Endocrinology of the Future
ICE 2024
21st International Congress of Endocrinology
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Endocrine conditions in children

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Disclosures

- Honoraria from:

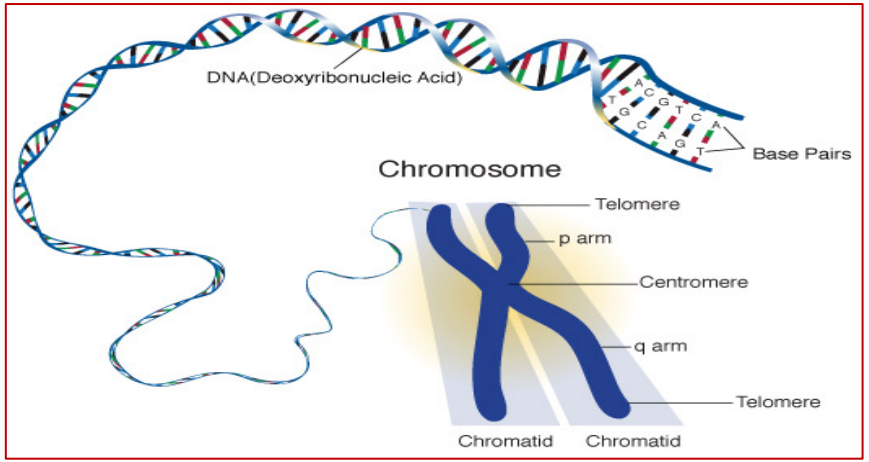
- Springer / Merck
- Pfizer

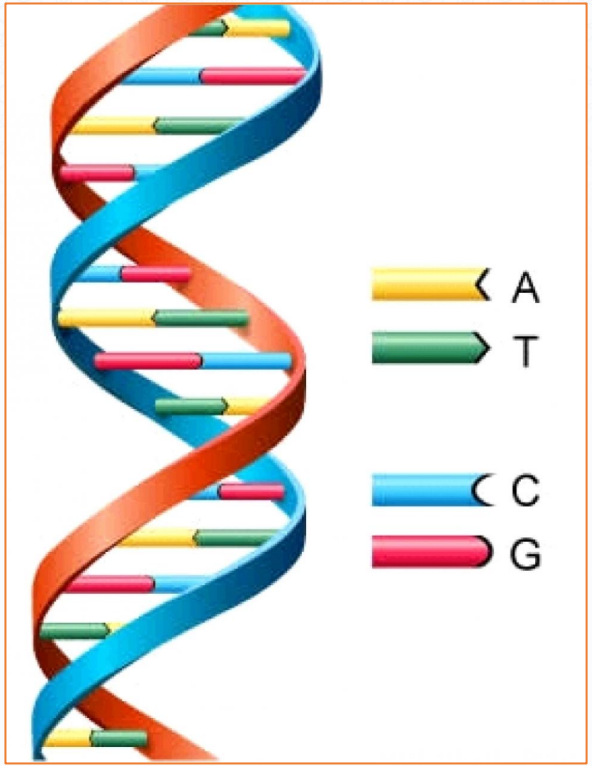
Introduction

- Genetics
  - Understanding inherited / chromosomal conditions
- Embryology
  - DSD
- Growth
  - GHD
  - Late effects
- Puberty
  - Early
  - Girls v Boys
- What else?

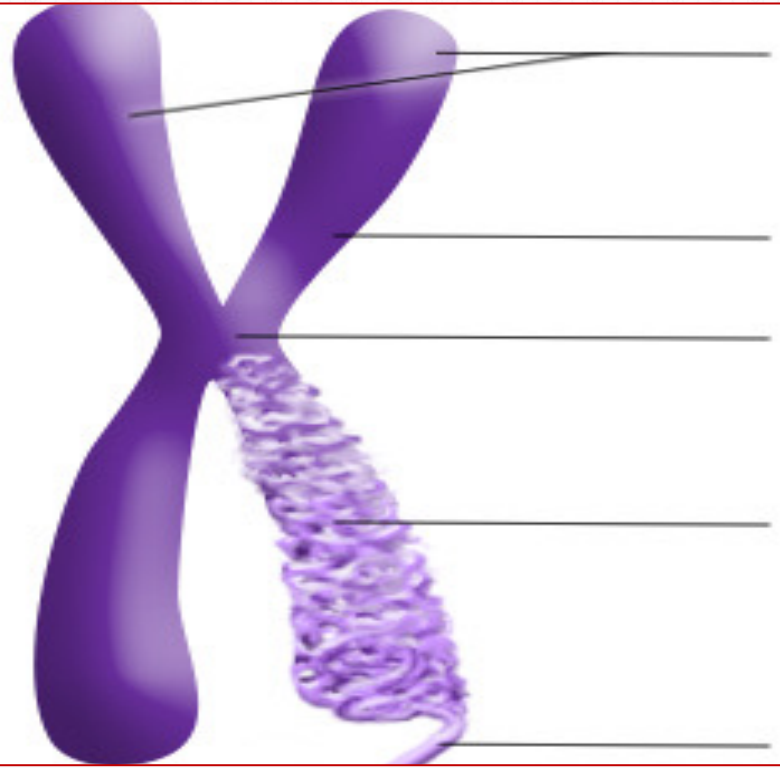
Genetics

- Knowledge of genetics paramount





Reading chromosomes



Two Identical Chromatids
One is an exact copy of the other and each contains one DNA molecule.

p arm – short arm structure

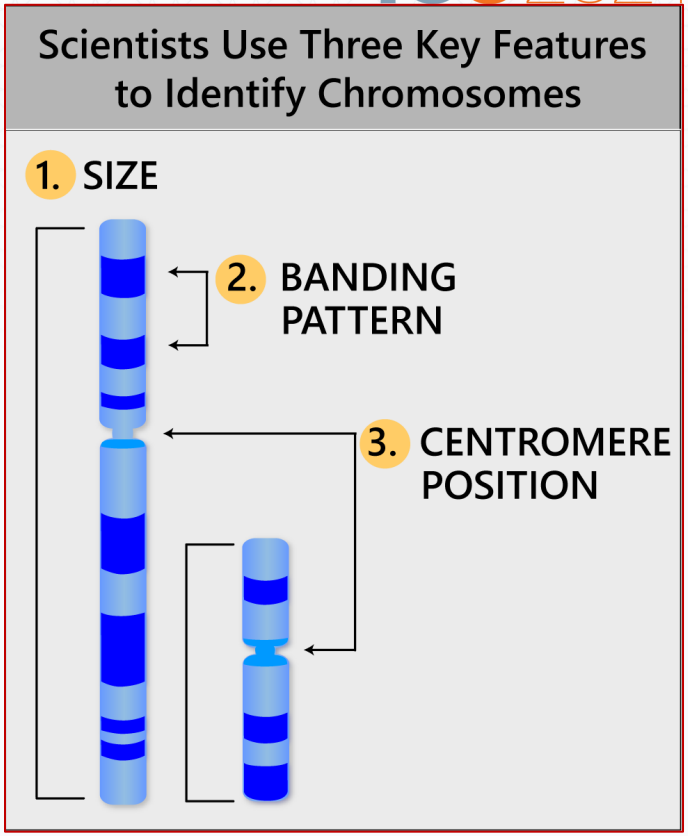
Centromere – constricted point of the chromosome

q arm – long arm structure

DNA molecule – long string like DNA

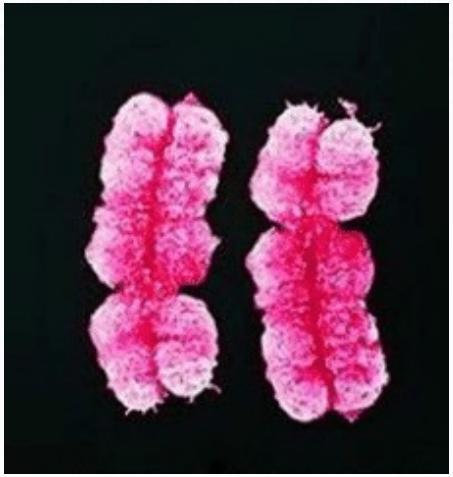
Reading chromosomes

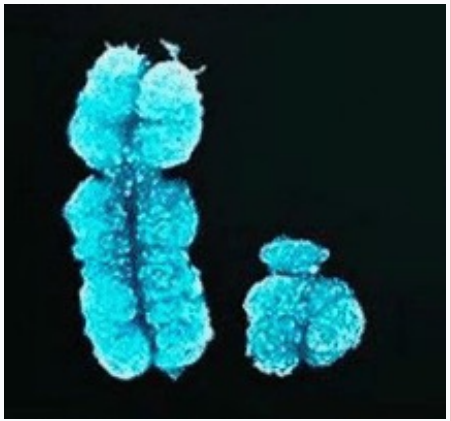
- Size
  - This is the easiest way to tell chromosomes apart
- Banding pattern
  - The size and location of the bands make the chromosome unique
- Centromere position
  - Centromeres appear as a constriction. They have a role in the separation of chromosomes into daughter cells during cell division (mitosis and meiosis)



The X and the Y

- The first 22 pairs of chromosomes are called autosomes
  - 44 autosomes
  - 2 sex chromosomes
    - Specify gender
      - XX – Female
      - XY – Male
  - Karyotype
    - Blood test to examine chromosomes in a sample of cells

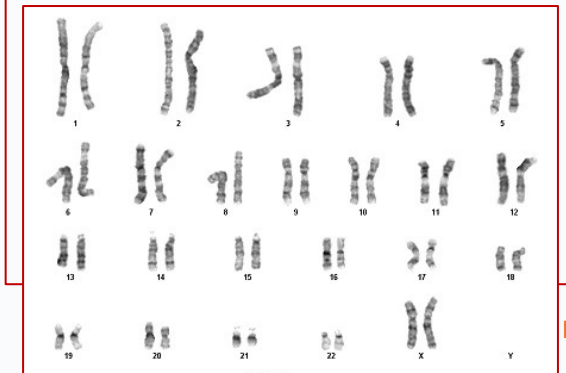




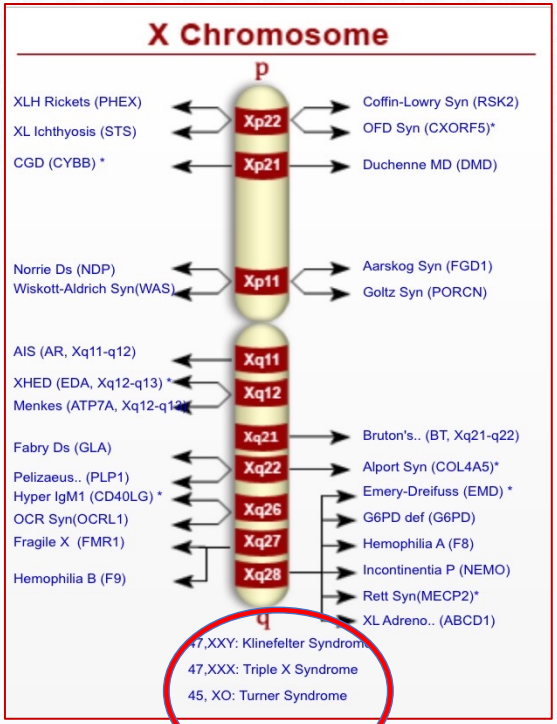
Using Karyotypes to diagnose genetic disorders

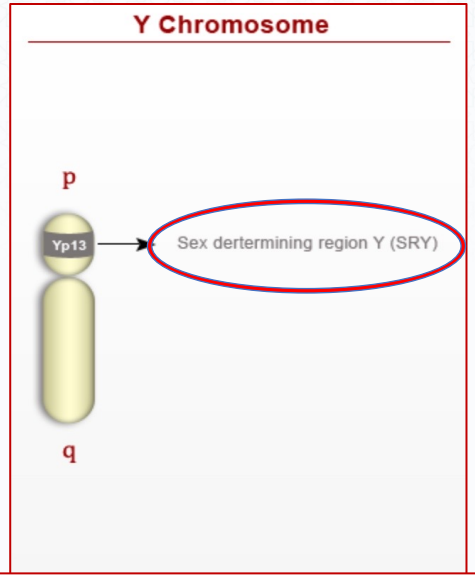
- Too many or too few chromosomes
  - Some chromosomes may be incorrectly distributed during meiosis
  - 3 copies
    - Trisomy
      - Down Syndrome – Trisomy 21
  - 1 copy
    - Monosomy

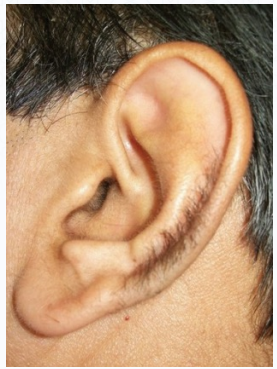
- Most of the time autosomal trisomy or monosomy are lethal
  - Some babies can be born with missing autosomes
- Involving sex chromosomes
  - Usually survive and relatively healthy



X and Y chromosomes







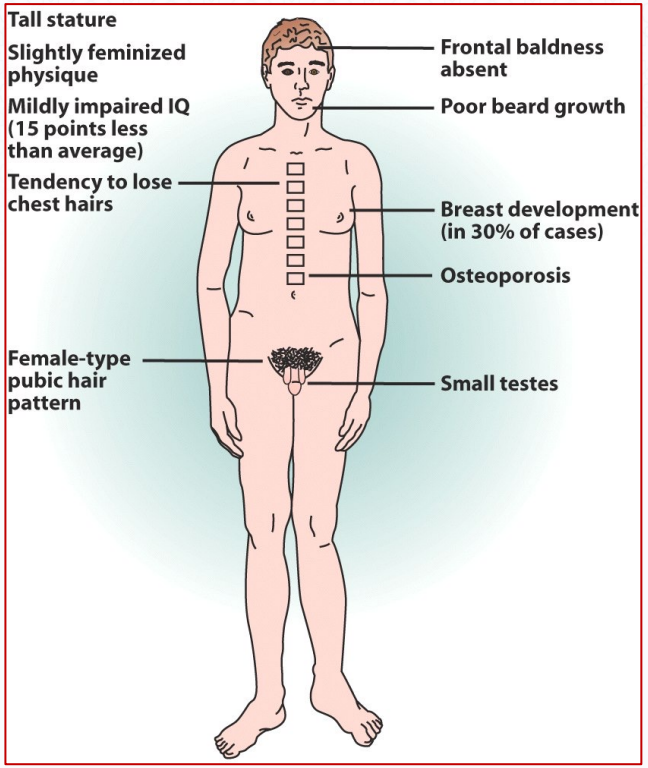
DOI: 10.7860/JCDR/2018/30757.11295
Review Article
Anatomy Section

Inheritance of Hypertrichosis Pinnae Auris-A Review of Literature

NEHA BARYAH[1], KEWAL KRISHAN[2], SANJEEV PURI[3], TANUJ KANCHAN[4]

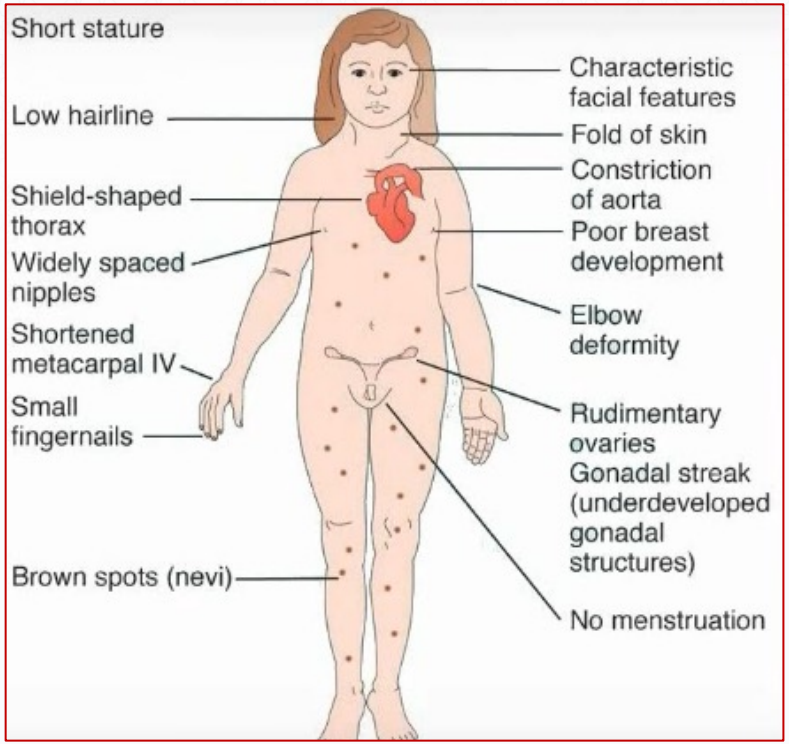
Klinefelter syndrome 47XXY

- Affects sexual development
  - Testes don't fully develop
  - Lower levels of testosterone
- Taller than average
- Many men only discover this when they seek help for infertility



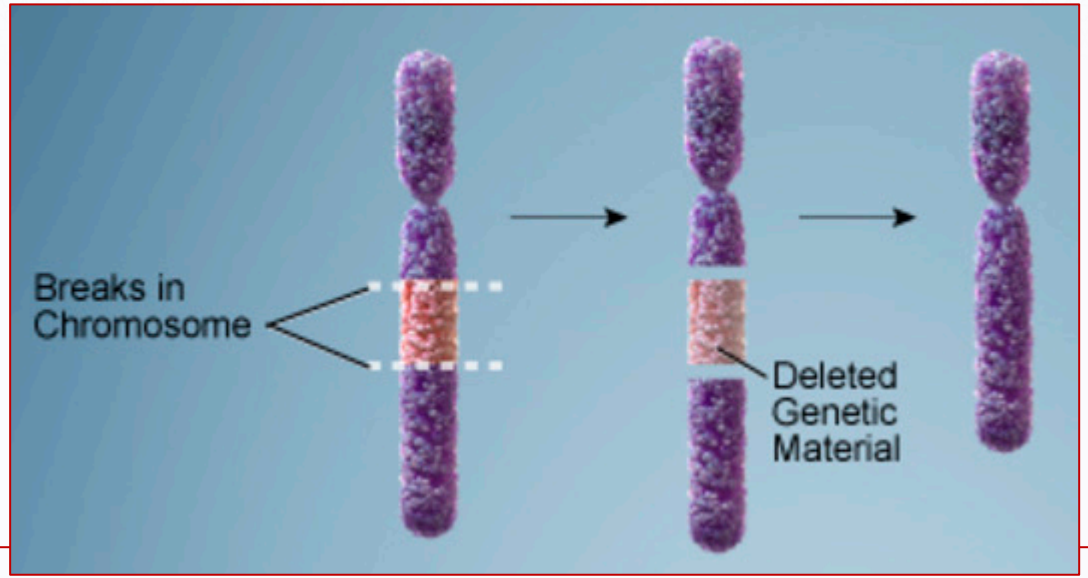
Turner syndrome X

- Only affects girls
- Affects growth and sexual development
  - Ovaries aren't developed properly
- 20%
  - Both X chromosomes present, but one is abnormal
- 30%
  - Missing the X in only some of the cells
    - Mosaicism
    - May have fewer symptoms



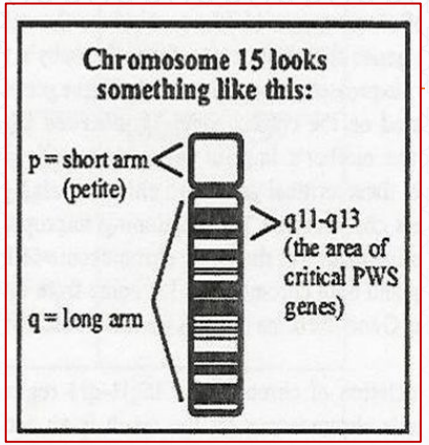
What about missing pieces?

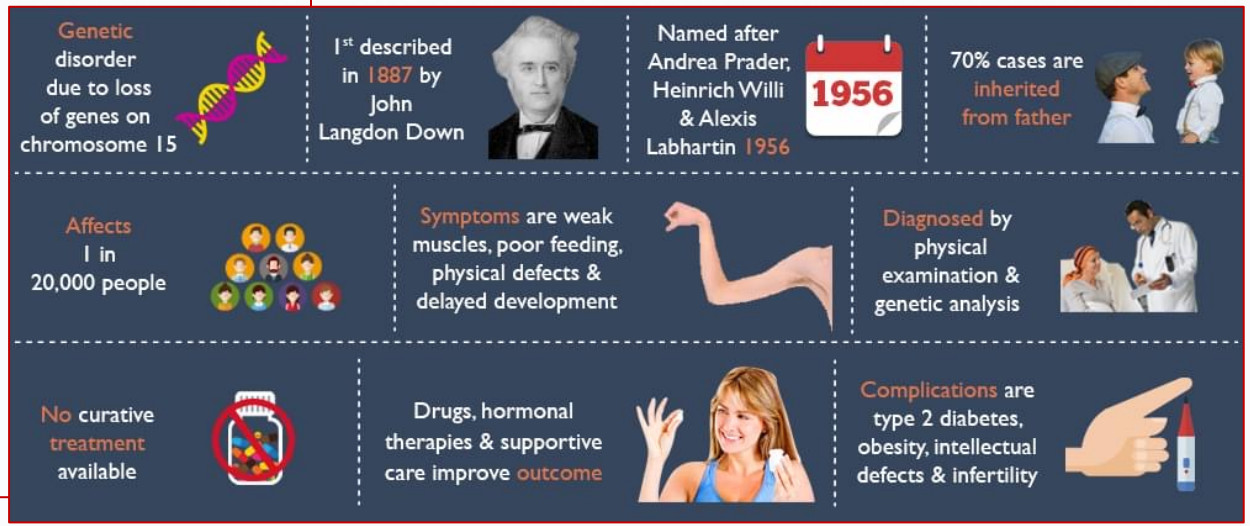
- **Chromosomal deletion**
- Some can be lost or rearranged during meiosis



Prader Willi Syndrome

- - Deletion on the long arm of Chromosome 15
- - Infants
  - Hypotonia
  - Poor feeding
  - Slow development
- - Childhood
  - Constantly hungry

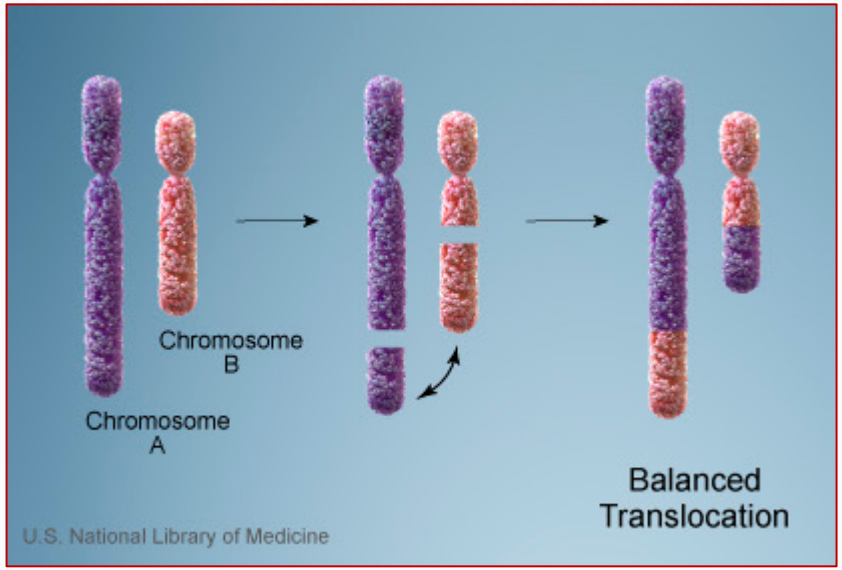




What about swaps?

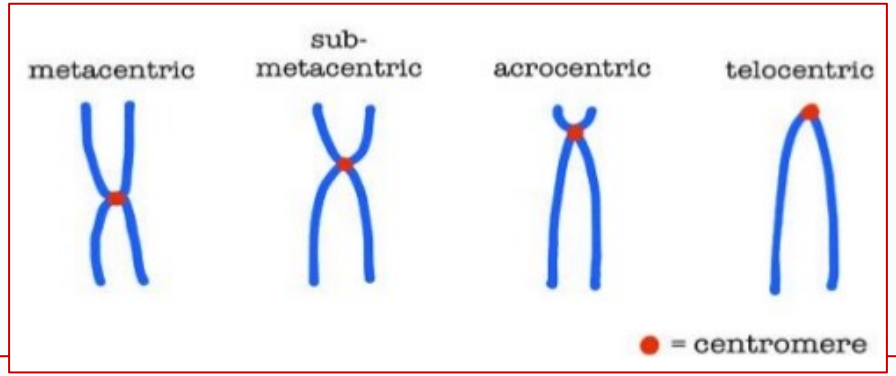
- **Chromosomal Translocation**

- Reciprocal
  - A swap between 2 chromosomes
  - Balanced
    - Individual has all healthy genes
  - Unbalanced
    - Where genes are duplicated or deleted



Translocations

- Robertsonian
  - When the long arms of two acrocentric chromosomes fuse at a centromere. The two short arms are lost, leaving a total of 45 chromosomes
    - Acrocentric chromosomes
      - Where the centromere is located near the end of the chromosome



Original article
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Ann Pediatr Endocrinol Metab 2013;18:111-115
Annals of Pediatric Endocrinology & Metabolism
apem

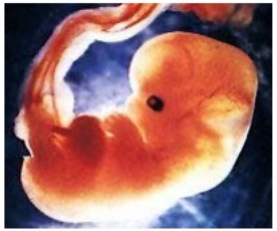
Various endocrine disorders in children with t(13;14)(q10;q10) Robertsonian translocation

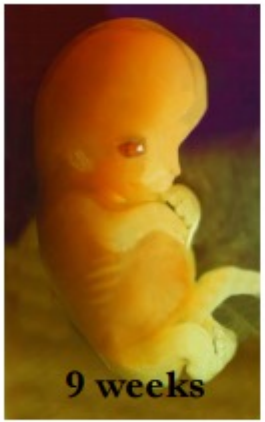
et al

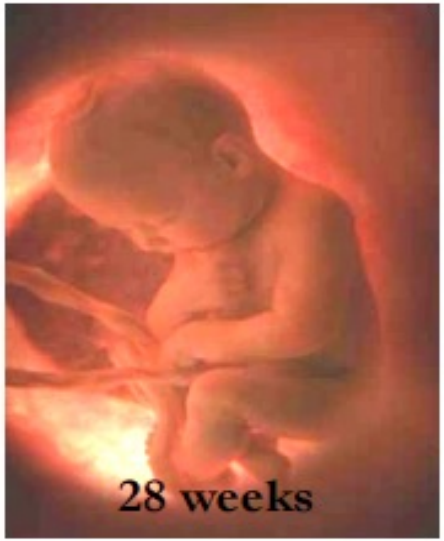
- Translocation (13;14) is one of the most frequent form with an approximate 75% among Robertsonian translocations

- t(13;14)(q10;q10) Robertsonian translocation shows various phenotypes from GHD to precocious puberty

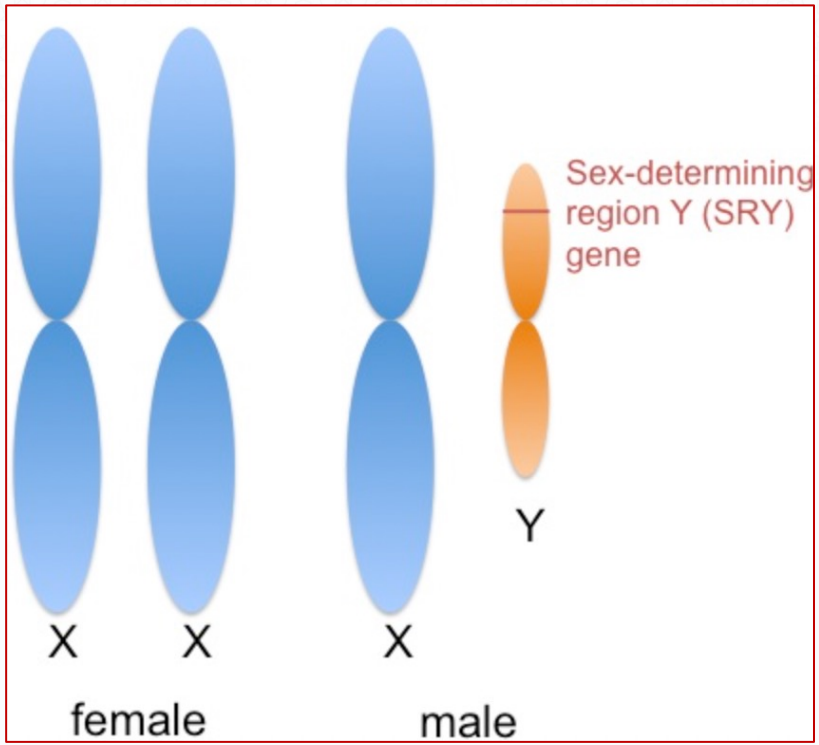
Embryology


6 weeks



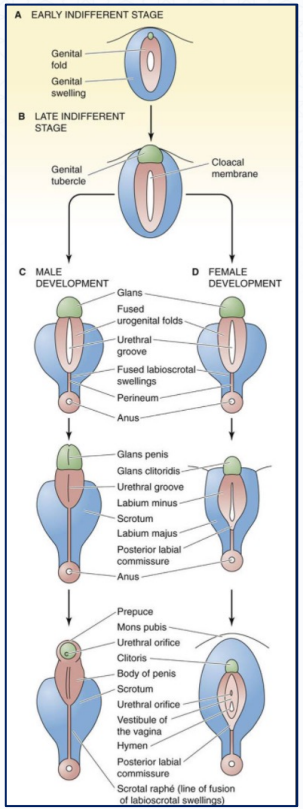


Determination of Sex: Back to the Y chromosome

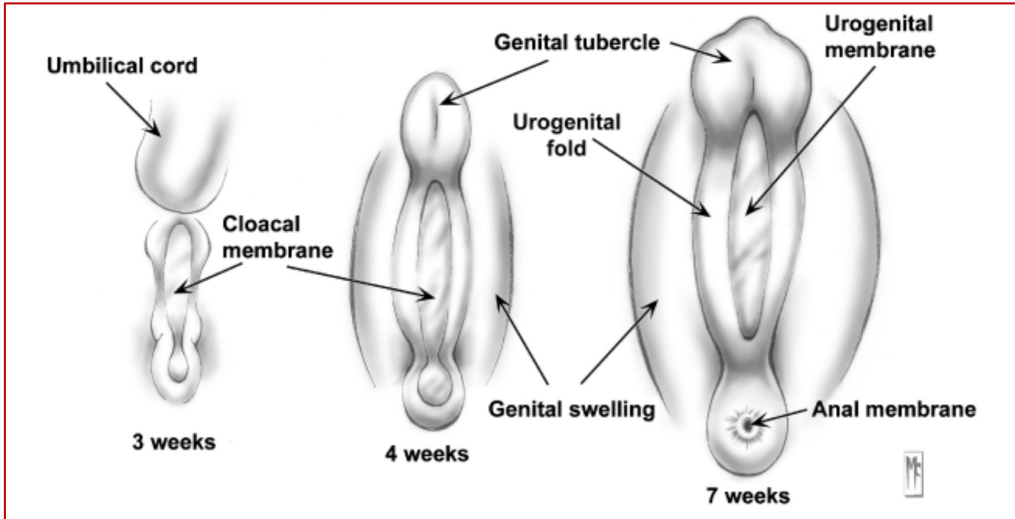


- SRY gene
- Signals sex-neutral tissue to develop into a pair of testes
- If SRY gene is missing or does not work

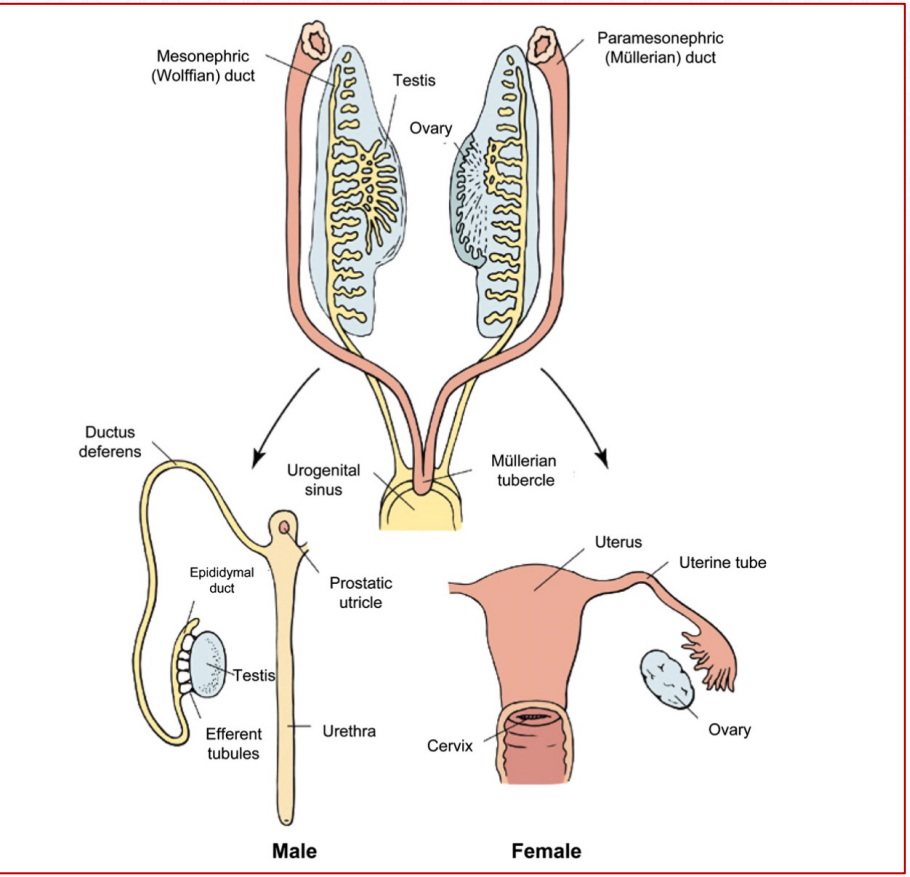
Embryology – 3 – 6 weeks



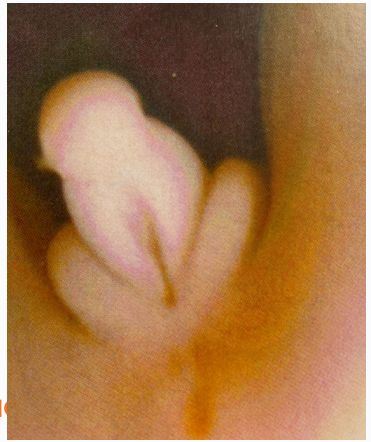
- Development of the external genitalia
- Cloacal membrane



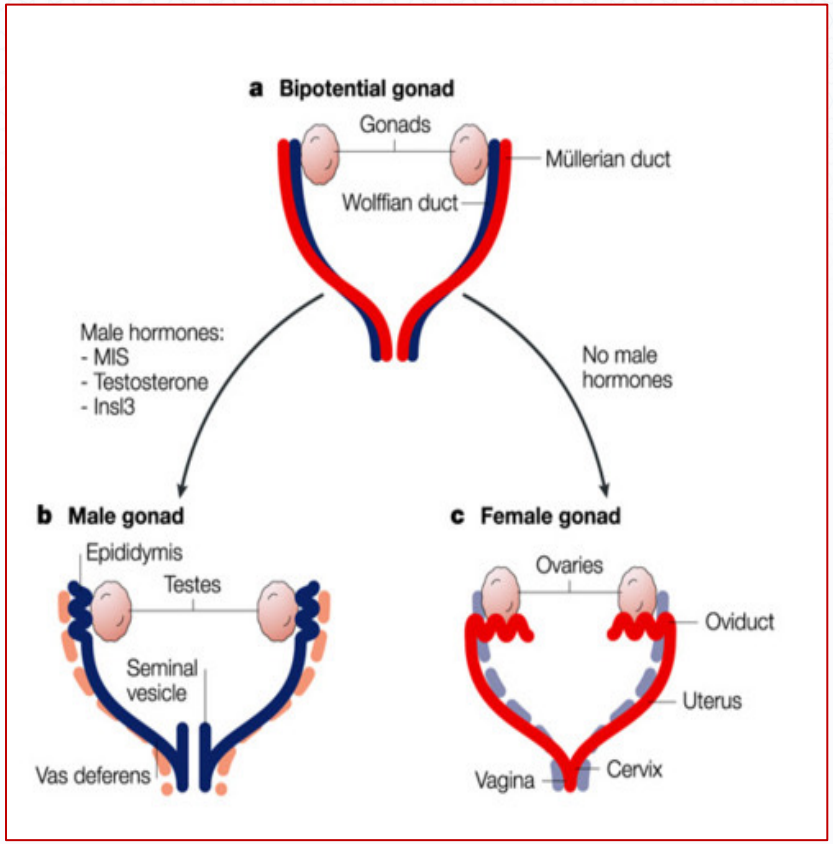
Embryology – 6 – 7 weeks



- Mullerian duct **FEMALE**
- Wolffian duct **MALE**

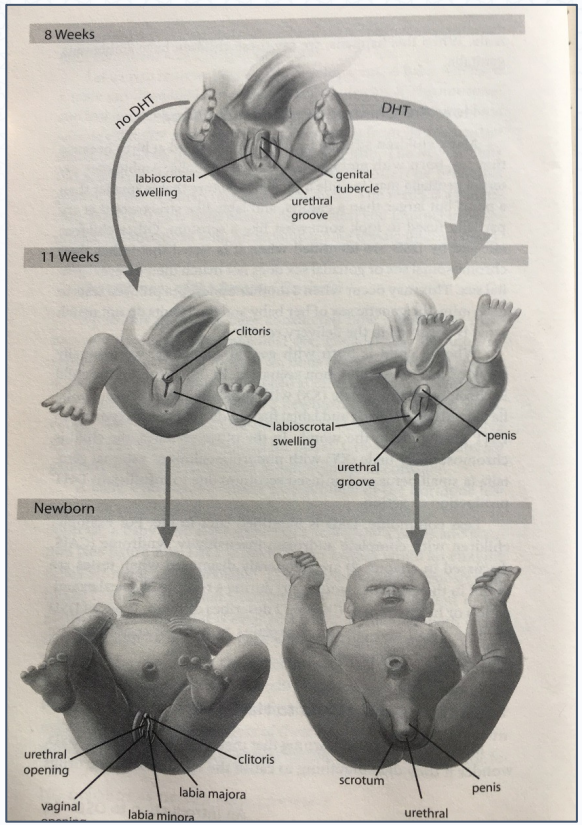


Genitalia development – 7-8 weeks



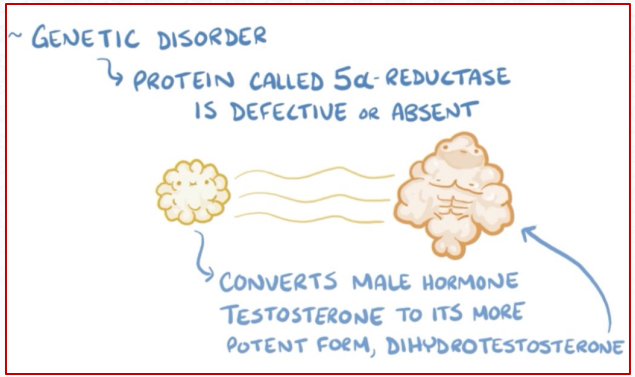
- Presence of XY chromosome
  - Triggers activation of SRY gene
  - Initiates development of a testis
  - Primary sex chords develop into Sertoli cells
    - Anti-Mullerian hormone (AMH)
    - Leads to regression of the Mullerian duct
  - Leydig cells produce testosterone
    - Stimulate Wolffian duct to form epididymis, vas deferens and seminal vesicles

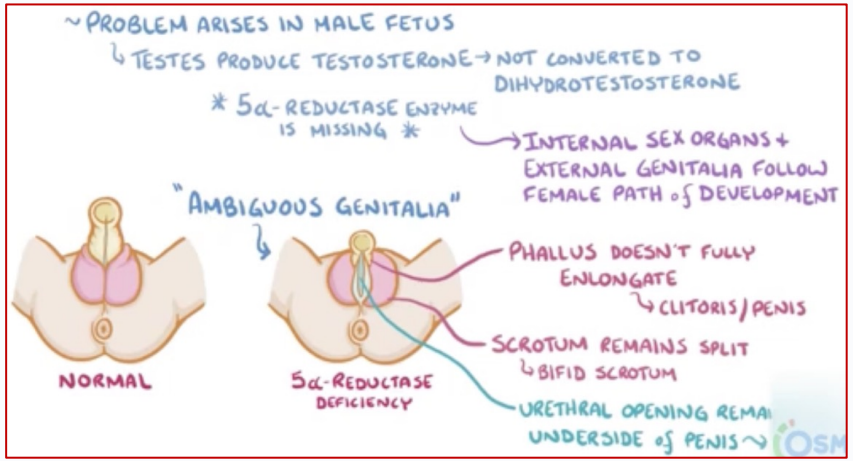
External genitalia development

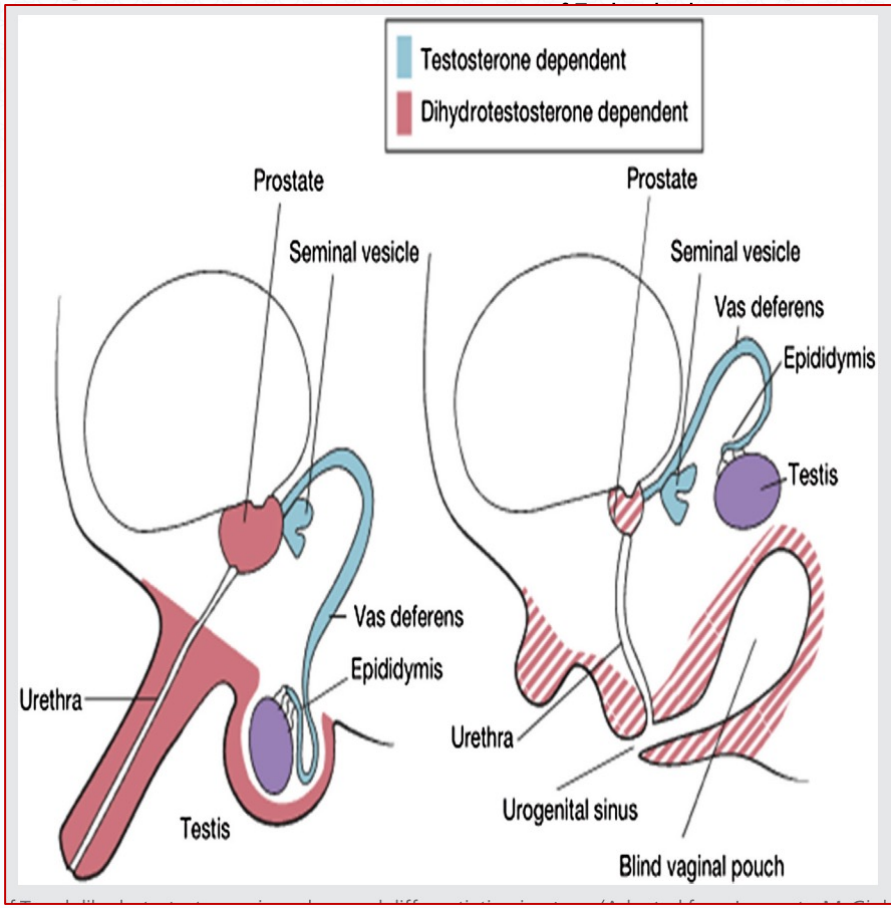


- A baby who doesn't make a byproduct of testosterone called dihydrotestosterone (DHT) will grow a vulva
- If a baby does make DHT, they will grow a penis and scrotum
- DHT is made in our bodies when an enzyme called 5α reductase is avaliable
  - This changes T to DHT

DSD - 5 α reductase deficiency

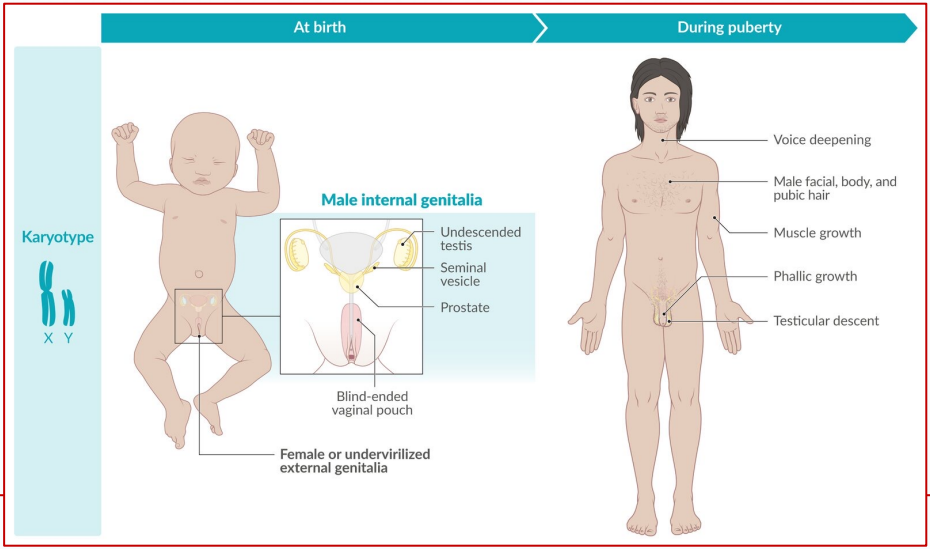






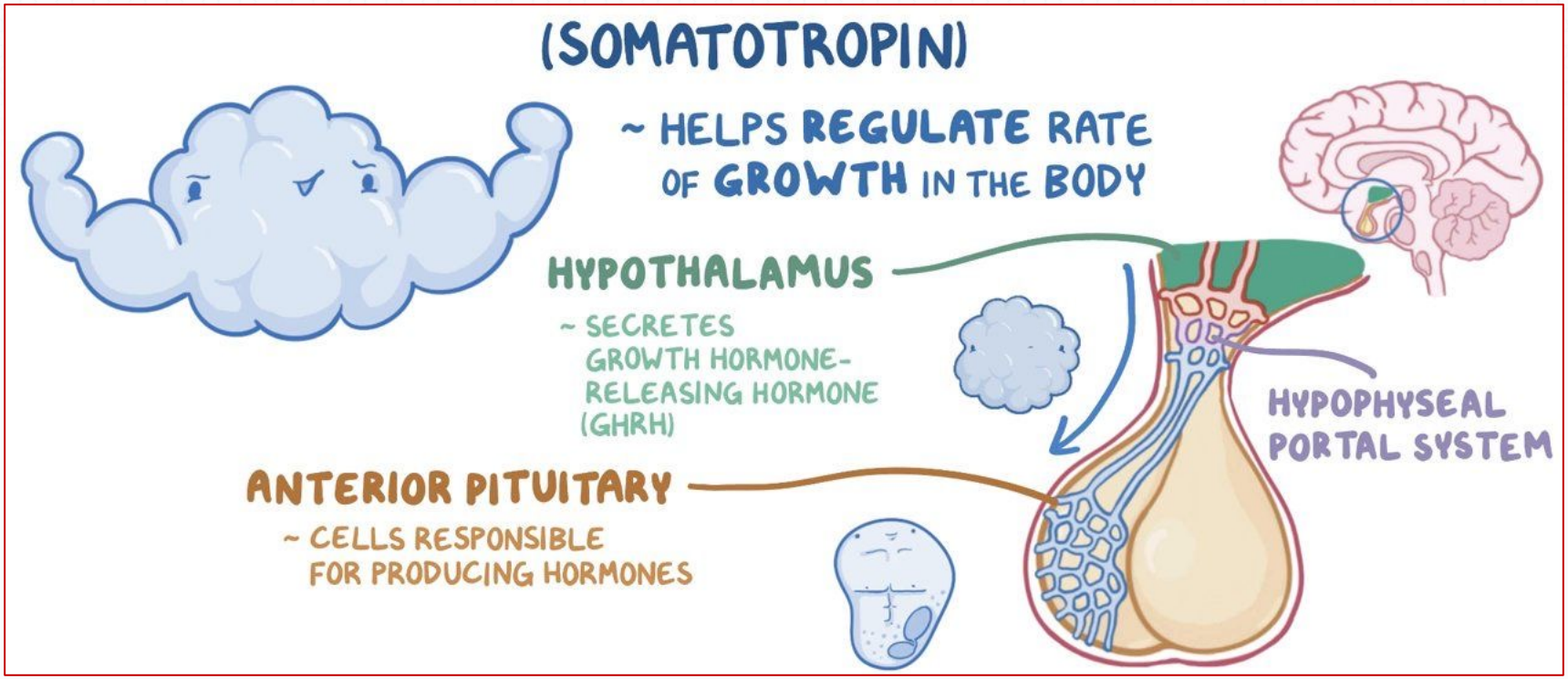
Other DSD

- Congenital Adrenal Hyperplasia (46 XX)
  - Ambiguous genitalia
- Complete Androgen Insensitivity Syndrome

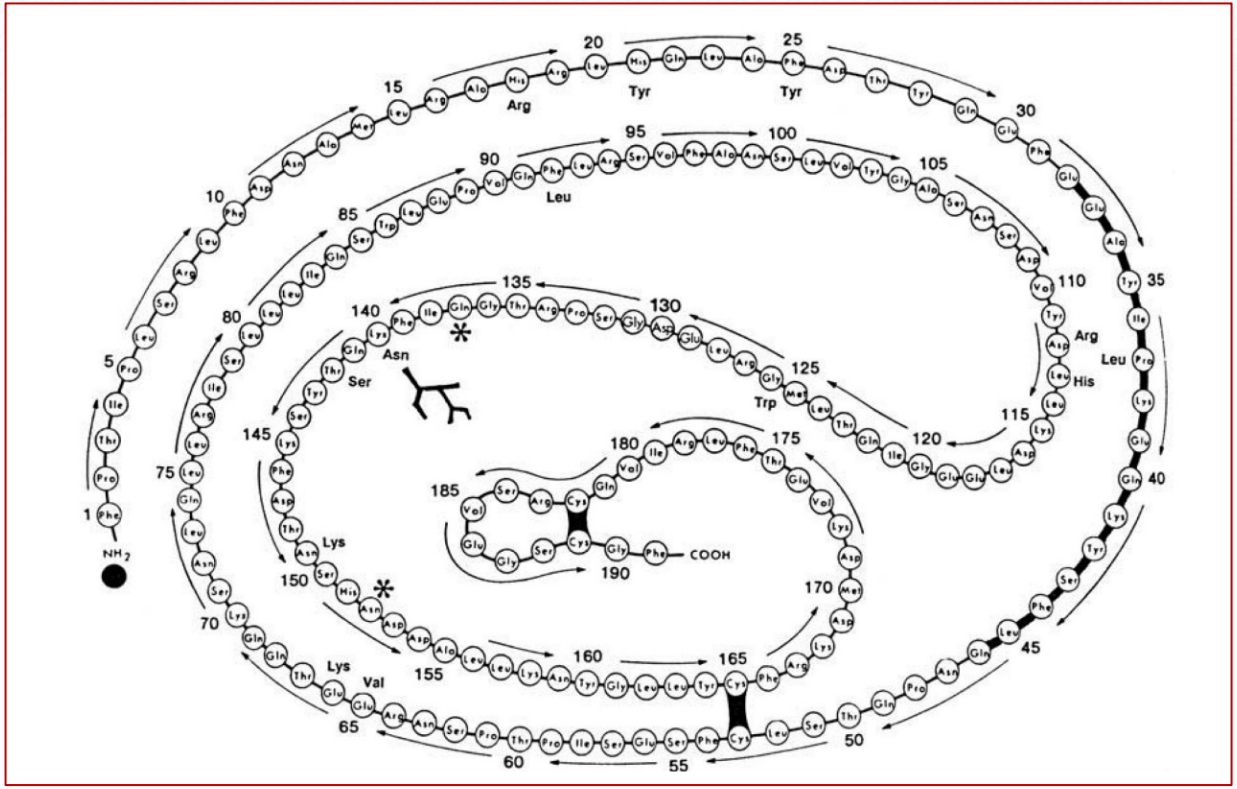


Sex Chromosome DSD	DSD 46,XY	DSD 46,XX
45,X (Turner Syndrome and variants)	Disorders of gonadal (testicular) development: 1) Complete gonadal dysgenesis (Swyer Syndrome) 2) Parcial gonadal dysgenesis 3) Gonadal regression 4) Ovotesticular DSD 5) CBX2 gene def. (ovaries + fem. ext. gen.)	Disorders of gonadal (ovarian) development: 1) Ovotesticular DSD 2) Testicular DSD (SRY+, duplication of SOX9), 46,XX males. Def. gen 3) Gonadal dysgenesis
47,XXY (Klinefelter Syndrome and variants)	Disorders of androgen synthesis or action: 1) Androgen biosynthesis defects (17-hydroxylase, 5αRD2, StAR protein, 3β-HSD, 17β-HSD) 2) Defects in androgen actions (CAIS, PAIS) 3) Defects in LH receptor (Leydig cell hypoplasia) 4) Defects in AMH or AMH receptor (Persistence Müllerian ducts syndrome)	Androgen excess: 1) Fetal (Defects in 21-hydroxilase, or 11-hydroxylase) 2) Fetoplacental (deficiencia de aromatasa, POR [P450 oxidoreductasa]) 3) Maternal (luteoma, exogenous androgens, etc)
45,X/46,XY (mixed gonadal dysgenesis, ovotesticular DSD)	Other (cloacal extrophy, severe hypospadias)	Other (cloacal extrophy, vaginal atresia, other)
46,XX/46,XY (chimeric, ovotesticular DSD)		

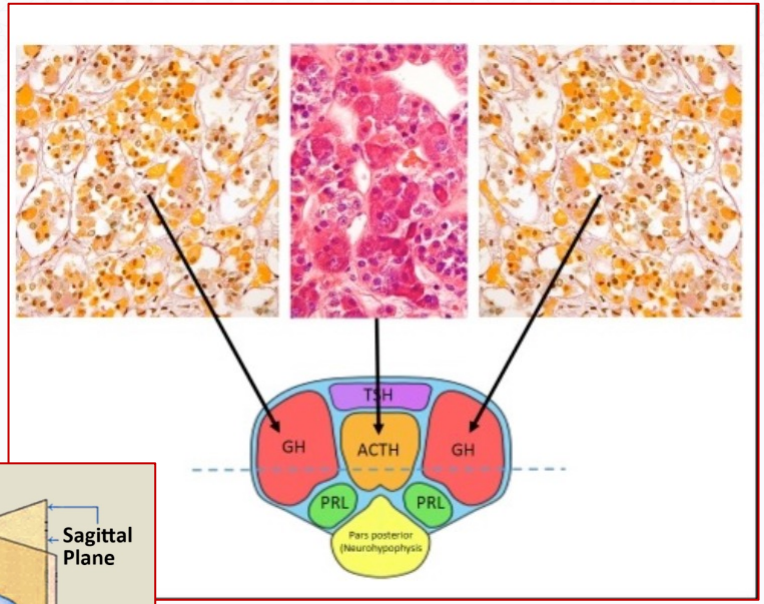
Growth – Growth hormone deficiency

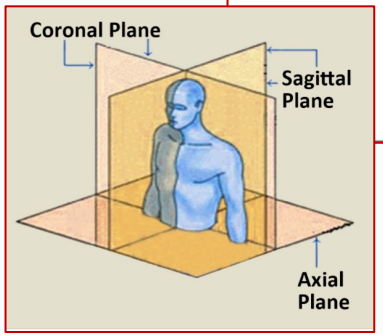


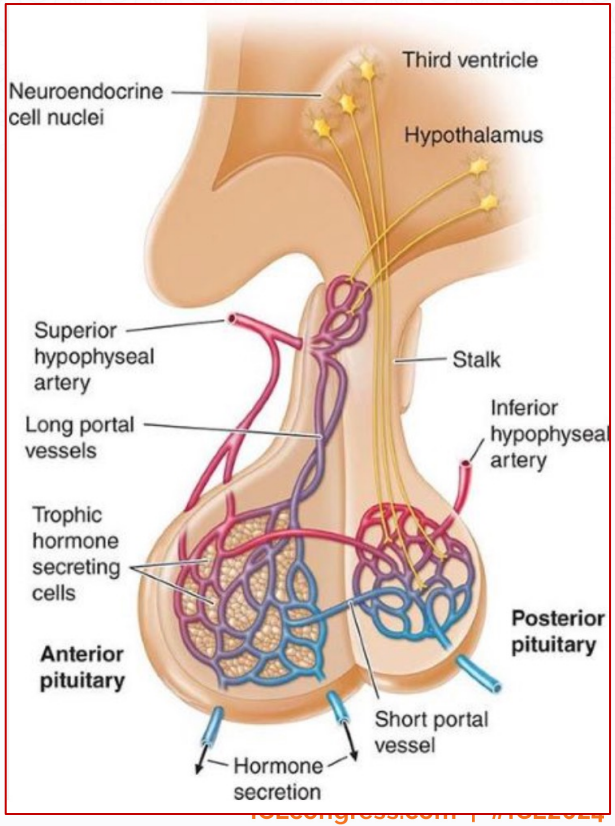
Growth hormone structure



Growth hormone – where?







Growth hormone deficiency - children

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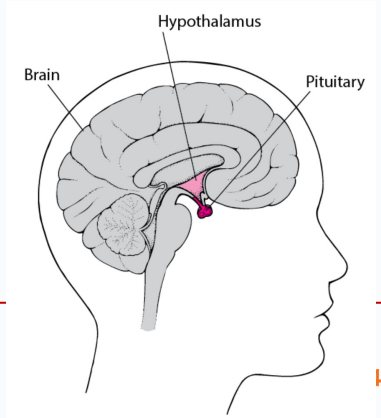
1-3 March 2024 | Dubai, UAE

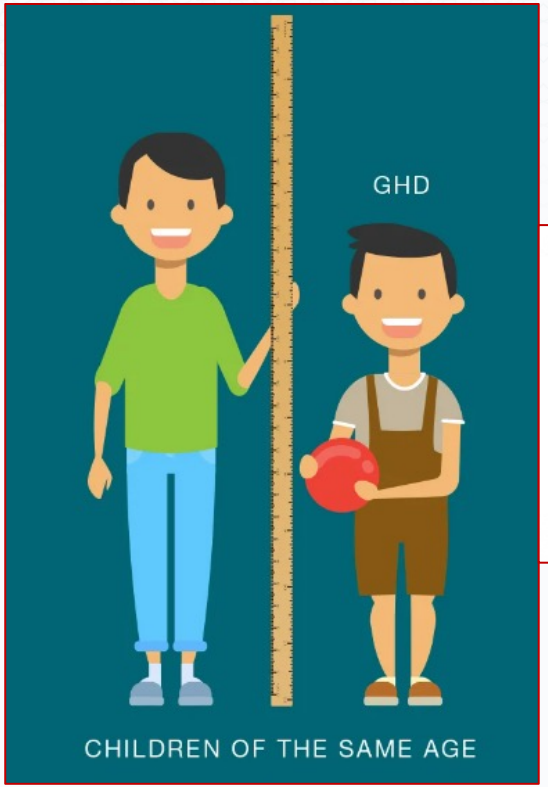
Growth failure associated with

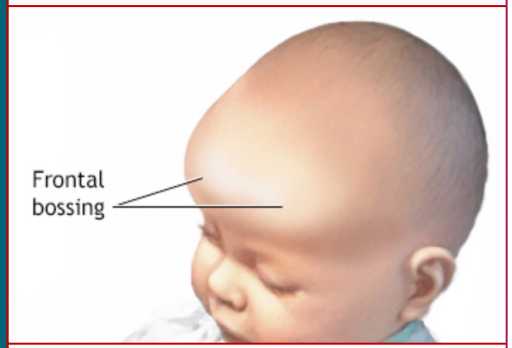
- **Growth hormone deficiency**
- Turner syndrome
- Noonan syndrome
- Prader Willi syndrome
- Chronic renal insufficiency
- Children born small for gestational age
- Short stature homeobox-containing gene (SHOX) deficiency

- Genetics
- Acquired GHD
  - Craniopharyngioma
  - Radiotherapy
- Birth trauma
- Neurological disease
  - Encephalitis
  - Meningitis
- Traumatic brain injury



Growth hormone deficiency





Consensus guidelines on diagnosis of GHD (GH Research Society)

When to consider investigation for GH deficiency:

1. Severe short stature, defined as a height more than 3 SD below the mean.
2. Height more than 1.5 SD below the mid-parental height.
3. Height more than 2 SD below the mean and a height velocity over 1 year more than 1 SD below the mean for age, OR a decrease in height SD of more than 0.5 over 1 year in children more than 2 years of age.
4. In the absence of short stature, a height velocity more than 2 SD below the mean over 1 year or more than -1.5 SD sustained over 2 years.
5. Signs indicative of an intracranial lesion.
6. Signs of MPHD.
7. Neonatal symptoms and signs of GHD (unexplained hypoglycaemia, prolonged jaundice, clinical appearance suggestive of GHD, microphallus and cryptorchidism).

Children

Biochemical investigations

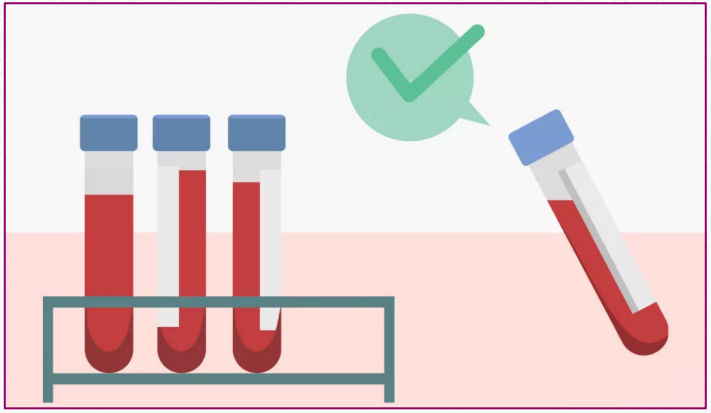
≤ 6 – 7 µg/L on GST x 2

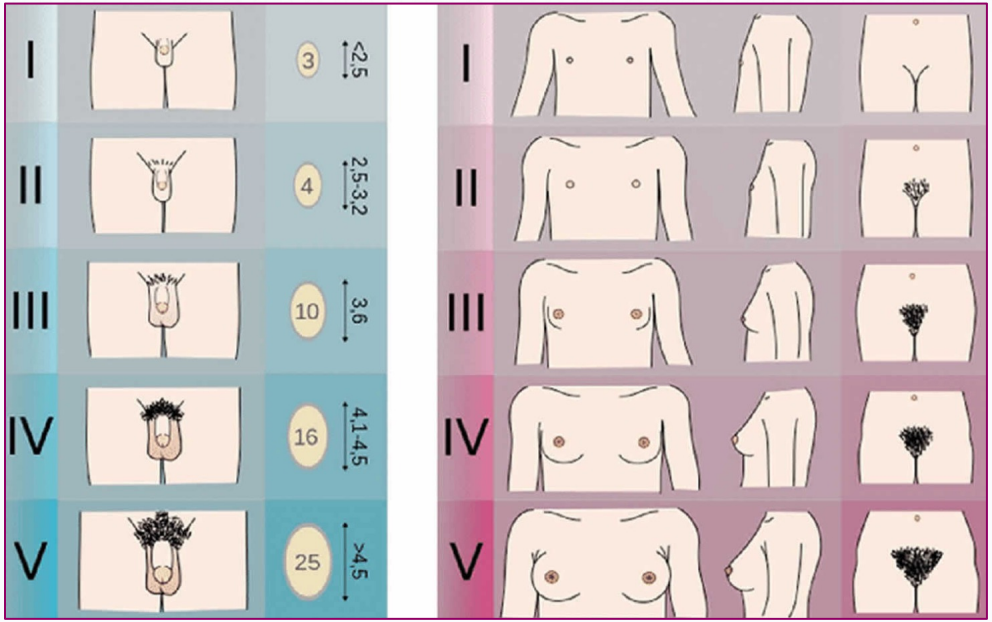
Radiological and genetic testing

Auxology

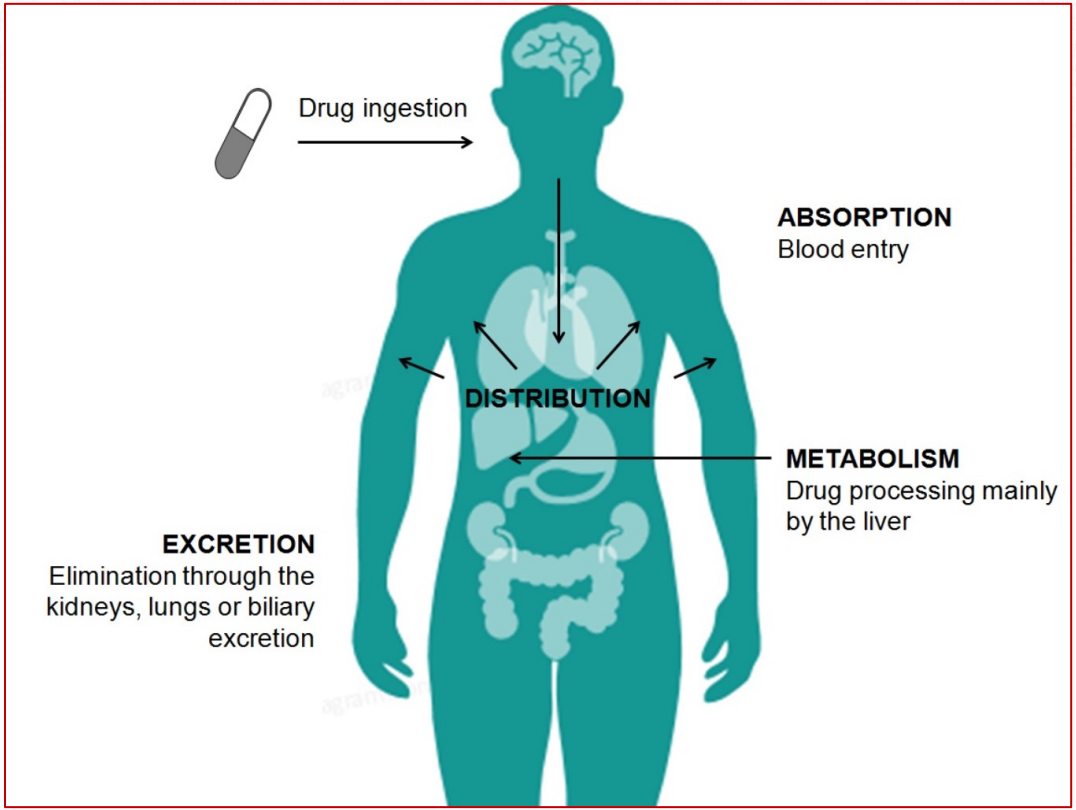
Physical examination

Pubertal staging

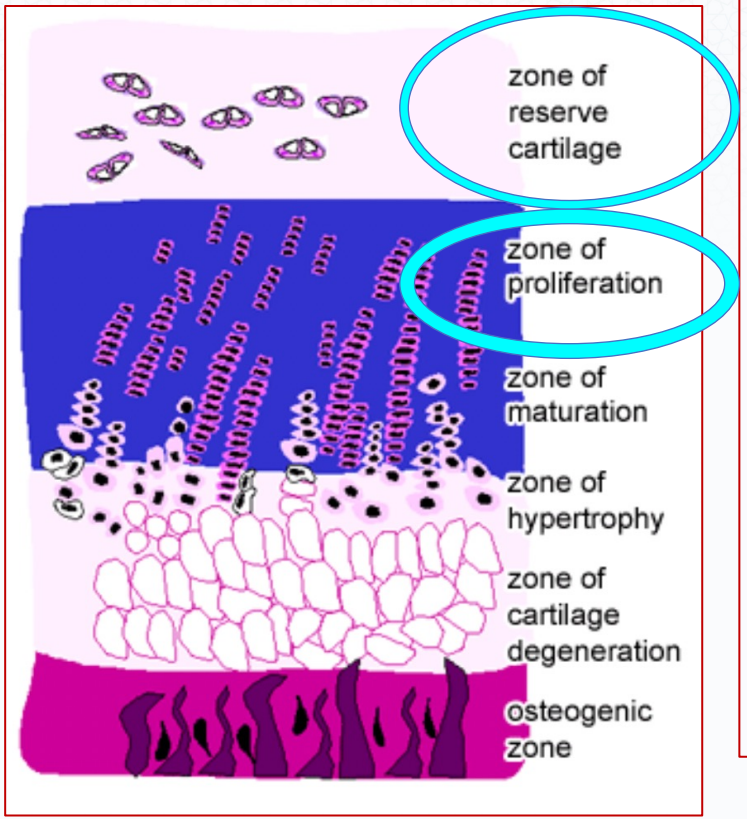




Growth hormone treatment



Epiphyseal growth plate



Cartilaginous tissue with specific functions since growth begins until epiphysis is closed after puberty

Three different zones

- The resting zone
  - Stem cells slowly replicate
- The proliferative zone
  - Generate clones of chondrocytes
  - Replicate at high rate
    - Align in columns
  - Replication decreases as move away from epiphysis, and form
- Hypertrophic zone
  - Cartilage attracts the blood vessels, osteoclasts, and differentiating osteoblasts, which remodel the newly formed cartilage into bone tissue.

GH treatment - children

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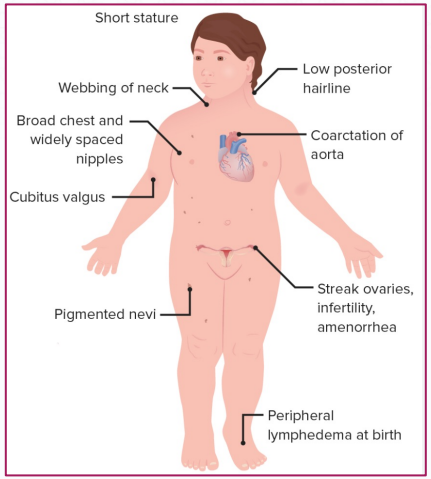
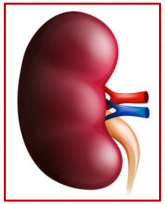
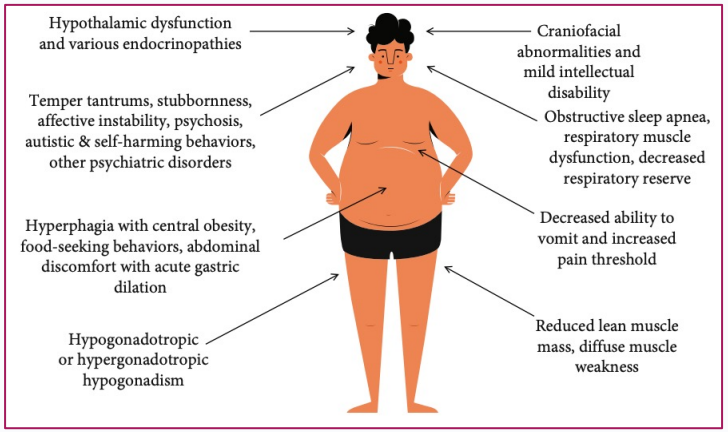
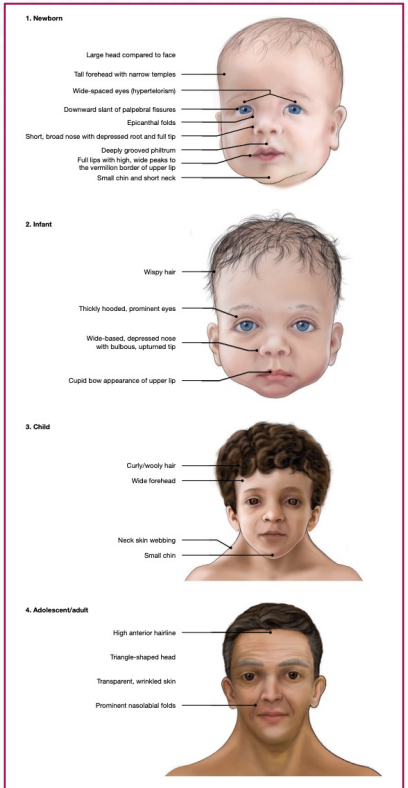




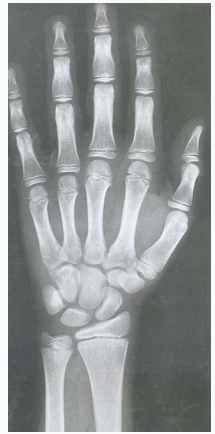




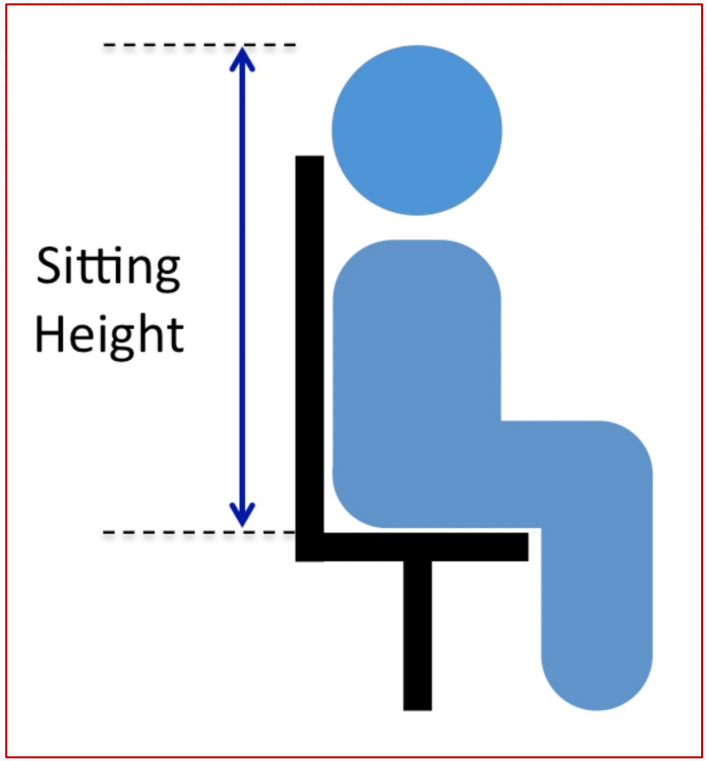
GH treatment - GHD

- Growth hormone device choice
- Dose dependent on condition
  - Weight calculated
- Regular clinic visits
  - 6/12 monthly
- Height velocity
- Adherence

- Bone age
- Thyroid Function Test
- Serum IGF1 and IGBP-3
- Metabolic panel, early am cortisol, FBC, HbA1C
- Dose adjustment
- Adverse Events



Late Effects of Childhood Cancer treatment



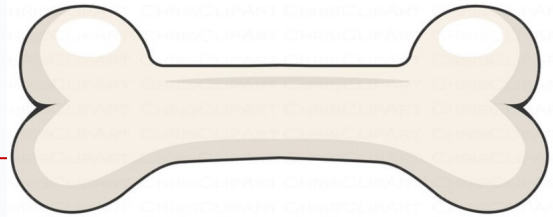
- Without growth hormone replacement therapy, virtually all patients who have received cranial radiation will have a final height below the 3rd centile.
- Onset of puberty also crucial
- Sitting height should be measured in children who received spinal irradiation

GH deficiency

- The result of both tumour and radiotherapy
- Occurs more quickly after higher (rather than lower) radiation doses
- Older children, who's growth and development is nearly finished, may get away without therapy in childhood
- The importance for it in adulthood is still

under review:

- General health, muscle and bone strength, quality of life



GH UK licenses

Company	Paediatric GHD	Adult GHD	TS	NS	PWS	SGA	CRI	SHOX
Nutropin Aq Ipsen	✓	✓	✓				✓	
Norditropin Novo Nordisk	✓	✓	✓	✓		✓	✓	
Genotropin Pfizer	✓	✓	✓		✓	✓	✓	
Omnitrope Sandoz	✓	✓	✓		✓	✓	✓	
Saizen Merck	✓	✓	✓			✓	✓	
Humatrope Lilly	✓		✓			✓	✓	✓

GH devices


oneclick
Nutropin AQ Pen


SurePal 5
SurePal 10
SurePal 15
24
Ngenia
mg
60
Ngenia
mg

What's new...?

Decrease Injection Frequency

Once-weekly LAGH vs daily GH injections

Potential to Improve Adherence

Decreased burden of treatment may increase patient compliance

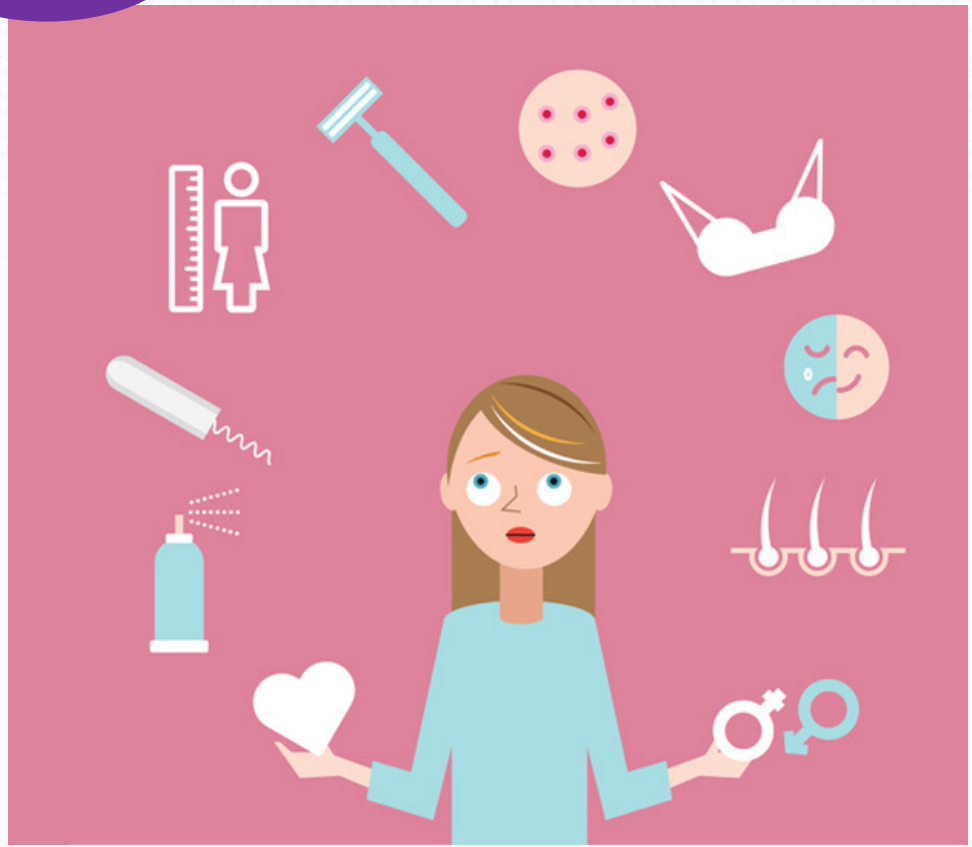
Potential to Maximise Efficacy

Adherence to therapy may improve treatment outcomes

Increased Flexibility

Offers patients and families therapeutic alternatives

Puberty – early or delayed?



Early (precocious) puberty

True precocious puberty: pubertal development caused by early activation of the hypothalamic-pituitary-gonadal axis

Pseudo-precocious puberty: pubertal development caused by sex steroids secreted without activation of the hypothalamic-pituitary-gonadal axis

Causes of True Precocious Puberty

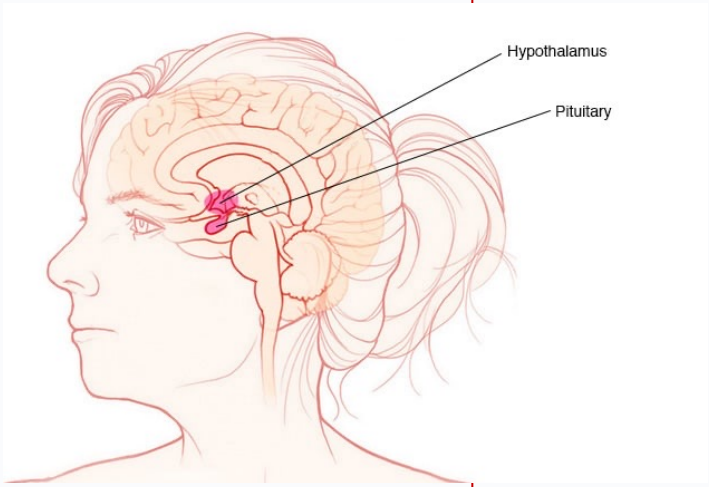
Organic CNS disruption:

- Tumours of the hypothalamic-pituitary region
- Post head injury / meningitis
- Neurofibromatosis
- Prematurity / Cerebral Palsy
- Hydrocephalus

Post cranial surgery or radiotherapy

Idiopathic

Genetics



Causes of Pseudo-Precocious Puberty

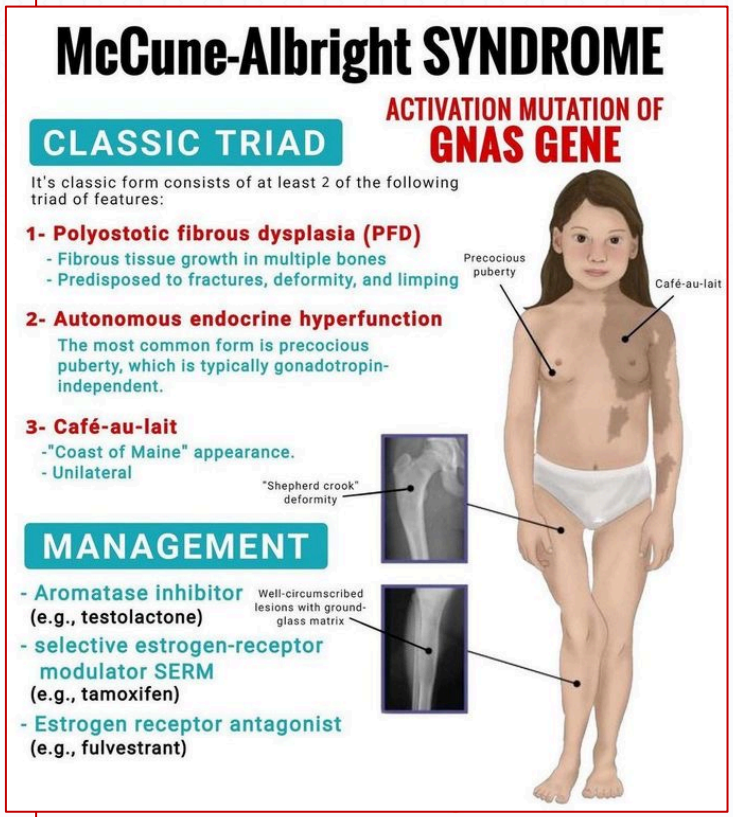
Sex steroids from the adrenal:

- Congenital adrenal hyperplasia
- Adrenal tumour
- Premature adrenarche (<6yr)
- Cushing's Syndrome

Sex steroids from the gonad:

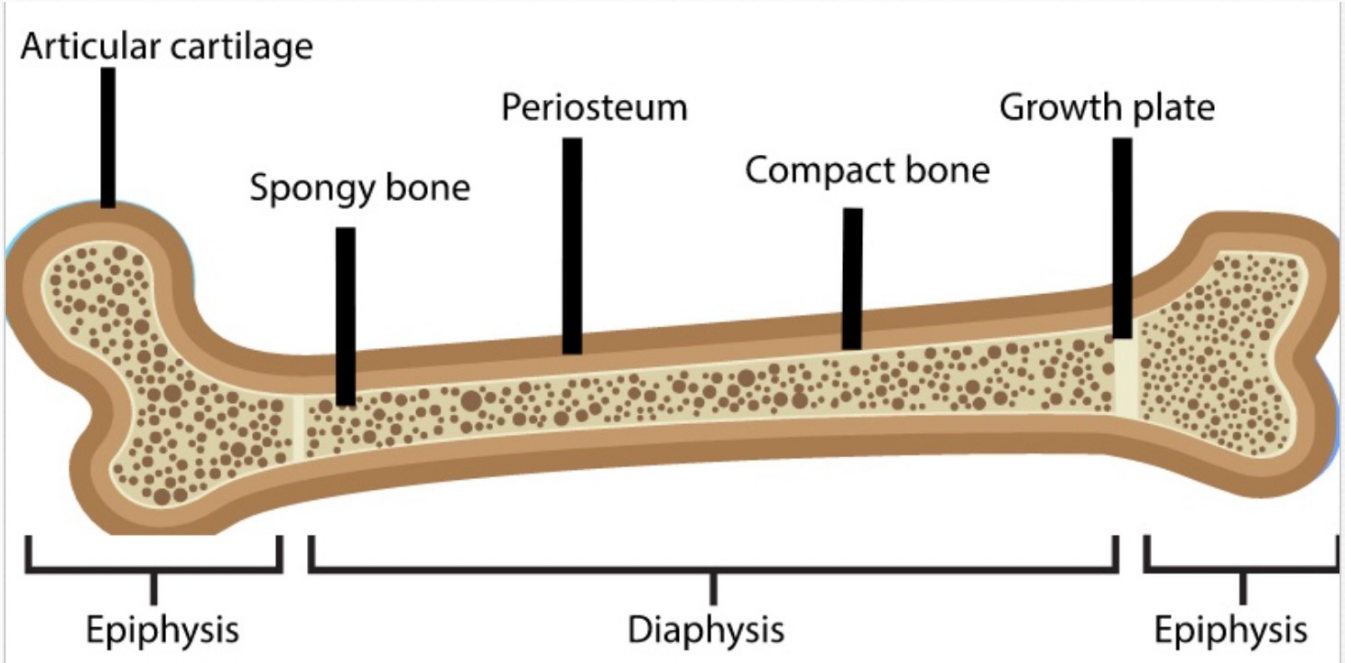
- Ovarian tumour, cysts
- McCune-Albright Syndrome
- Testotoxicosis
- HCG – secreting (germ cell) tumours

Exposure to exogenous steroids



Management

Main goal is to prevent early fusion of the epiphyseal growth plates

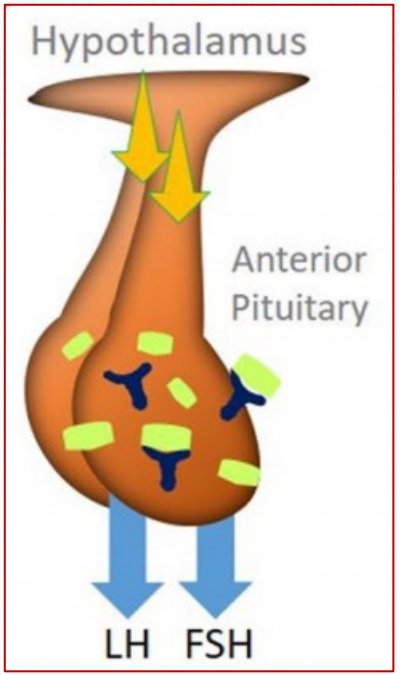


GnRH analogues

Artificially created molecules

Similiar to the actual GnRH

Affinity for GnRH receptors in the pituitary gland



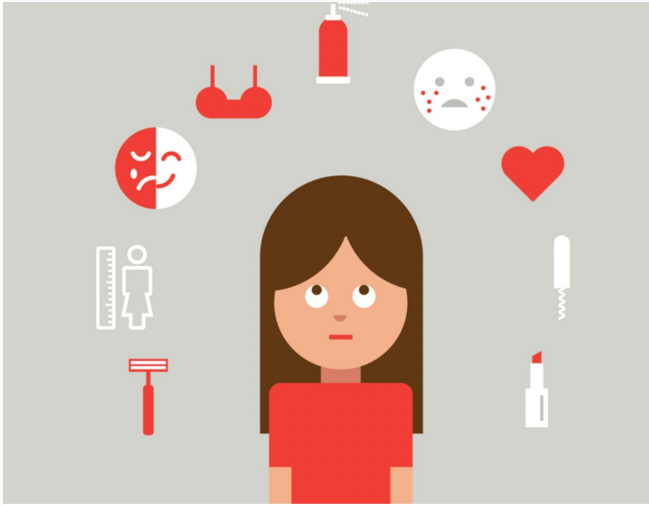
Girls

What are the signs of CPP in girls?

Breast development before 8 yrs

Pubic hair before 8 yrs

Menarche before 10 yrs



Breast development between 8 – 9yrs –

Investigate if:

Onset of development before 8 yrs

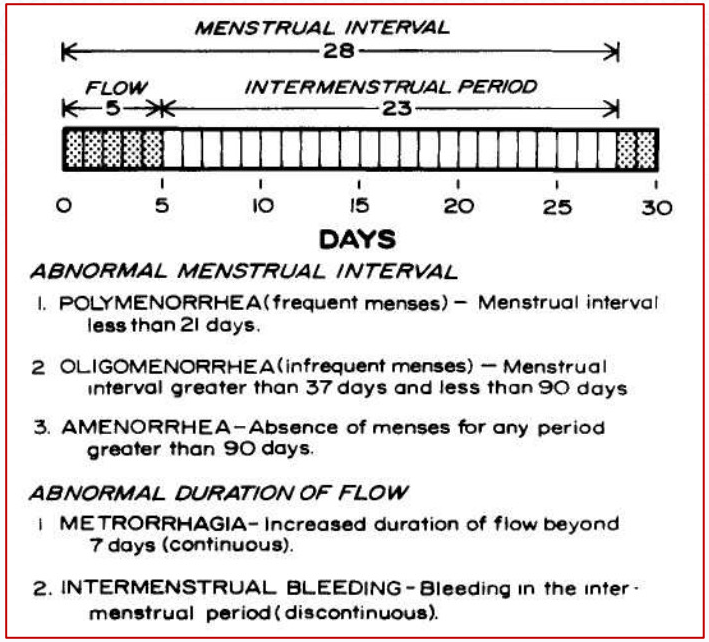
HV >6cm/yr

- Adult height prognosis below target height

Rapid progression of pubertal development (from one stage to another in less than 6 months)

Clinical evidence of a neurogenic aetiology

Period problems



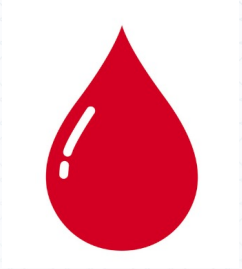
ABNORMAL MENSTRUAL INTERVAL

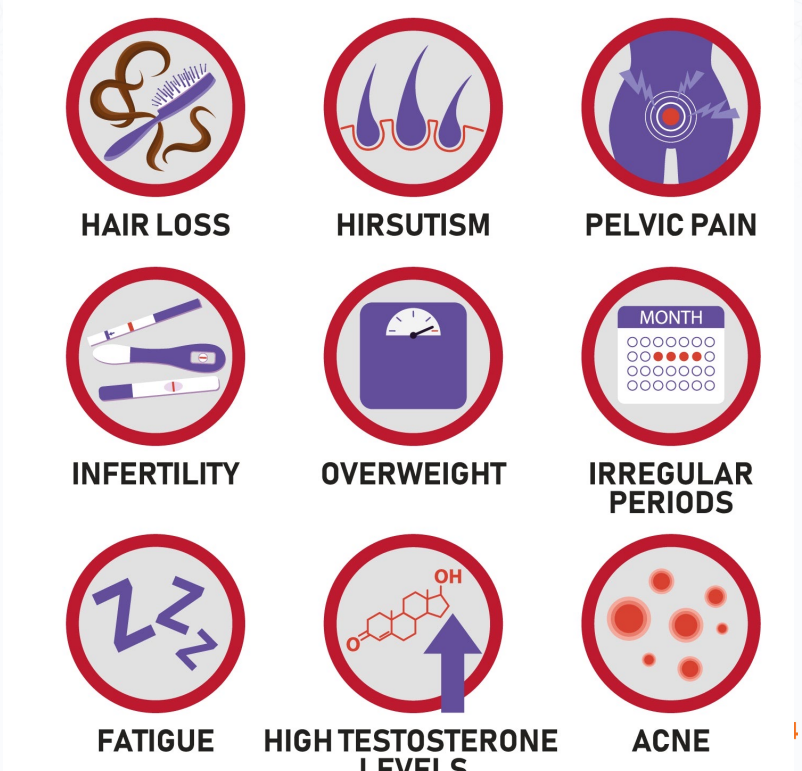
1. POLYMENORRHEA (frequent menses) – Menstrual interval less than 21 days.
2. OLIGOMENORRHEA (infrequent menses) – Menstrual interval greater than 37 days and less than 90 days
3. AMENORRHEA – Absence of menses for any period greater than 90 days.

ABNORMAL DURATION OF FLOW

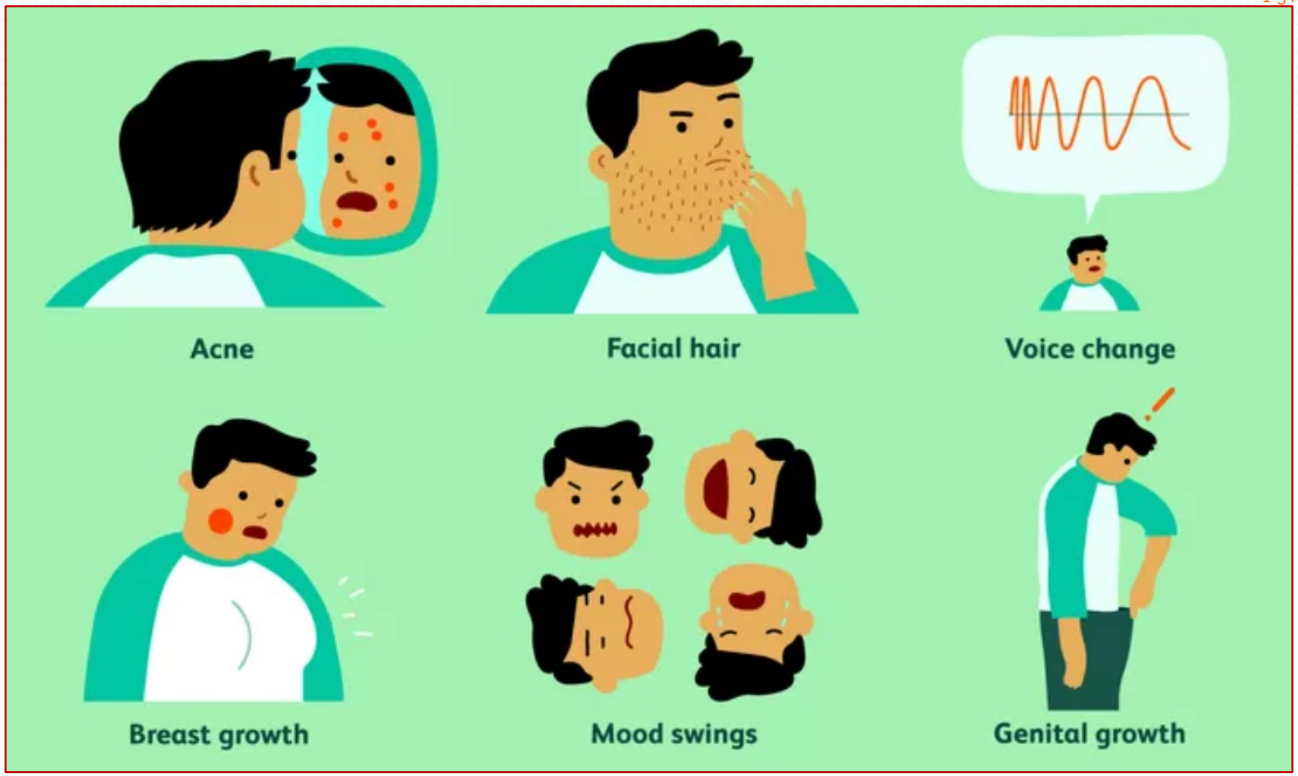
1. METRORRHAGIA – Increased duration of flow beyond 7 days (continuous).
2. INTERMENSTRUAL BLEEDING – Bleeding in the inter-menstrual period (discontinuous).

- Polycystic Ovarian Syndrome





Boys

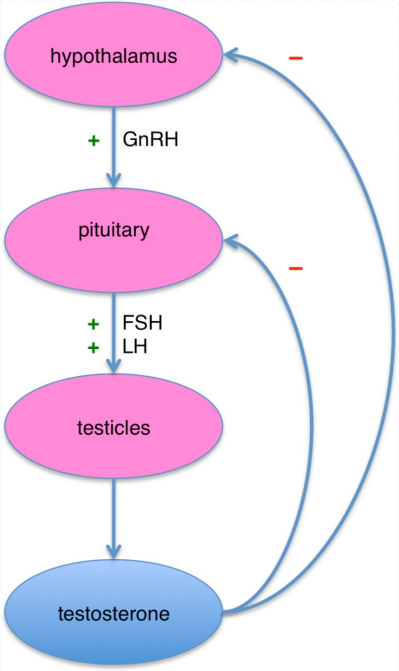

Acne
Facial hair
Voice change
Breast growth
Mood swings
Genital growth

What are the signs of CPP in boys?

1 – Testicular enlargement
Increased FSH production
Testosterone stimulation

2 – Penis growth / pubic hair growth / scrotal changes

3 – Acne / voice change / facial hair / body odour /increased
muscle mass



CPP in boys

- No cause for CPP can be found in up to 2/3 of girls

- Identifiable cause is more likely in boys

The main concern with boys..

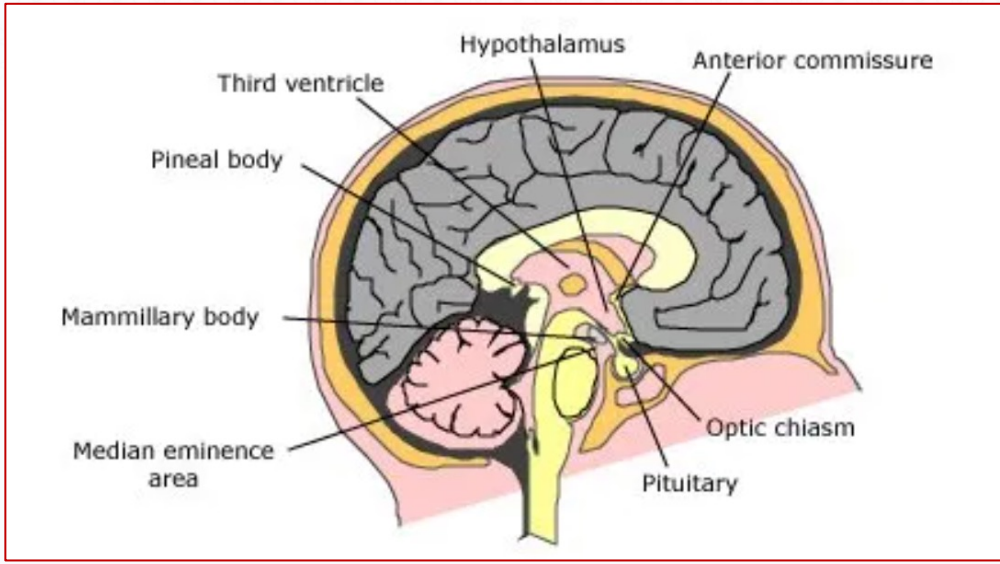
Central nervous system findings such as brain tumours or congenital malformations are more frequently observed in boys who present with precocious puberty

The most common cause?

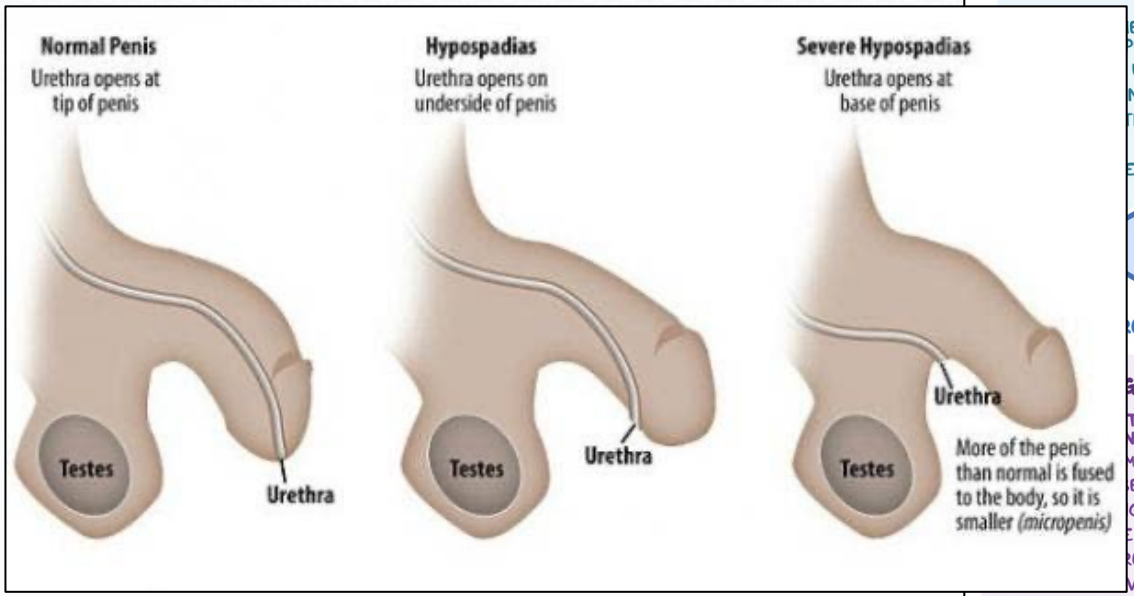
Hypothalamic Hamartoma

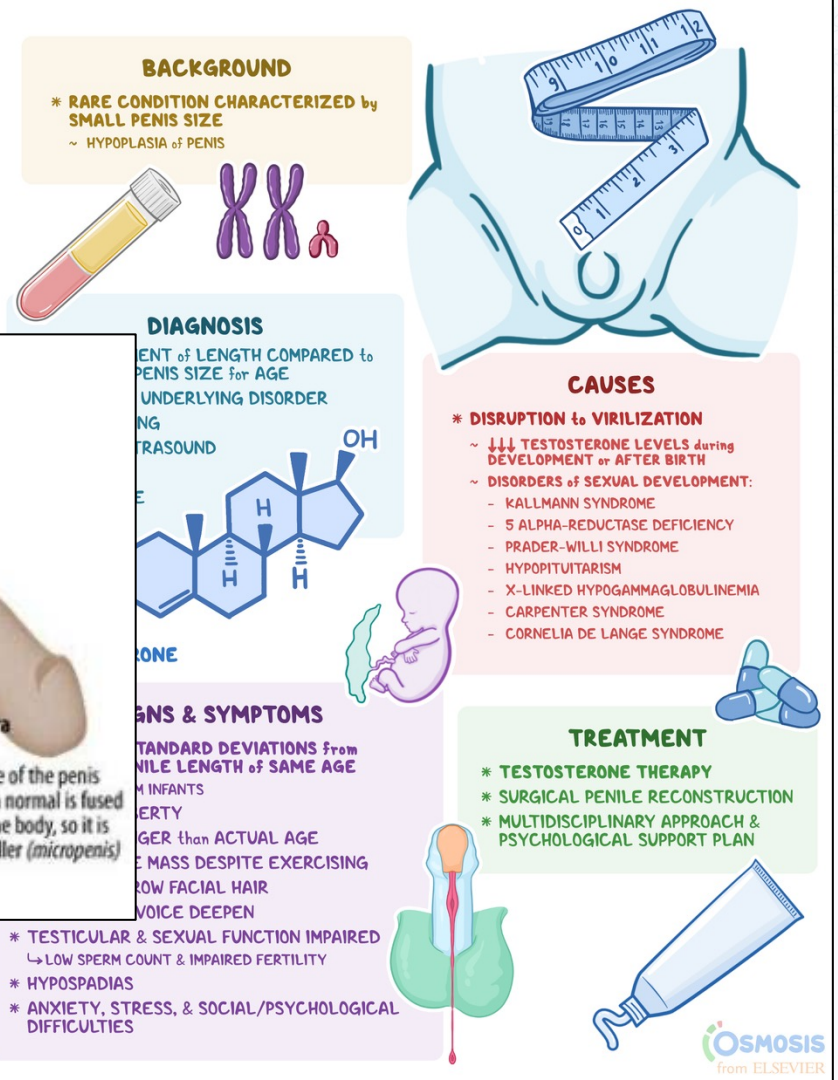
- Congenital
- Benign
- Collection of neural tissue
  - Base of third ventricle

- Incidence: 1: 100,000 children



Penile anomalies



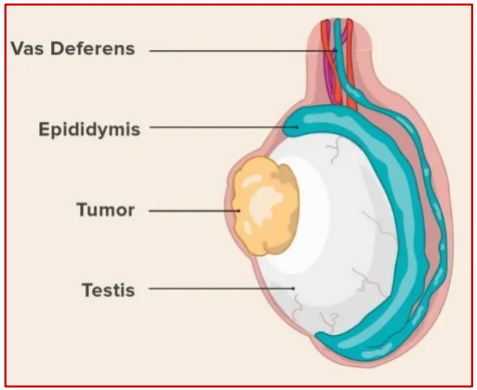


Testicular tumours

- Testicular tumours are rare in children
- Painless scrotal mass is the most frequent clinical presentation.
-
- Tumour markers and hormone levels (testosterone) contribute to the diagnosis and management of a testicular mass in boys.
- Ultrasonography is the best imaging modality to study testicular tumours.

Tumour types

- Yolk sac tumour
  - Pre-pubertal
- Teratoma
  - Pre-pubertal
- Dermoid cyst
- Epidermoid cyst
- Germ cell tumours
- Seminoma



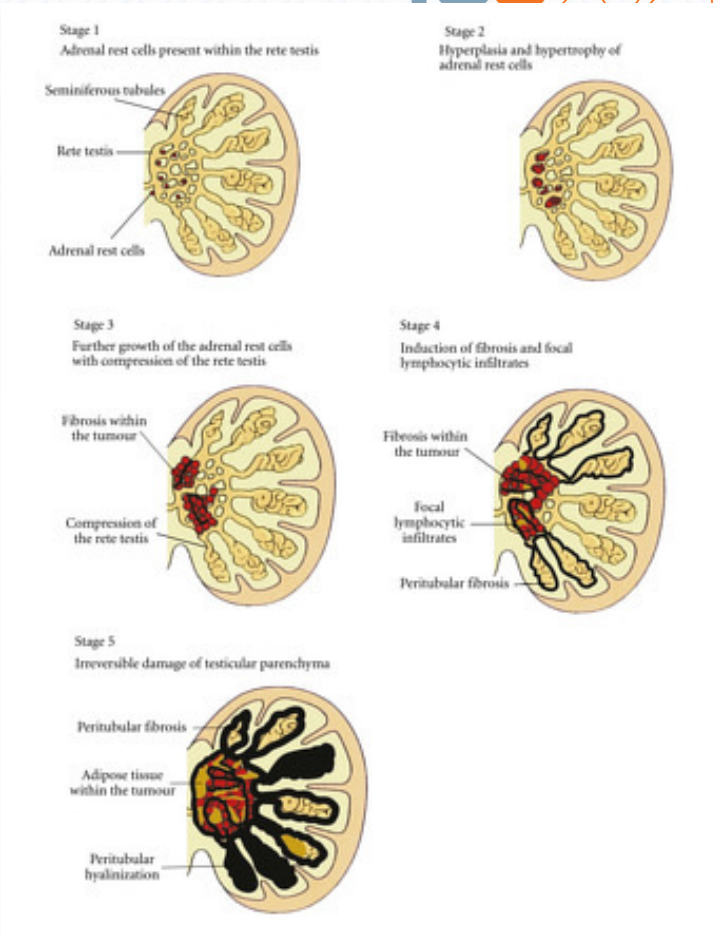
- Embryonal carcinoma
- Choriocarcinoma
- Mixed germ cell tumours
- Sex cord-stromal tumours
  - Leydig cell
  - Sertoli cell
  - Juvenile granulosa cell tumour
- Gonadoblastoma

TARTs

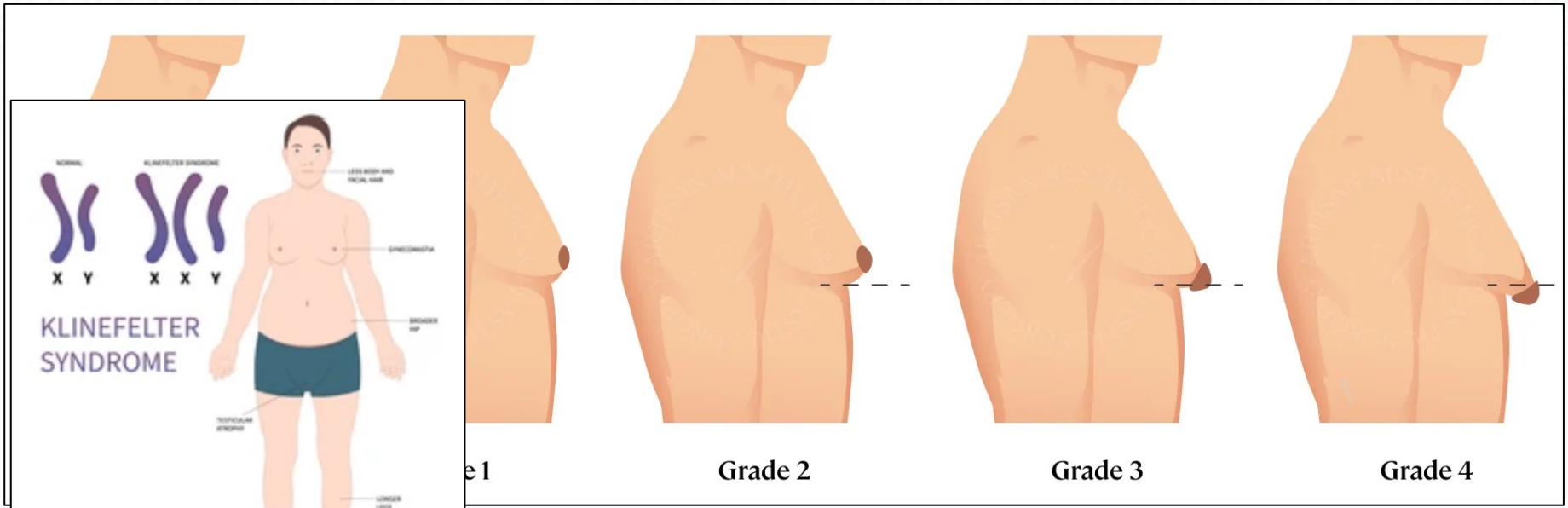
Testicular adrenal rest tumours (TARTs) are rare tumours associated with congenital adrenal hyperplasia (CAH).

CAH is an autosomal recessive disorder of the adrenal gland characterized by an enzymatic defect in the adrenal steroid hormone production pathway, leading to low cortisol and aldosterone levels.

The lack of negative feedback from cortisol causes the pituitary gland to release an increased amount of adrenocorticotropic hormone (ACTH), resulting in adrenal hyperplasia



Gynaecomastia



What else?

- Congenital Hypothyroidism
  - Neonatal thyroitoxicosis
- Other growth / puberty disorders
  - Growth hormone insensitivity
  - Noonan syndrome
  - SHOX deficiency
  - Idiopathic short stature
  - Delayed puberty
- Adrenal disorders
  - CAH
  - Addison's disease
- Multiple Endocrine Neoplasia
  - Von Hippel Lindau disease

In conclusion

- Background knowledge required
- Working with families / children
  - Adherence
- Impact of diagnoses at different ages
- Transition to adulthood
- Multi-disciplinary team work
- Role of the nurse specialist
- So much more!

Thank you

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