WHAT COMES UNDER THE DSD UMBRELLA?

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CONFLICT OF INTEREST DISCLOSURE

- Invited lectures at pharmaceutical company meetings
  - Merck
  - Sandoz
- International paediatric endocrine nurse advisory board
  - Merck

INTRODUCTION

- Introduction to DSD
- Classification
- Hormones involved in DSD
- Embryology reminder
- ‘Normal’ reproductive systems
- Chromosomes reminder
- What is a DSD
- MDT approach
- Diagnostic process
- The CNS role in DSD

WHAT IS A DSD?

- Congenital conditions in which development of chromosomal, gonadal or anatomic sex is atypical

- True genital ambiguity
  - 1 in 5000 / 1 in 4500 births

- Genital anomalies
  - 1 in 300 births

What words do you associate with DSD?

REVISED NOMENCLATURE: CHICAGO CONSENSUS 2006

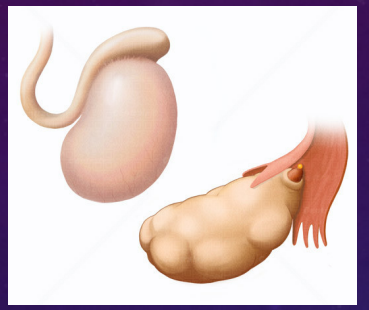
Previous	Revised
Intersex	Disorders of sex development (DSDs)
Male pseudohermaphrodite	
Undervirilization of an XY male	46,XY DSD
Undermasculinization of an XY male	
Female pseudohermaphrodite	
Overvirilization of an XX female	46,XX DSD
Masculinization of an XX female	
True hermaphrodite	Ovotesticular DSD
XX male or XX sex reversal	46,XX testicular DSD
XY sex reversal	46,XY complete gonadal dysgenesis

CLASSIFICATION OF DSD

- **46,XY DSD (under virilised genetic male)**
  - Disorders of testicular development
    - Ovotesticular DSD
  - Disorders of androgen synthesis / action
    - CAIS
  - Others
    - Hypospadias
- **46,XX DSD (over virilised genetic female)**
  - Disorders of ovarian development
    - Ovotesticular DSD
  - Androgen excess
    - CAH

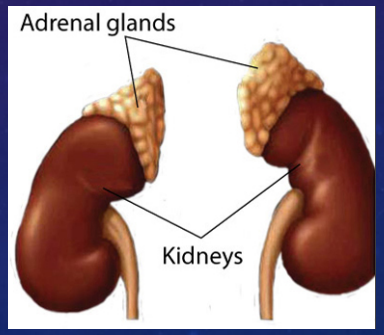
- **Sex chromosome DSD (variable)**
  - Turner syndrome
  - Klinefelter syndrome
  - Mixed gonadal dysgenesis

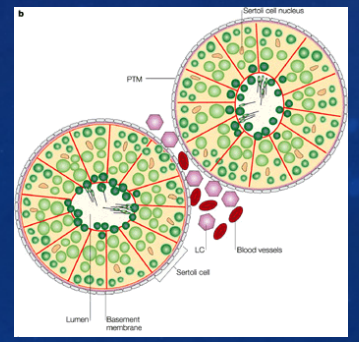
ENDOCRINOLOGY IN SEX DEVELOPMENT



HORMONES INVOLVED IN SEX DEVELOPMENT

- Produced in the placenta, adrenal glands and developing gonads
- **Androgens** synthesized by the Leydig cells from 8 to 9 weeks are one of the key regulators
  - Control Wolffian ducts and external genitalia development
- **AMH** (MIH) produced by the Sertoli cells
- Insulin like hormone 3 (**INSL3**) made by the Leydig cells
- **Oestrogens** from the foetal / maternal ovary
- Pathway for steroid hormone synthesis
- **HCG**



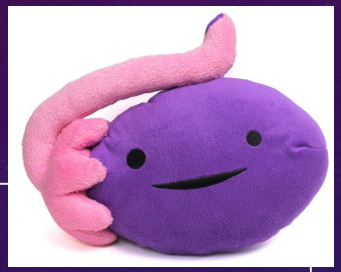


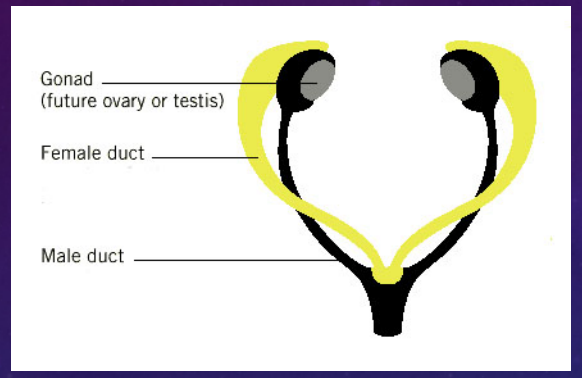
HCG

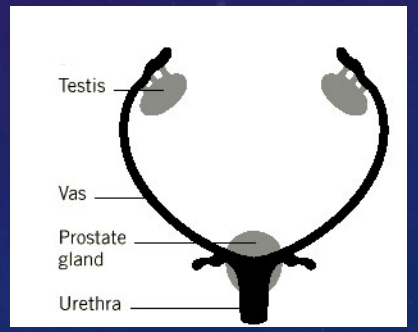
- Serum levels of foetal testosterone mirror HCG, suggesting that the placenta has an important role in the early years of male sexual development
- Key masculinising effects during second half of gestation
  - Growth of penis and scrotum, and testicular descent
  - Probably regulated by foetal hypothalamus
    - Babies with congenital hypopituitarism and anencephaly have micropenis, hypoplastic scrotum and cryptorchidism
- Now see very premature infants with IUGR
  - These boy babies are inadequately masculinised
    - Consistent with inadequate placental HCG to stimulate testosterone production from the foetal Leydig cells during a critical phase of sex development

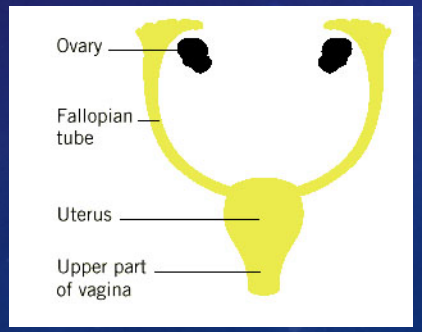
EMBRYOLOGY REMINDER

FORMATION OF INTERNAL STRUCTURES



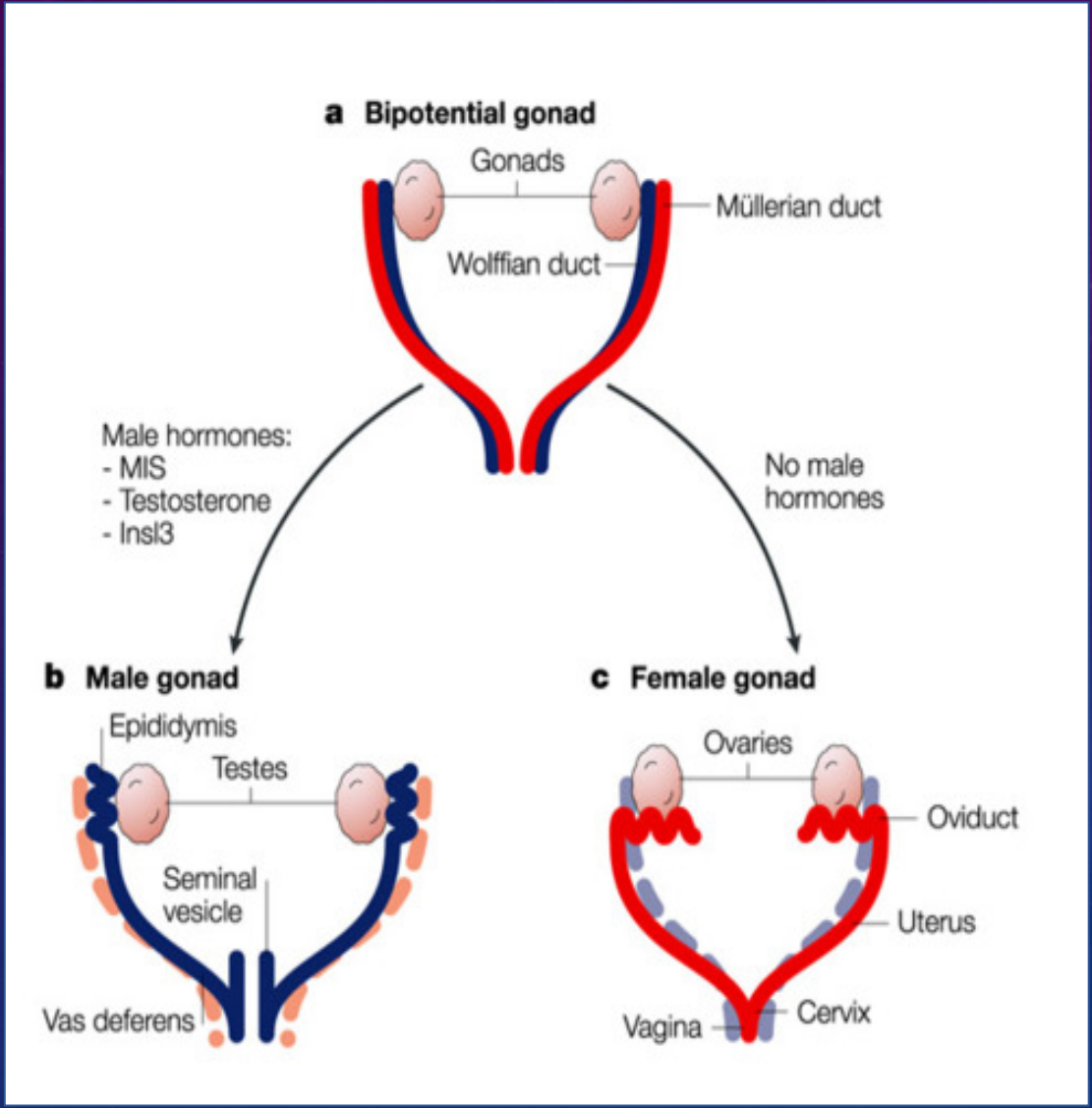






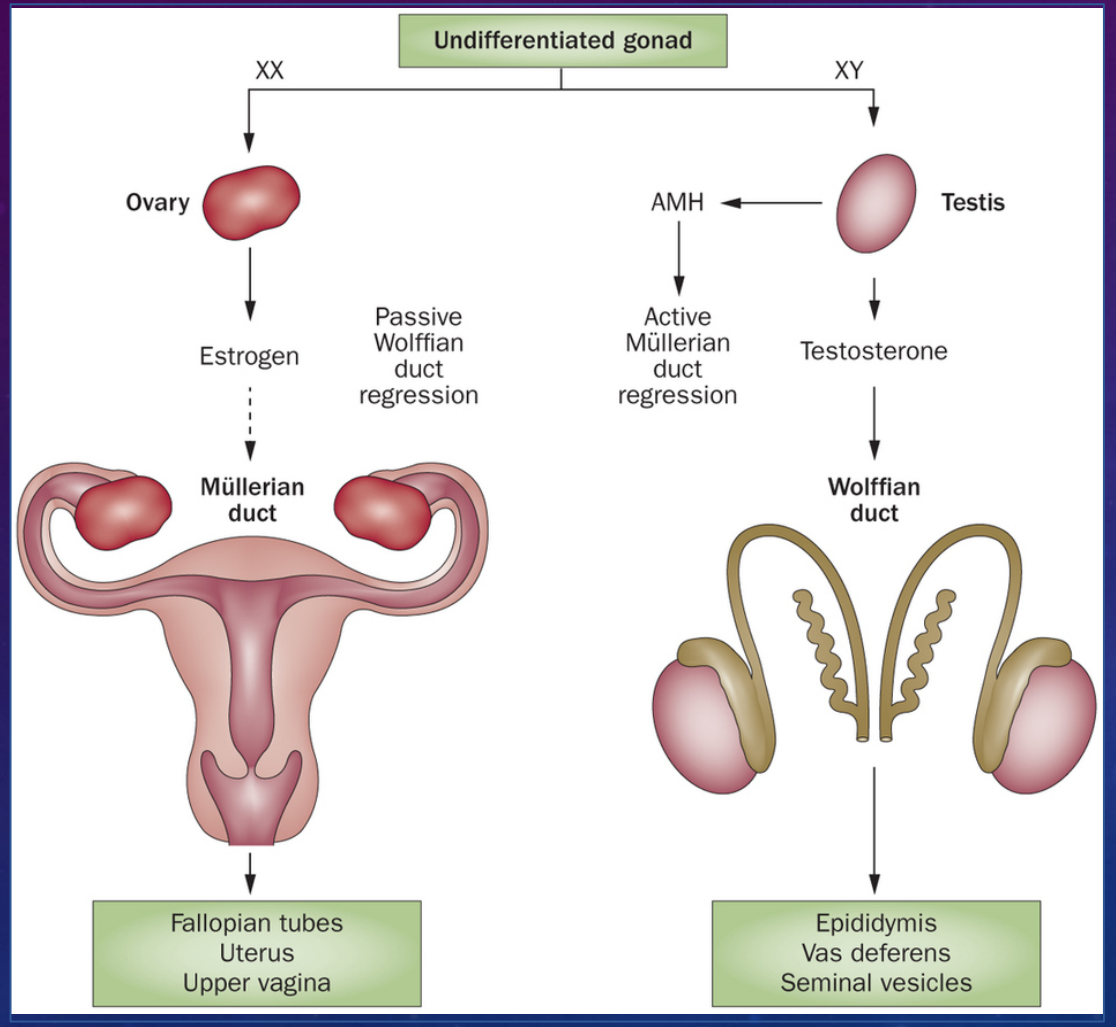
- Foetal ovaries
  - Make small amounts of testosterone and AMH (anti Mullerian hormone)
- Foetal testes
  - Make lots of both hormones
- The presence or absence of these hormones influences the development of the internal sex ducts:
  - Mullerian ducts
    - Found in boy and girl foetuses, but disappear in boys when the testes make AMH (Mullerian Inhibiting Hormone)
    - Forerunners of the uterus, cervix, fallopian tubes and upper portion of the vagina
  - Wolffian ducts
    - Found in all foetuses but disappear in girls as they have no testes to produce testosterone
    - Forerunners of vas deferens, epididymides, prostate gland and seminal vesicles

GENITALIA DEVELOPMENT – 7-8 WEEKS



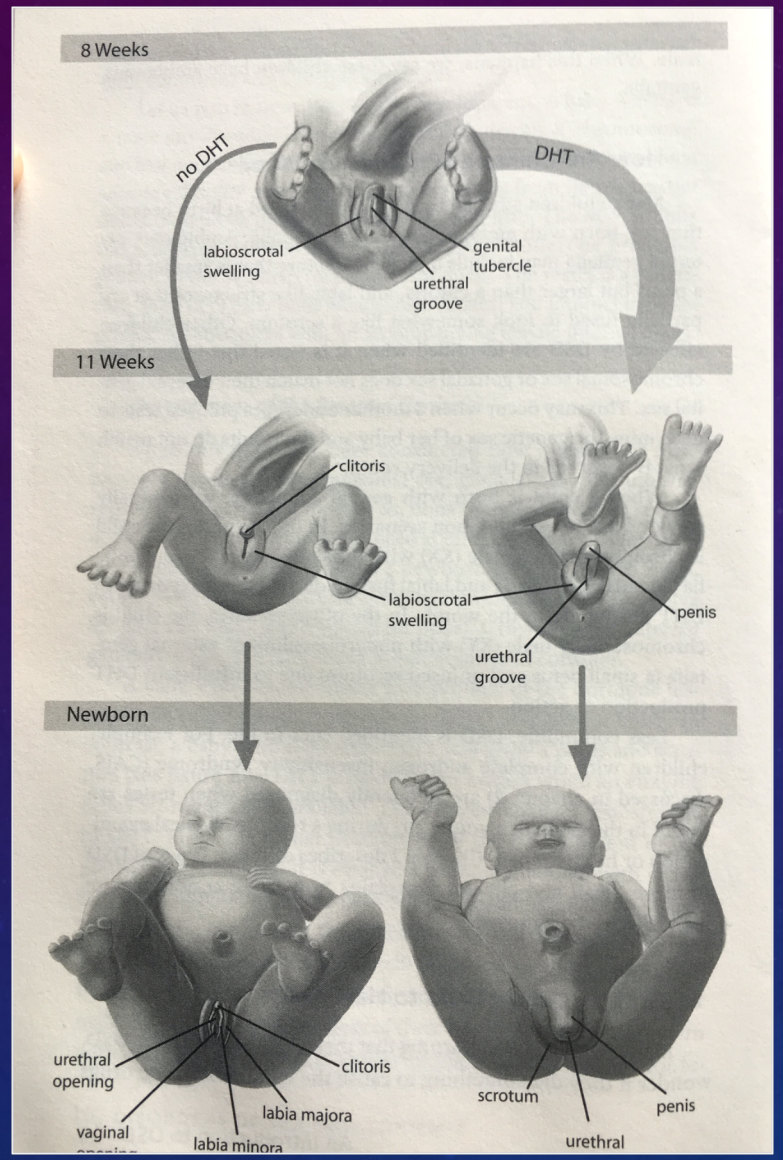
- **7-8 weeks**
  - Presence of XY chromosome
    - Triggers activation of SRY gene
    - Initiates development of a testis
    - Primary sex chords develop into Sertoli cells
      - AMH
      - Leads to regression of the Mullerian duct
    - Leydig cells produce testosterone
      - Stimulate Wolffian duct to form epididymis, vas deferens and seminal vesicles

GENITALIA DEVELOPMENT



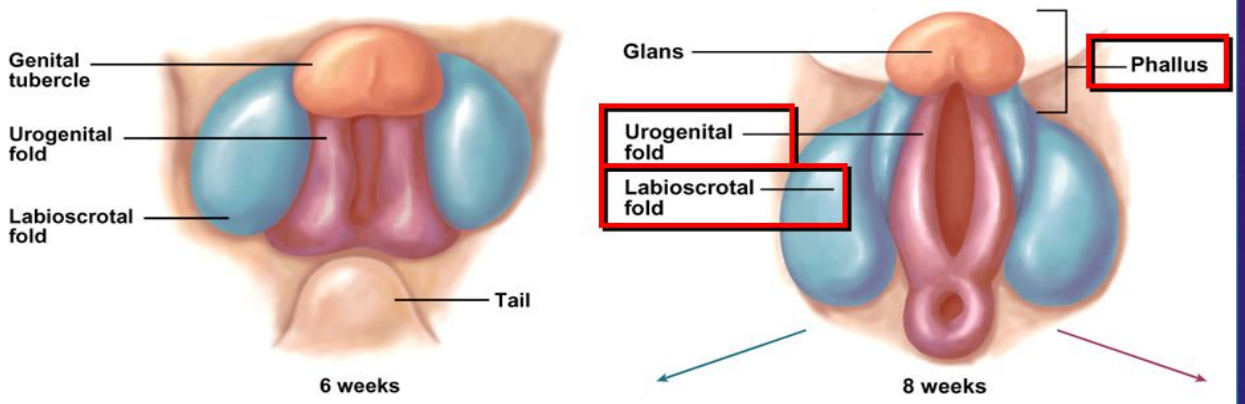
- External genitalia remains same until 8 weeks
  - Central genital tubercle
  - Masculine – DHT
    - Penis
  - Female
    - Only enlarges a small amount to form the clitoris

EXTERNAL GENITALIA DEVELOPMENT

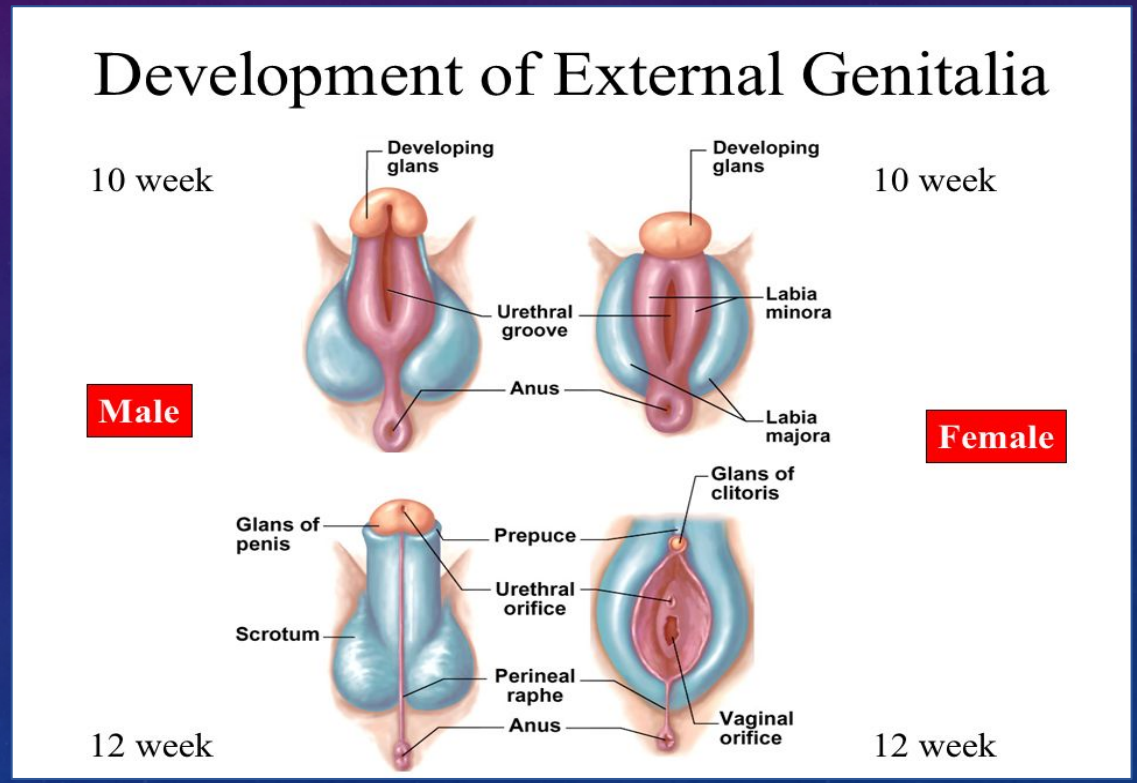


- A baby who doesn't make a byproduct of testosterone called dihydrotestosterone (DHT) will grow a vulva
- If a baby does make DHT, they will grow a penis and scrotum
- DHT is made in our bodies when an enzyme called 5α reductase is available
  - This changes T to DHT

EXTERNAL GENITAL DEVELOPMENT

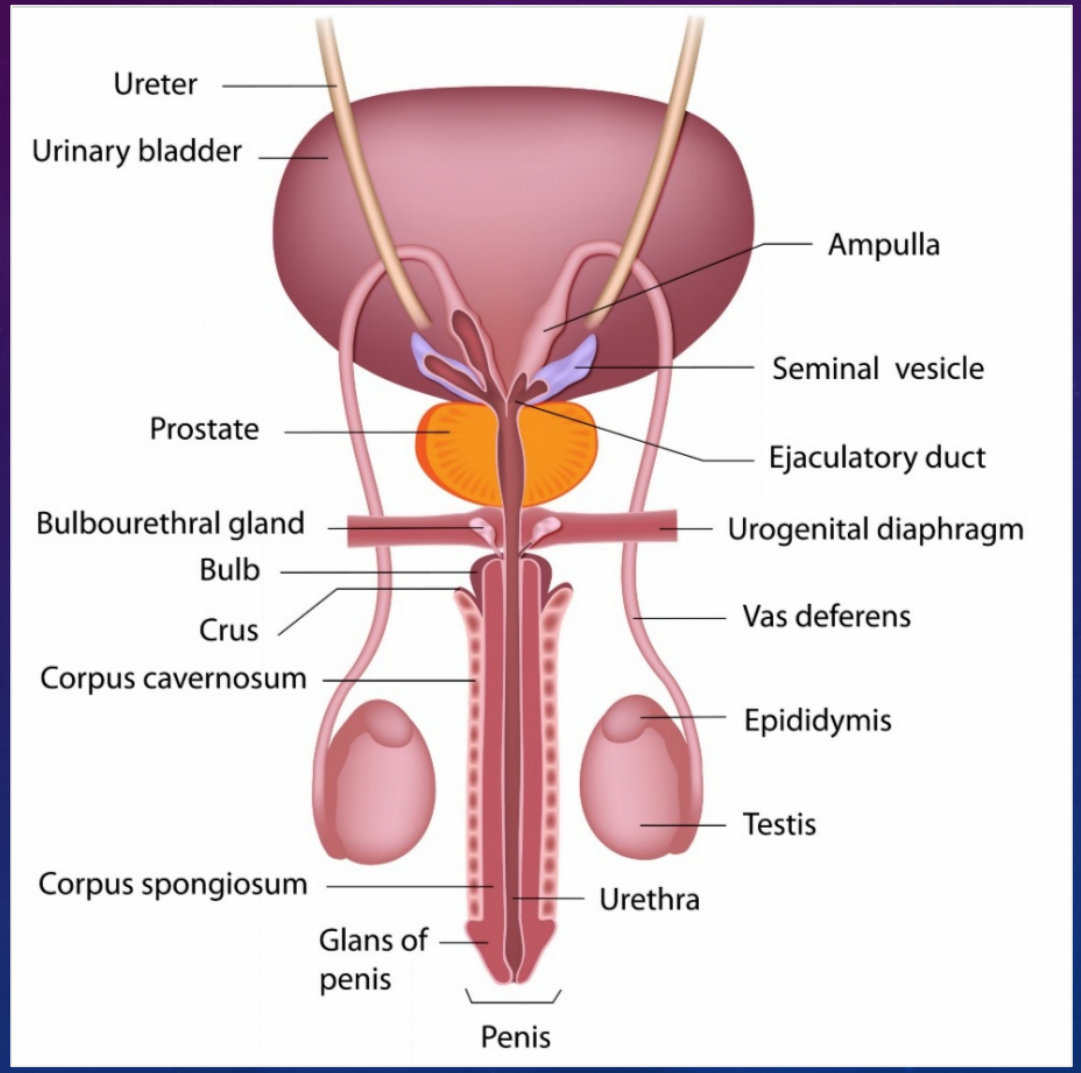


- All 8 week old fetuses have same 3 structures
  - by end of week 9, begin to show sexual differentiation
  - distinctly male or female by end of week 12

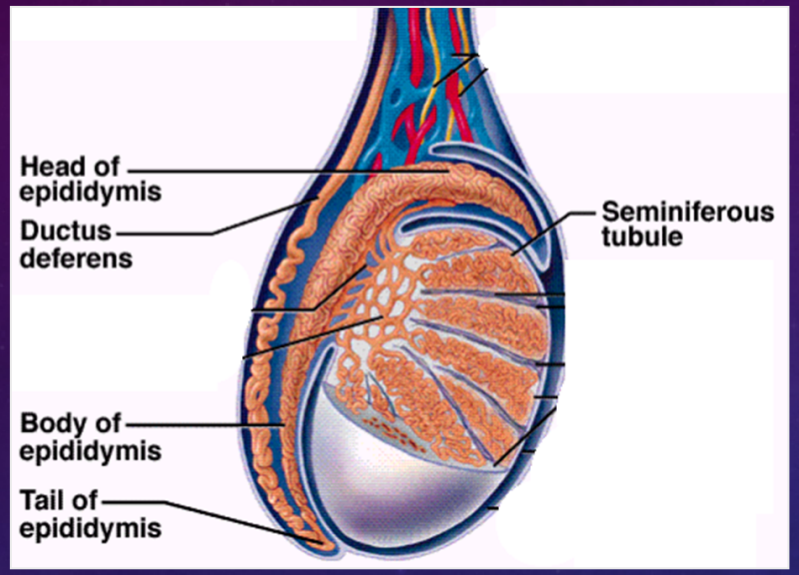


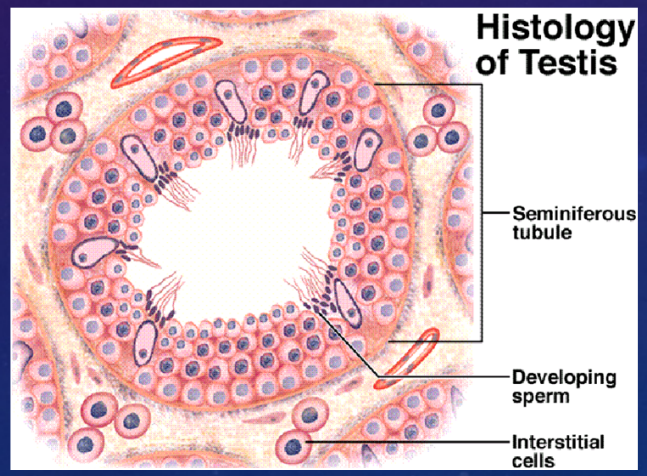
A REMINDER OF THE REPRODUCTIVE SYSTEMS

THE MALE REPRODUCTIVE SYSTEM



TESTES

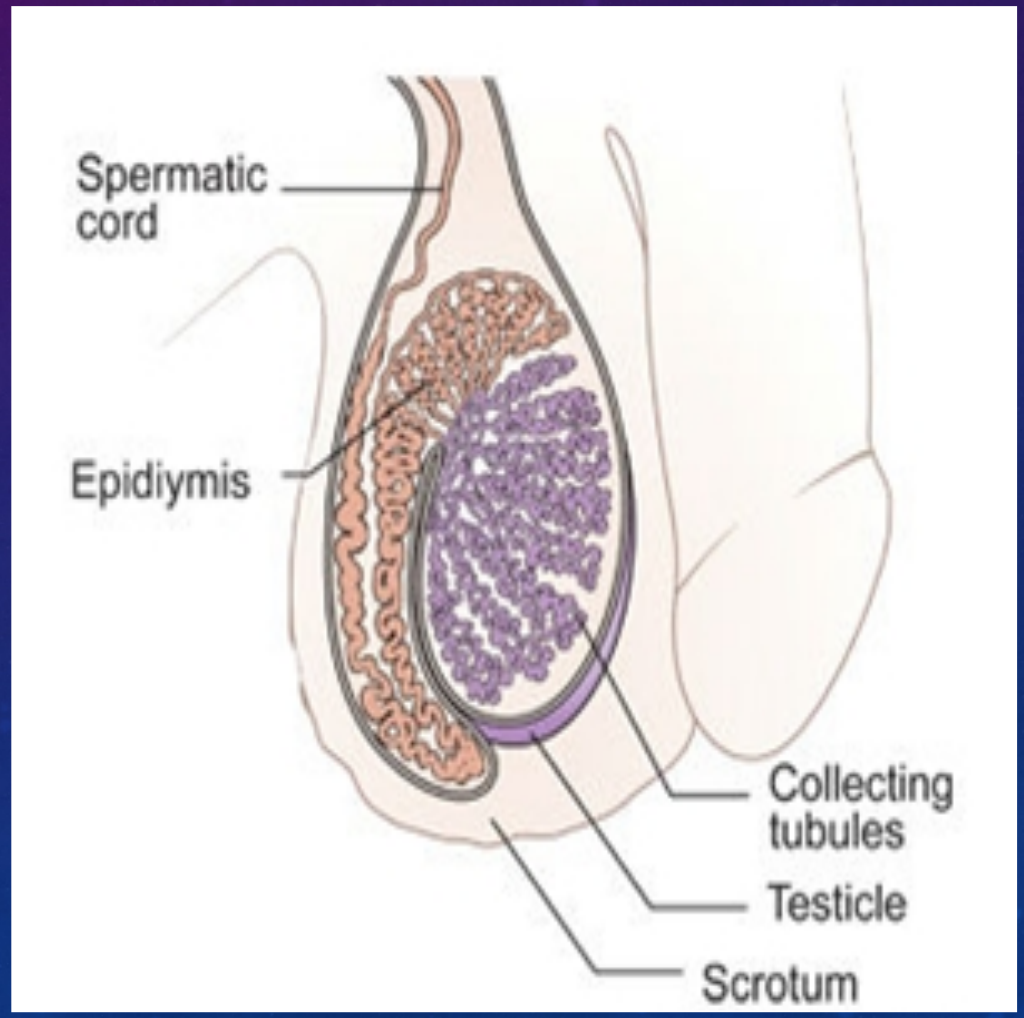




- Produce sperm cells
- Developed from germ cells in seminiferous tubules
- Secrete testosterone by interstitial / Leydig cells

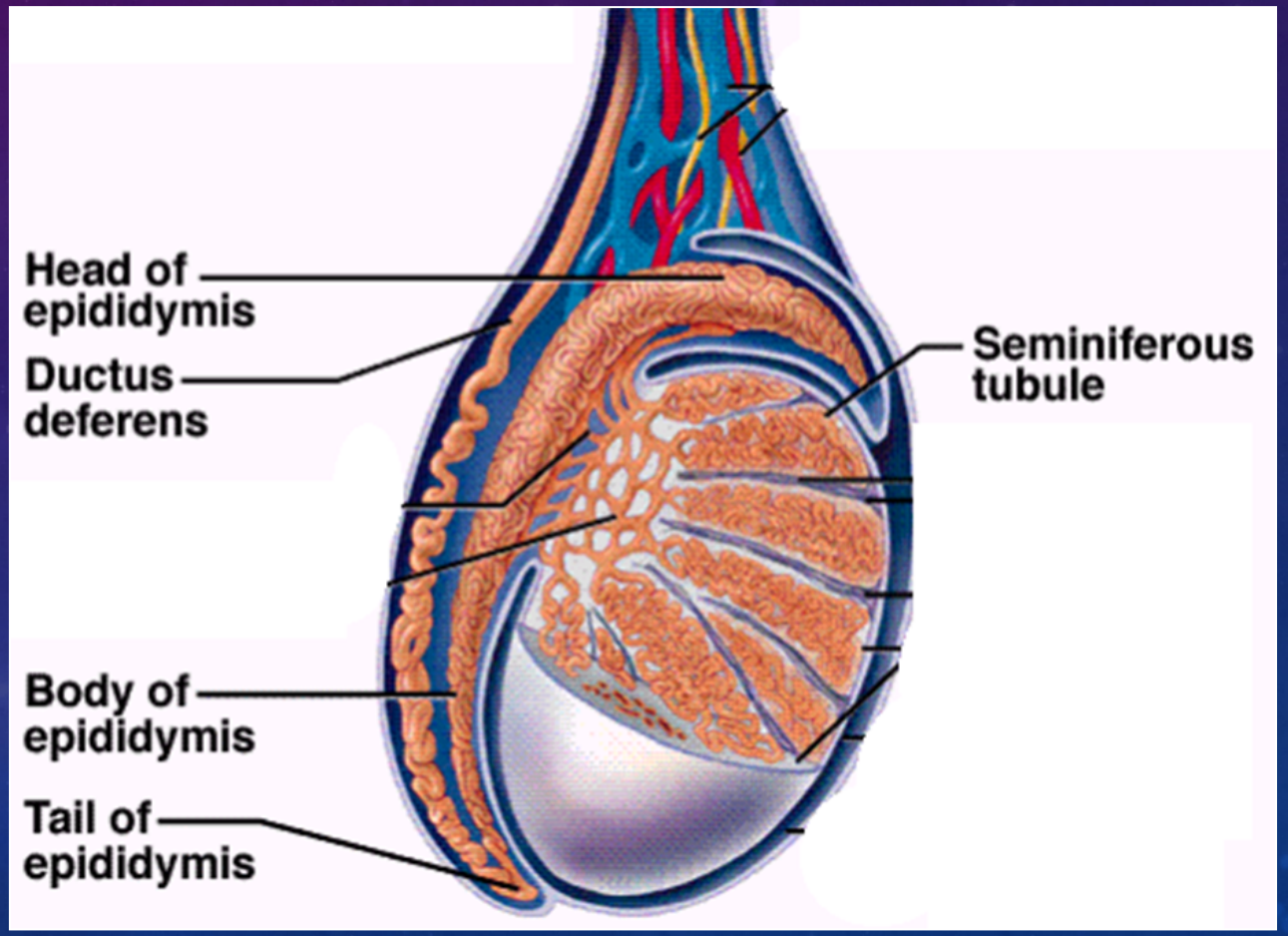
LEYDIG CELLS

- Found adjacent to the seminiferous tubules in the testicle
- Produce testosterone in the presence of LH
    - LH binds to receptors within the cell

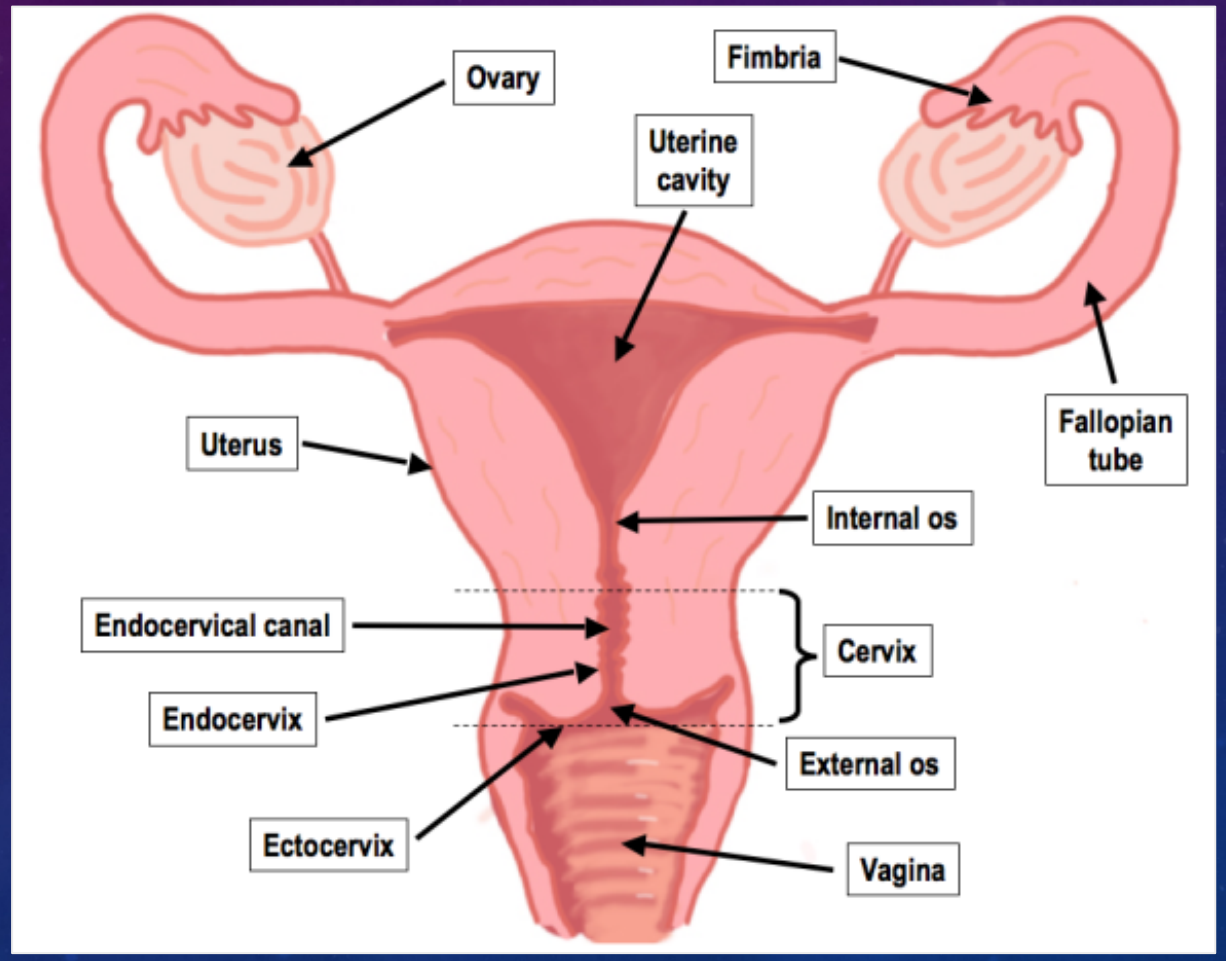


EPIDIDYMIS

- Storage site of sperm cells
- Absorbs about 90% of the fluid secreted by the testis
- Sperm remain stored here for 40 – 60 days
  - Absorbed if not ejaculated prior to that time

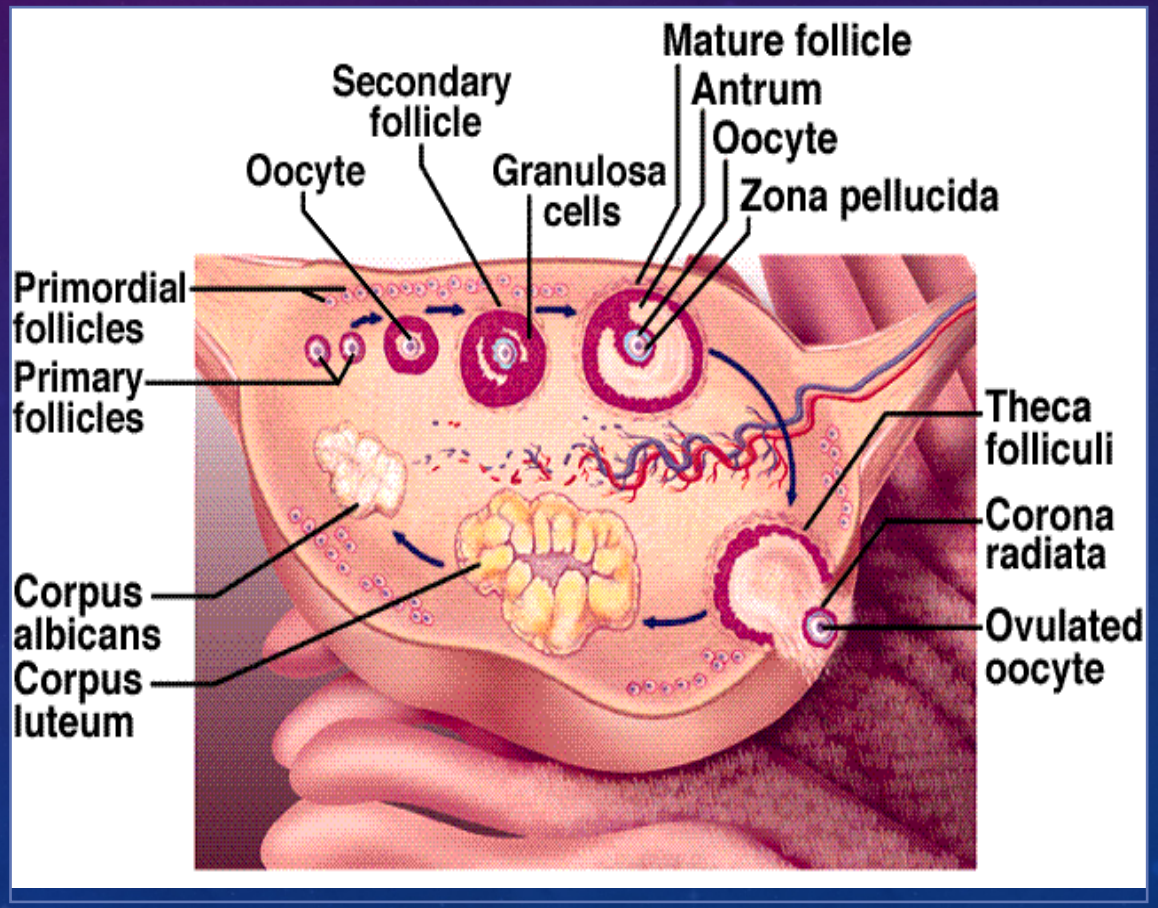


THE FEMALE REPRODUCTIVE SYSTEM



THE OVARY

- Produce oocytes (oogenesis
  - Most primary oocytes undergo a process of degeneration called ***atresia***. Only 2 million remain at the time of birth, and by puberty, only 400,000 remain
  - Only one oocyte is ovulated each 28-day cycle
- Produce hormones:
  - **Oestrogen**
  - **Progesterone**
  - **Inhibin**
  - **Androgens**
- The release of an oocyte does not alternate between the two ovaries and seems to be random
- After removal of an ovary, the remaining one produces an egg every month



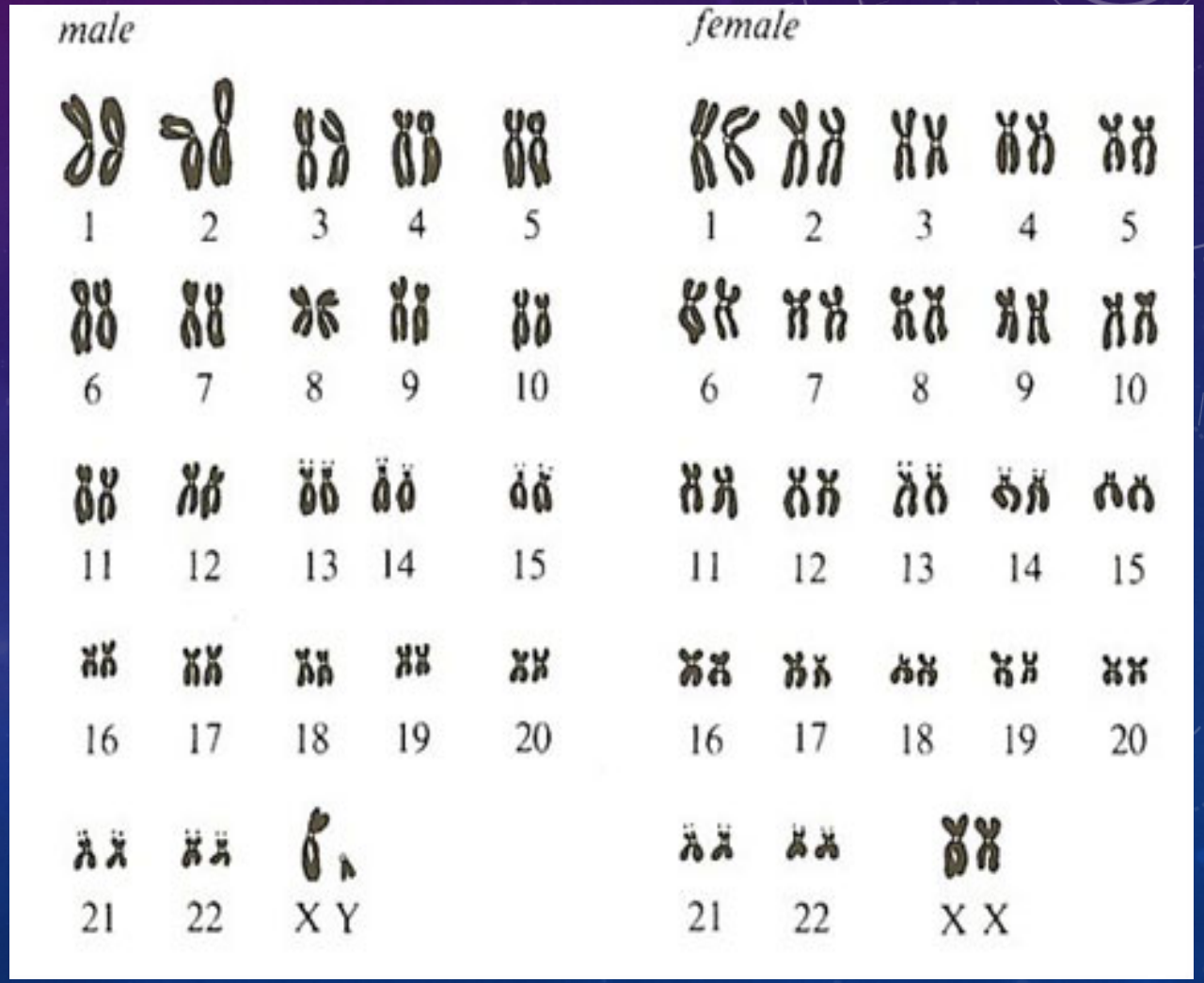
DIFFERENT DSD

- 46 XY DSD
- 46 XX DSD
- Sex chromosome DSD

CHROMOSOMES OVERVIEW

XX AND XY CHROMOSOMES

- XX – genotypic female
- XY – genotypic male
- Half of sperm cells carry the X chromosome, and half carry the Y chromosome
- The SRY gene present on the Y chromosome will act as a signal for the pathway for maleness
  - Starts off virilisation
- Can also have a chromosomal arrangement that is contrary to phenotypic sex
  - XX males
  - XY females
  - Abnormal number of sex chromosomes may be present
    - **DSD**

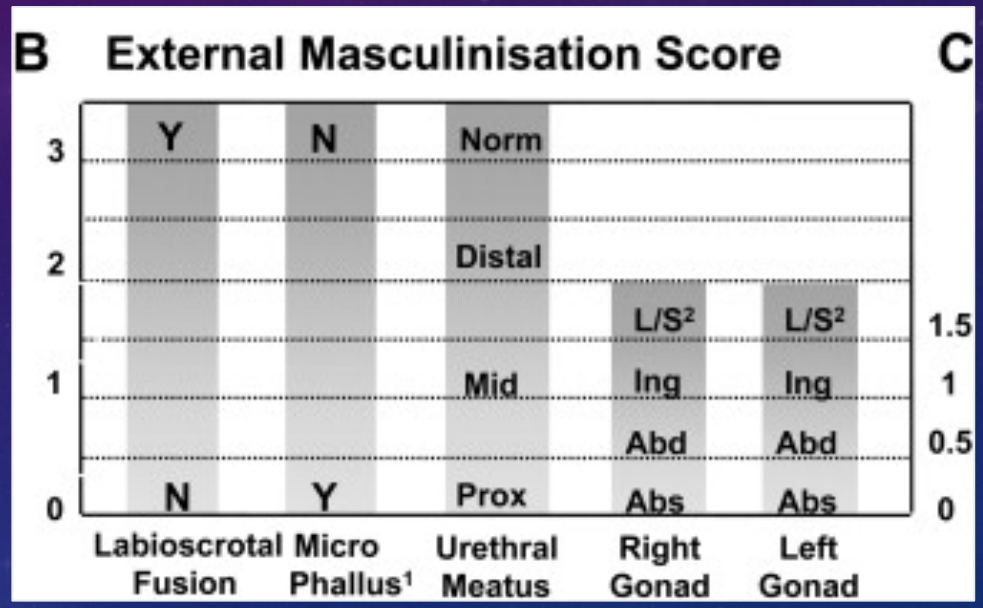


46XY DSD - PRESENTATION

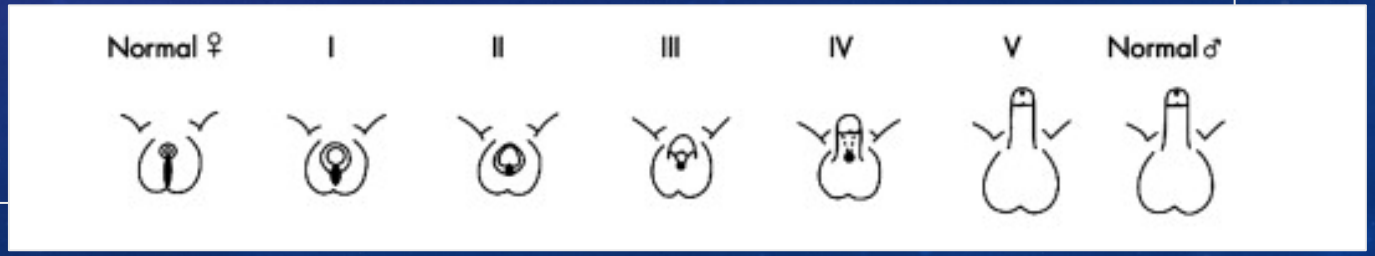
- Absence of secondary sexual characteristics in an adolescent boy
- Hypospadias
- Ambiguous genitalia at birth
- Primary amenorrhea in an adolescent child with a complete female phenotype
- Variation depends on 2 factors:
  - Degree in disturbance of androgen production or action
  - Point at which this disturbance occurs during sex development
- Anatomic presentation can be classified by using clinical rating scales

CLINICAL RATING SCALES

- External Masculinisation Scale
  - Score of < 7 is considered ambiguous

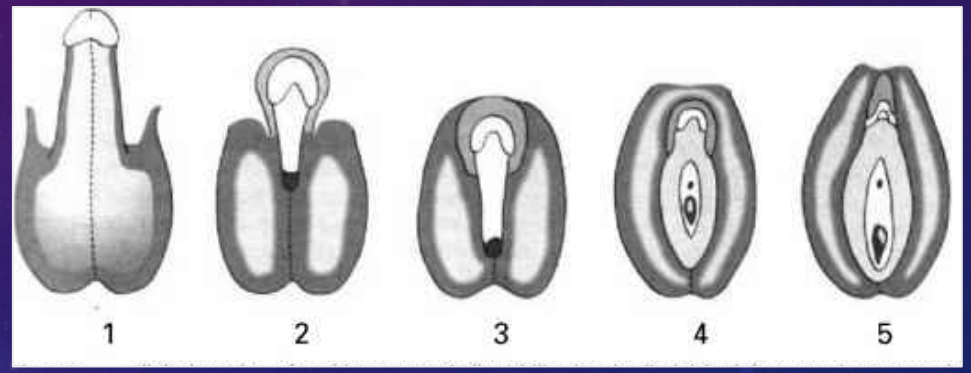


- Virilisation of XX individudals (Prader)

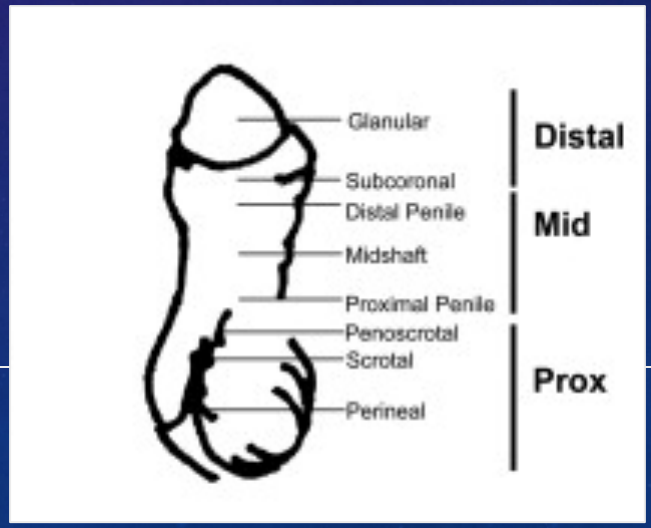


CLINICAL RATING SCALES

- Androgen Insensitivity (Quigley)



- Hypospadias classification



46XY- ANDROGEN INSENSITIVITY SYNDROME

- Complete absence of androgen action from the time of early foetal development results in a child with a typical female external phenotype (CAIS)
- *Partial* action of androgens during foetal development causes hypospadias
  - Micropenis can occur
  - Cryptorchidism
- Mullerian structures may be present or absent
  - If AMH not released, then internal structures may remain as female
  - Must determine if present as will have a bearing on fertility if raised female
- Gonadal germ cell cancer risk
  - Increased in testes with impaired development and presence of Y chromosome material
    - PAIS and raised as male – strict cancer surveillance
    - CAIS and raised as female – prophylactic gonadectomy

Model Hanne Gaby Odiele reveals she is intersex to 'break taboo'

24 January 2017 | Europe

Share

Hanne Gaby Odiele had two major operations, as a child and a teenager

A top fashion model has revealed that she is intersex, saying that she hopes speaking out will help break a taboo.

Hanne Gaby Odiele, 29, was born with undescended testicles, which were removed when she was 10 after doctors warned that they could cause cancer.

Intersex people are born with a mixture of male and female sex characteristics.

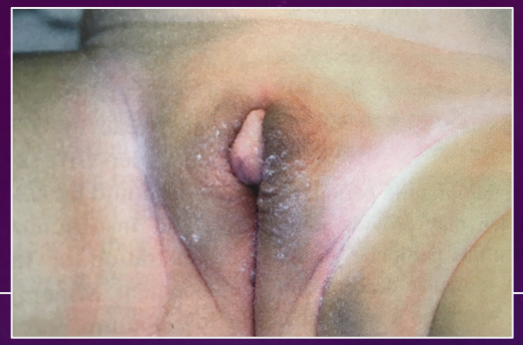
According to the United Nations, the condition affects up to 1.7% of the world's population.

Ms Odiele, originally from Belgium, was born with androgen insensitivity syndrome (AIS).

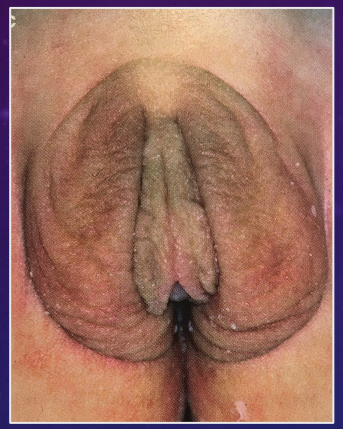
Video: disorders of sex development

A urologist explains different disorders of sex development, how they affect children and treatment options. Lexy, who was diagnosed with partial androgen insensitivity syndrome, explains why she started hormone therapy at the age of 34

CAIS / PAIS

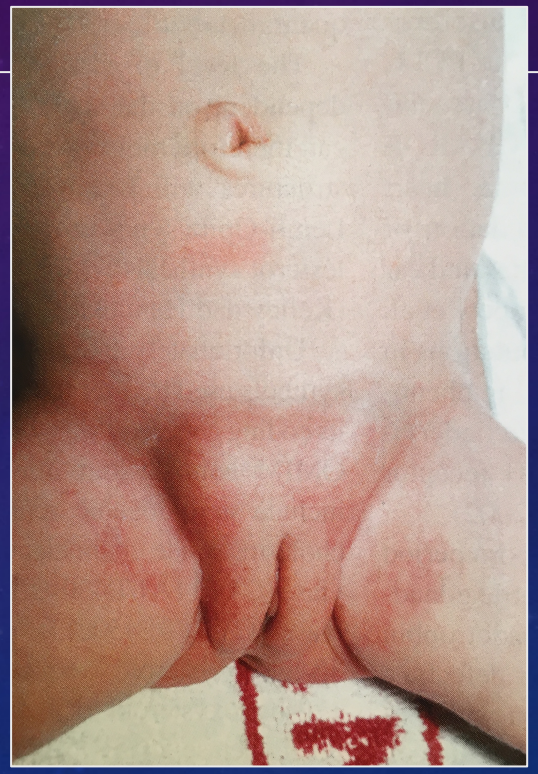


- PAIS
  - Showing minimal virilisation of phallus and genital folds



  - More virilised, where the genitalia show unfused labio-scrotal folds, but pigmentation and wrinkling more noticeable, with a larger phallus

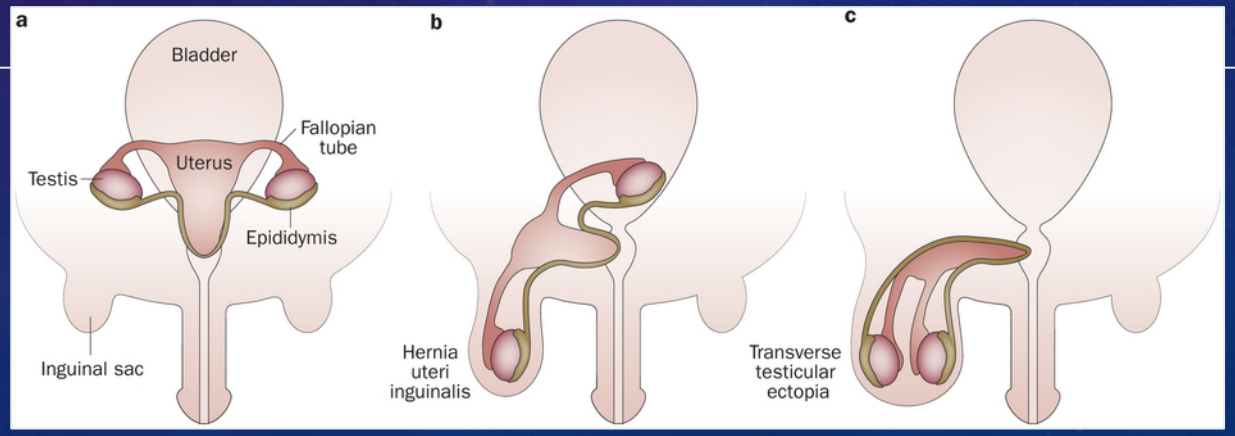
- CAIS



  - Showing normal female external genitalia, but visible gonads in the groin

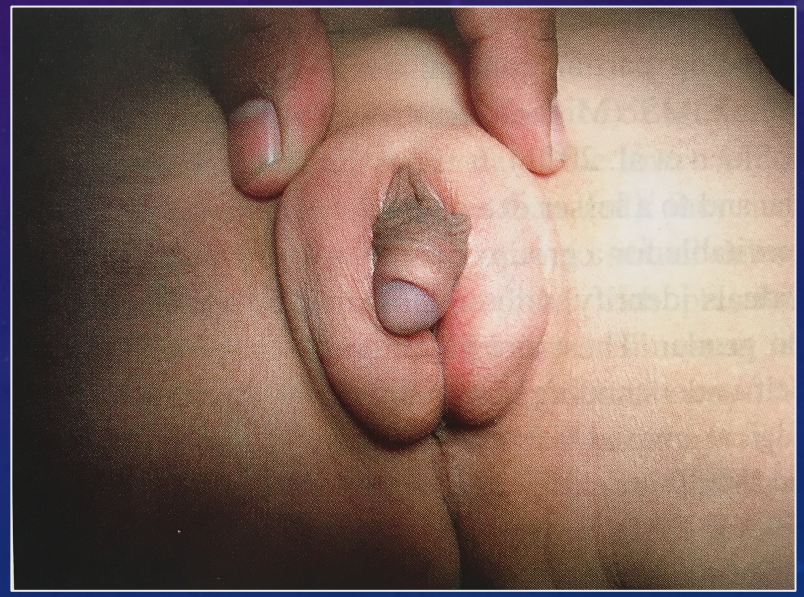
46XY - PERSISTENT MULLERIAN DUCT SYNDROME

- Mutations in the gene encoding AMH
  - Lead to persistence of Mullerian duct organs in a 46XY individual
- Usually present
  - Cryptorchidism
  - Uterine remnants only apparent on examination, or later inguinal herniation



46XY GONADAL DYSGENESIS

- This occurs when there is disruption in the testicular developmental pathway toward mature Sertoli and Leydig cells
- Usually leads to:
  - Small testes with poor androgen-production capacity
  - Presence of mullerian structures
  - Elevated gonadotrophins from puberty
    - Primary gonadal failure



- Inadequate early androgen production leading to bifid scrotum and severe chordee of phallus

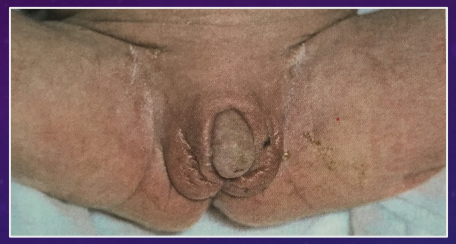
46XX PRESENTATION

- Ambiguous genitalia
  - More than half of all infants born with AG are 46XX
    - Due to in utero exposure of androgens
    - Source may be adrenal (CAH) or testicular
- Complex congenital malformations
  - Cloacal extrophy, or bladder extrophy
- Gradual clitoris enlargements during childhood
  - Non classical CAH
- Abnormal developments at puberty
  - Primary amenorrhoea
    - No breast or pubic hair development (46XX gonadal dysgenesis or steroid biosynthetic defects) OR
    - Normal breast and pubic hair development (Mullerian duct agenesis)
    - Normal breast development but little or no pubic hair (CAIS)

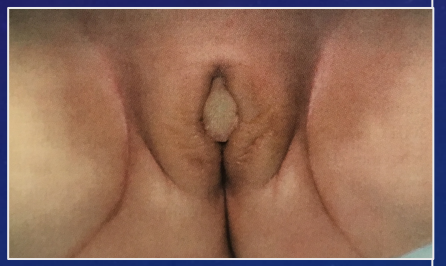
46XX CAH

- Baby will have been exposed to excess male hormone in-utero
- The genitalia will look like a boy's:
  - Labia will fuse to look like a scrotum
  - Clitoris enlarges and looks like a penis
- Can sometimes be so severe, sex assignment is difficult
  - Need karyotype
  - Will still have normal internal structures
  - Surgery may be needed to correct outer appearance
    - CONTROVERSIAL

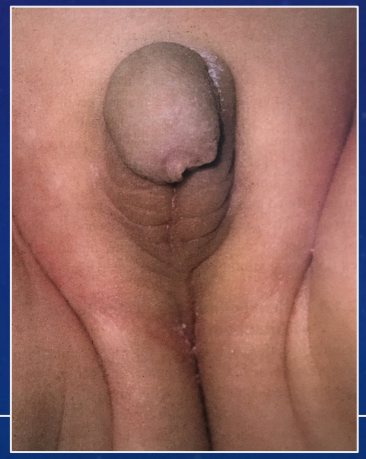
- Exposure to prenatal androgens and Prader 3 virilisation at birth



- Same baby at age 8 weeks at the time of genital reconstruction, showing some regression of virilisation after starting steroid treatment

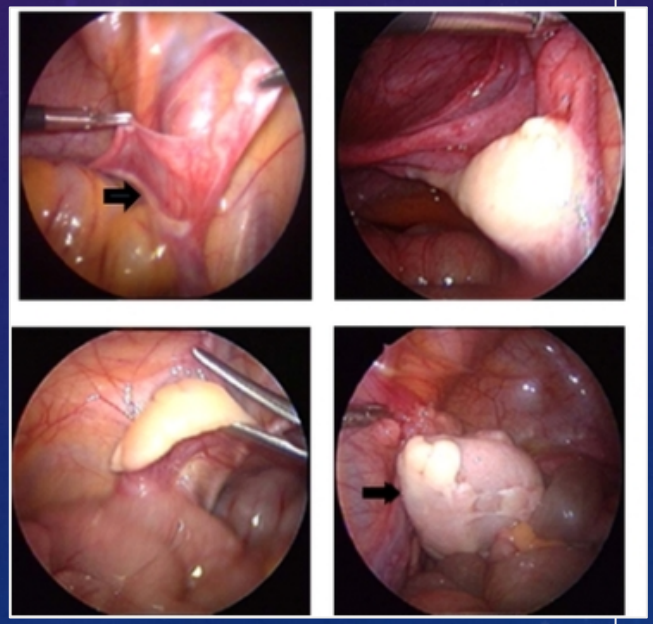


- Another baby girl with a more severe form of 21OHD, leading to more severe virilisation (Prader IV)



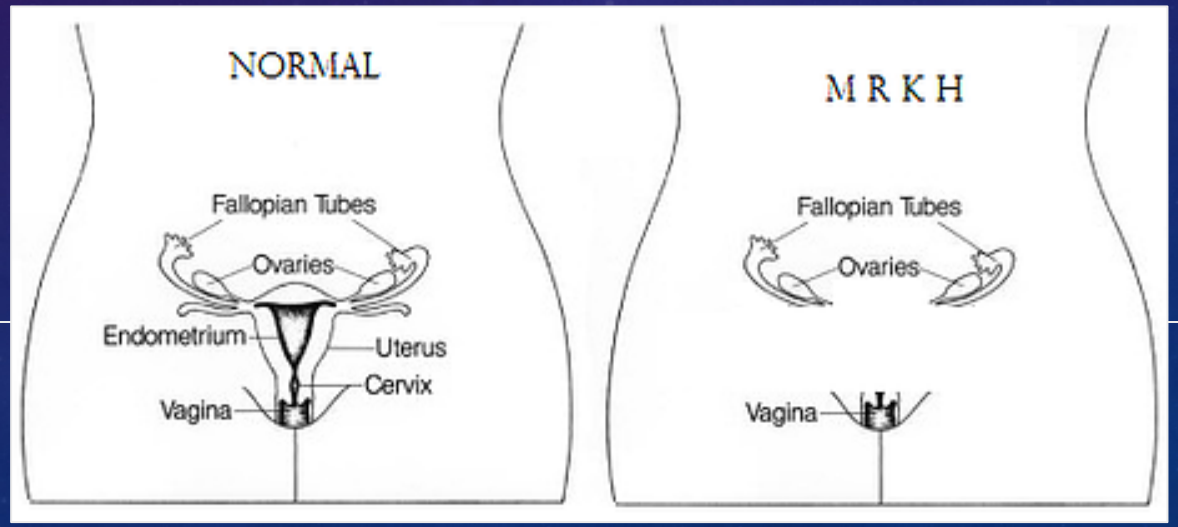
46XX GONADAL DYSGENESIS

- Mutations in FSH receptor gene has been identified
- ‘Pure’ without features of TS
- Streak gonads are present due to germ cells not forming properly
  - Mostly composed of fibrous tissue
- Characterised by primary amenorrhoea with or without secondary sexual characteristics



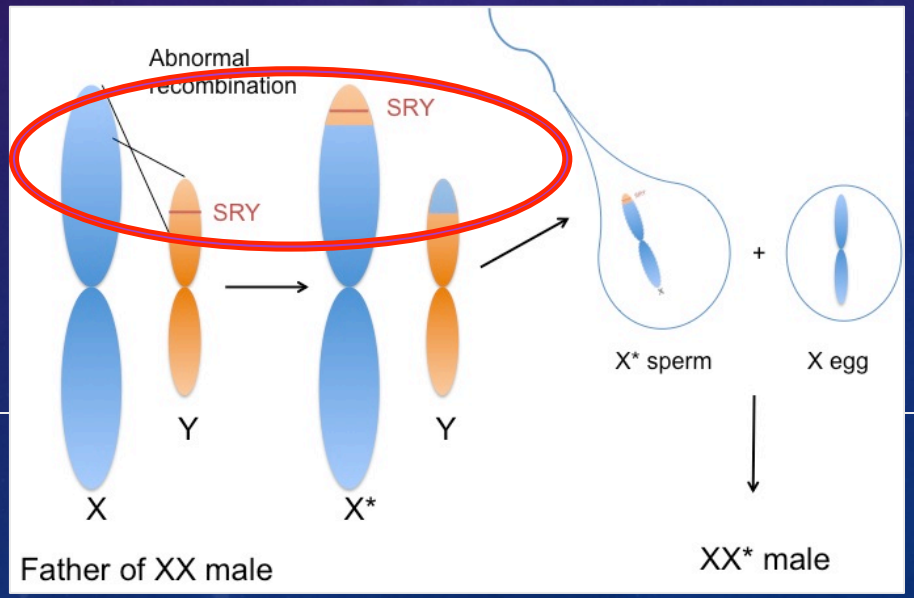
46XX MULLERIAN DUCT AGENESIS

- Vaginal agenesis usually associated with an absent uterus and fallopian tubes but with normal ovarian development
  - Mayer–Rokitansky–Küster–Hauser syndrome



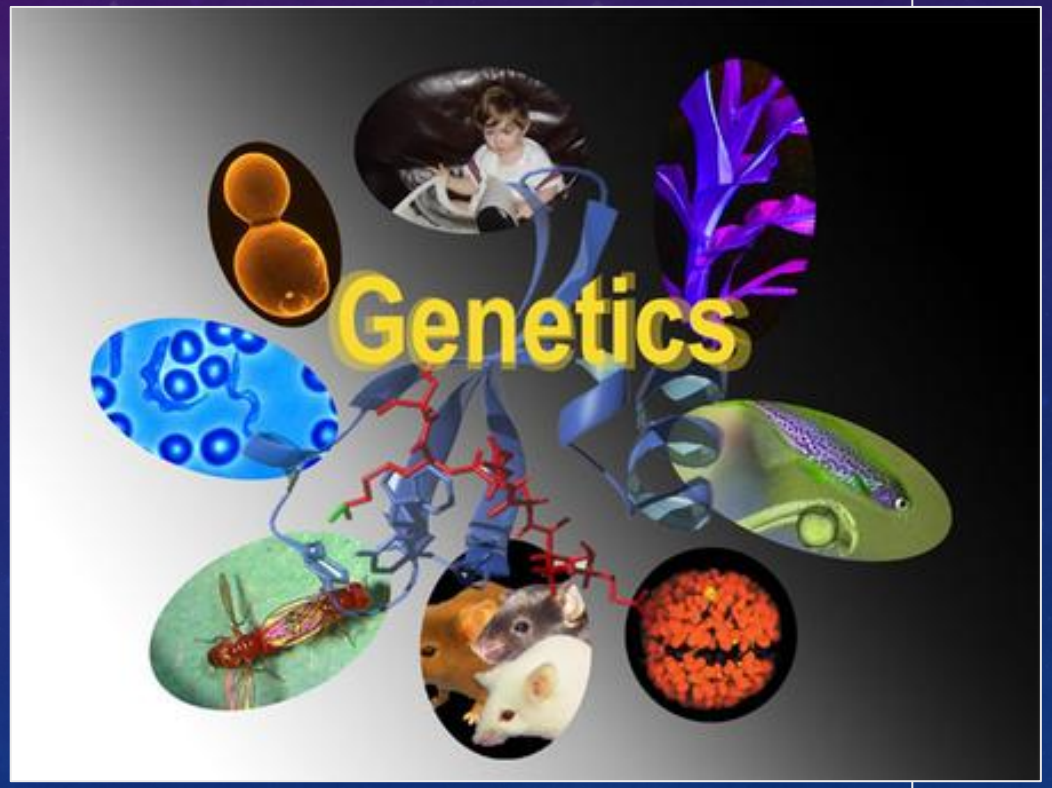
46XX TESTICULAR DSD

- 1 in every 20,000 males with testes has a 46XX karyotype
- Translocation of SRY to the tip of one of the X chromosomes has occurred
- Phenotypical similarities between 46XX men and those with Klinefelter Syndrome
  - 46XX men shorter
  -



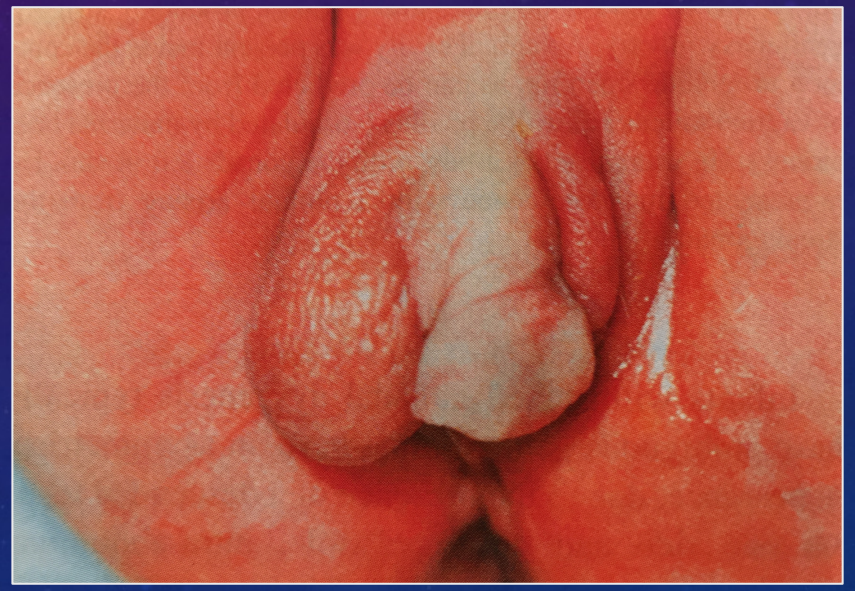
SEX CHROMOSOME DSD

- 46XX Ovo-testicular DSD
- Klinefelter Syndrome
- Turner Syndrome
- 45X / 46XY



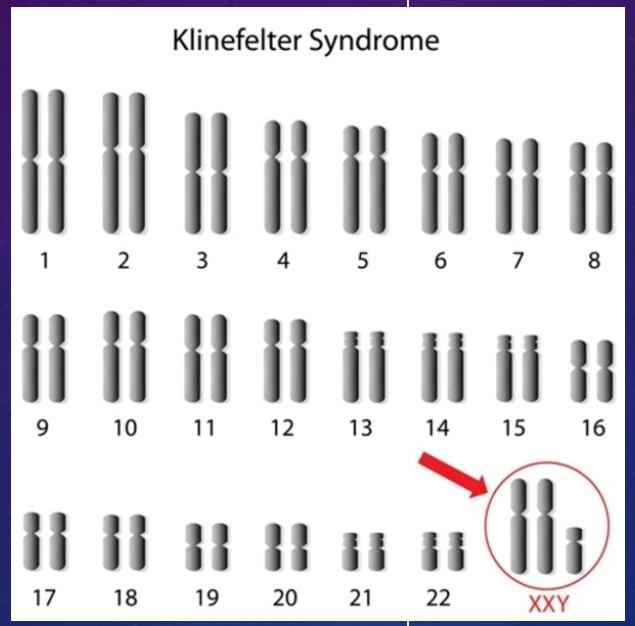
46XX OVO-TESTICULAR DSD

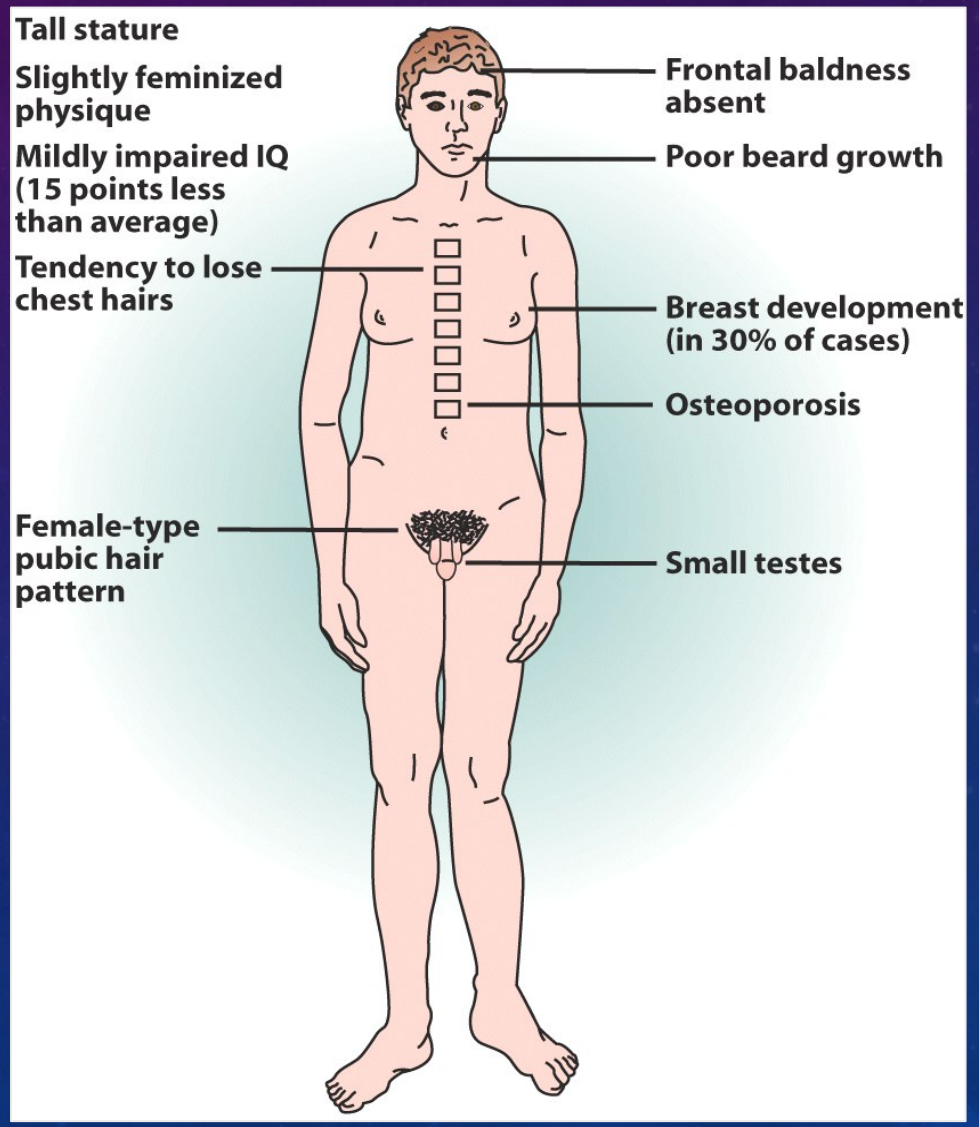
- Specific type of gonadal dysgenesis
  - Presence of ovarian follicles and seminiferous tubules in the gonads
- Distribution in the gonads vary
  - 89% of ovotestes, ovarian and testicular elements are evenly distributed
- Testicular tissue undergoes atresia at a faster rate than ovarian tissue
- Phenotype varies
  - Often testis on right and ovary on left
- Small number of women can become mothers
- Paternity never reported
  - Gonad most likely to function will be the ovary
  - Gonadal cancer risk in 46XX ovo-testicular DSD is low risk
    - May be fertile oocytes
    - Spermatogenesis absent
      - Excise testicular component if it can be identified
      - If not, leave till puberty and remove tissue that is producing the unwanted hormones



KLINEFELTER SYNDROME 47XXY

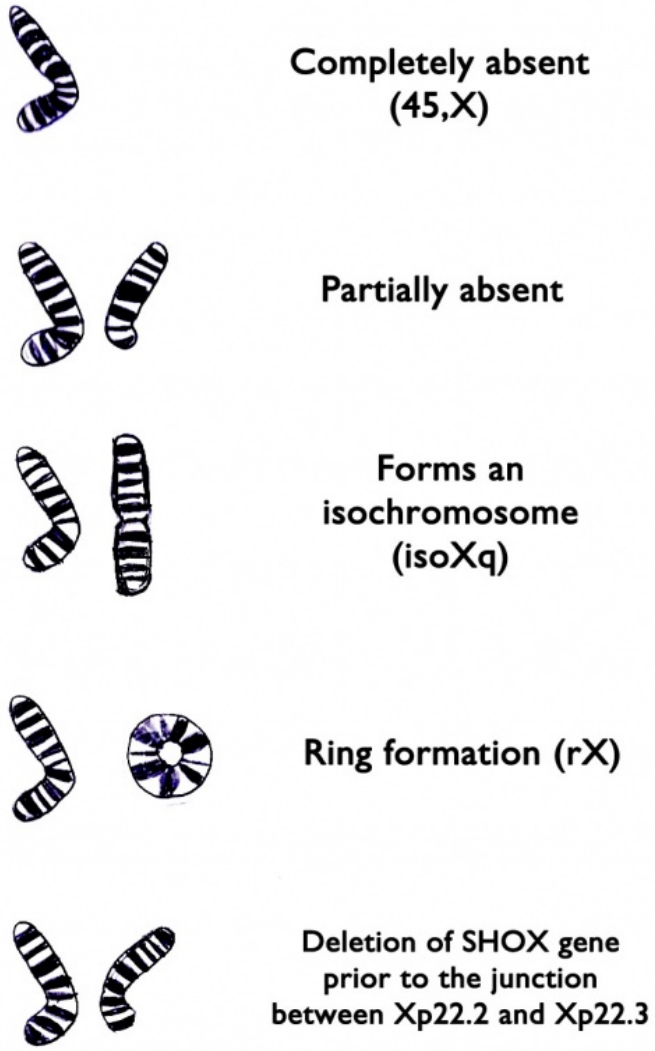
- Affects sexual development
  - Testes don't fully develop
    - Oligospermic
  - Lower levels of testosterone
- Taller than average
- Many men only discover this when they seek help for infertility





TURNER SYNDROME

- Only affects girls
- Affects growth and sexual development
  - Ovaries aren't developed properly
- In TS the second sex chromosome is either:
  - Completely absent (45,X) (Monosomy X)
  - Partially absent
  - Forms an isochromosome (isoXq), possessing a long arm duplication (q) and being devoid of a short arm (p)[
  - In a ring formation (rX)[
  - Is devoid of the homeobox gene, **SHOX** (short stature homeobox)
- Any of these variations of the second sex chromosome may occur with or without cell line **mosaicism**
  - Missing the X in only some of the cells
  - May have fewer symptoms
  - *All except 1% of 45X foetuses are miscarried*



45X/46XY DSD

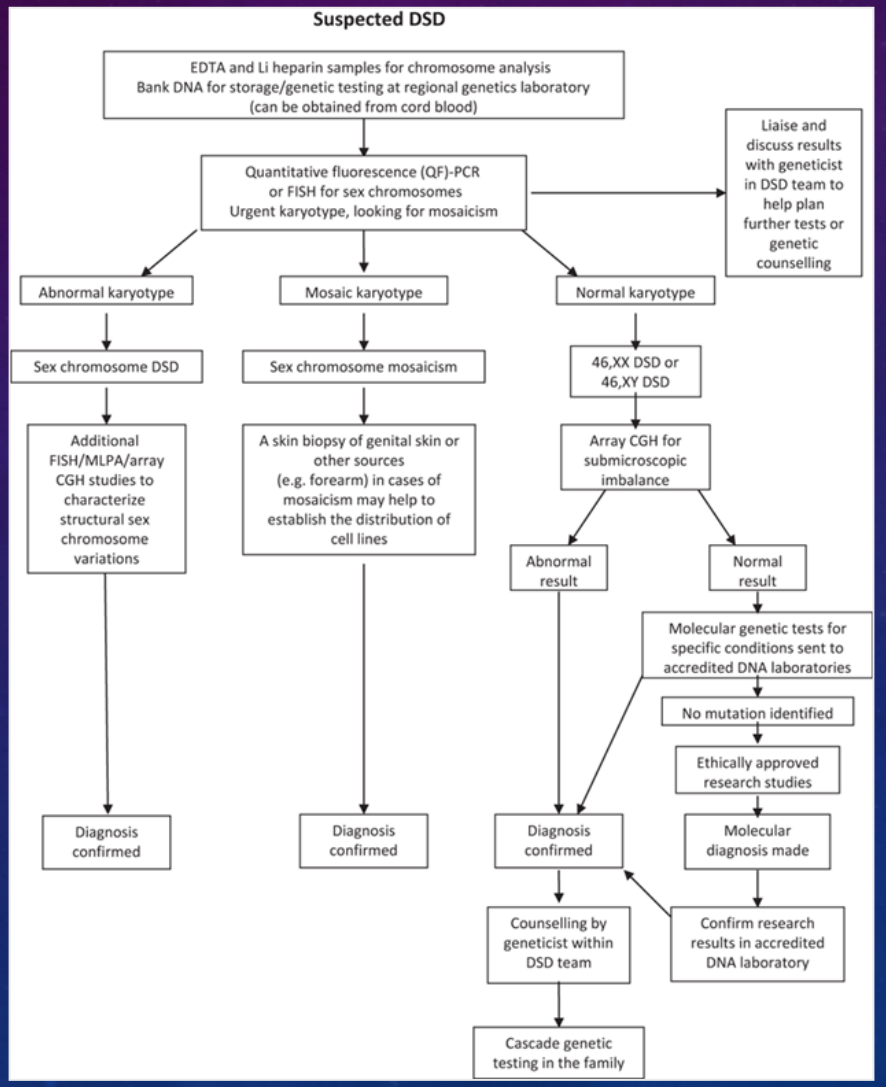
- Right gonad has a reasonable testis which has descended into a hemi-scrotum
- Left side gonad was intra-abdominal streak gonad
- Vaginal cavity present
- Raised a boy, gonads left insitu
- Re-presented in adolescence with a tumour arising from the streak gonad

- Wide range of phenotypes
  - 95% - normal male
    - SS and dysgenetic testes
  - Female phenotype
    - Features of TS (where karyotype has Y chromosome)
- Mixed gonadal dysgenesis
  - Asymmetrical appearance
- 75% have a uterus
- SS in 84%
  - GH therapy
- Abnormalities of urinary tract and CVS may be present
  - Similiar to those of TS

DSD MDT TEAM


Biochemist
Pathologist & Histopathologist
Imaging & Urodynamics
Local Paediatrician
+/- Surgeon / Urologist
+/- Midwives / Nurses
Endocrinologist
Urologist
Psychologist
CNS
Gynaecologist
Reproductive medicine
Clinical & Molecular genetics
General Practitioner & Social Work
Community and Religious Leaders
Ethicist

MAKING THE DIAGNOSIS *(AHMED, 2011)*



To ARRANGE:

- Pelvic and abdominal (renal) USS
- Clinical photography (if parents consent)
- General Bloods: U&E, Cortisol, ACTH, testosterone, inhibin B and AMH, FSH and LH
- USP (if not done or as back up sample); urinalysis for proteinuria (if not done)
- Bloods for DNA storage (if parents consent)
- Consider other investigations as required (e.g. synacthen test, LHRH test, PRA, aldosterone, prolactin/TFTs/IGF1)
- Cancel tests if samples not necessary (e.g. AMH in CAH) or duplicated (e.g. USP being done)

ON ADMISSION "MEET AND GREET" THE PARENTS, EXPLAIN WHAT WILL HAPPEN AND WHO THEY WILL SEE, AND FOCUS ON SUPPORT AS WELL AS THE PLANNED "TESTS" – appreciate how tired and stressed they are, and maintain their privacy; let them have time together to talk and reflect

46,XX

If CAH suspected (common):
PRIOR TO TREATMENT: Cortisol, PRA, Aldosterone, 17-OHP, A4, DHEAS, 11-deoxycortisol, USP
Short synacthen test only after day 3

Ovotesticular DSD (rare):
AMH, inhibin B, testosterone, consider early EUA and laparoscopy

Aromatase deficiency (v rare); also clitoromegaly of prematurity and structural variants

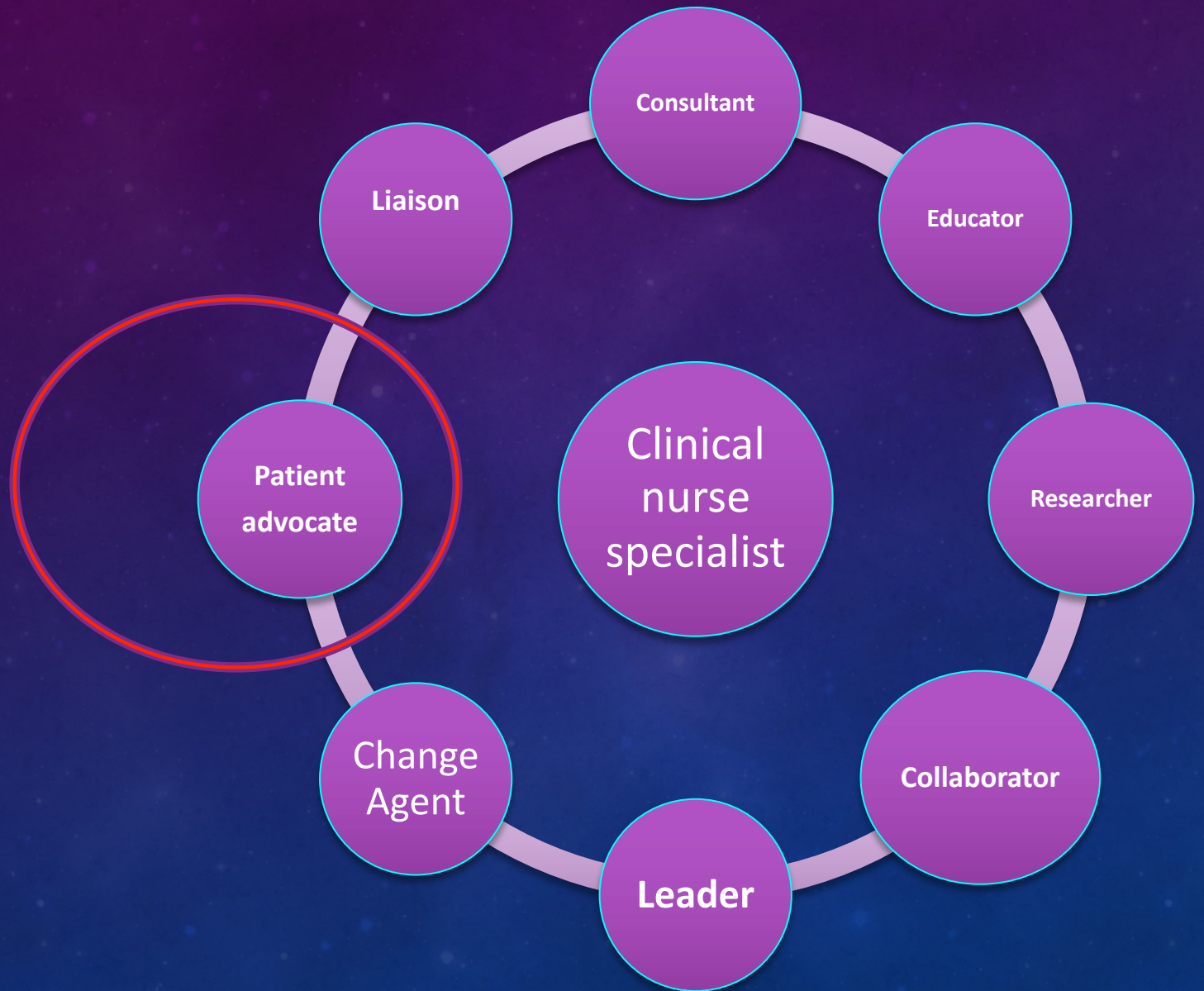
46,XY

Ensure **adrenal function** adequate (**rare**):
ACTH, cortisol, synacthen
Is it **dysgenesis, steroidogenic defect or androgen resistance**?
AMH, inhibin B, testosterone, LH/FSH, USP;
Consider 3 day/3 week hCG stimlation test

45,X/46,XY

AMH, inhibin B, testosterone, LH/FSH;
Consider 3 day/3 week hCG stimlation test or early EAU/laparoscopy;
ECHO, TFTs, renal USS, Turner screening, audiology etc

CLINICAL NURSE SPECIALIST ROLES



CNS ADVOCATE ROLE – AT DIAGNOSIS

- Ensure referring team has parents admission leaflet
- Liaising with the MDT
  - From the referring team and also the team being referred to
  - Is the baby well / hospitalised
  - Are they requiring transport / nurse escort / will that nurse stay with patient
- Liaising with the ward
  - Ensure GnRH, Synacthen and HCG in stock on ward if need be
- Liaising with the parents!
- Prepare information packs for parents
  - DSD families leaflet
  - Cortisol deficiency booklets
  - CAH information
  - CNS contact details

- How is the baby feeding
  - Breast pump, bottles, quiet area available
  - Bottle feeding – enough milk
- Ensure parents bring
  - Phone chargers, nappies, wipes, books etc, lists of questions
  - Maternity notes, child health care notes, referral letters
  - Money for parking
- Can they speak English
  - Arrange interpreter, prepare translated information

CNS ADVOCATE ROLE - ONGOING

- Key liaison and support for family
- Involvement in support groups / support group days
- Be knowledgeable in specific condition and long term implications
  - Prepared for discussions on puberty and adolescence and beyond
- Liaise with adult DSD / gynaecology teams
- Patient and family empowerment

CONCLUSION..

- Brief overview of DSD conditions
  - Many more complex variants
  - Diagnosis
  - Management
  - Treatment
  - Links with adrenal and gynaecology
  -

Sleeping Hermaphroditus