hair: longer coarser darker hair that grows

on the scalp ,pubic ,and armpit areas in both adult men and women.

In hirsutism The hair is often dark and coarse instead of the light, fine, colorless hair .



A. Vellus Hair. B. Terminal Hair

WHAT CAUSES HIRSUTISM?

- Hirsutism is either due to increase of the androgen hormones or to the hirsutism" .

highsensitivityofthe hair follicle to androgens "idiopathic

- The androgens hormones that may increased :-

-androgen : "ovarianoradrenalorigin".

1 Testosterone : mostly ovarian origin Dehydroepiandrosterone sulfate
2 (DHEAS) : adrenal origin
3 Androstenedione :adrenal or ovarian origin

We should rule out the exogenous intake of androgens which can cause hirsutism and acne .

So based on the previous slide, any disorder that increase the androgens levels is a cause of hirsutism :-

- Polycystic ovarian syndrome : most common
- Congenital adrenal hyperplasia.
- Ovarian tumors.
- Adrenal tumors. Cushing disease. Drugs.(carbamazepine , fluoxetine , isotretinoin ,
- olanzapine , pregabalin , systemic corticosteriods, oral contraceptive) Idiopathic
- hirsutism : increased cutaneous sensitivity of the skin to normal circulating. levels of
- androgens.

POLYCYSTIC OVARY SYNDROME

- Acomplex endocrine disorder affecting women of childbearing age characterized by increased androgen production and ovulatory dysfunction.

Leading cause of An-ovulatory infertility and Hirsutism.

The syndrome is characterized by :

- menstrual irregularity
- Hyperandrogenism: both clinical (hirsutism, acne, or male-pattern balding) and biochemical (elevated serum androgen concentrations).

How to diagnose PCOS?

Rotterdam criteria(2outof 3 withexclusion of other causes)

-Menstrual irregularity

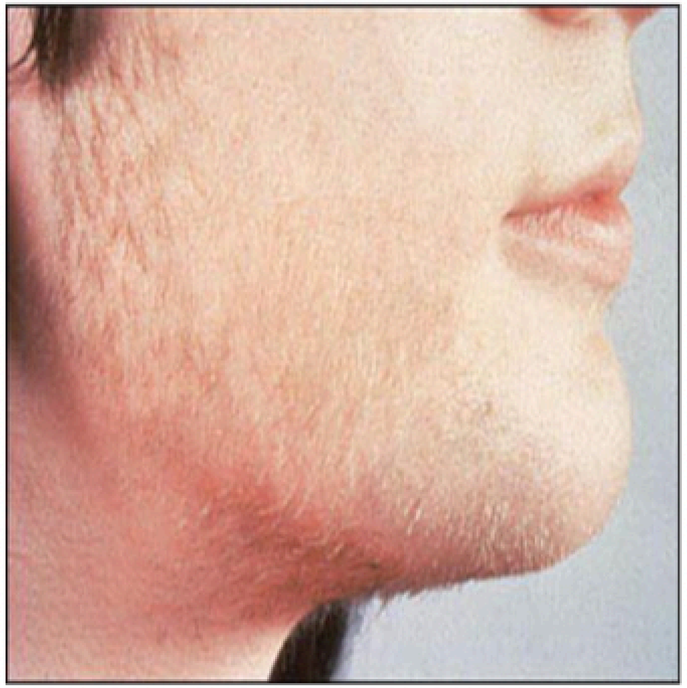
- due to anovulation or oligo-ovulation

-Hyperandrogenism

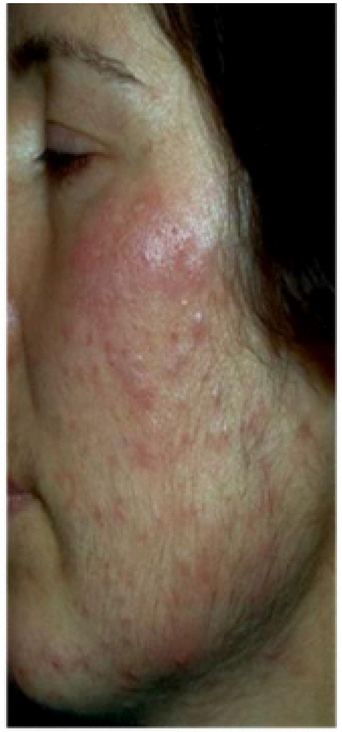
- Clinical or Biochemical Evidence

-Polycystic ovaries by TVUS

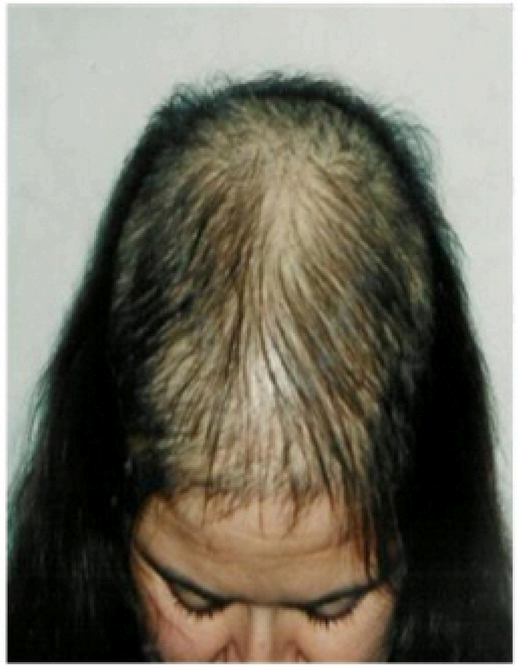
- Bilateral
- Presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter and/or increased ovarian volume.



Hirsutism



Acne



Alopecia

CONGENITAL ADRENAL HYPERPLASIA

- a group of autosomal recessive disorders, each of which involves a deficiency of an enzyme involved in the synthesis of cortisol, aldosterone, or both.
- The phenotype can vary from clinically in apparent disease (occult or cryptic adrenal hyperplasia) to a mild form of disease that is expressed in adolescence or adulthood
- (non classicadrenal hyperplasia)to sever disease that results in adrenal insufficiency (classicadrenal hyperplasia).

HOW TO DIAGNOSE LATE ONSET CAH ?

The classical type the patient diagnosed early in infancy due to presense of ambiguous genitalia and electrolyte imbalnce .

The non classical type will be diagnosed late in adulth oodin patients who have similar picture to pcos (hirsutism, irregular cycle).

So How to diagnose late onset CAH?

- Its diagnosed by marked increase in 17-hydroxyprogesterone greater than >1000 ng/dL after adrenocorticotropic stimulation

OVARIAN TUMORS

- Hirsutism caused by anandrogen-secreting tumor usually occurs later in life and progresses rapidly when compared with PCOS.

  sex cord stromal neoplasia : Sertoli-Leydig cell tumors, granulosa-theca cell tumors .

- •Androgen–secreting ovarian tumors are rare“only 5% of all ovarian tumors”, and present with hirsutism and virilization which may manifest as sever alopecia, deepening Of voice, and clitoromegaly.

- Laboratory tests: Testosterone level is markedly elevated. (more than 150ng/dL)

- Many of these tumors can be identified by vaginal us.

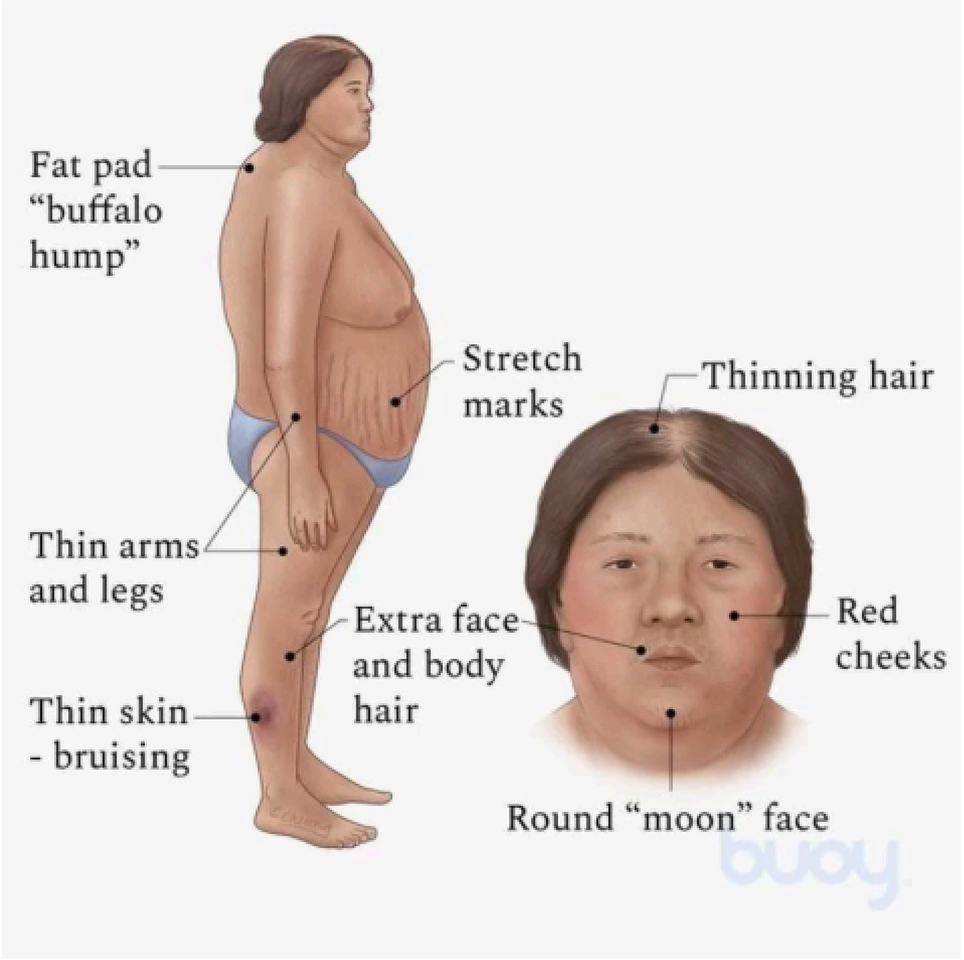
ADRENAL TUMORS

- Rare cause of androgen excess.
- most are carcinoma that often secrete not androgen (mostly dheaanddhea-s)
- Examination: Physical examination will show evidence of virilization.
- Laboratory tests: elevated serum dhea-s >700 microgram /dl is suggestive of anadrenal tumors.
- Imaging: CT OR MRI SCAN will show an abdominal-flank mass.
- Picture the same as the patient presented with ovarian tumor but the investigation is different.
- Many of these tumors can be identified by vaginal us.

CUSHING DISEASE

- Adrenal over activity due to acorticotroph adenomasecreting ACTH excessively results not only inexcessive secretion of cortisol but also of adrenal androgens, typically result in hirsutism.
- Although the majority of women who have Cushing's disease have hirsutism, only a very small fraction of women with hirsutism have Cushing's disease.
- Centralobesity, hirsutism, moonface, buffalohump, purple striae on abdomen, acne.
- Laboratorytests: blood serum cortisol testing , 24-hour urinary free cortisol testing and dexamethasone suppression test

CUSHING DISEASE



IDIOPATHIC HIRSUTISM

- Idiopathic hirsutism defines : the hirsutism that occurs in association with regular menses, normal ovarian morphology, and normal plasmatic androgen levels.
- It is a diagnosis of exclusion after elimination of other etiologies.
- It represents about 10% of all cases of hirsutism and 50%of cases of mild hirsutism.

How To Approach The Patient ?

History

- **Onset And Progression =**
  >When did she notice increased hair growth
  >Is the onset sudden or gradual?
  (PCOS typically have a peripubertal /Androgen secreting tumors usually occur late in life)
  Rapid or slow progression (very rapid in androgen secreting tumors)
- **Distribution And Pattern**
  > Which areas are affected? (face, chest, abdomen, back, thighs)
  >Any associated acne, oily skin, or scalp hair loss? (androgenic features)

History

- **Menstrual Hx =**
  >Are your menstrual cycles regular?
  >Any history of infertility?
  >Menarche (first period)?
- **Symptoms Suggesting Virilization** (sign of high androgen levels)
  > Deepening of voice?
  > Increase in muscle mass
  >Breast size reduction?
  > Clitoral enlargement?

History

- **Associated Symptoms** =
  >Recent weight gain or central obesity?
  >Striae (stretch marks), easy bruising (Cushing's)?
  > Fatigue, mood changes?
- **Drugs Hx** = (steroids, danazol, phenytoin, DHEA)
- **Family Hx** = Several conditions that cause hirsutism, including congenital adrenal hyperplasia and polycystic ovary syndrome, run in families.

Physical examination

اللهم أبدل جوع أهلنا شبعاً و
خوفهم أمناً و ضعفهم قوة

Physical Examination

- **General Inspection**

>Hair distribution → Use Ferriman–Gallwey score to quantify severity (scores hair growth in 9 androgen-sensitive areas).

>Type of hair → Coarse, pigmented terminal hair vs fine vellus hair.

>Signs of virilization → Deep voice, increased muscle mass, male pattern baldness, breast atrophy, clitoromegaly.

>Skin changes → Acne, seborrhea, oily skin.

>Body habitus → Central obesity (PCOS, Cushing's).

>Acanthosis nigricans → Marker of insulin resistance (common in PCOS).

Physical Examination

- **BMI & Waist to hip ratio =** (Obesity pattern helps identify PCOS or Cushing's.)
- **Breast examination** → Atrophy suggests virilization; galactorrhea suggests hyperprolactinemia.
- **Pelvic examination (if indicated)** → Look for clitoromegaly (tumor suspicion) or signs of androgen excess.

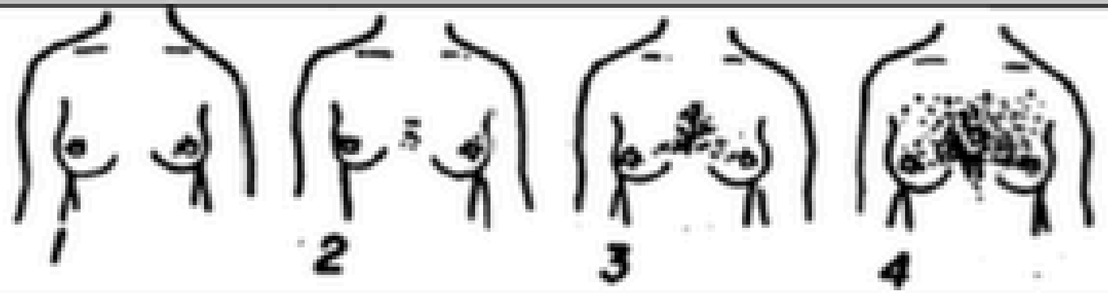
- **Scoring the Hirsutism**

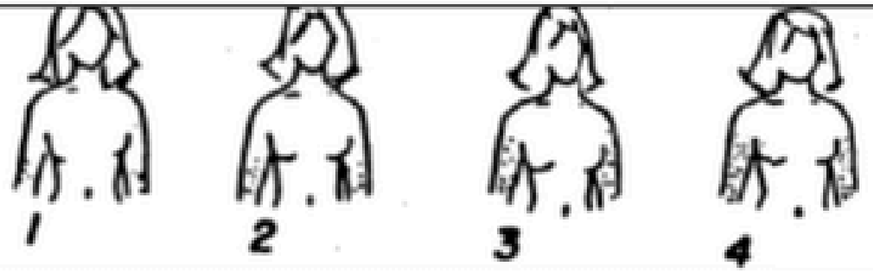
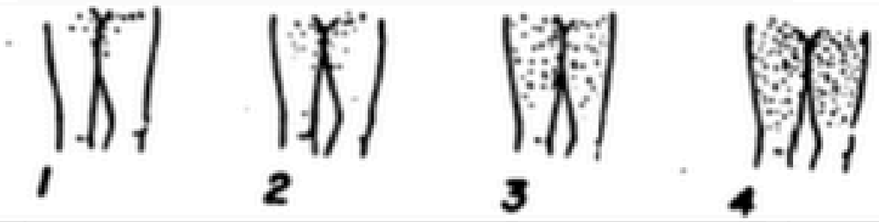
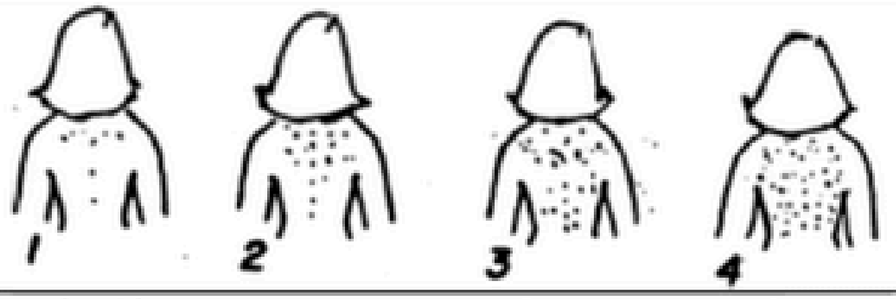
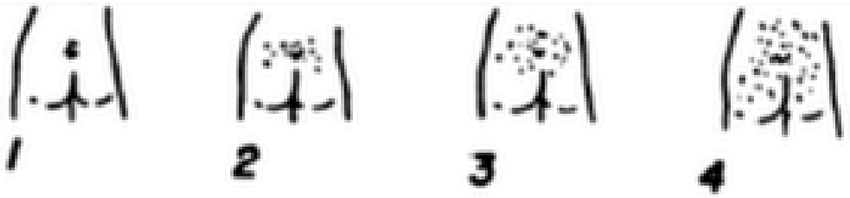
  Ferriman–Gallwey Score:

  Is the presence of terminal hair in a female body in a male-type pattern, includes hair on 9 body areas:

  (upper lip, chin, chest, upper and lower abdomen, upper and lower back, upper arm and thigh.)

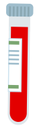
  - Score each from 0 (no hair) to 4 (extensive hair).
  - ⩾8 usually considered diagnostic of hirsutism.

Body Area	Date of exam :		
Upper Lip		Score	
Chin		Score	
Chest		Score	
Upper Abdomen		Score	

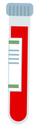
Lower Abdomen		Score	
Arms		Score	
Thigh		Score	
Upper Back		Score	
Lower Back		Score	
		TOTAL SCORE	

Investigation

- **Mainly based on your judgement regarding to history and examination. So, it is <u>diagnosed clinically</u>.**



Free testosterone (more than 150ng/dL) = suggest ovarian tumor ⟶ Next step : pelvic ultrasound



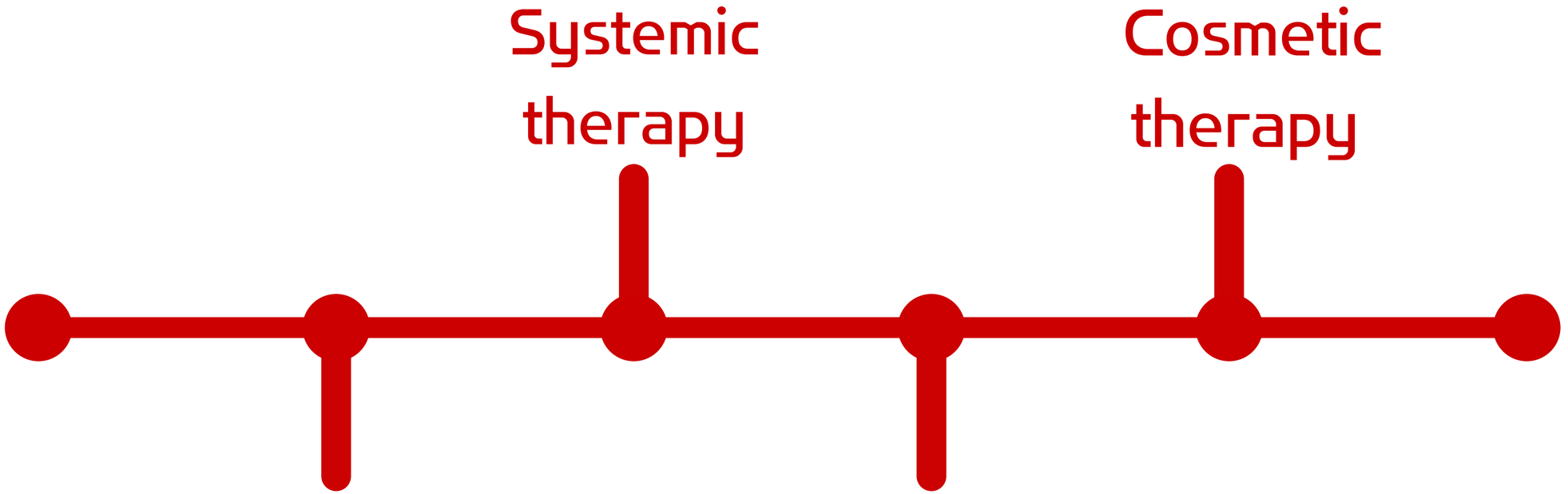
Dehydroepiandrosteron sulfate (DHEAS) = elevated suggest adrenal cause ⟶ Next step : CT / MRI
Not elevated suggest PCOS ⟶ Next step : LH:FSH

17-hydroxyprogesterone = Screen for congenital adrenal hyperplasia (CAH)

Note

- High testosterone + normal DHEAS → ovarian tumor/PCOS
- High DHEAS + normal testosterone → adrenal tumor/CAH
- Both very high → consider ovarian/adrenal tumor
- Mildly elevated both → PCOS
- All 3 test are normal → idiopathic hirsutism

Management

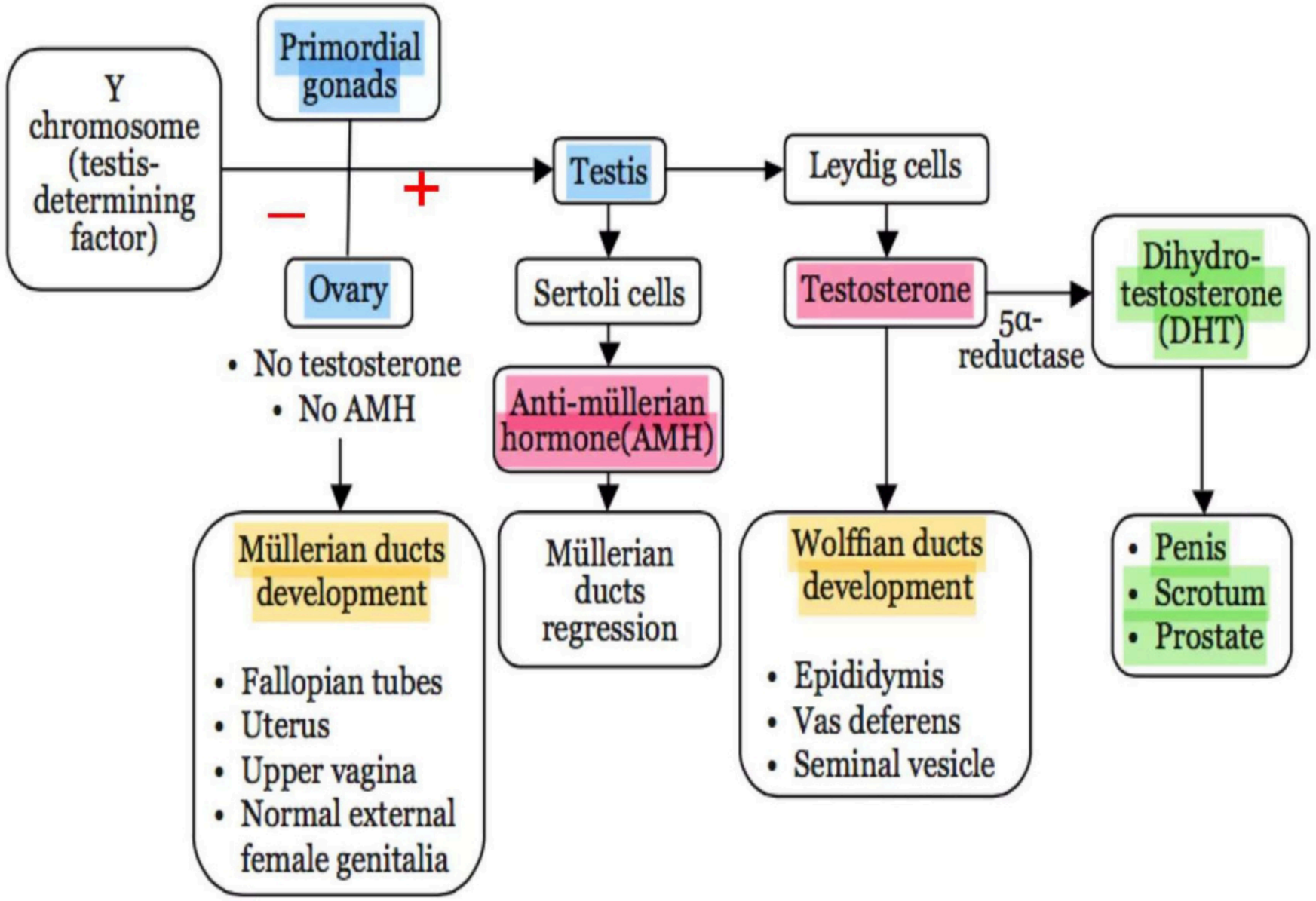

Systemic therapy
Cosmetic therapy
Remove the source of excess androgen
Topical therapy

Management

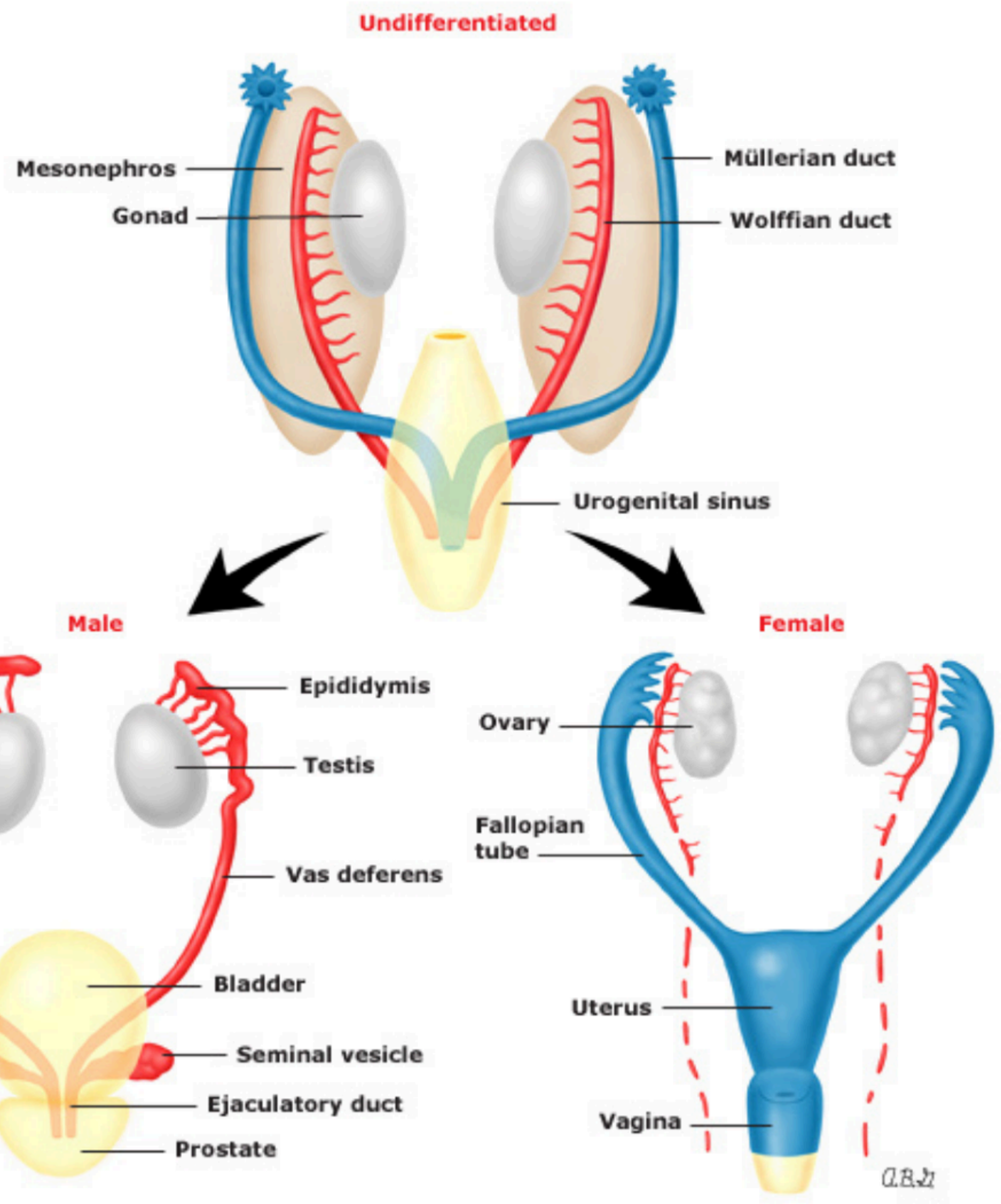
- Treat the cause
- Systemic therapy = Oral contraceptive
  Spironolactone
  Flutamide
  Finasteride
- Topical therapy = Eflornithine (Vaniqa)
- Cosmotic therapy = Bleaching , shaving, waxing, laser

Definition

- Infants born with genitals that do not appear typically male or female, or that have an appearance discordant with the chromosomal sex are classified as having a **difference (or disorder) of sex development (DSD**.
- DSDs with a genital appearance that is sufficiently atypical to prompt evaluation occur in approximately 1 in 4500 live births



Simplified model for sexual differentiation and the development of internal and external genitalia.


Undifferentiated
Mesonephros
Gonad
Müllerian duct
Wolffian duct
Urogenital sinus
Male
Female
Epididymis
Testis
Vas deferens
Bladder
Seminal vesicle
Ejaculatory duct
Prostate
Ovary
Fallopian tube
Uterus
Vagina

Normal sexual differentiation

	GONADS	INTERNAL GENITALIA	EXTERNAL GENITALIA
TIMING (I U)	7-9Week	8-1 I Week	8-20 Week
EMBRYONIC ORIGIN	Genital ridge	Wolffian (male) Mullerian (female)	-genital tubercle -genital fold - Genital swelling
DETERMINIG FACTOR	TDF (encoded as SRY gene on Yp)	Testosterone Anti-mullerian H.	Di-hydro-testosterone

Table 2: Major causes of disorders of sex development (DSD) according to karyotype

46,XX Karyotype		
46,XX DSD	• Congenital adrenal hyperplasia (CAH)	◦ Enzyme deficiency ▪ 21α-hydroxylase ▪ 11β-hydroxylase ▪ 3β-hydroxysteroid dehydrogenase
	• Ovarian/adrenal tumours (mother–child)	
	• Exposure to exogenous medication (synthetic progestin preparation)	
Ovotesticular DSD		
46,XY Karyotype		
46,XY DSD	• Lack of synthesis of testosterone	◦ Testicular differentiation ▪ pure gonadal dysgenesis ▪ absence of Leydig cells or luteinising hormone receptor ▪ testicular regression ▪ gonadotrophin hormone deficiency ◦ Enzyme deficiency in testosterone pathway ▪ 20,22-desmolase ▪ 17,20-lyase ▪ 3β-hydroxysteroid dehydrogenase ▪ 17α-ketoreductase
	• Lack of synthesis of dihydrotestosterone	◦ 5α-reductase deficiency
	• End-organ-unresponsiveness (resistance)	◦ Partial ◦ Complete
Ovotesticular DSD		
Multiple or local congenital anomalies		
Mixed Karyotype		
Ovotesticular DSD 46,XX/46,XY		
Mixed gonadal dysgenesis 45,X/46,XY		

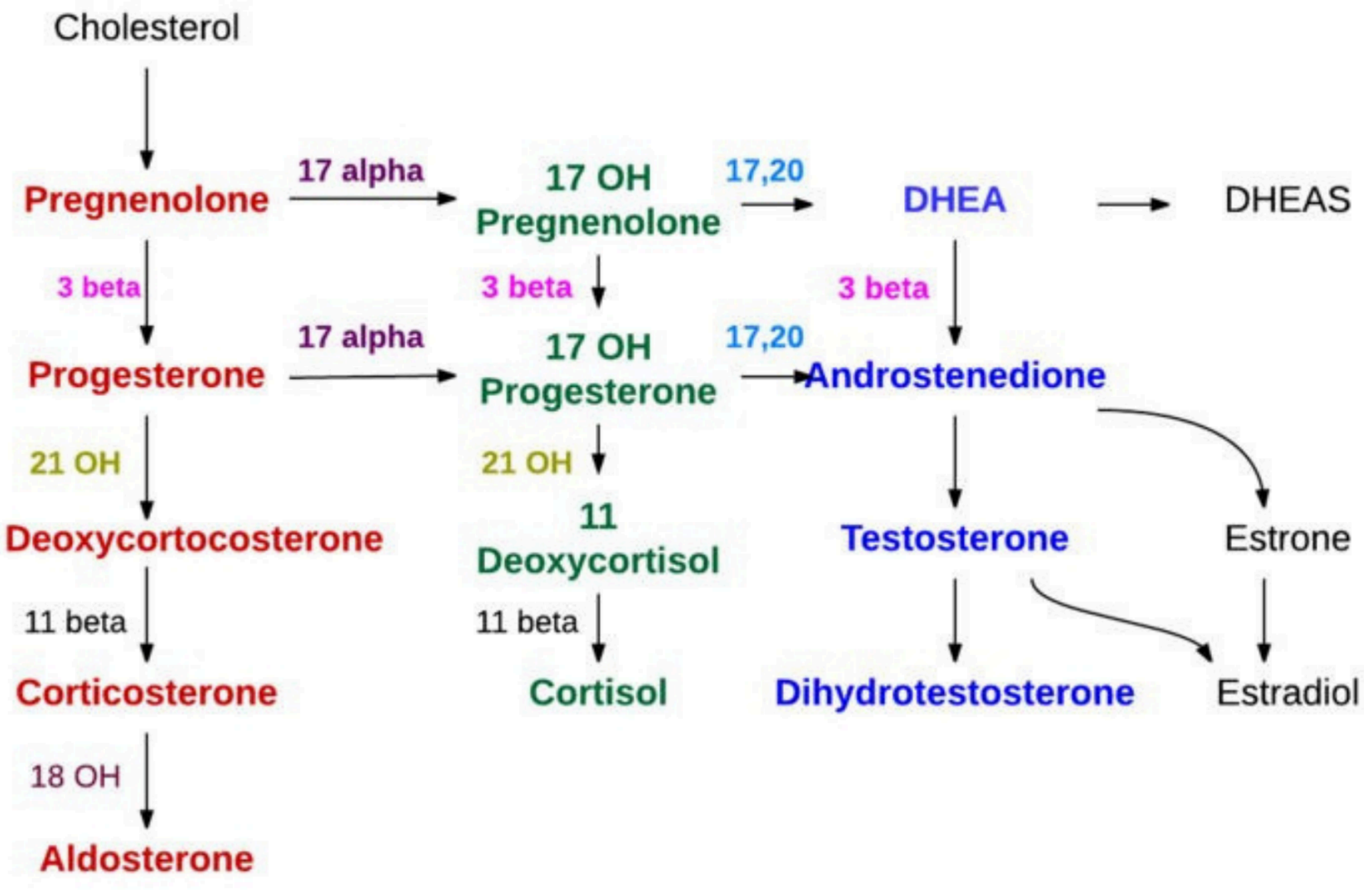
46XX

46XY

Congenital Adrenal Hyperplasia [CAH]

- Definition :Congenital adrenal hyperplasia (CAH) are any of several autosomal recessive diseases resulting from mutations of genes for enzymes mediating the biochemical steps of production of mineralocorticoids, glucocorticoids or sex steroids from cholesterol by the adrenal glands (steroidogenesis)*
- Incidence: the most common, 45%
- Sub-types:

1- 21 hyroxylase deficiency (classic CAH- commonest)
2- 11 β hyroxylase deficiency
3- 3 β hydroxy-steriod dehydrogenase deficiency
4- 17 α hyroxylase deficiency
5- PORD (P450 oxido-reductase deficiency)


Cholesterol
Pregnenolone
17 alpha
17 OH Pregnenolone
17,20
DHEA
DHEAS
3 beta
3 beta
3 beta
Progesterone
17 alpha
17 OH Progesterone
17,20
Androstenedione
21 OH
21 OH
Deoxycortocosterone
11 Deoxycortisol
Testosterone
Estrone
11 beta
11 beta
Corticosterone
Cortisol
Dihydrotestosterone
Estradiol
18 OH
Aldosterone

Classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency

- accounts for approximately **95 percent of CAH** and is the most frequent cause of atypical genital appearance in general.
- can be diagnosed based on **elevated serum 17-OHP**.
- Decreased activity of 21-hydroxylase results in **decreased production of cortisol and aldosterone** and **overproduction of adrenal androgens.**
- Affected infants with 21-hydroxylase deficiency often have **salt wasting**, which causes hyponatremia with hyperkalemia, dehydration, and hypotension, and they are at risk for the life-threatening complication of adrenal crisis.

Other types of congenital adrenal hyperplasia

- 11-β hydroxylase deficiency patients are protected from the symptoms associated with adrenal crisis, although they are subject to others such as *hypertension* due to salt retention and *ambiguous genitalia in females*.
- 17α-hydroxylase deficiency results in *ambiguous external genitalia in males* and lack of pubertal development or menstrual cycles (amenorrhea) in *females*.
- 3-β-hydroxysteroid dehydrogenase deficiency leads to *ambiguous genitalia in males and females*. In both genders it can lead to salt-wasting.

- Congenital lipoid adrenal hyperplasia may cause *early death* due to adrenal crisis. *Males have ambiguous genitalia*. Both males and females, if they survive, would likely be infertile.
- PORD (P450 oxidoreductase deficiency) presents with signs and symptoms that may resemble 21-hydroxylase deficiency, 17-hydroxylase deficiency, or a combination of the two enzyme deficiencies. Some cases have been associated with a *skeletal disorder* known as *Antley-Bixler syndrome*.

CAD - diagnosis

- **Prenatal**:
  - Detection of elevated amniotic fluid level of **17-OHP, 21 deoxycortisol & androstendione.**
  - **first trimester chorionic villus sampling and testing the fetal DNA** for a particular CAH gene mutation known to occur in the family (most accurate).
- **Postnatal**:
  - Clinically- ambiguous genitalia
  - Levels of 17-OHP, 21 deoxycortisol, androstendione, cortisol
  - Electrolyte disturbance

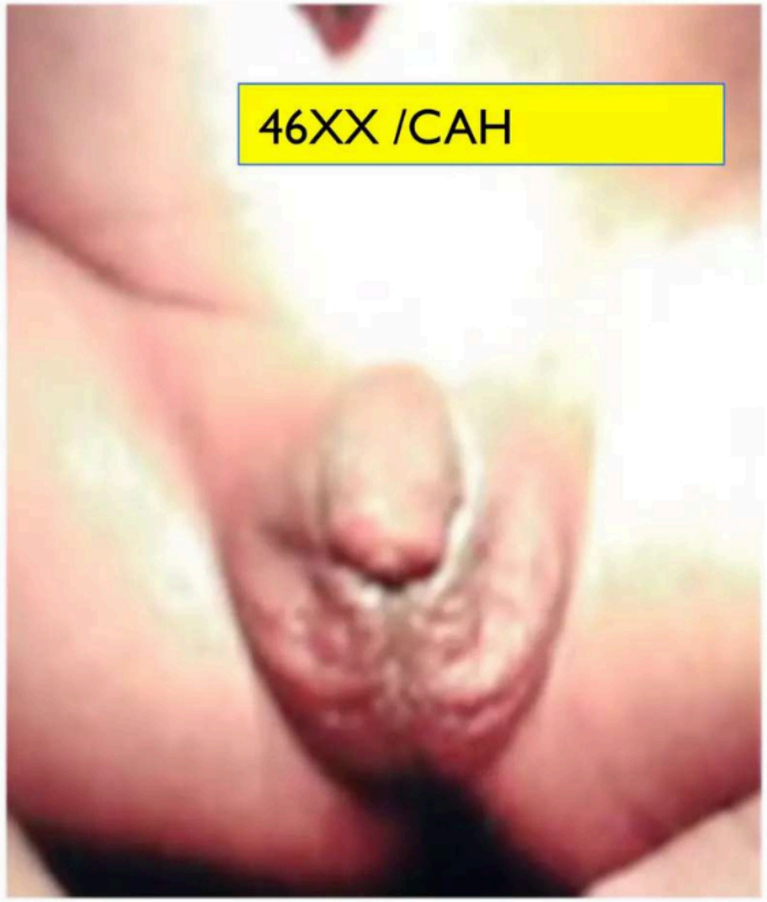


Figure 2: Ambiguous genitalia in a 46,XX patient known to have congenital adrenal hyperplasia due to 21α-hydroxylase deficiency. Note the complete masculinisation, with normal looking hyperpigmented male genitalia (but no palpable testes).

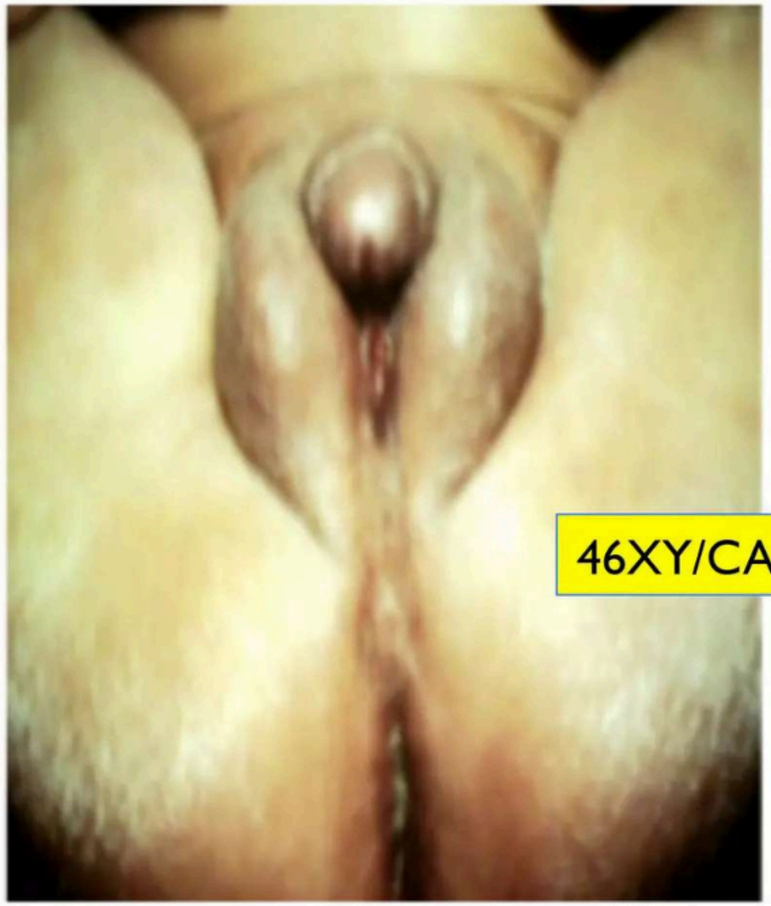


Figure 3: Ambiguous genitalia in a 46,XY patient known to have congenital adrenal hyperplasia due to 3β-hydroxysteroid dehydrogenase deficiency. Note the pigmented, short, curved phallus, central urogenital slit, and separated labioscrotal testis.

CAH - Treatment

PRENATAL TREATMENT

-The rationale for prenatal treatment is to treat the fetus with a *glucocorticoid (dexamethazone DEX)* via the mother, in order to suppress the fetal adrenal androgen production that is increased in fetuses with severe forms of CAH (the salt-wasting and simple virilizing variants).

- Indicated in mother that has previously given birth to a child with severe CAH at 6-7th week of next pregnancy.

CAH - Treatment

PRENATAL TREATMENT

- The dose given is 20 µg/kg body weight/day, based on pre-pregnancy weight and maximum 1.5 mg/day, in three divided doses.
- A few weeks later, around week 12, prenatal diagnosis is performed on fetal DNA obtained from a chorionic villous biopsy (CVS).
- In healthy fetuses and in CAH affected boys treatment will be stopped while affected girls will be treated until term.

CAH - Treatment

Post-natal treatment

A- Medical:

1- hydrocortisone (10 mg/day) OR
2- prednisone (3.5-5 mg/m^2 surface area] *monitoring of treatment by 17 OHP (range 500 – 4000 ng/dl)*

B- Surgical:

1- *general consideration*

- Patient is genetically female and potentially fertile.
- Surgical correction must be after medical control .
- Parents must be counseled about the procedure

2-*Surgical procedures:*

- Reduction of clitoris size (amputation, clitoral recession)
- Division of labio-scrotal folds (introito-plasty)

Other disorders

- TURNER SYNDROME.
- Androgen Insensitivity syndrome(AIS).
- Swyer syndrome.

TURNER'S SYNDROME

- **A genetic condition that occurs in females who have a missing or abnormal X chromosome (sex chromosome).**
- phenotype is female.
- genotype is:

-Classical monosomy (45XO).

-Mosaicism (45XO/46XX).

-Abonrmal x chromosome.

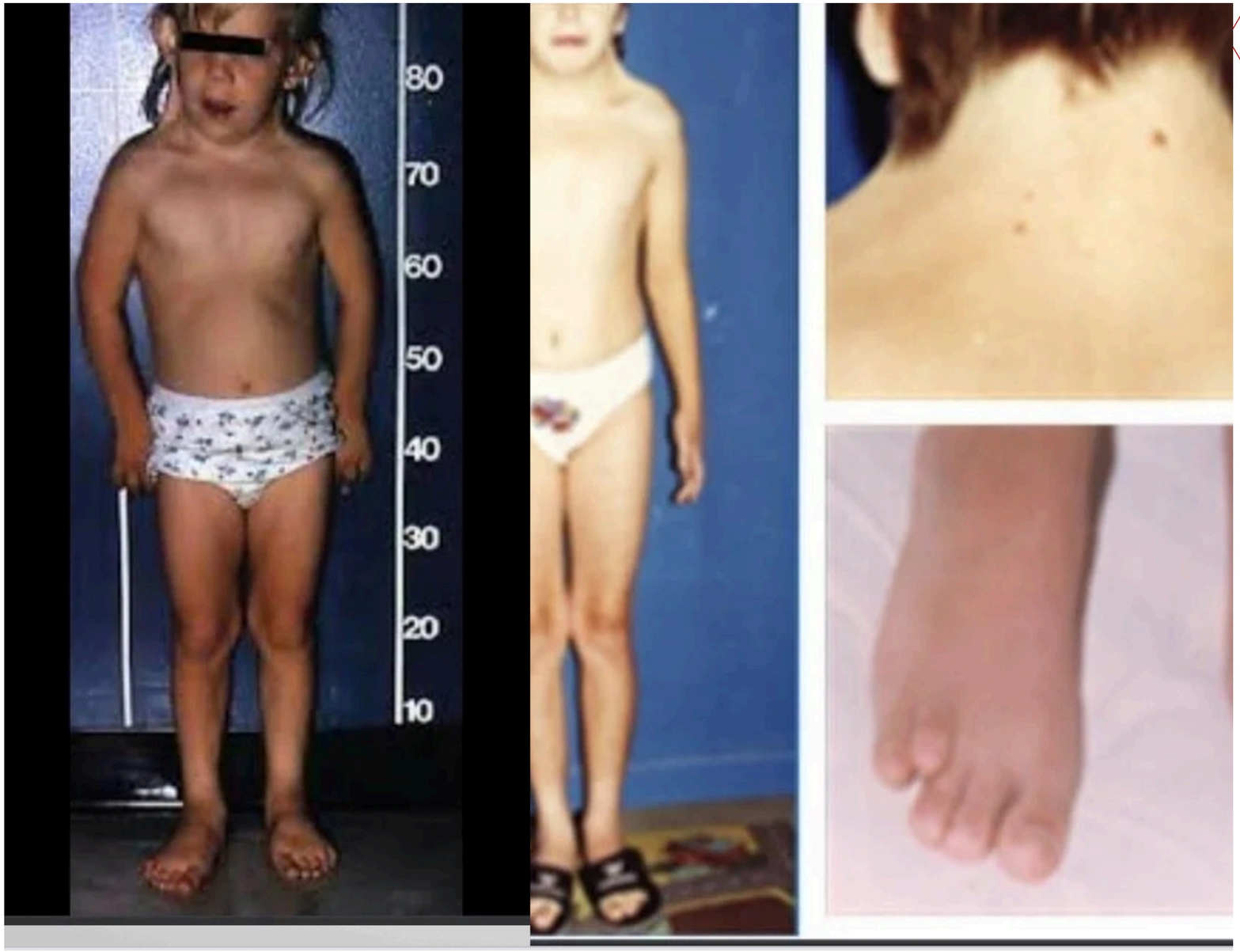
- Complete or partial absence of x-chromosome.
- MC chromosomal abnormality in female.
- Mainly diagnose clinically.
- Ovarian tissue in affected individuals, referred to as ‘streak gonads’, primarily consists of connective tissue with either no follicles or only a few atretic follicles.

-Clinical features:

- short stature.
- webbing of the neck.
- wide carrying angle.
- Widely spaced nipples (shield chest).

-Associated medical conditions:

- coarctation of the aorta.
- inflammatory bowel disease, sensorineural and conduction deafness.
- renal anomalies.
- endocrine dysfunction, such as autoimmune thyroid disease.


80
70
60
50
40
30
20
10

-Presentation:

Present with delayed puberty (primary amenorrhea and absent of secondary sexual characteristics).

-Diagnosis:

1.karyotyping test (confirmatory test).

2.clinically.

3.US.

4.labs:(High FSH and LH levels.)

-Management:

1. Growth hormon therapy (in childhood).

2. HRT (in adolescence).

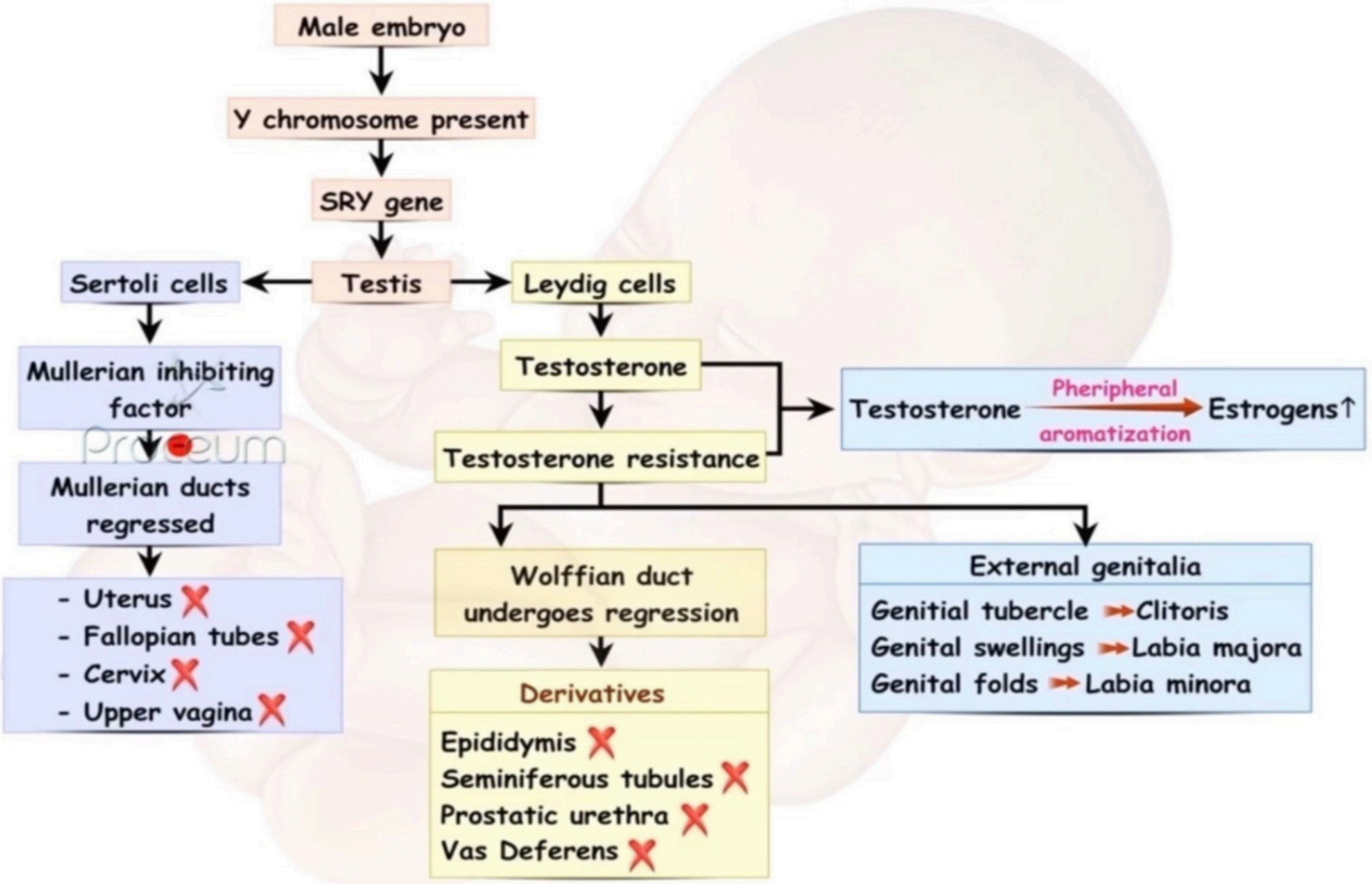
3.fertility treatment.

4. Managing Associated Health Issues.

Androgen Insensitivity syndrome(AIS)

- X-linked recessive inheritance.
- The phenotype is female.
- The genotype is (46XY).

TESTICULAR FEMINIZATION SYNDROME



1. SRY gene is present so testes form normally (testes)
2. testes secrete AMH, leading to the regression of the Müllerian ducts (no uterus).
3. Testes secrete Testosterone but androgen receptor don’t respond (androgen receptor gene mutation), so the external genitalia do not virilize and instead undergo female development (female external genitalia)

In cases of partial androgen insensitivity, the androgen receptor can respond to some extent with limited virilization. The child is usually diagnosed at birth with ambigous genitalia.

Presentation:

1. primary amenorrhea at puberty.
2. if the testes are in the inguinal canal they can cause a hernia in a younger girl.
3. Dyspareunia
4. Infertility.

Management:

1. counseling and Psychological support .
2. Surgical intervention.
3. HRT.

Swyer syndrome

complete Gonadal dysgenesis.

-Phenotype is female.

-Genotypes is 46XY.

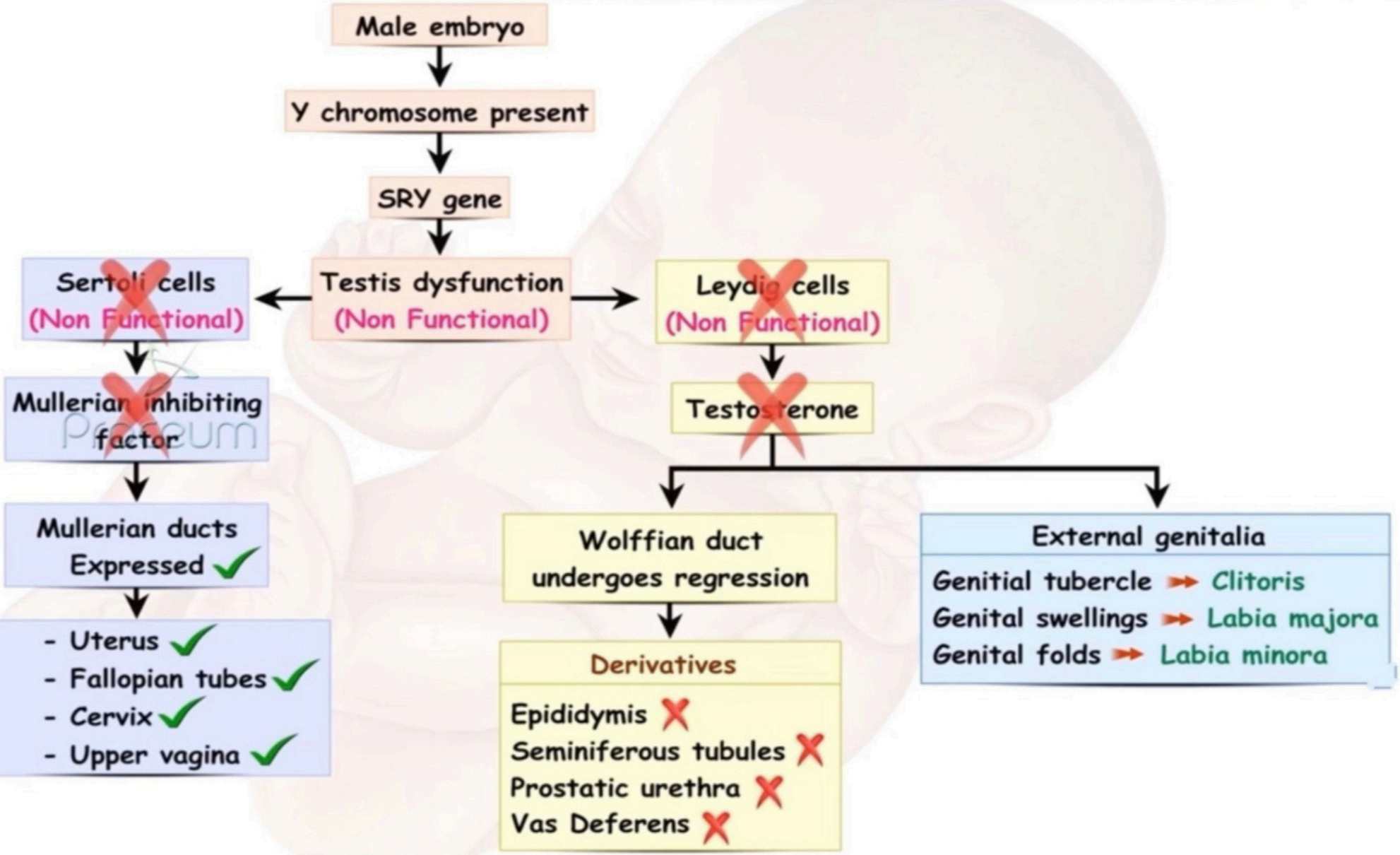
1. SRY gene is mutated (no testes).

2. No testosterone (normal female genitalia).

3.No anti- Mü llerian hormone (fallopian tube, uterus and vagina present).

4.streak gonads that does not produce any hormones (no secondary sexual characteristics).

SWYER SYNDROME (GONADAL DYSGENESIS)



-Presentation:

Present with delayed puberty (primary amenorrhea and absent of secondary sexual characteristics).

-Management:

1. Remove streak gonads (risk of germ cell tumor gonadoblastoma).
2.Puberty must be induced with oestrogen and pregnancies have been reported with a donor oocyte.

THANK YOU