An introduction to Differences in Sex Development (DSD)

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Disclosures

Honoraria
- Pfizer
- Sandoz
- Ipsen

Educational / Travel grants
- Society of Endocrinology

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Photographs

- Please note the photographs in this presentation are of a sensitive nature
- They are not patient identifiable

Hutson, J. M., G. L. Warne and S. R. Grover, Eds. (2012).
Disorders of Sex Development: An Integrated Approach to Management.
New York, Springer

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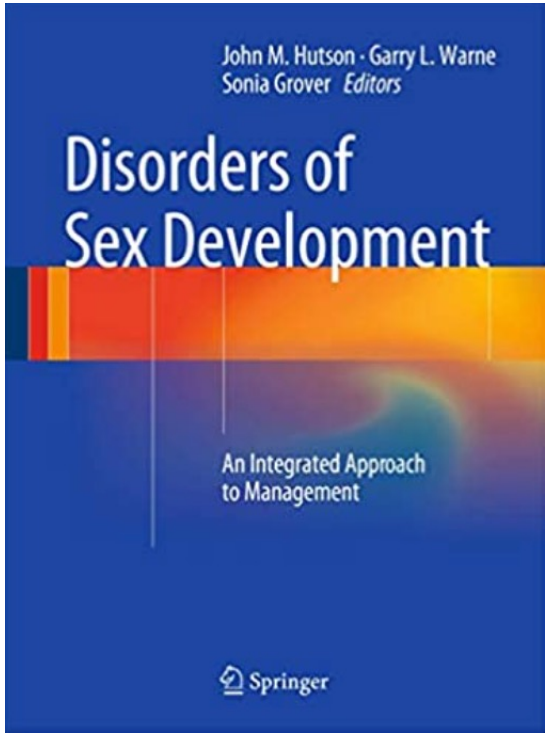

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Introduction

- Sex determination
- DSD classification
- Types of DSD
- The CNS role
- Patient support
- UK data
- International focus

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Normal sex development

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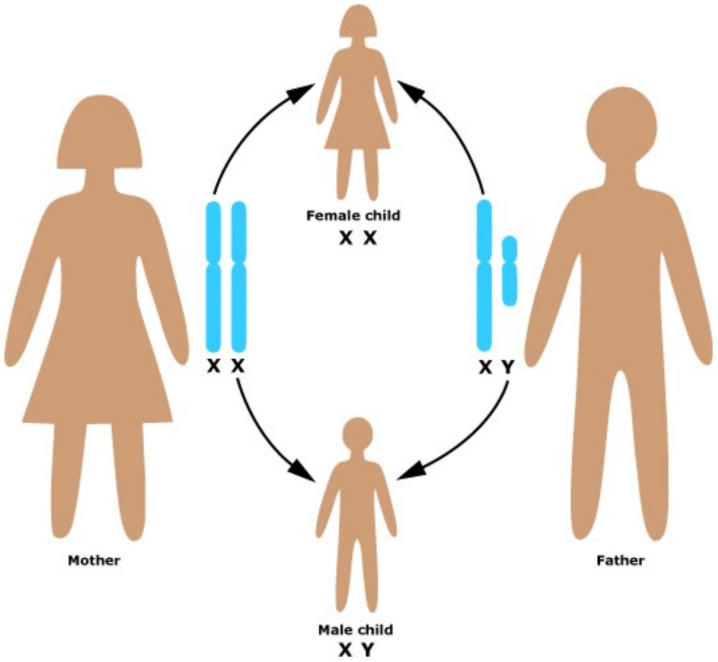
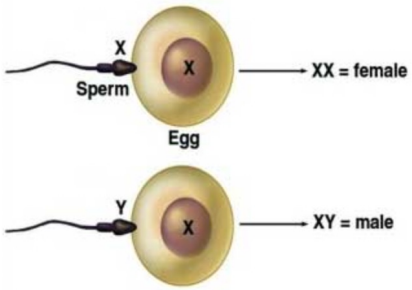
Determination of Sex



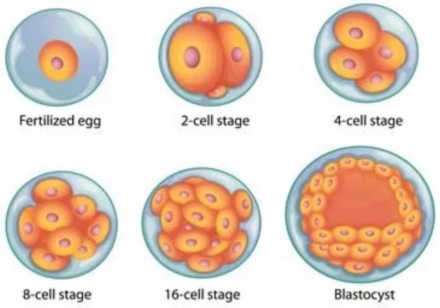
www.uptodate.com
Graphic 76396



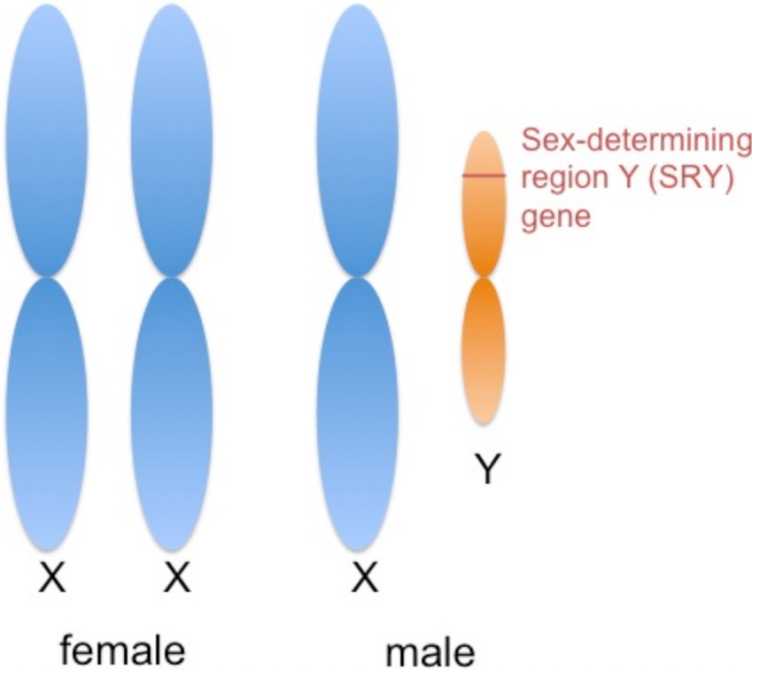
www.whhealth.weebly.com

- XX – Female
- XY – Male
- Sex chromosome division
  - Blastocyst

(Hiort, 2017)



Determination of Sex – 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

Sekido & Lovell-Badge, 2008

Wisniewski et al, 2012

?

https://amasianv.files.wordpress.com/2012/08/xx-male1.jpeg

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SRY gene location

North East Thames Regional Genetics Service

FISH

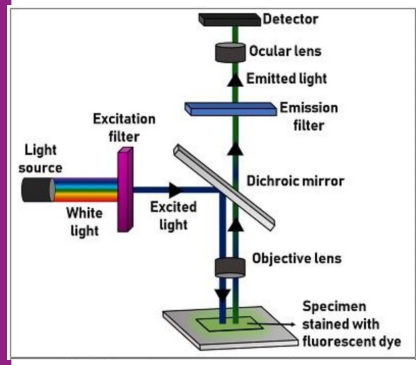
Fluorescence **i**n **s**itu **h**ybridization

Cytogenetic technique

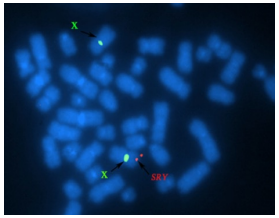
Can detect genetic abnormalities

Sample viewed under Fluorescence Microscopy

Bishop, 2010



www.biologyreader.com



Full Karyotype

- Blood cultures are grown and harvested to yield metaphase cells which are analysed using light microscopy.

? Possible sex chromosome abnormality

- A targeted 30 cell score for the sex chromosomes is performed
  - Not a full karyotype

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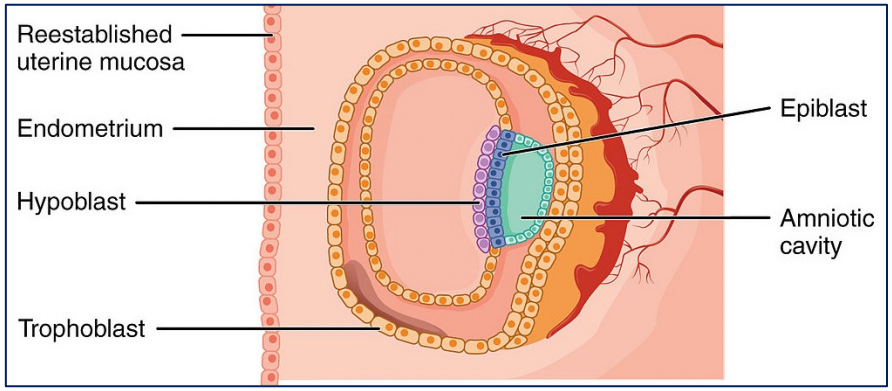
Embryology – first 2 weeks

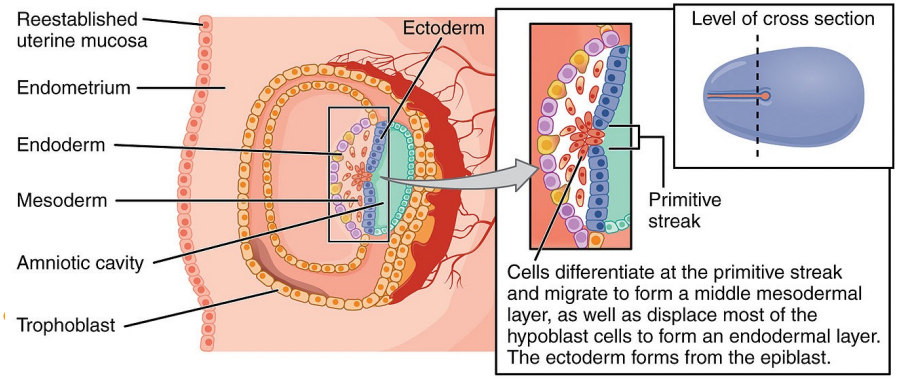
- Blastocyst
  - Implantation



Trophoblast

Dividing into layers

- Gastrulation
  - Day 14



- Ectoderm
- Mesoderm
- Endoderm

Webster & DeWreede, 2016

www.teachmeanatomy.info

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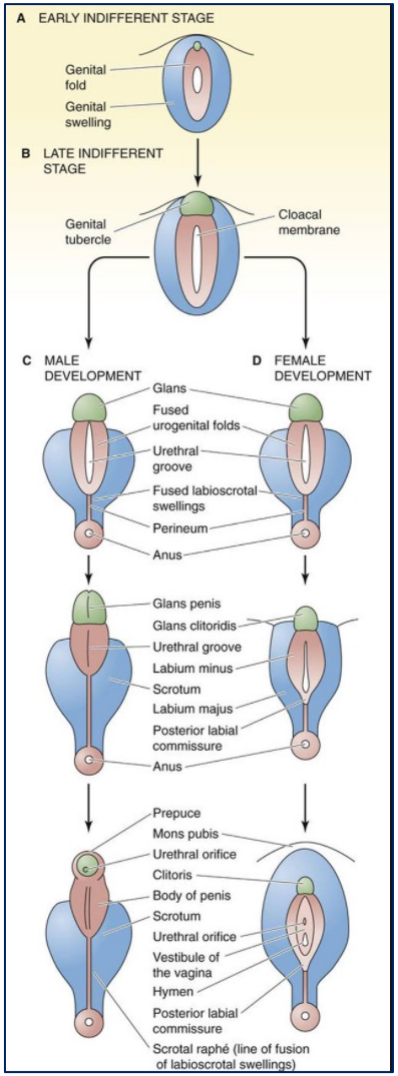
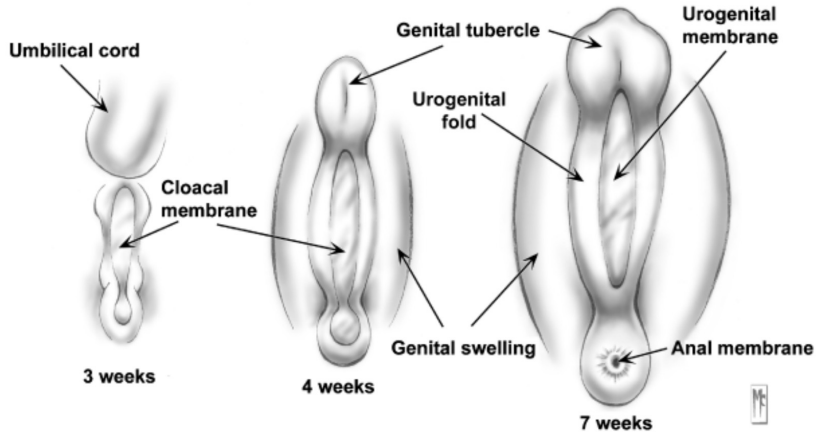
Embryology – 3 – 6 weeks



- Development of the external genitalia
- Cloacal membrane



Yamada, 2003

www.doctorlib.info

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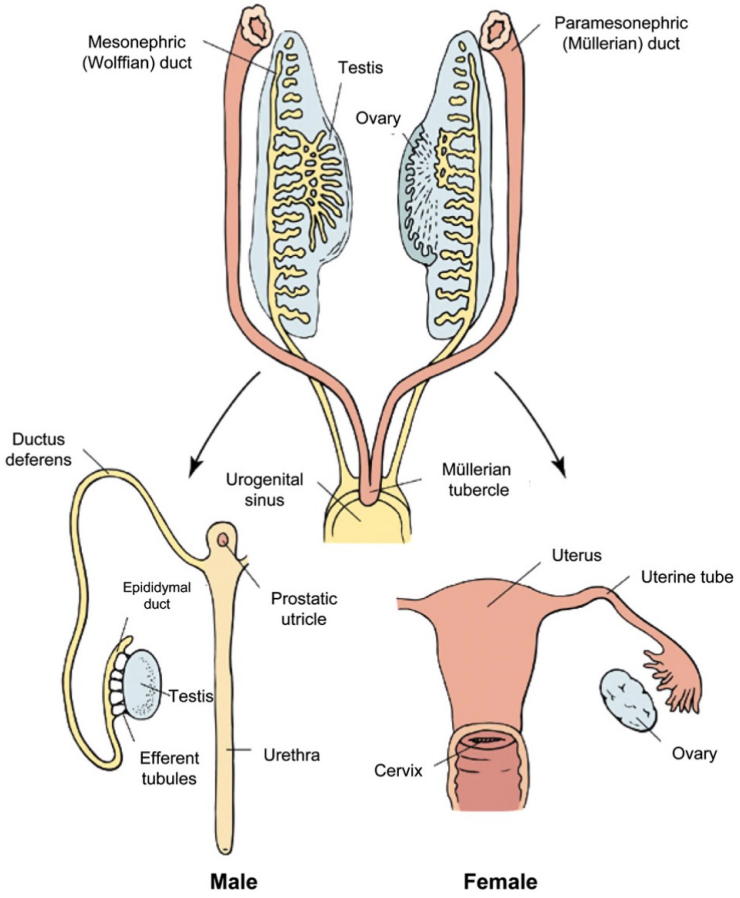
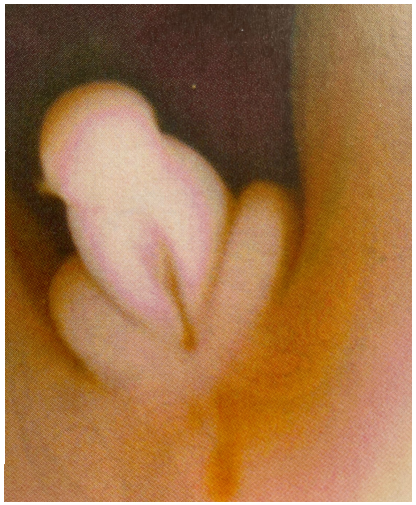
Embryology – 6 – 7 weeks



Mullerian duct
FEMALE
- Paramesonephric duct

Mesonephric duct
MALE
- Wolffian duct



Biason-Lauber, 2009
Hutson, 2012

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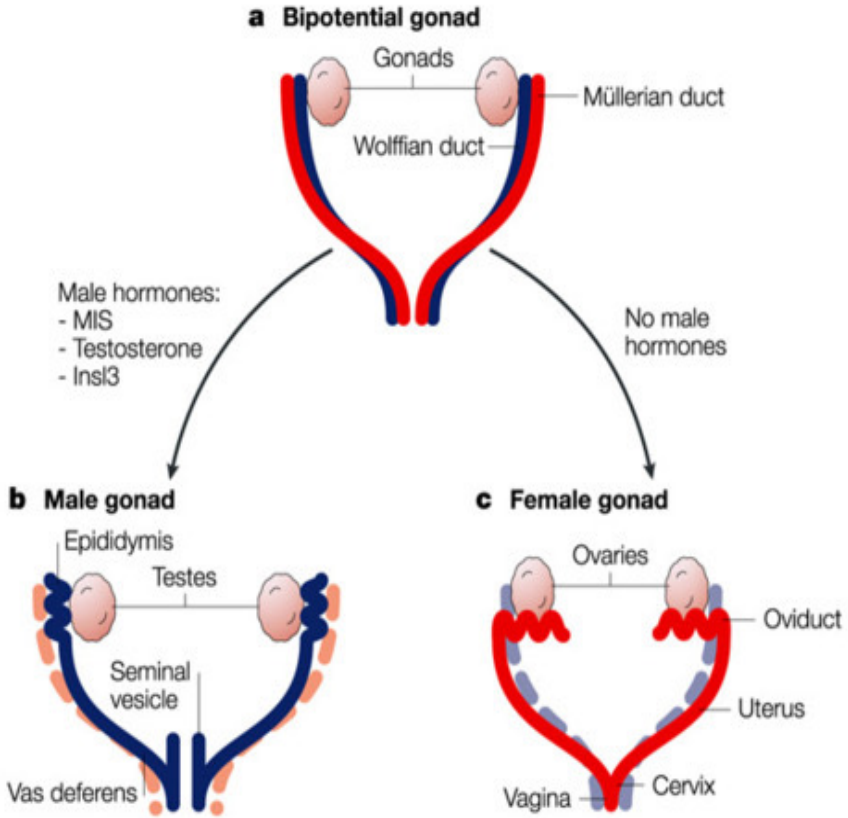
Genitalia development – 7-8 weeks



- 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

Davies, 2019

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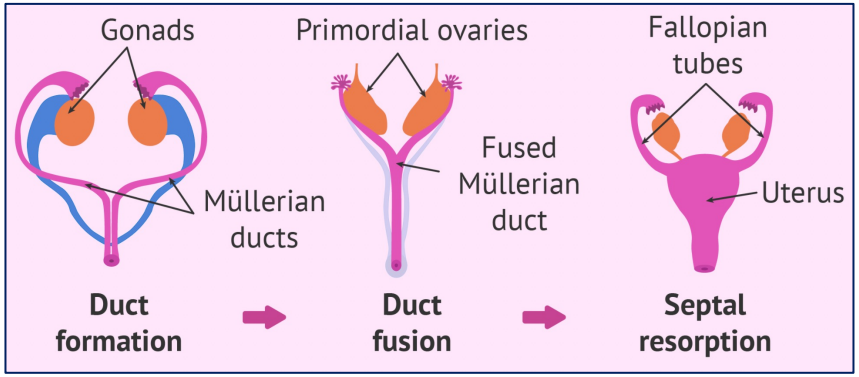
Sexual differentiation

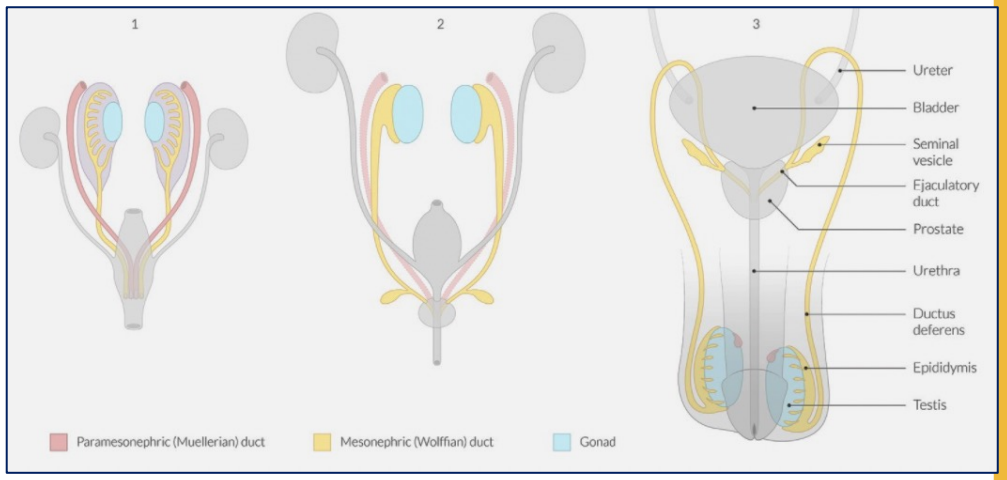
- Mullerian Ducts
  - Initially present in both sexes
  - Regress under the influence of AMH

- Wolffian Ducts
  - Regress in the female

www. https://www.invitra.com/en/uterine-malformations/uterus/-

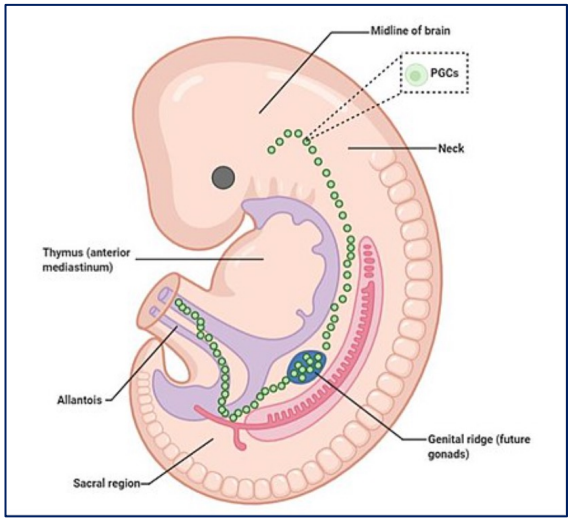


www. https://www.amboss.com/us/knowledge/Development_of_the_reproductive_system



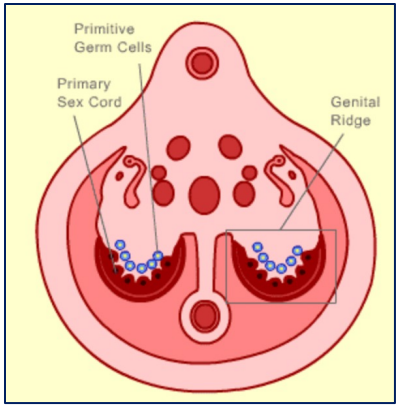
Gonadal development

- Gonads
  - Intermediate mesoderm
  - Mesodermal epithelium
  - Germ cells



https://en.wikipedia.org/wiki/Primordial_germ_cell_migration

- Primordial germ cells (PGC)
  - Precursors for gametes
  - Migrate from the embryo's yolk sac to the genital ridge



- Here, they are incorporated into the primary sex cords

- Fingerlike projections that have formed over the previous week

https://*www.jaypeedigital.com/eReader/chapter/9789386261205/ch1#*

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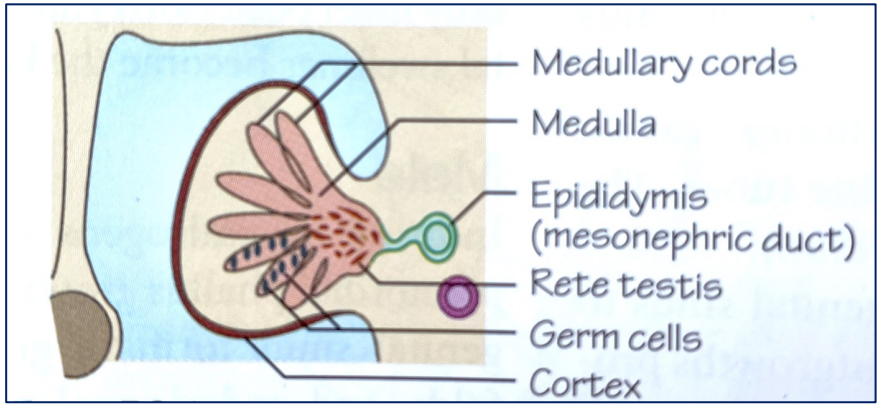
The Testis

Testis development
- SRY gene

After arrival of PGC
- Sex determination occurs

(Cool & Capel, 2009)

SRY
- Interacts with DNA



Webster & DeWreede, 2016

- Leydig cell development
- Rete Testis
- Seminiferous tubules

Webster & De Wreede, 2016

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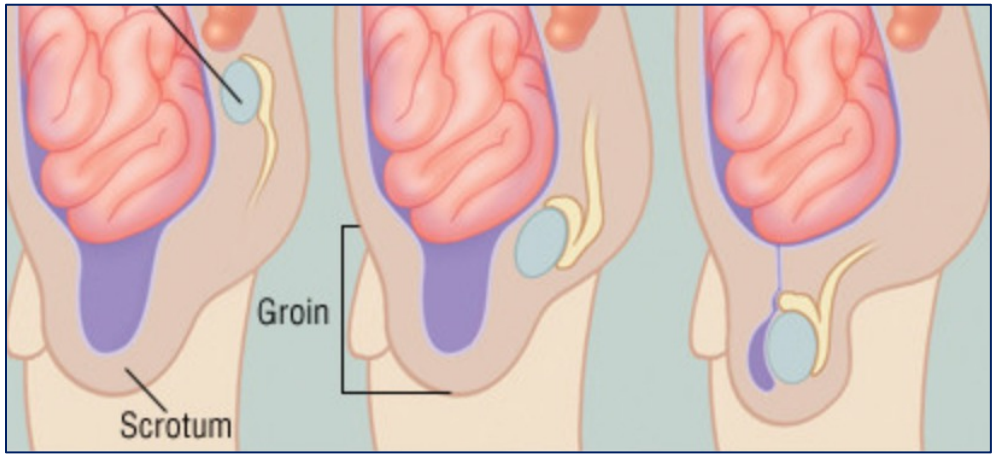
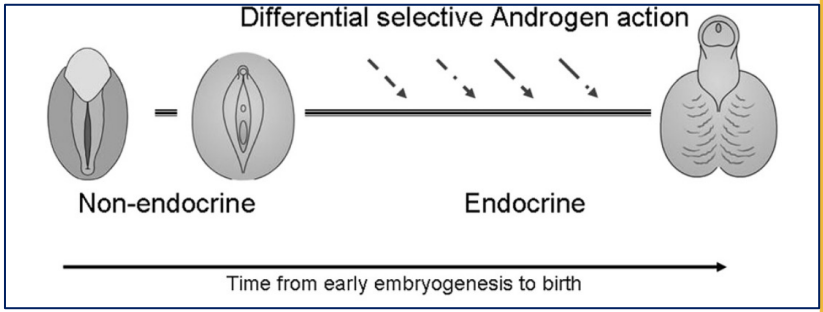
The Testis



- Androgens
- AMH
  - Androgen insensitivity syndrome

Makela et al, 2019



https://www.health.harvard.edu/a_to_z/undescended-testicle-a-to-z

Hiort, 2013

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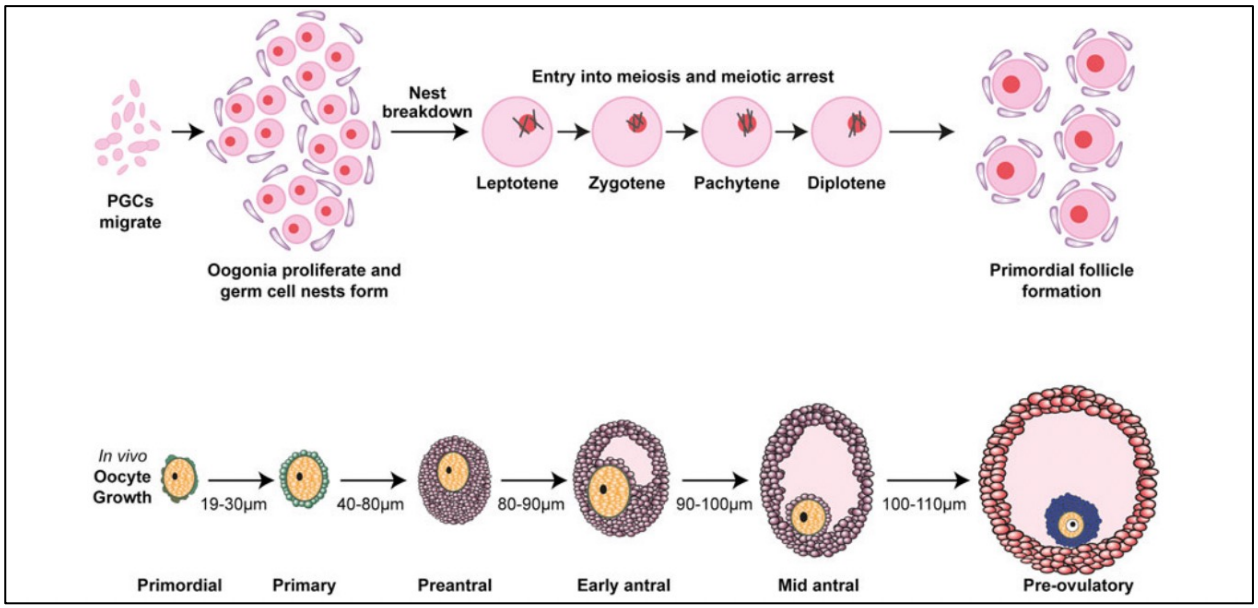
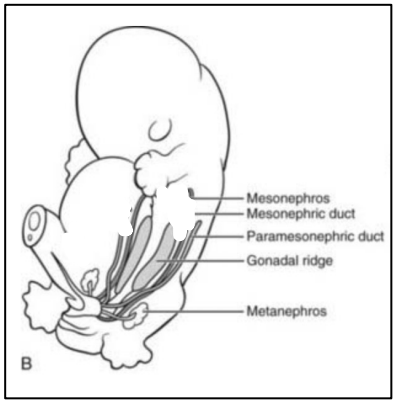
The Ovary

- Genetic influence
  - WTN4
    (Vainio et al, 1999)
- Week 6 of gonadal development

- Oocyte maturation

Telfer & Anderson 2019





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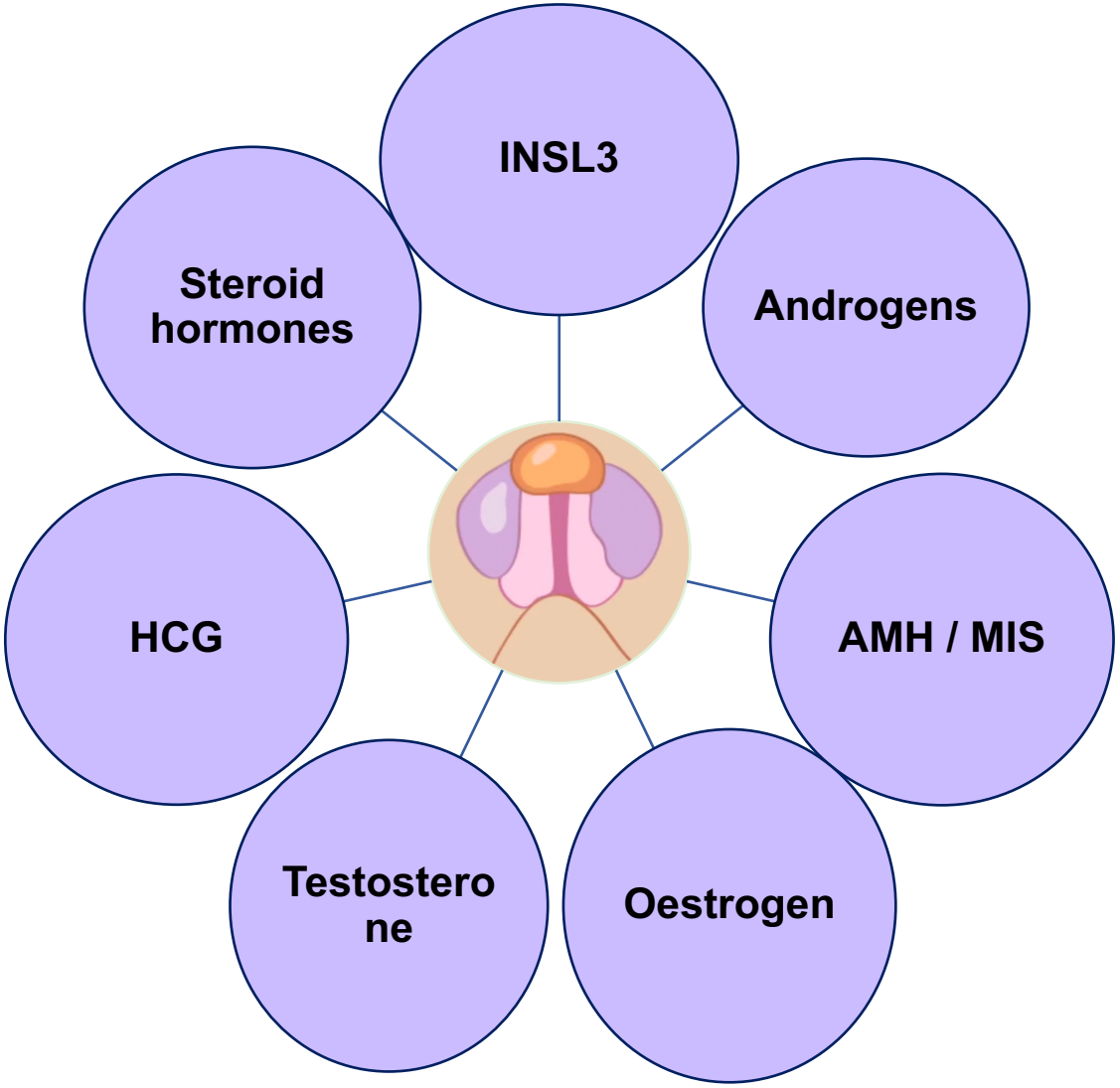
Hormones



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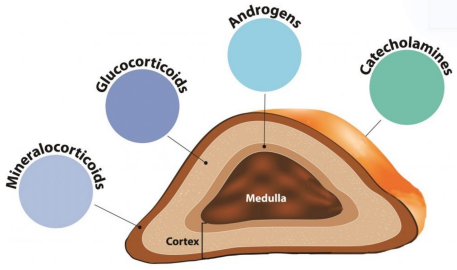
Hormones overview

DHT

Dihydrotestosterone

Androgens



Zhu & McGinley, 2009

https://www.hormones-australia.org.au/the-endocrine-system/adrenal_gland/

Testosterone

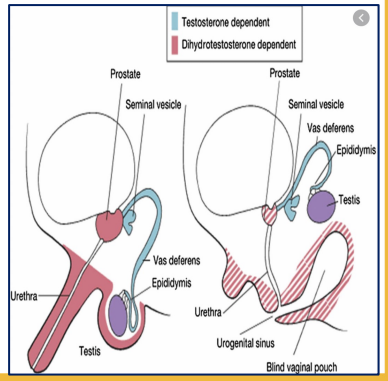
Steroid formed from cholesterol in the Leydig cells

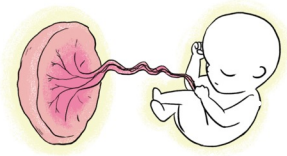
AMH

- Anti-Mullerian Hormone
- Produced by Sertoli cells
- Secreted into Wolffian ducts
- Secreted into Mullerian ducts
  - Trigger regression in the male

INSL3

- INSulin Like Hormone
- Produced by Sertoli cells
- Stimulates growth of genito-inguinal ligament

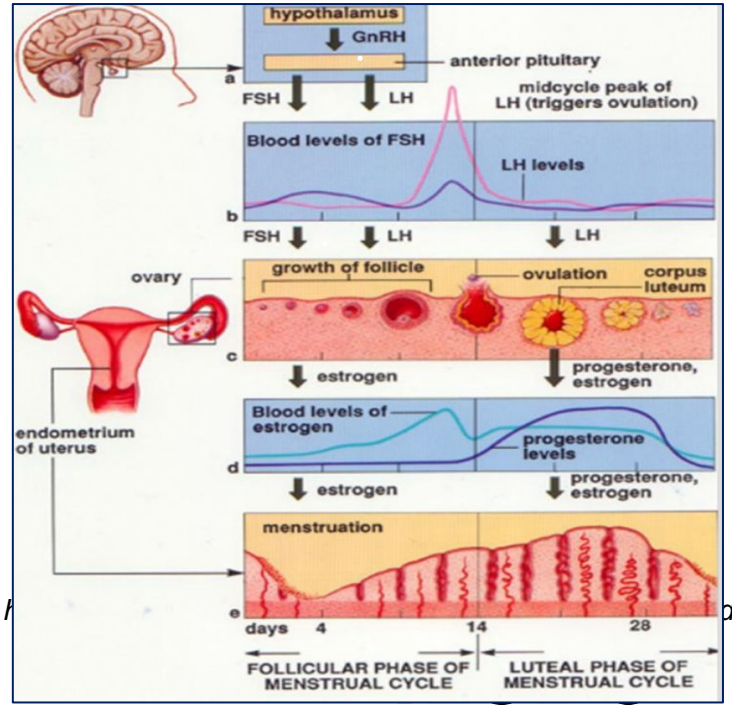




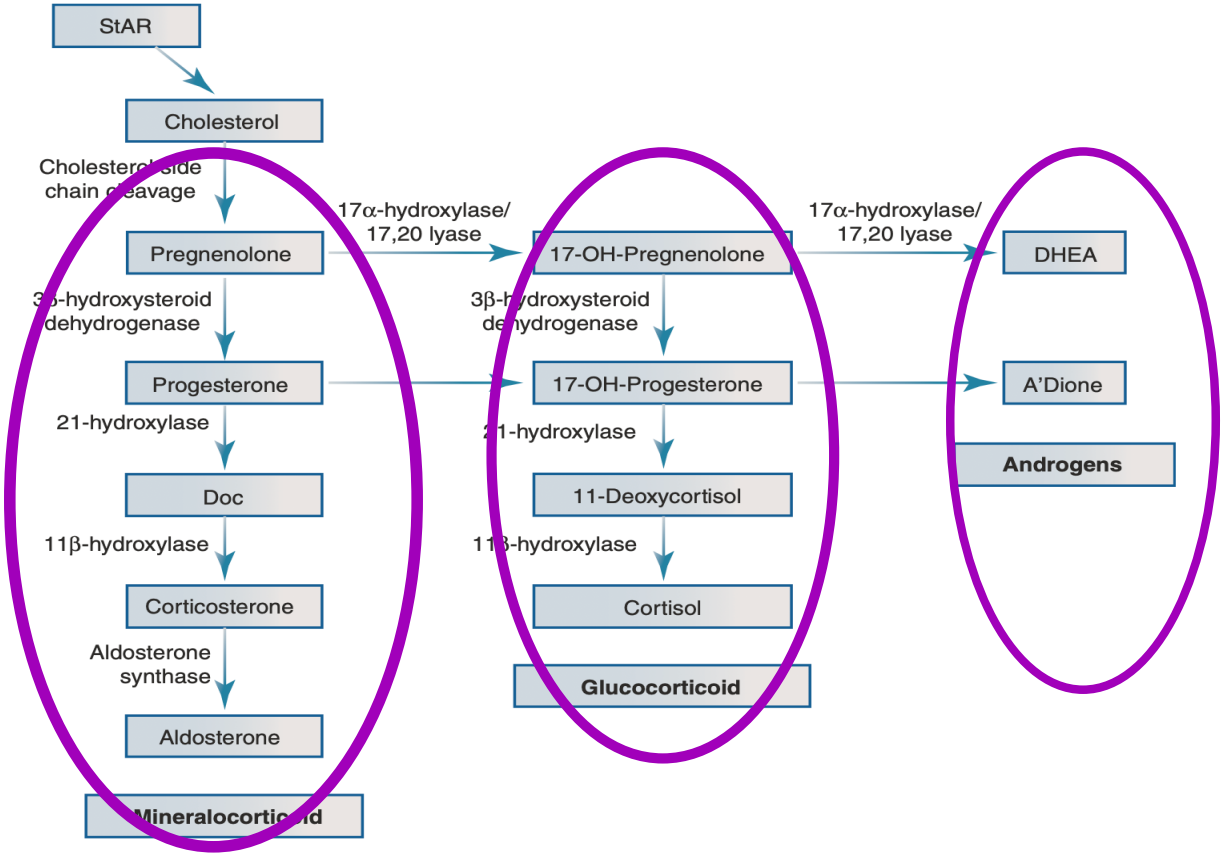
Hormones overview

- **HCG**
  - Human Chorionic Gonadotrophin
- 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
    - Babies with congenital hypopituitarism and anencephaly have micropenis, hypoplastic scrotum and cryptorchidism

- **Oestrogen**
  - Ovaries
  - Placenta



Adrenal steroid pathway



Yeoh, 2019; Turcu & Auchus, Endocrinol Metab Clin North Am, 2015

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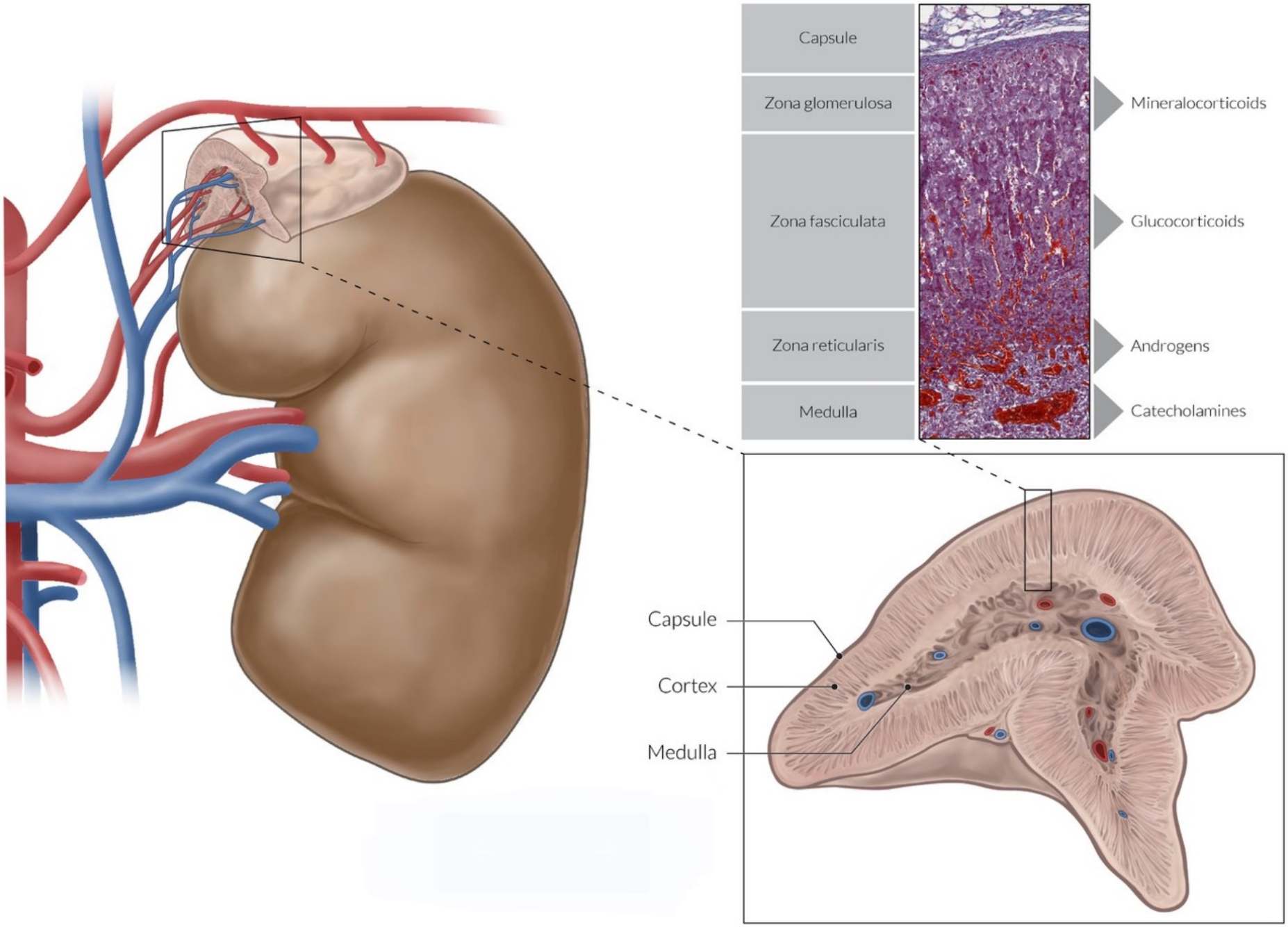
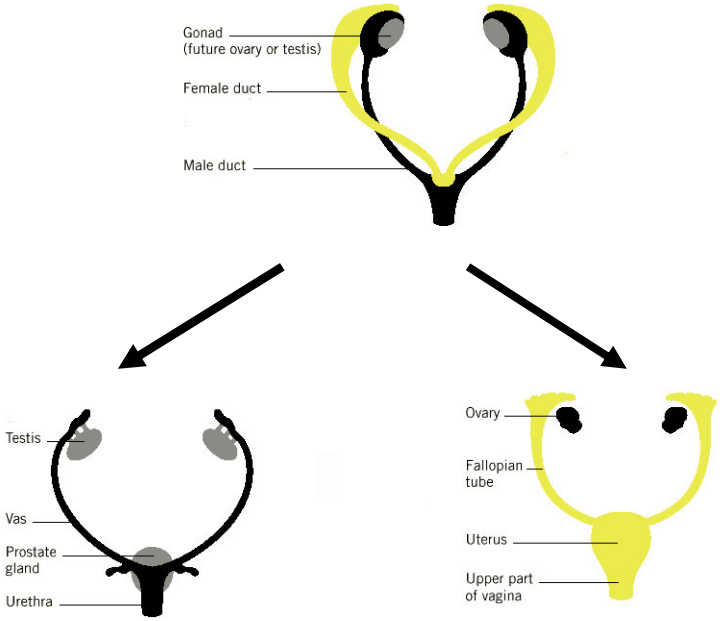

Capsule
Zona glomerulosa
Zona fasciculata
Zona reticularis
Medulla
Mineralocorticoids
Glucocorticoids
Androgens
Catecholamines
Capsule
Cortex
Medulla

Formation of internal structures

https://iheartguts.com/



Foetal ovaries

Make small amounts of testosterone and AMH

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

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Differences in sex development

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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

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

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Classification of DSD

- **46,XY DSD (under virilised genetic male)**
  - Disorders of testicular development
    - Ovotesticular DSD
  - Disorders of androgen synthesis / action
    - Complete Androgen Insensitivity Syndrome
  - Others
    - Hypospadias
- **46,XX DSD (over virilised genetic female)**
  - Disorders of ovarian development
    - Ovotesticular DSD
  - Androgen excess
    - Congenital Adrenal Hyperplasia
- **Sex chromosome DSD (variable)**
  - Turner syndrome
  - Klinefelter syndrome
  - Mixed gonadal dysgenesis

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XX and XY chromosomes

- XX – genotypic female

- XY – genotypic male

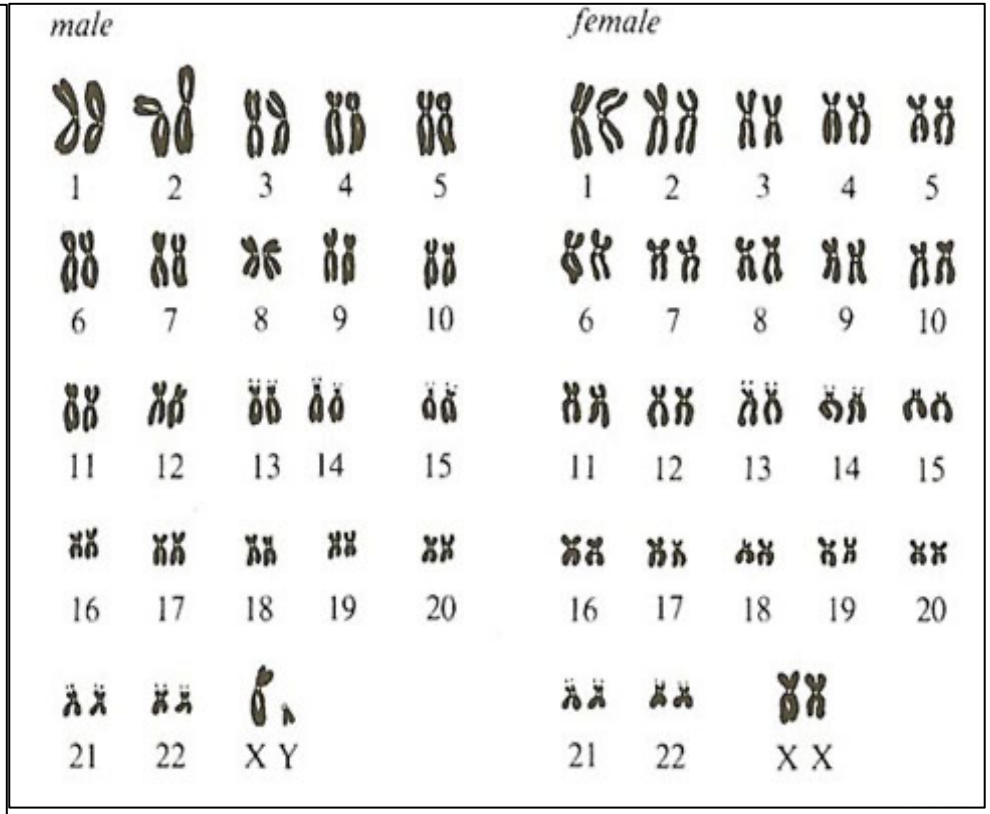
- Half of sperm cells carry the X chromosome, and half carry the Y chromosome

- The SRY gene present on the Y chromosome will act as a signal for the pathway for maleness
  - Starts off virilization

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



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Clinical Examination

- - Thorough general physical examination
  - - Any dysmorphic features
    - - Syndromes associated with DSD
    - - Signs of systemic illness
      - - Metabolic problems

- Genital examination
  - Urethral opening position
  - Palpable gonads outside inguinal canal / Labio-scrotal folds
    - Usually be testes
  - Anogenital distance
  - Degree of rugosity
  - Pigmentation of labio / scrotal tissue
    - Virilisation

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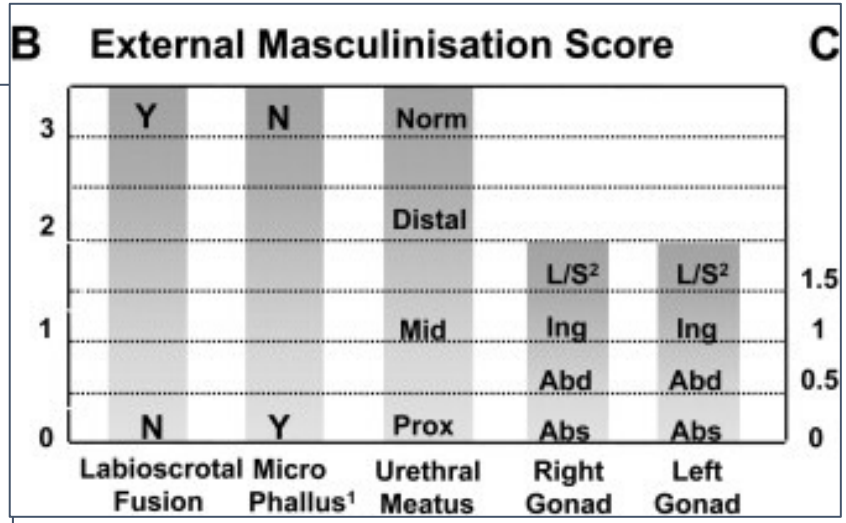
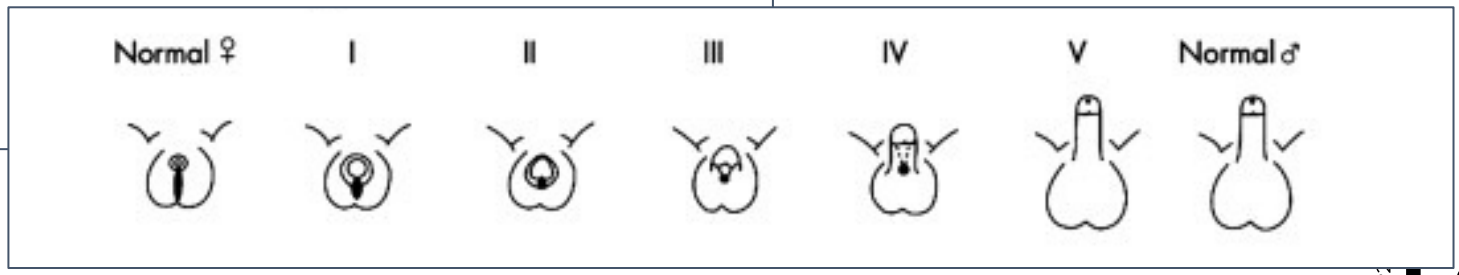
Clinical Rating Scales

External Masculinisation Scale

Score of < 7 is considered ambiguous

Virilisation of XX individudals (Prader)





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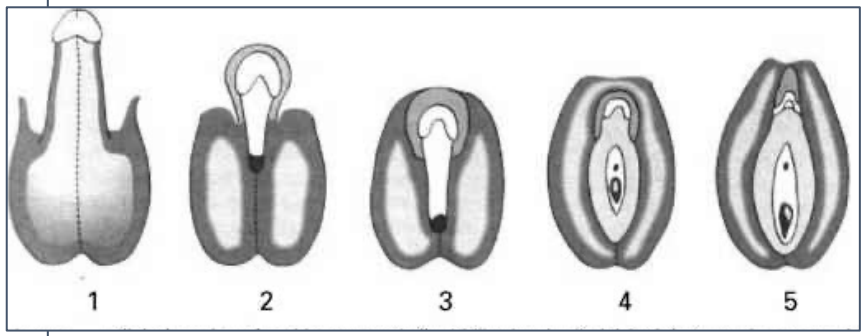
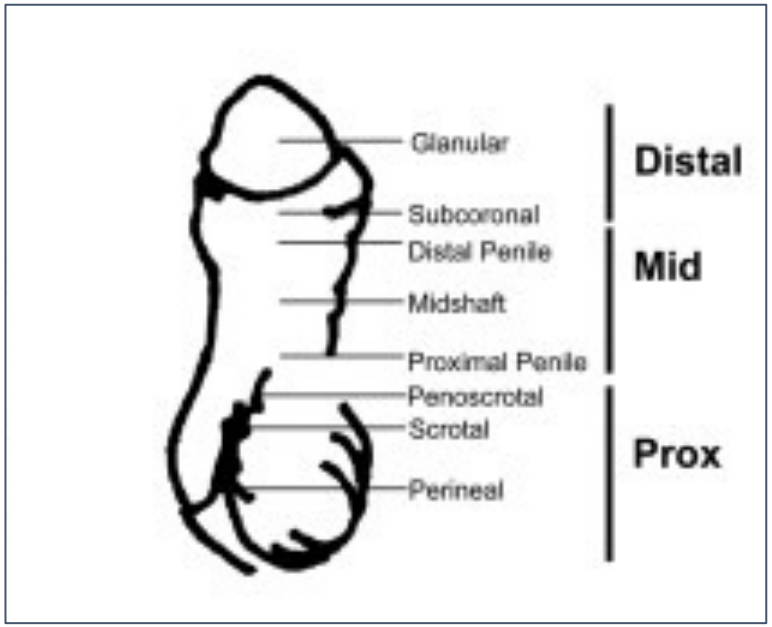
Clinical Rating Scales

- Androgen Insensitivity (Quigley)



- Hypospadias classification



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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

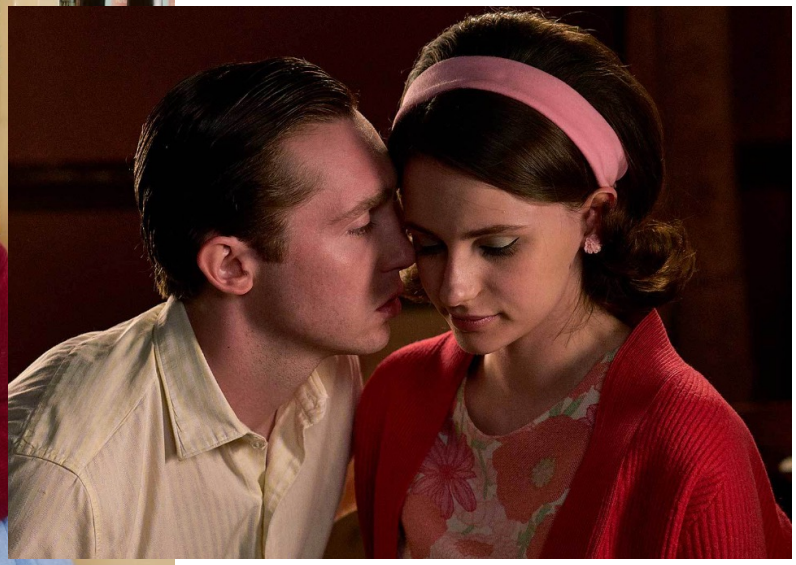
46XY- Androgen Insensitivity Syndrome

- *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 (PAIS)
  - 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

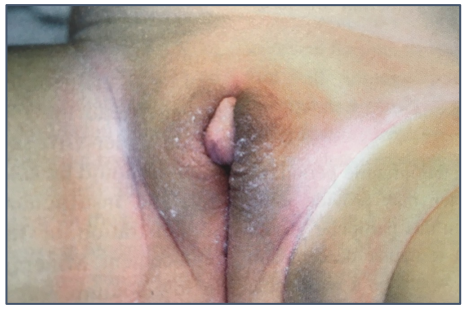
- Gonadal germ cell cancer risk
  - Increased in testes with impaired development and presence of Y chromosome material
    - PAIS and raised as male – strict cancer surveillance
    - CAIS and raised as female – prophylactic gonadectomy - ? Childhood / Puberty



Supermodel comes out as intersex: 'My body isn't really male or female,' Hanne Gaby Odiele reveals

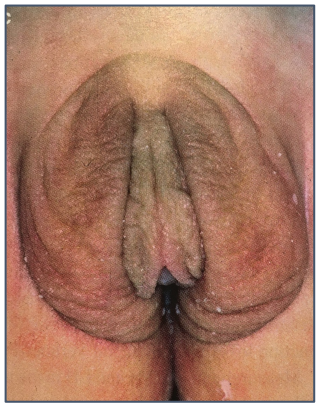
Supermodel wants to break the 'taboo' surrounding the syndrome of being born with sex characteristics that aren't entirely male or female

https://www.teenvogue.com/story/hanna-gaby-odiele-explains-how-she-found-out-she-is-intersex



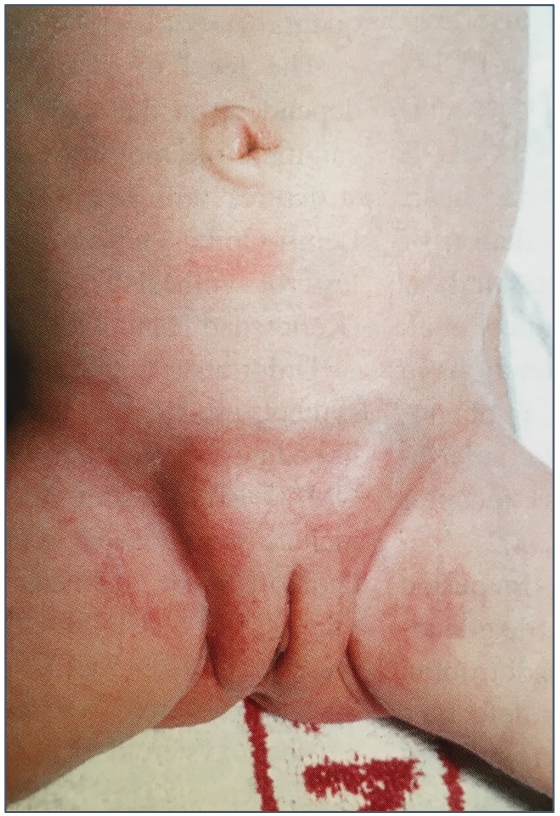
CAIS / PAIS

- 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

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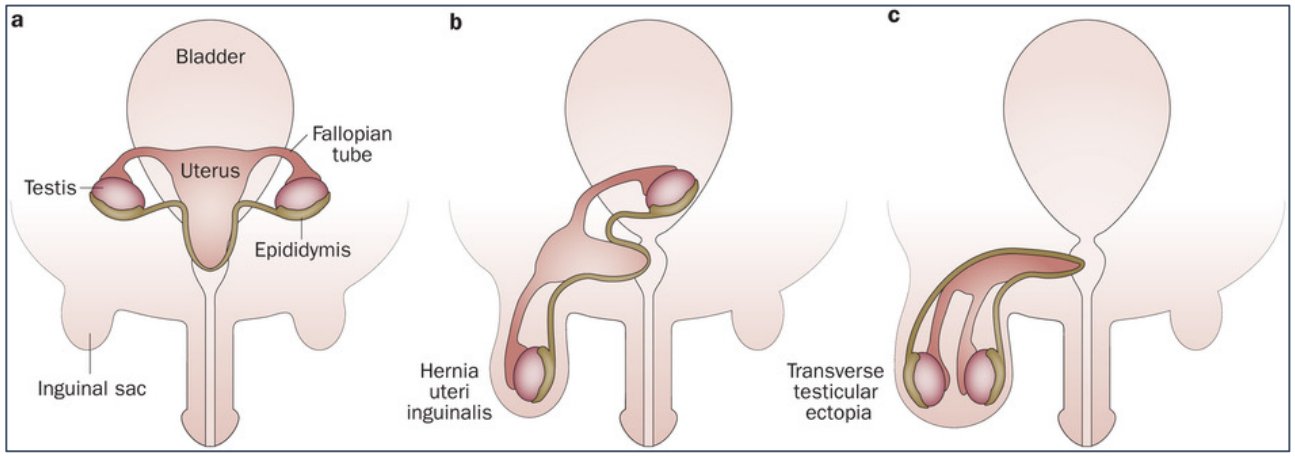
46XY - Persistent Mullerian Duct Syndrome

- 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

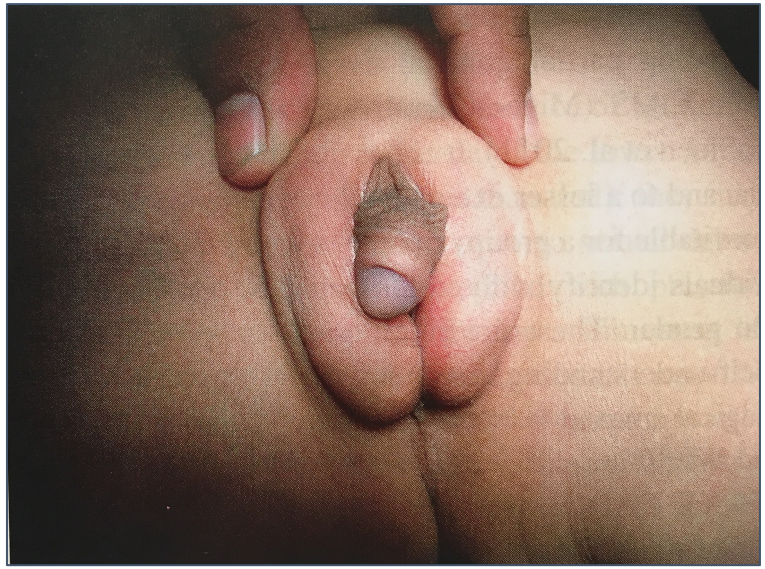


46XY Gonadal Dysgenesis

- 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

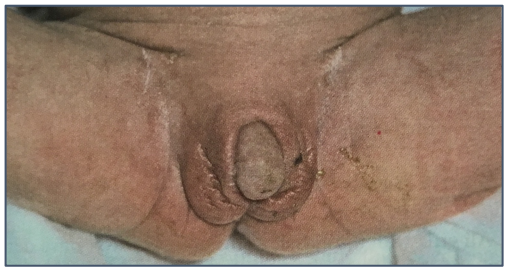
  leading to bifid scrotum and severe chordee of phallus



46XX Presentation

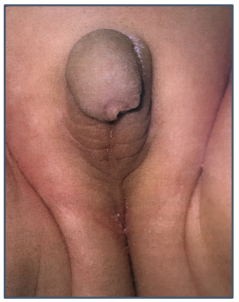
- Ambiguous genitalia
  - More than half of all infants born with AG are 46XX
    - Due to in utero exposure of androgens
    - Source may be adrenal (CAH) or testicular
- Complex congenital malformations
  - Cloacal extrophy, or bladder extrophy
- Gradual clitoris enlargements during childhood
  - Non 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)

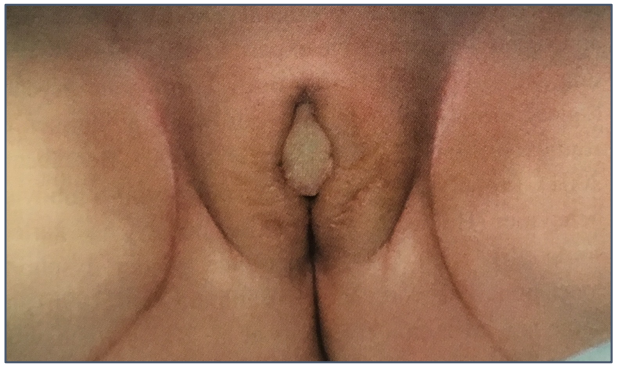
46XX CAH



- 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

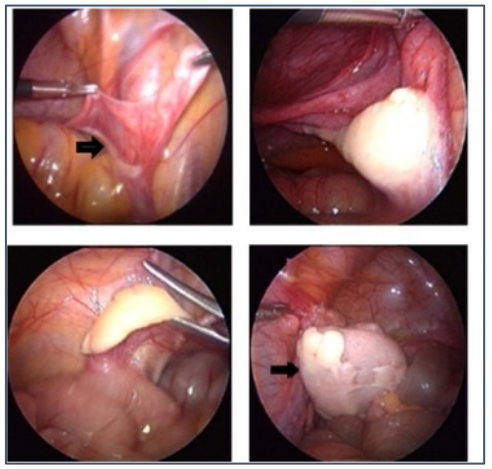
- Exposure to prenatal androgens and Prader 3 virilisation at birth
- Same baby at age 8 weeks at the time of genital reconstruction, showing some regression of virilisation after starting steroid treatment
- Another baby girl with a more severe form of 21OHD, leading to more severe virilisation (Prader 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

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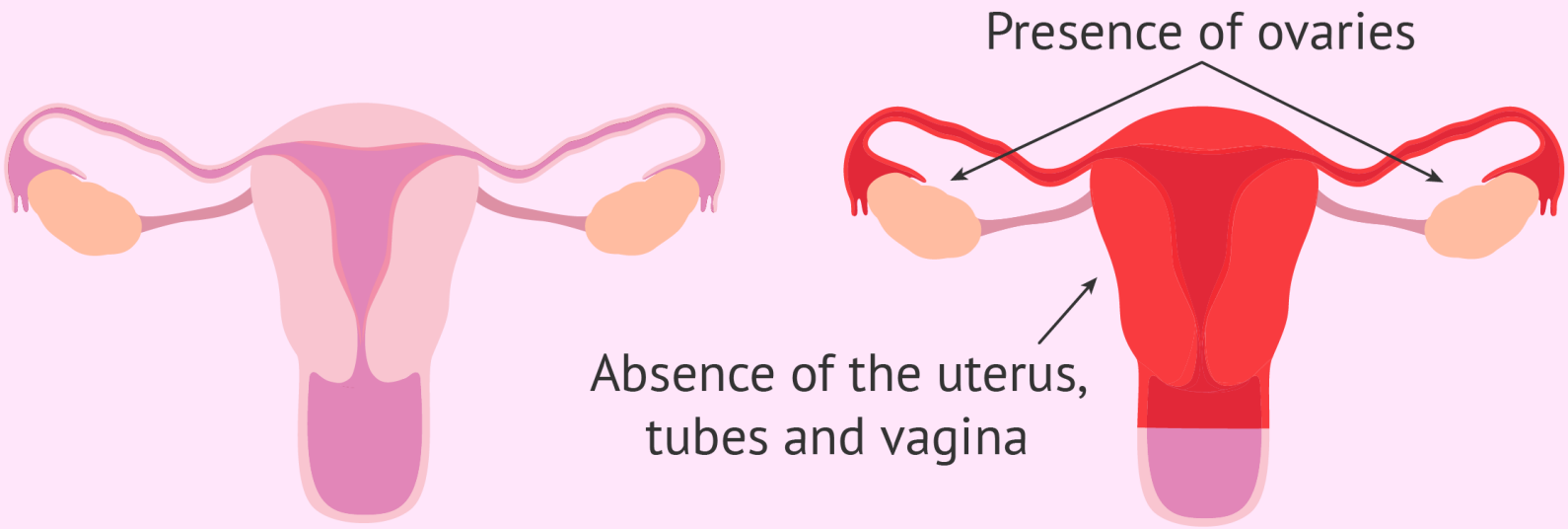
46XX Mullerian Duct Agenesis

Vaginal agenesis usually associated with an absent uterus and fallopian tubes but with normal ovarian development

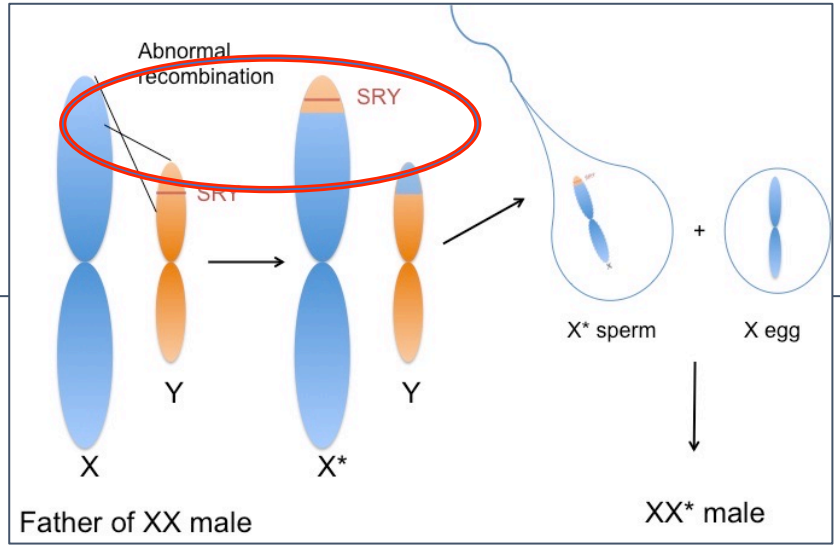
Mayer–Rokitansky–Küster–Hauser syndrome



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



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Sex Chromosome DSD

46XX Ovo-testicular DSD

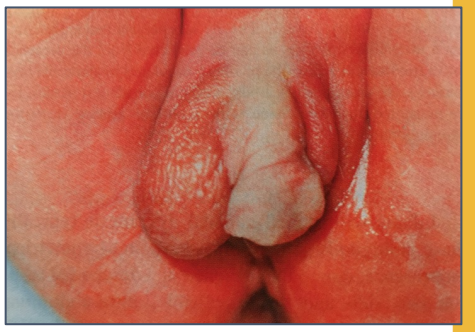
Klinefelter Syndrome

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



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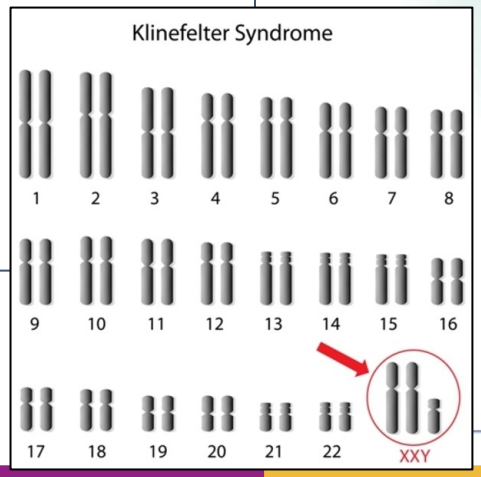
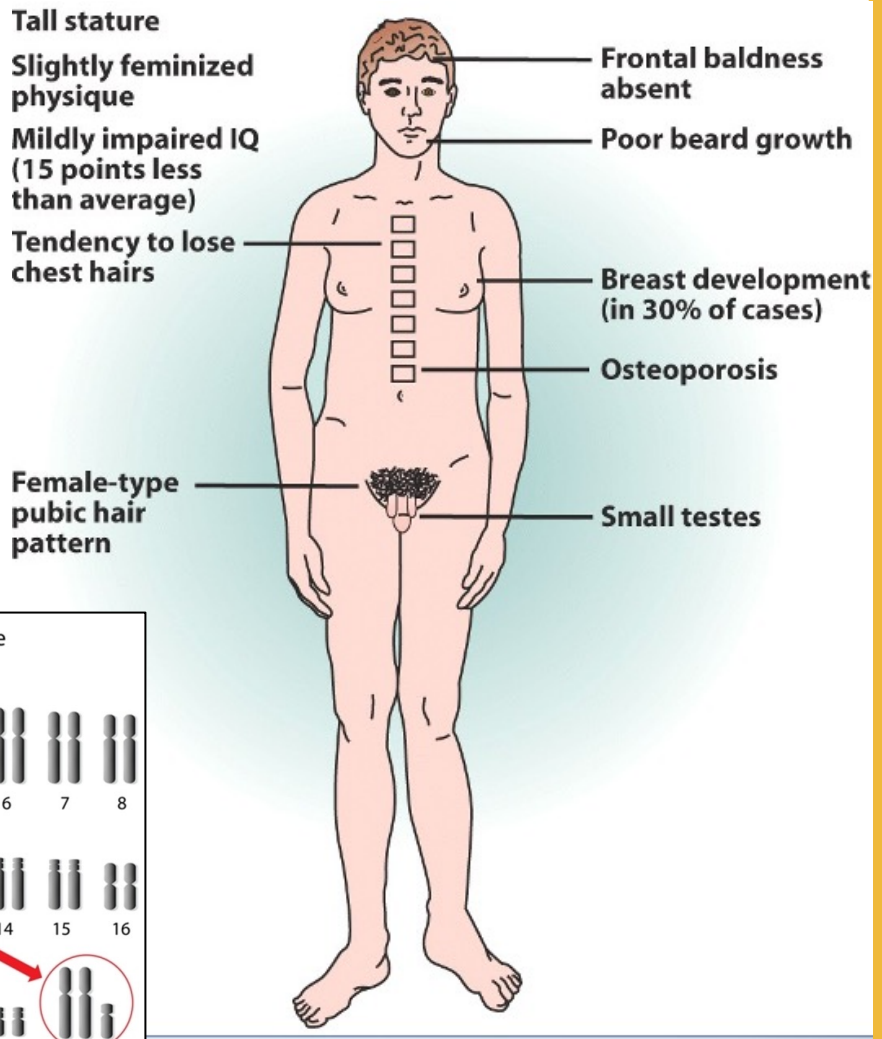
Klinefelter syndrome 47XXY

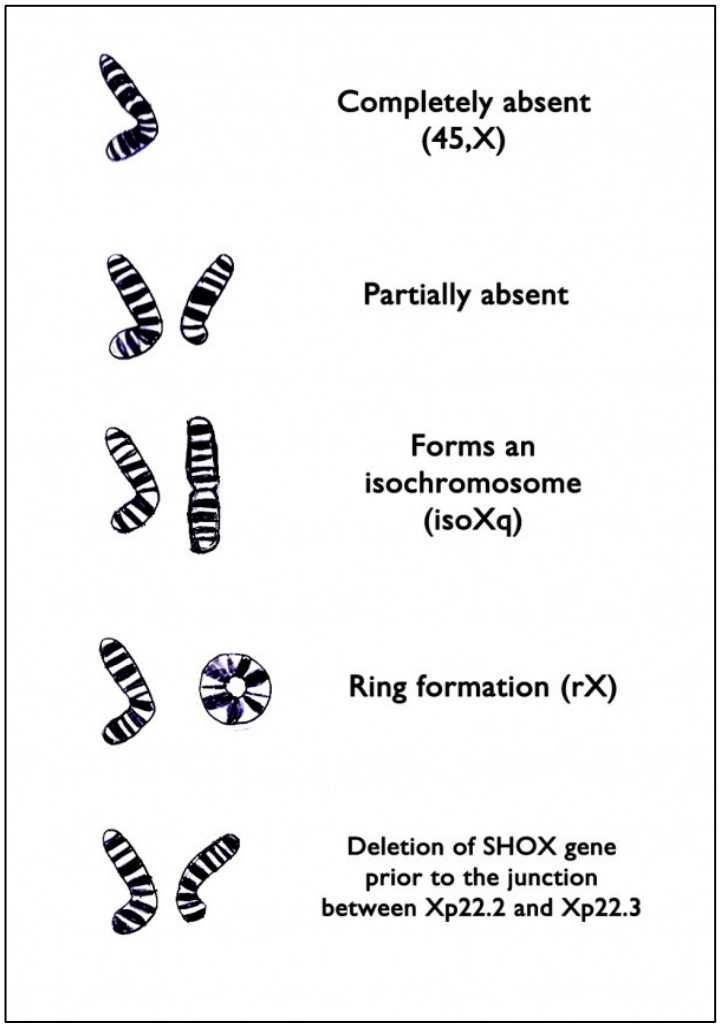
- Affects sexual development
  - Testes don't fully develop
    - Oligospermic
  - Lower levels of testosterone
- Taller than average
- Many men only discover this when they seek help for infertility





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



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

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CNS role

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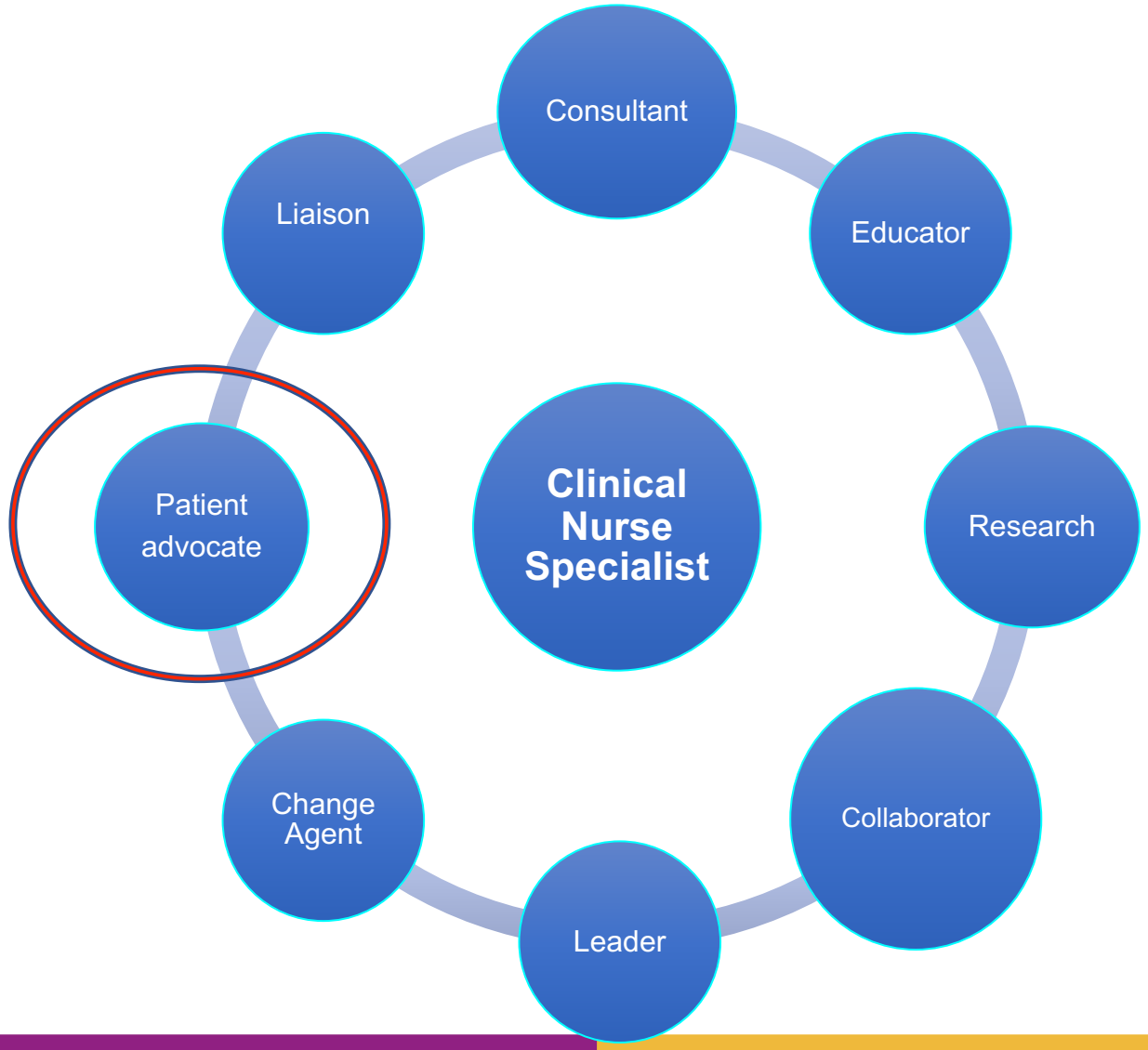
Clinical Nurse Specialist roles



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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 various members of MDT to arrange ward visit
  - Liaising with Biochemistry / Ultrasound / Photography
- 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

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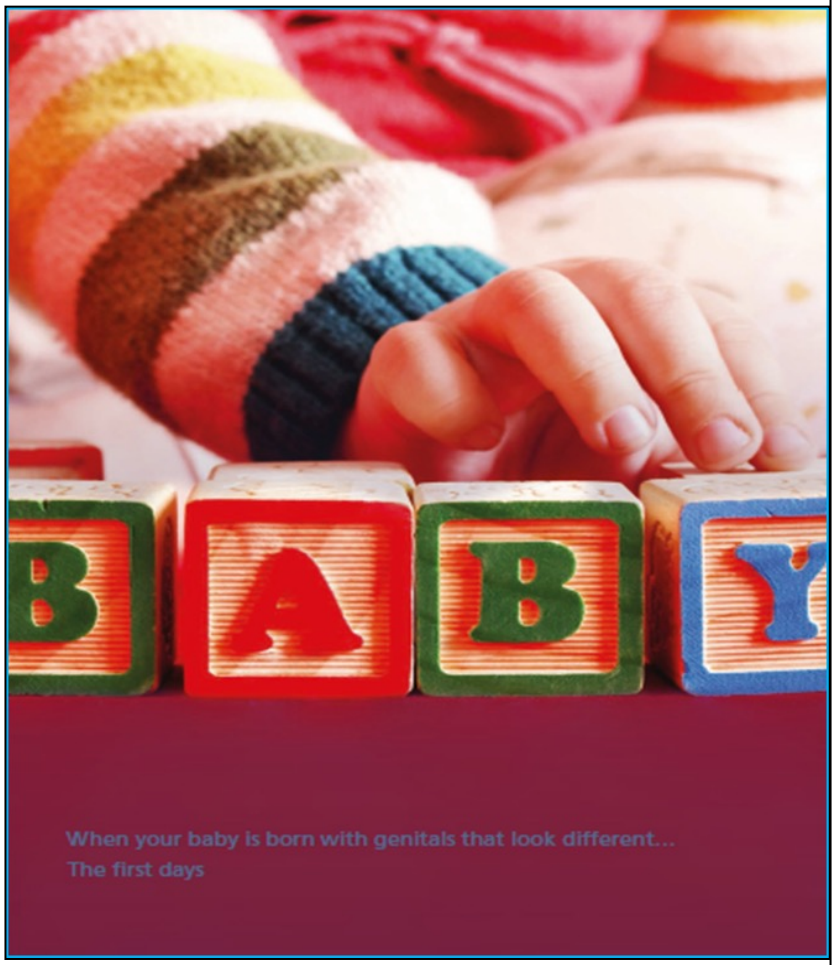
Family Support - dsdfamilies



- dsdfamilies.org
- UK based support group
  - Information and support resource for families with children, teens and young adults with a DSD
  - Links to other support groups throughout the UK
    - CAH, TS, Hypospadias, Klinefelter, AIS
  - Links to international DSD support groups

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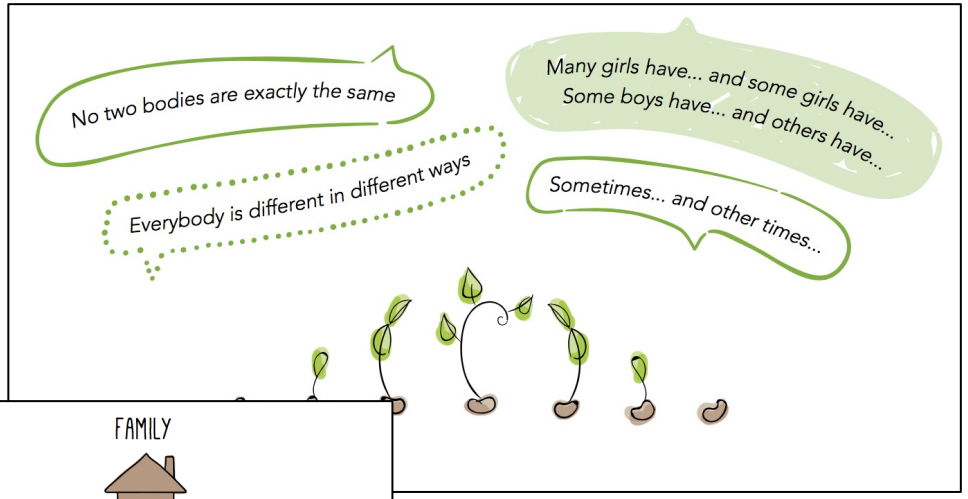
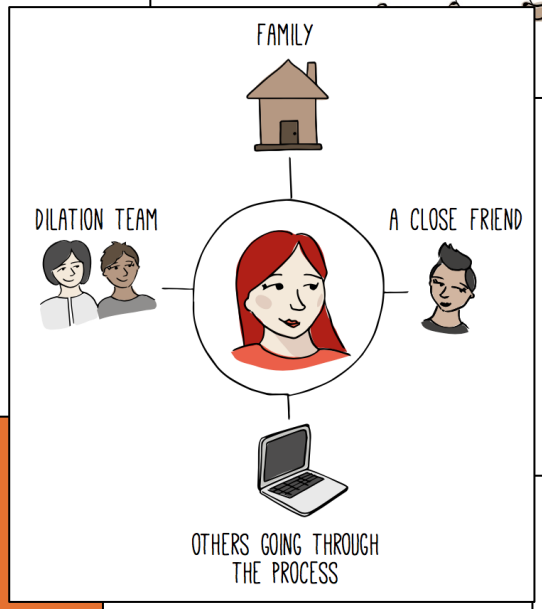
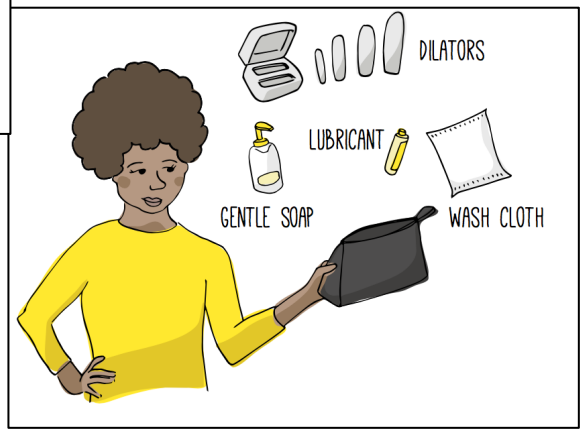
dsdfamilies.org

- Advice
  - How to talk to others
  - How to talk with teenagers
  - Dilatation



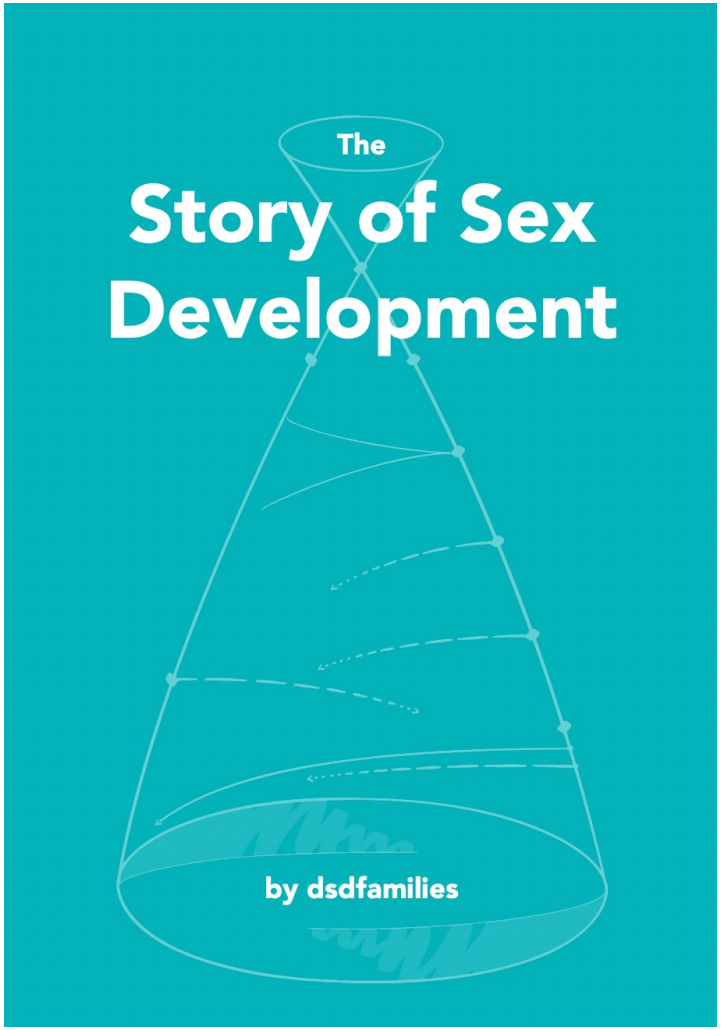




Top Tips for Talking

about differences of sex development

Story of Sex Development



dsdfamilies

www.dsdfamilies.org
@dsdfamilies

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UK Statistics

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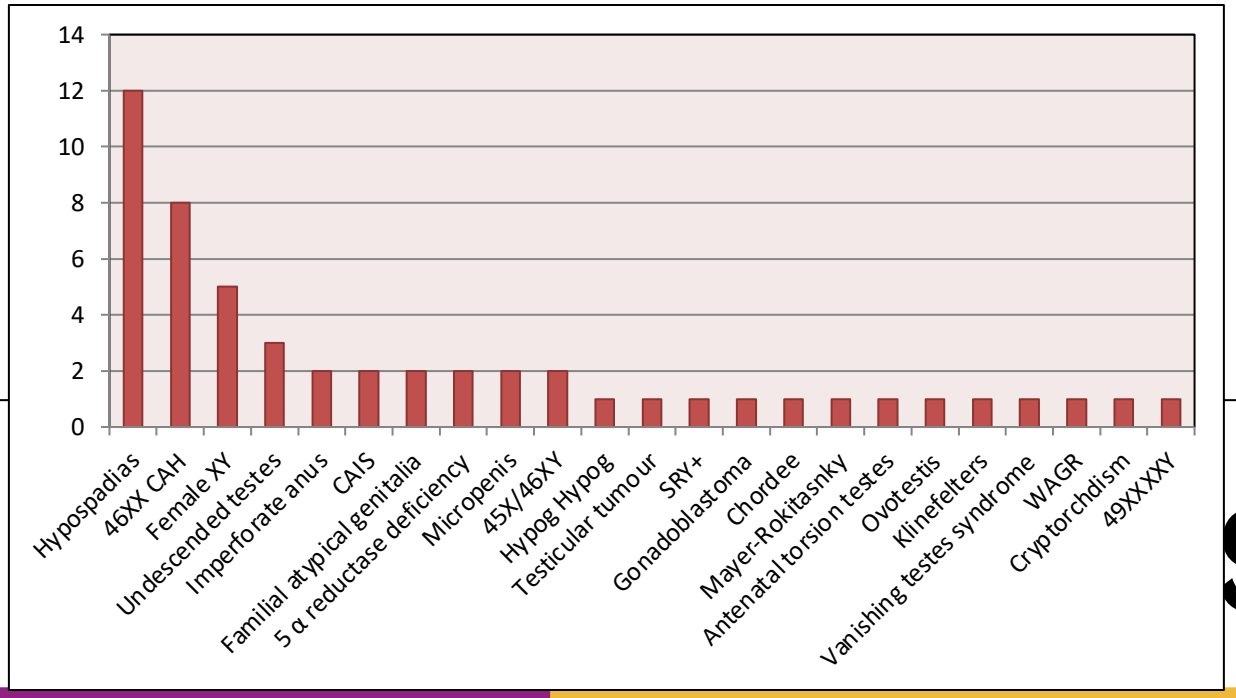
GOSH DSD diagnosis statistics - 2015

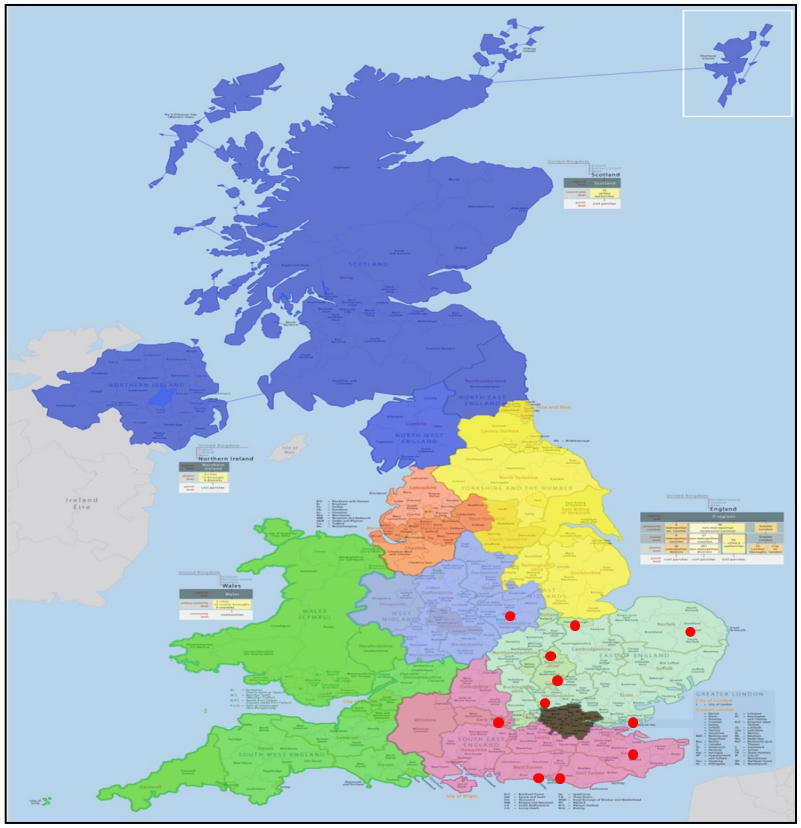
53 new referrals over one year

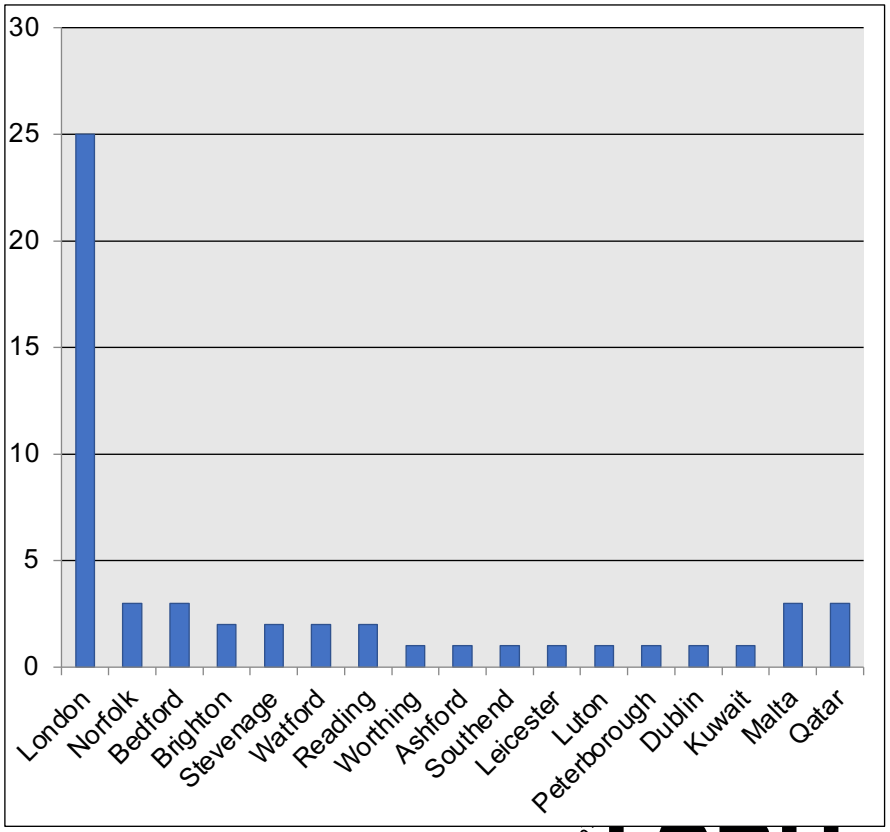
Averaging 6 a month



SBU

DSD referral areas





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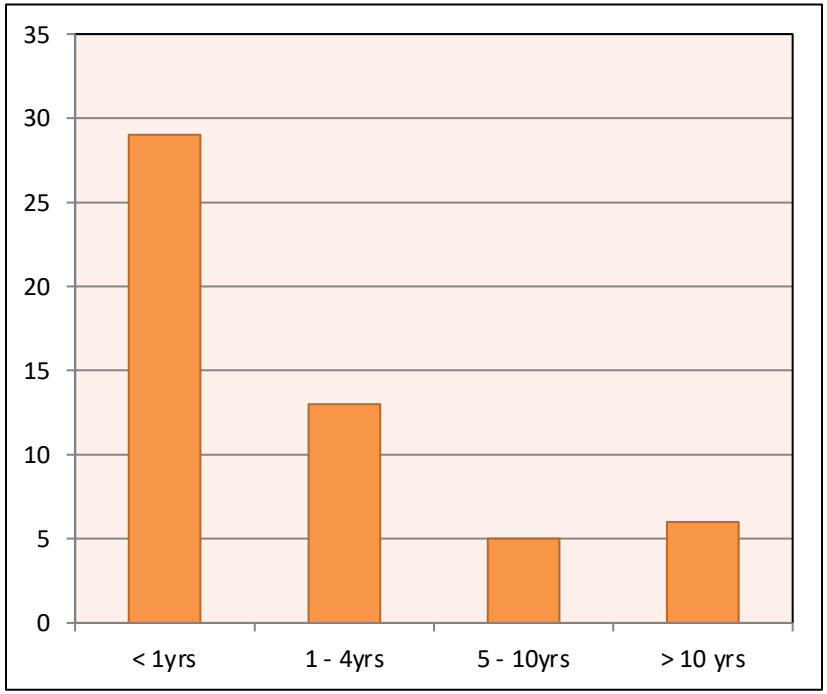
DSD ages of referral at GOSH



- Infants
  - Usually present with atypical genitalia
- Adolescents
  - Atypical sexual development
    - Micropenis
    - Cryptorchidism
    - Referrals from other centres
      - Previous hypospadias surgeries
      - Familial atypical genitalia
      - CAIS

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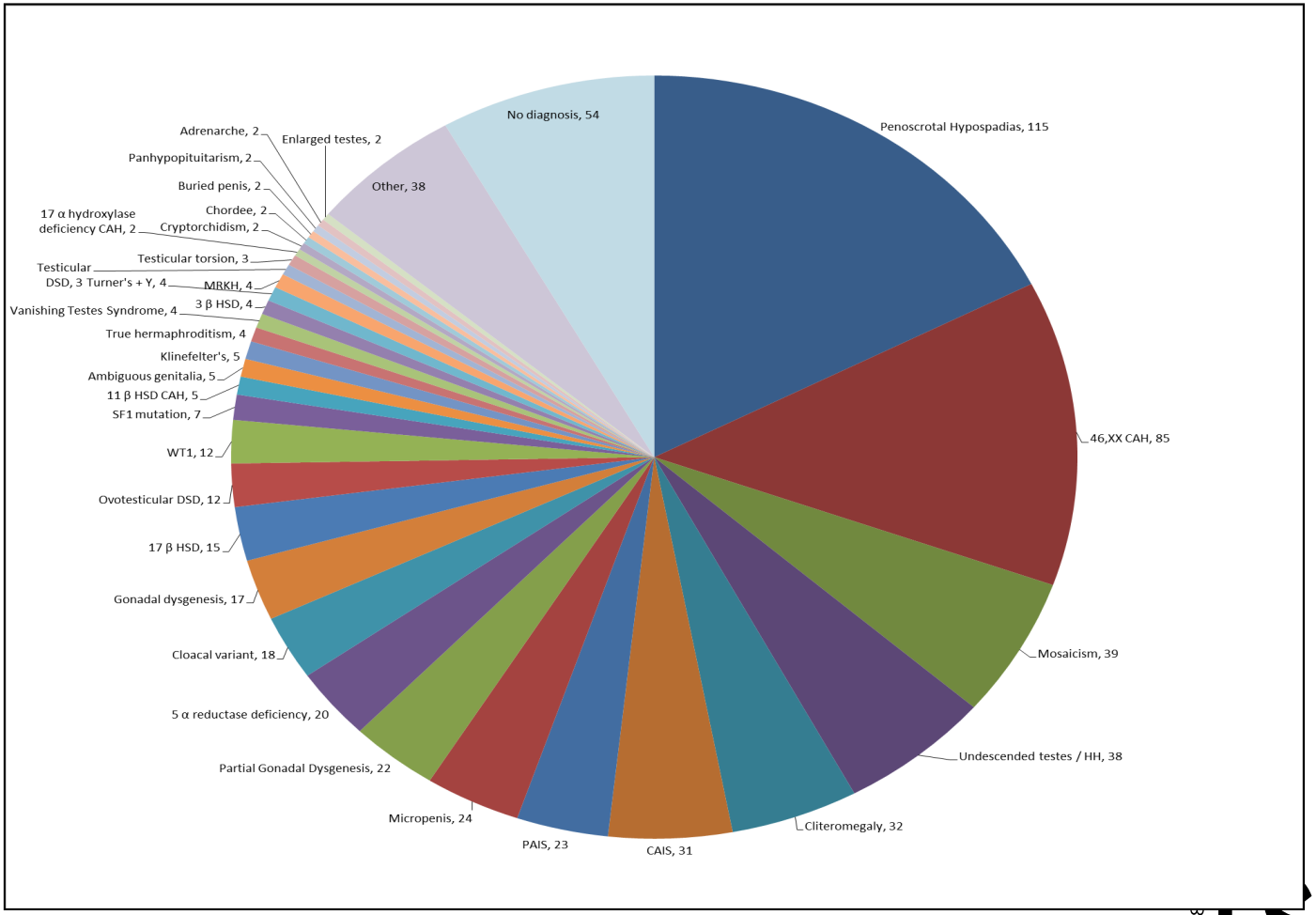
GOSH DSD data over 21 years N= 657



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- SCDSD11.2%
- 46,XY DSD 61.1%
- 46,XX DSD 27.7%
- Most children (80.1%) presented as neonates, usually with atypical genitalia, adrenal insufficiency, undescended testes or hernias

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https://doi.org/10.1210/jendso/bvac165
Advance access publication 28 October 2022
Clinical Research Article

ENDOCRINE SOCIETY

OXFORD

A Single-Center, Observational Study of 607 Children and Young People Presenting With Differences of Sex Development (DSD)

Elim Man,[1,2,3] Imran Mushtaq,[4] Angela Barnicoat,[5] Polly Carmichael,[6,7] Claire R. Hughes,[2,8] Kate Davies,[2,9] Helen Aitkenhead,[10] Rakesh Amin,[2] Charles R. Buchanan,[11] Abraham Cherian,[4] Nikola J. Costa,[10] Sarah M. Creighton,[12] Patrick G. Duffy,[4] Emma Hewson,[6] Peter C. Hindmarsh,[2,13] Louisa C. Monzani,[6] Catherine J. Peters,[2] Philip G. Ransley,[4] Naima Smeulders,[4] Helen A. Spoudeas,[1,2] Dan Wood,[4,14,15] Ieuan A. Hughes,[16] Harshini Katugampola,[2] Caroline E. Brain,[2] Mehul T. Dattani,[1,2,*] and John C. Achermann[1,2,*]

International Statistics

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South Africa *(Ganie et al, 2016)*

- 416 children
- 46 XY - 57.5%
  - Androgen synthesis action
    - Ovotesticular DSD
      - Single most common diagnosis amongst black African patients with ambiguous genitalia
- 46 XX - 33%
  - CAH
- MSC - 9.5%
  - TS – 2/3
  - Late presentation

- Lack of biochemistry tests
- Lack of advanced molecular techniques (WES)
  - Likely to alter classification of their cohort
  - WES
    - Can detect mutation s in known DSD genes

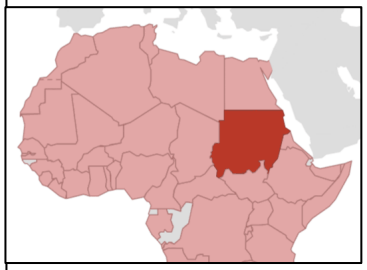
DE GRUYTER J Pediatr Endocrinol Metab 2016; aop

Yasmeen Ganie*, Colleen Aldous, Yusentha Balakrishna and Rinus Wiersma

Disorders of sex development in children in KwaZulu-Natal Durban South Africa: 20-year experience in a tertiary centre

Sudan *(Abdullah et al, 2012)*

- 5 year retrospective study of PE clinic
- 156 DSD patients
  - 46 XX - 44%
    - CAH
  - 46 XY – 29%
    - AIS



DE GRUYTER DOI 10.1515/jpem-2011-0467 — J Pediatr Endocr Met 2012; 25(11-12): 1065–1072

Mohamed Ahmed Abdullah*, Umsalama Saeed, Asjjad Abass, Karib Lubna, Arabi Weam, Abdelbassit S. Ali and Imad F. Elmwla

Disorders of sex development among Sudanese children: 5-year experience of a pediatric endocrinology clinic

- 60% referred to specialized clinics
  - Some families refuse
    - Finance
    - Stigma
  - Some left without action
    - Aetilogy spiritual
      - Not treated by Western medicine
- 70% deliveries at home
  - Midwives and young Drs not trained
- Sex assignment
  - Guesswork
    - Has to be done before naming ceremony
      - No later than 2 weeks
- SSIS
  - Sudan Scientific Intersex Society
    - MDT only in Khartoum
- Investigations
  - Costly ($300 per patient)
  - Unavailable
- Early surgery opted for
  - Culture
  - Religious directives

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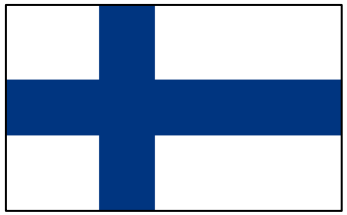

Finland *(Kohva et al, 2018)*

- 550 patients 2004 – 2014
  - 46 XY – 54%
  - MSC – 37%
  - 46 XX – 9%
- Most common
  - Bilateral cryptorchidism
    - Klinefelter
  - TS (child health care clinic)
    - Mean age of diagnosis 4 years
      - Decceleration of growth
        - Finnish growth data?
        - National child measurement programme UK – Reception / Year 6
        - Finland – 20 height measurements from post birth – 12 years

Endocrine CONNECTIONS | E Kohva *et al.* | DSDs: timing of diagnosis and management | 7:4 | 595–603

RESEARCH

Disorders of sex development: timing of diagnosis and management in a single large tertiary center

E Kohva[1,2], P J Miettinen[1], S Taskinen[1,3], M Hero[1], A Tarkkanen[1,2] and T Raivio[1,2]

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[2]Faculty of Medicine, Department of Physiology, University of Helsinki, Helsinki, Finland
[3]Department of Pediatric Surgery, Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

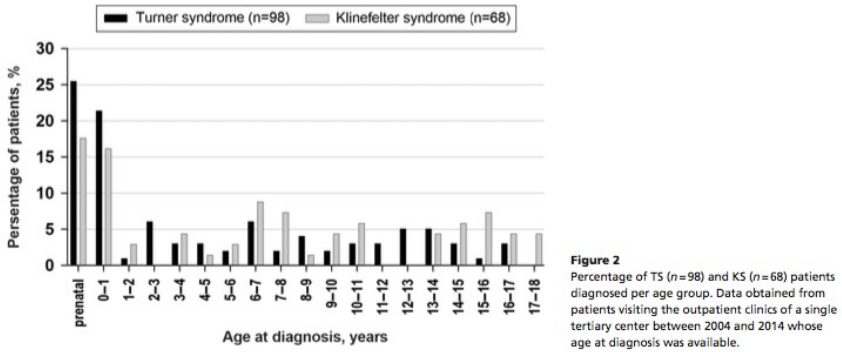

Figure 2
Percentage of TS ($n=98$) and KS ($n=68$) patients diagnosed per age group. Data obtained from patients visiting the outpatient clinics of a single tertiary center between 2004 and 2014 whose age at diagnosis was available.

Conclusion

- Understanding of sex development
- Understanding of DSD
- COMPLEX
  - Treatment
  - Management
  - Advocate

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