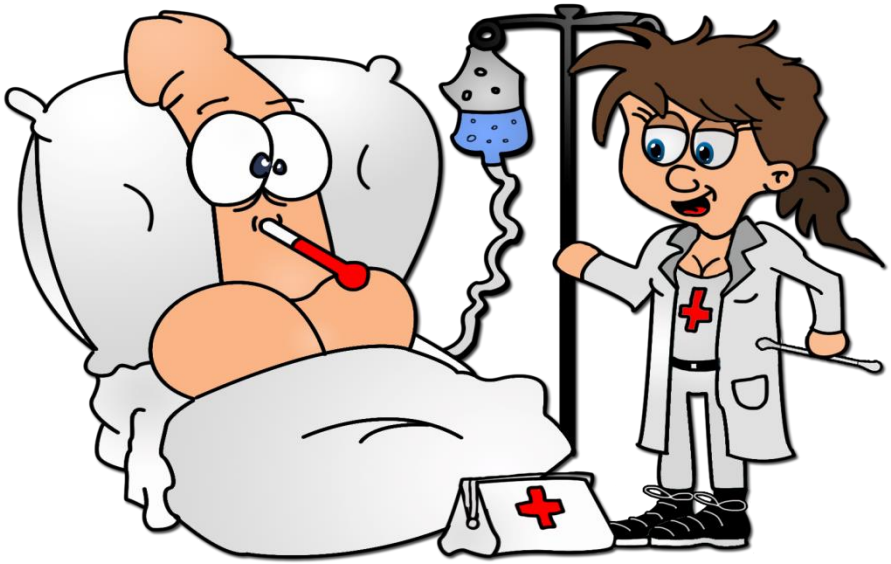
Variaties in GeslachtsOntwikkeling



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UZ GENT

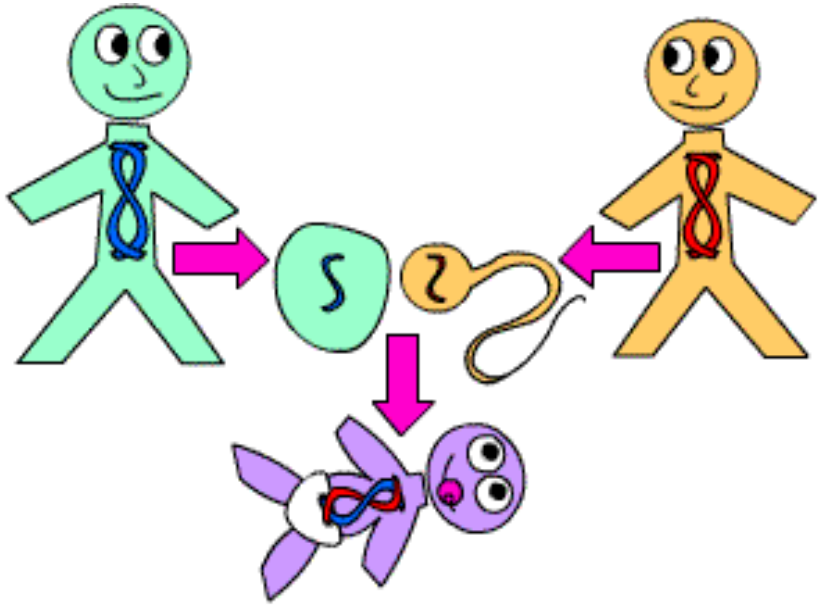
GESLACHT

Biologisch geslacht

Gespecialiseerde organismen: male and female types (or sexes)

Combineren en mixen genetische aspecten

Sexuele reproductie als mix van gameten om nieuwe organisme te creeren die genen van beide ‘ouders’



SEKS VS GENDER ?

Sex : biology, anatomy: MALE VS FEMALE

external sex organs

internal sex organs

Secundaire seksueel ontwikkeling bij puberteit

Gender: Kwaliteiten en Gedrag ,verwacht door de maatschappij M/F

Gender roles :

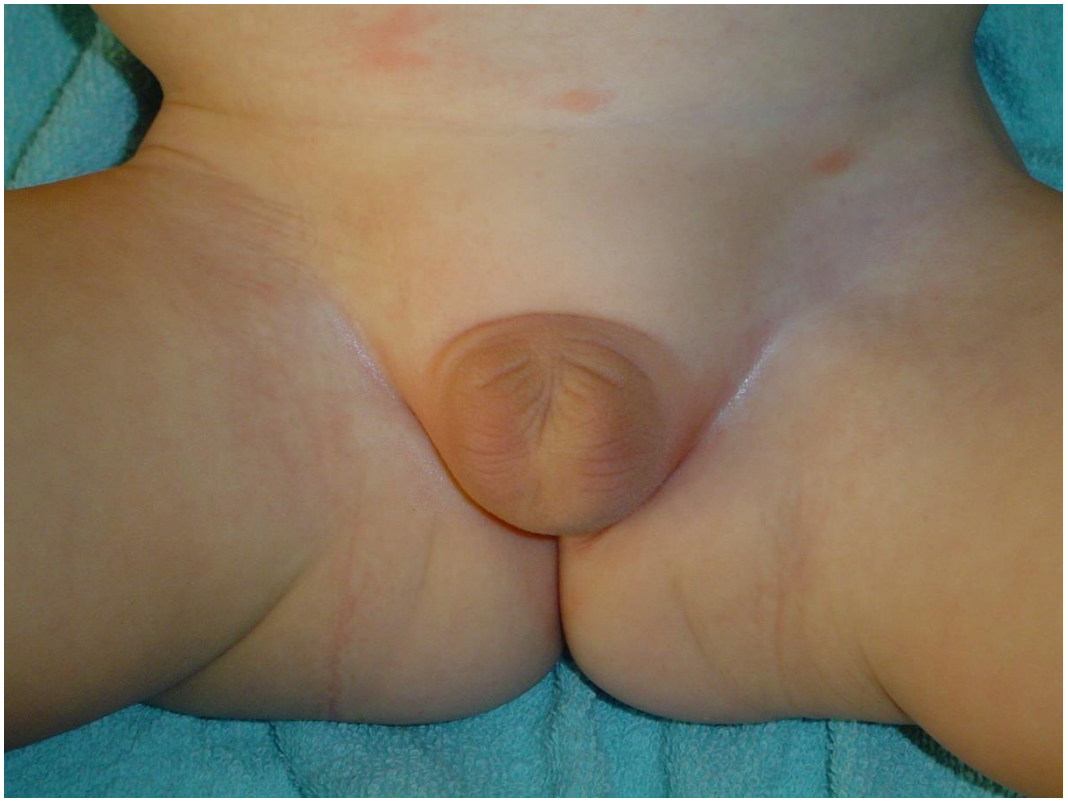
Aangeleerde gedragen, ~ educatie, economie.

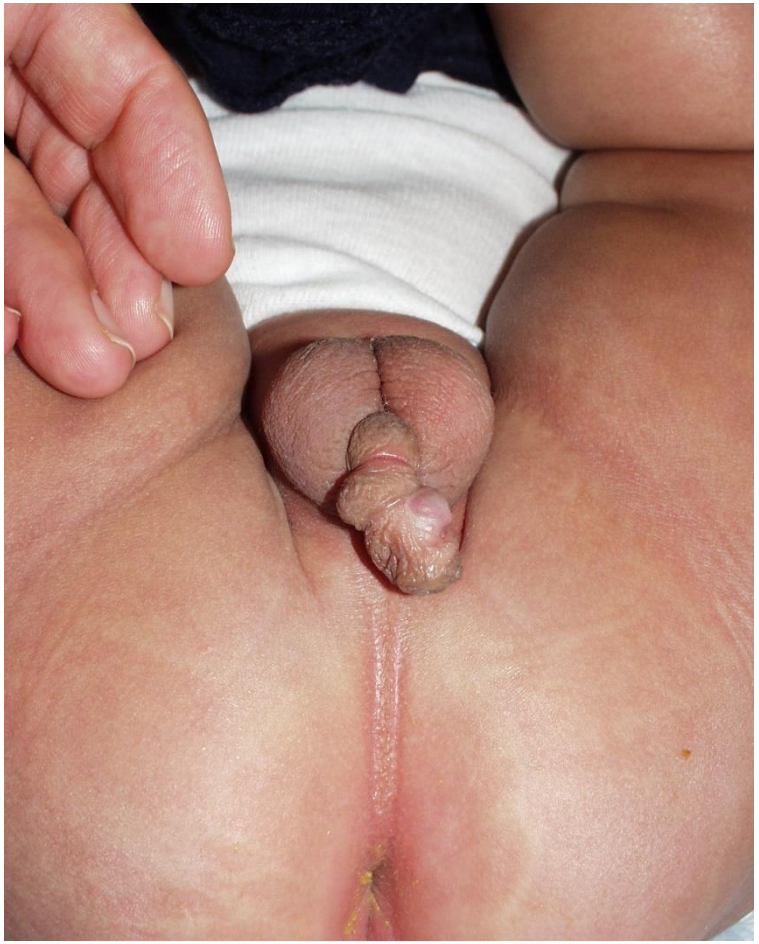
Grote variaties volgens culturen.

Evolutie // tijd, gedefinieerd door maatschappij

Gender identity. Subjectief maar continu en persisterend gevoel van onszelf als man of vrouw

Variaties in Geslachts ontwikkeling





VARIATIES ?

Aangeboren condities :

ontwikkeling

van chromosome

gonaden

anatomische geslacht

ATYPISCH is:

micropenis

clocale exstrofie

blaas exstrofie

..

CONSENSUS STATEMENT ON MANAGEMENT OF INTERSEX

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Consensus Statement on Management of Intersex Disorders

Peter A. Lee, Christopher P. Houk, S. Faisal Ahmed and Ieuan A. Hughes

Pediatrics 2006;118;e488
DOI: 10.1542/peds.2006-0738

CONSENSUS STATEMENT ON MANAGEMENT OF INTERSEX

PREVIOUS NAME	NEW NAME
Intersex	Disorders of sex development (DSD)
Male Pseudohermaphrodite	46,XY DSD
Female Pseudohermaphrodite	46,XX DSD
Trae Hermaphrodite	ovotesticular DSD
XY sex reversal	46,XY complete gonadal dysgenesis
XX male	46,XX testicular DSD

WAAROM ?

Accurater voor diagnostiek

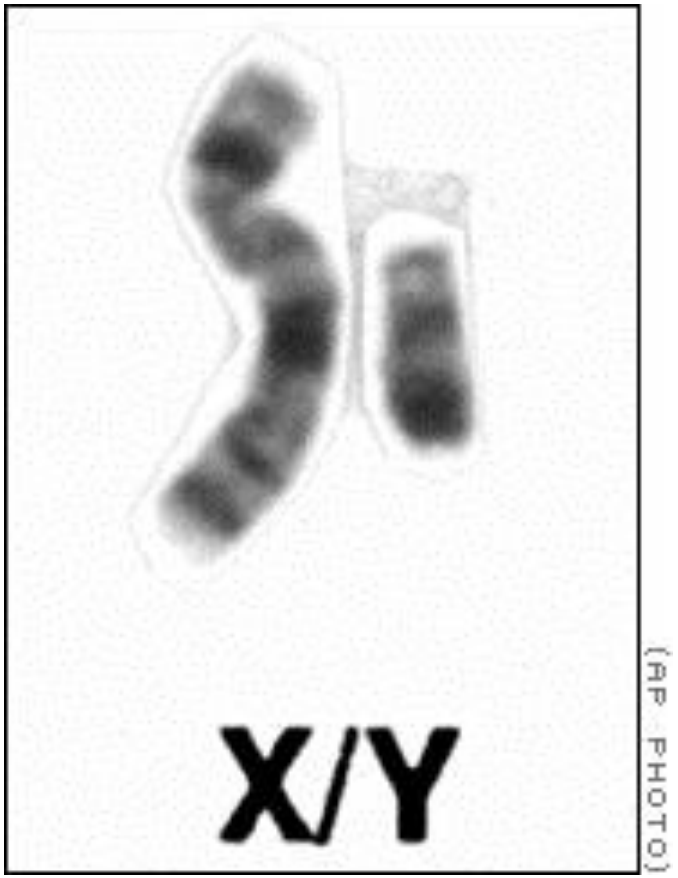
Descriptief

Reflecteert genetische etiologie

Houdt rekening van de spectrum van de fenotypische variaties

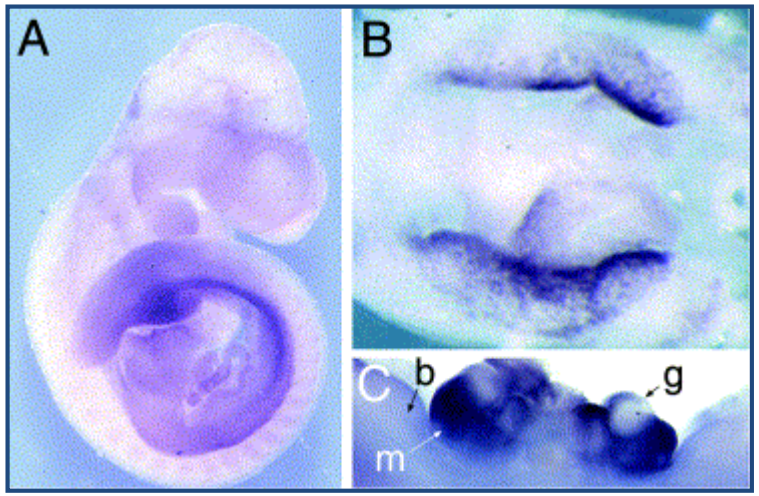
Sex Chromosome DSD	46,XY DSD	46,XX DSD
A: 45,X (Turner Syndrome and variants) **B: 47,XXY (Klinefelter Syndrome and variants)** **C: 45,X/46,XY (mixed gonadal dysgenesis, ovotesticular DSD)** **D: 46,XX/46,XY (chimeric, ovotesticular DSD)**	**A: Disorders of gonadal (testicular) development** 1. Complete gonadal dysgenesis (Swyer syndrome) 2. Partial gonadal dysgenesis 3. Gonadal regression 4. Ovotesticular DSD	**A: Disorders of gonadal (ovarian) development** 1. Ovotesticular DSD 2. Testicular DSD (eg SRY+, dup SOX9) 3. Gonadal dysgenesis
	B: Disorders in androgen synthesis or action 1. Androgen biosynthesis defect (eg 17 Hydoxysteroid dehydrogenase deficiency, 5α reductase deficiency, StAR mutations 2. Defect in androgen action (eg CAIS, PAIS) 3. LH receptor defects (eg Leydig cell hypoplasia, aplasia) 4. Disorders of AMH and AMH receptor (Persistent Mullerian Duct Syndrome)	**B: Androgen excess** 1. Fetal (eg 21 hydroxylase deficiency, 11 hydroxylase deficiency) 2. Fetoplacental (aromatase deficiency, POR) 3. Maternal (luteoma, exogenous, etc)
	C: Other (eg severe hypospadias, cloacal extrophy)	**C: Other** (eg cloacal extrophy, vaginal atresia, MURCS, other syndromes)

Where does it start?



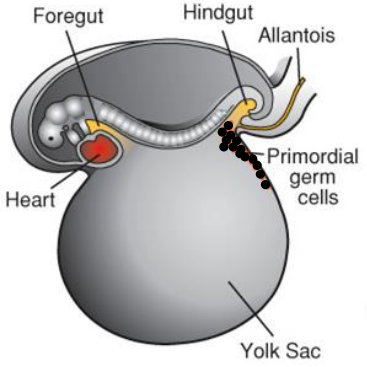
Sexual development

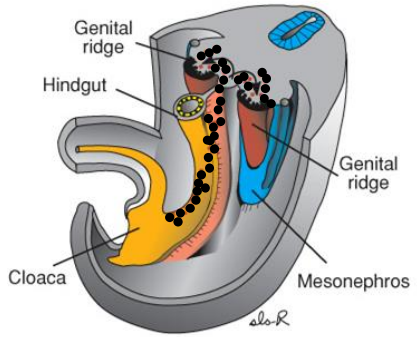
Week 4 - 6



WT1, Sf1, DAX1

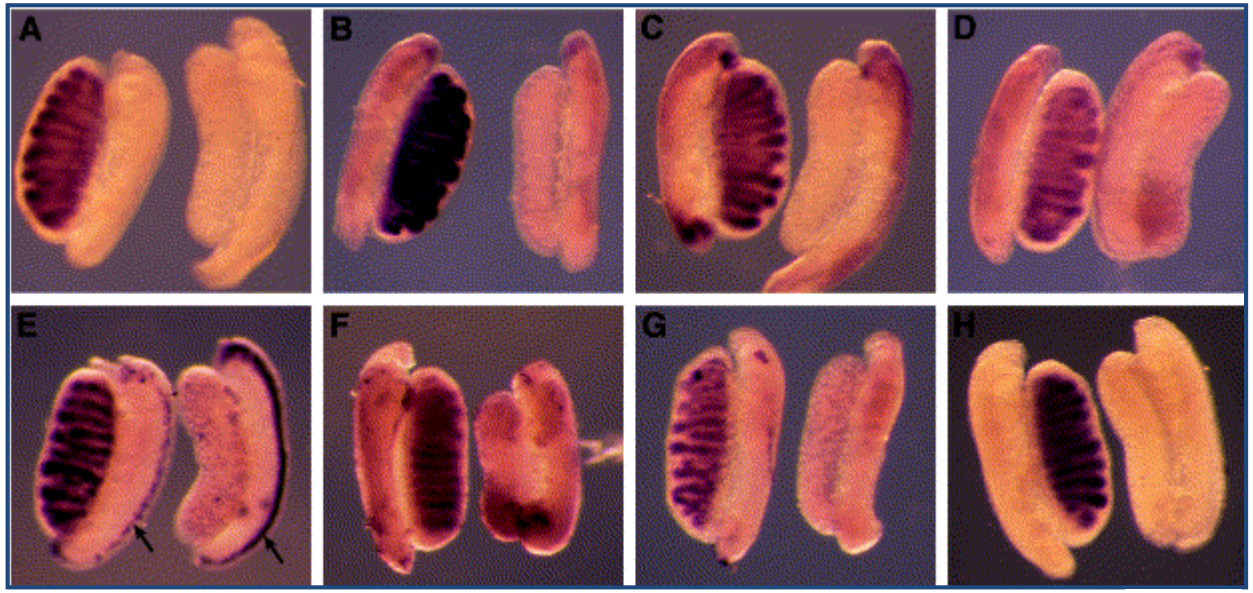
Lhx9, M33, Emx2





C-KIT/SCF

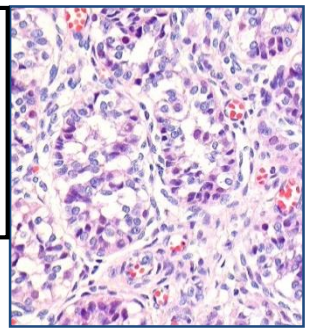
Sexual development

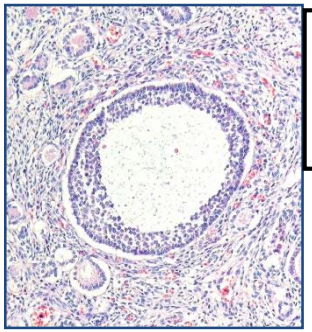


Week 6 - 13

SRY, SOX9, AMH, SF1

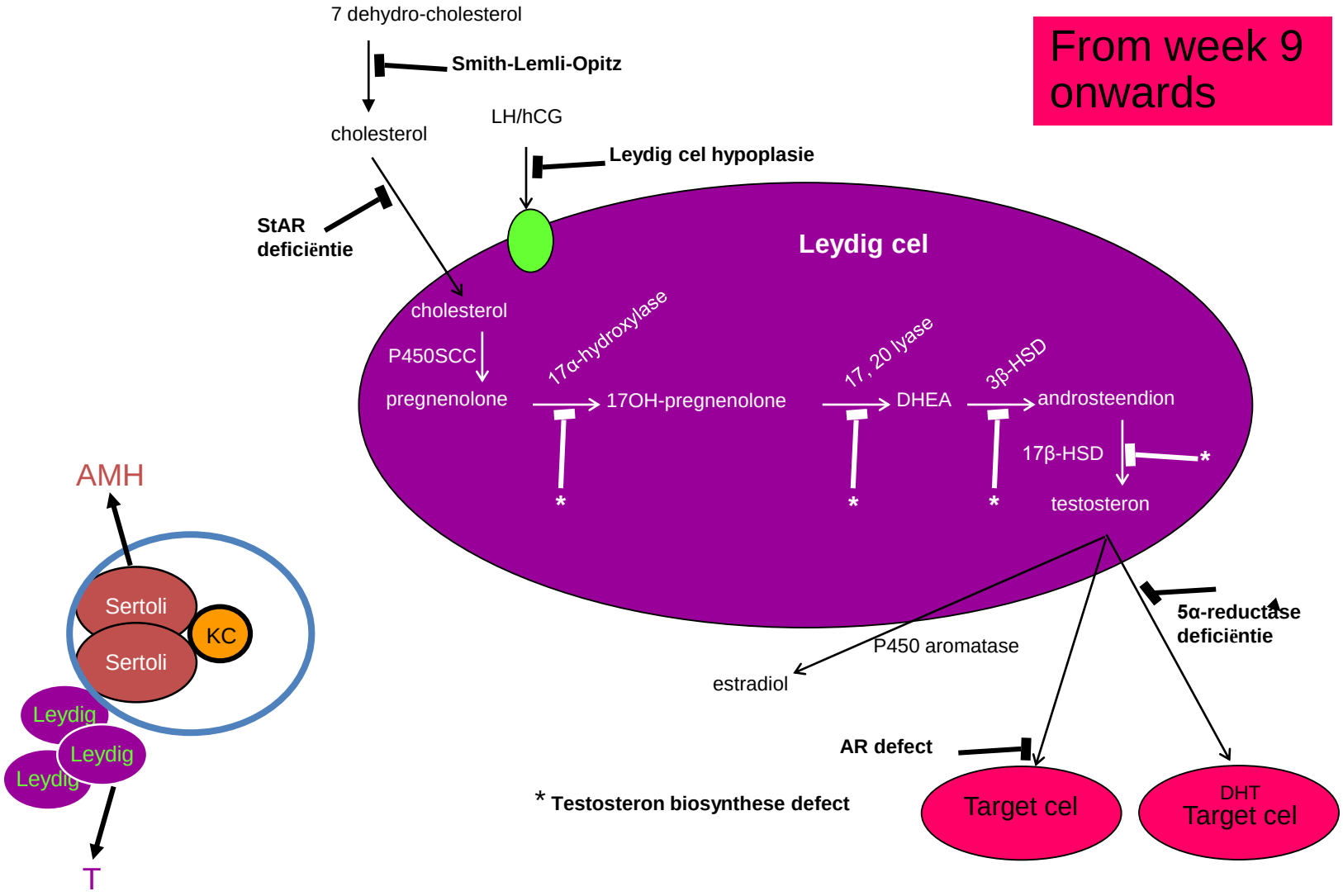
DHH, ATRX, DMRT1, ...



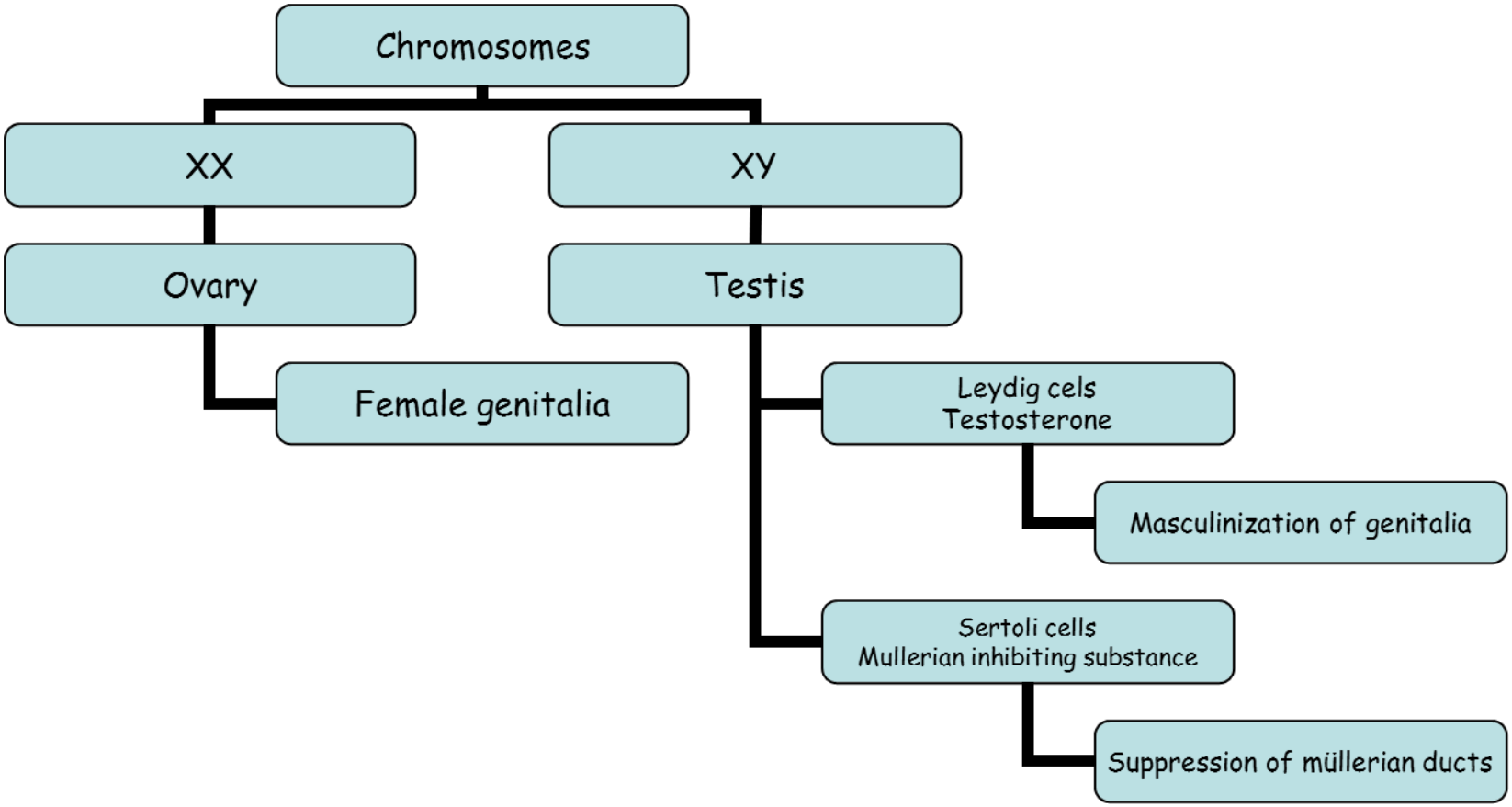


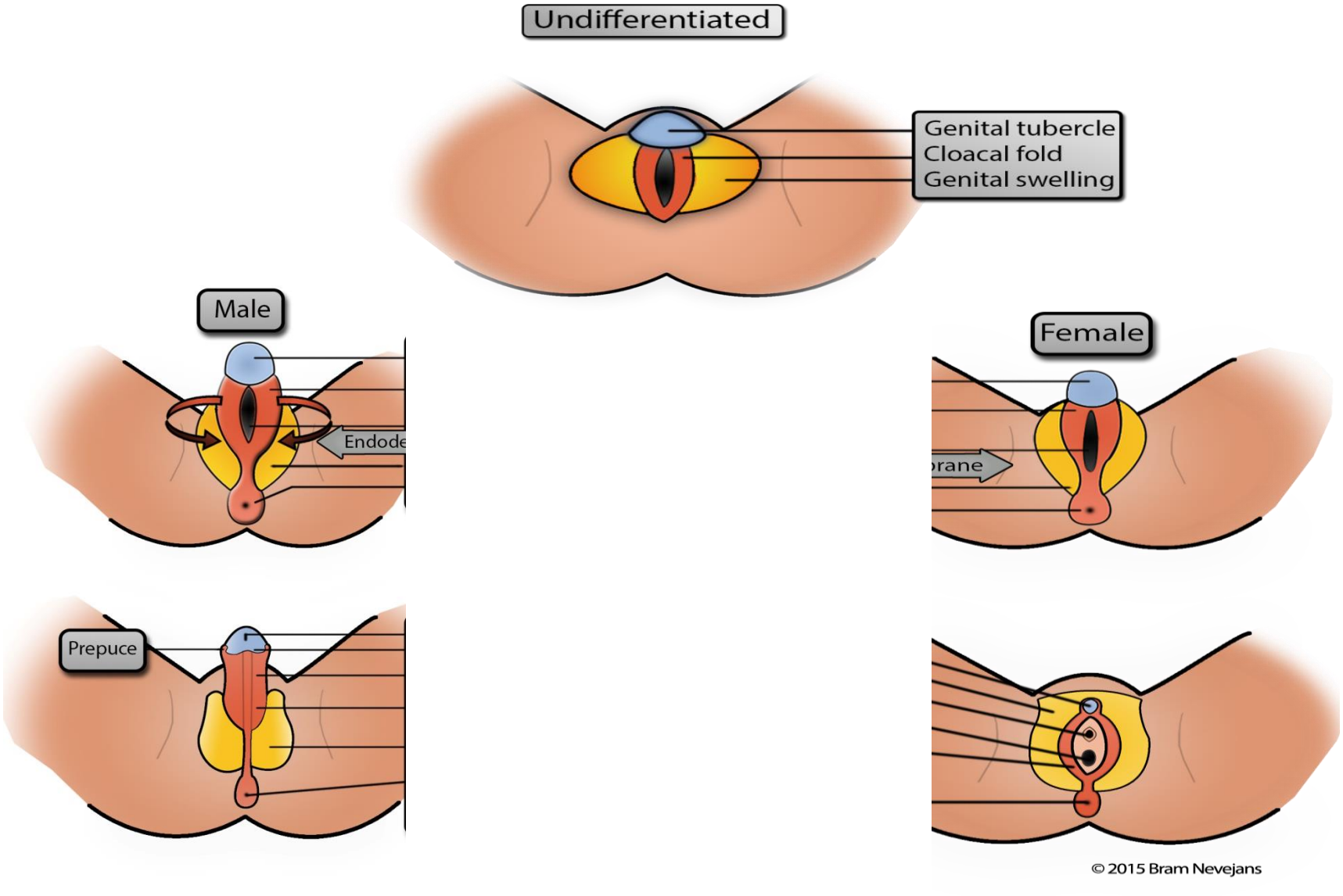
DAX1, FOXL2, RSPO1

Sexual development

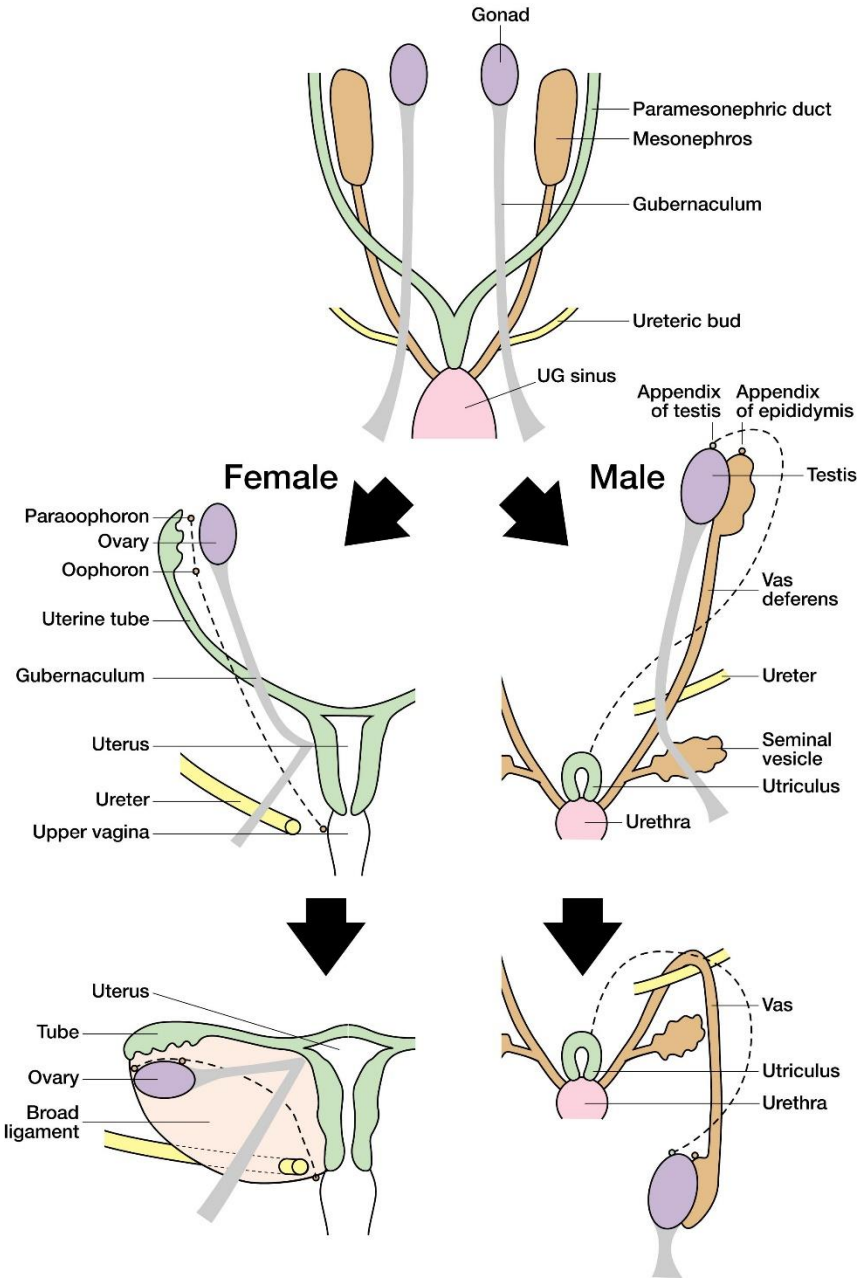


Normal sexual differentiation



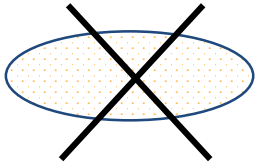


STARTS AT THE **BEGIN** OF THE DEVELOPMENT



Slide Duncan Wilcox

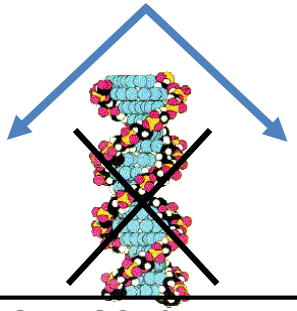
Disorders of Sex Development

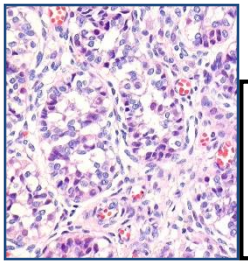


WT1, Sf1, DAX1

Lhx9, M33, Emx2

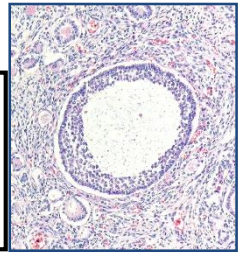
Gonadal dysgenesis

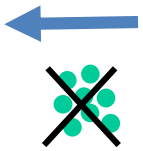


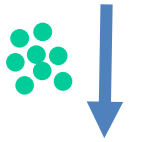


SRY, SOX9, AMH, SF1

DHH, ATRX, DMRT1, ...







Undervirilisation

Star

HSD3B2, CYP17

HSD17B3

AR

SRD5A2

Overvirilisation

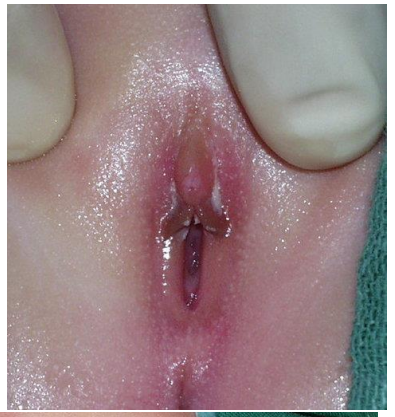
CYP21

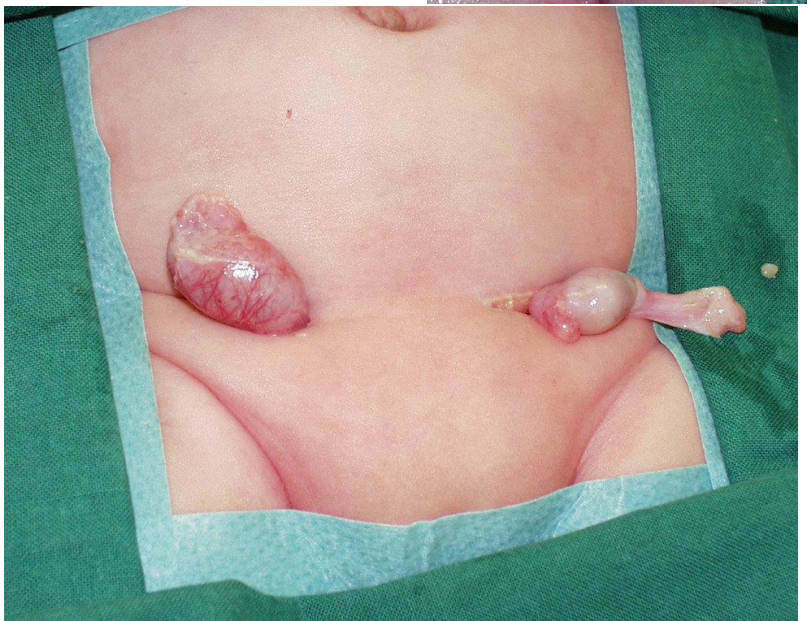
CYP11B1

CYP19

Disorders of sexual development

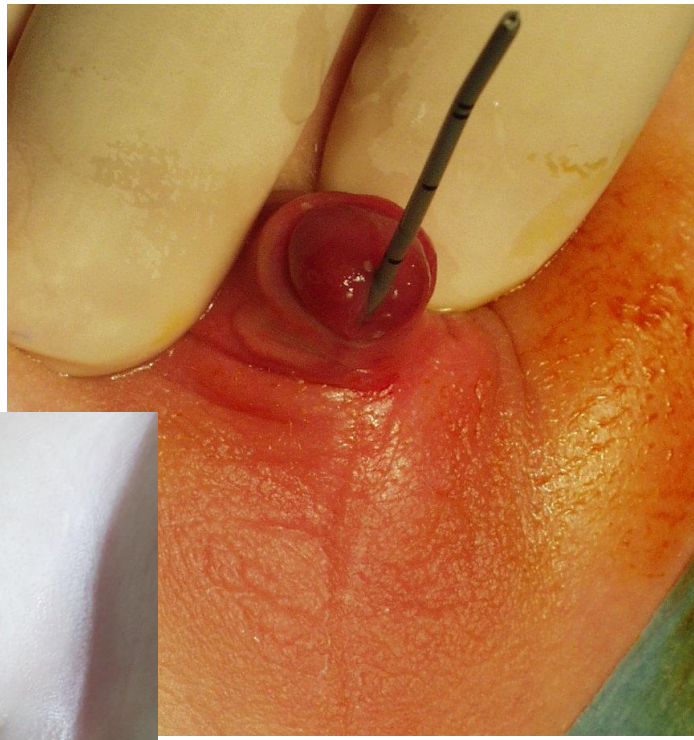
- Mismatch normal phenotype and normal genotype
  - CAIS
  - 46 XX testicular DSD “XX male”
  - 46 XY complete gonadal dysgenesis “Swyer syndrome” (XY female)

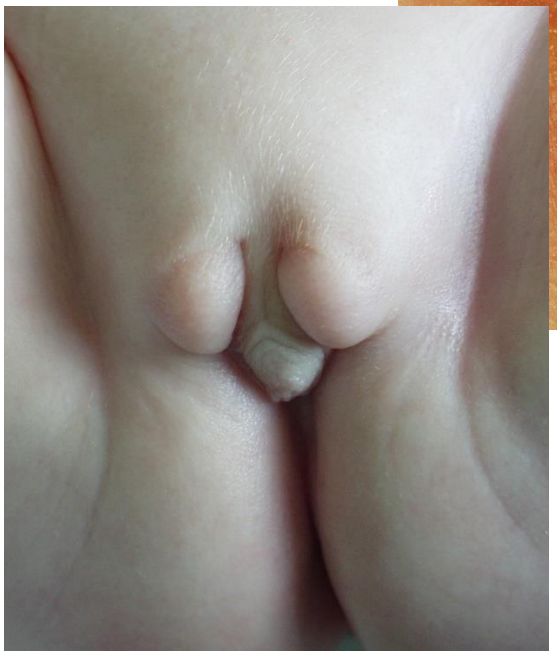




Disorders of sexual development

- Ambiguous genitalia
  - With normal karyotype
  - With abnormal karyotype



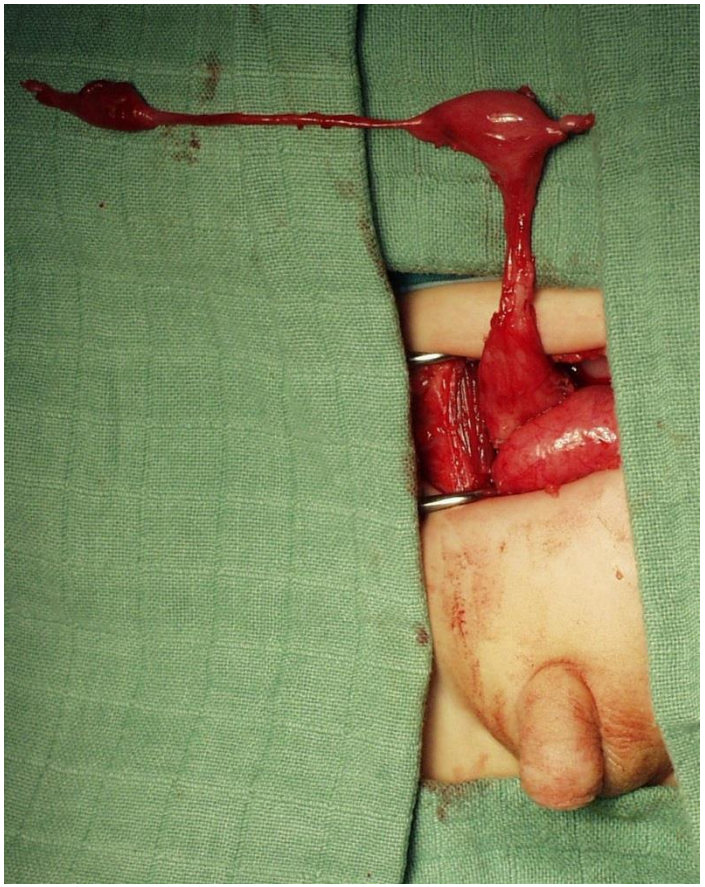


Ambiguous genitalia

- With normal karyotype
  - CAH
  - PAIS
  - 5 alpha reductase deficiency

Ambiguous genitalia

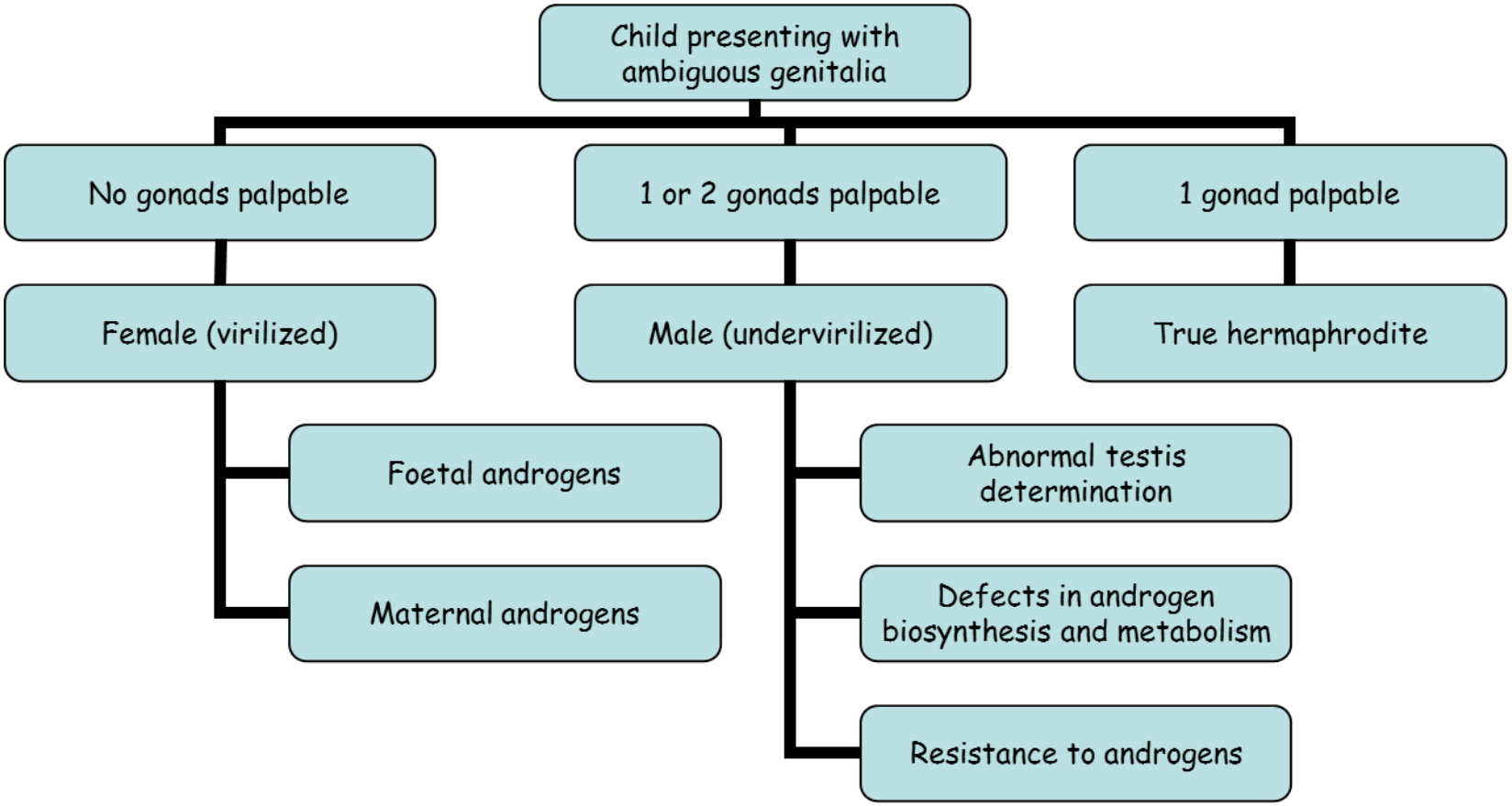
- With abnormal karyotype
  - Ovotesticular DSD "True hermaphroditism"
  - sex chromosome DSD "Mixed gonadal dysgenesis"



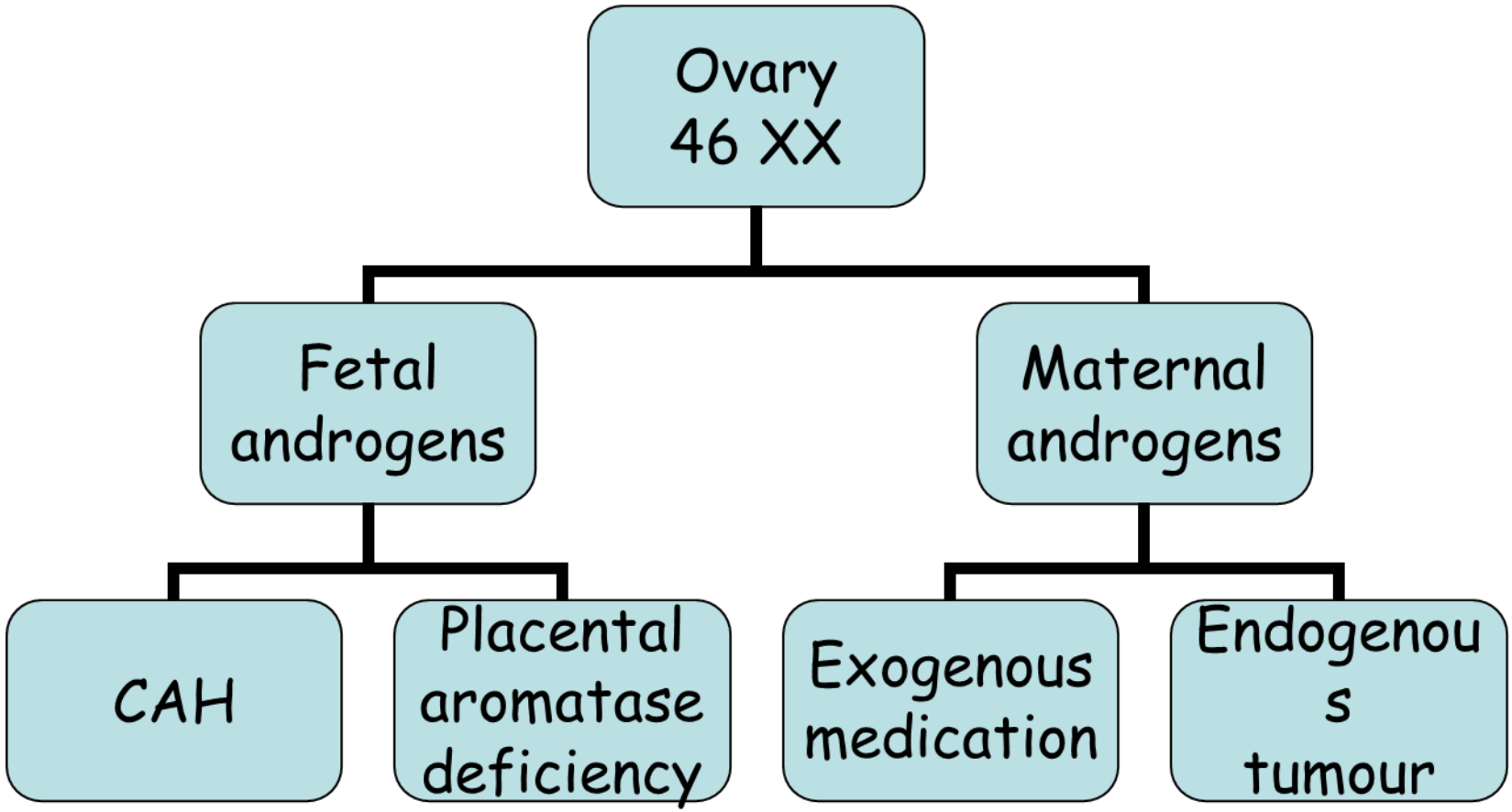
Ambiguous genitalia

- Virilized female
  - Fetal androgens
  - Maternal androgens
- Undervirilized male
  - Impaired testosterone metabolism
  - Androgen insensitivity syndrome
  - Persitent mullerian duct syndrome
- Disorders with dysgenetic gonads
  - (Pure gonadal dysgenesis)
  - Mixed gonadal dysgenesis
- True hermaphroditism

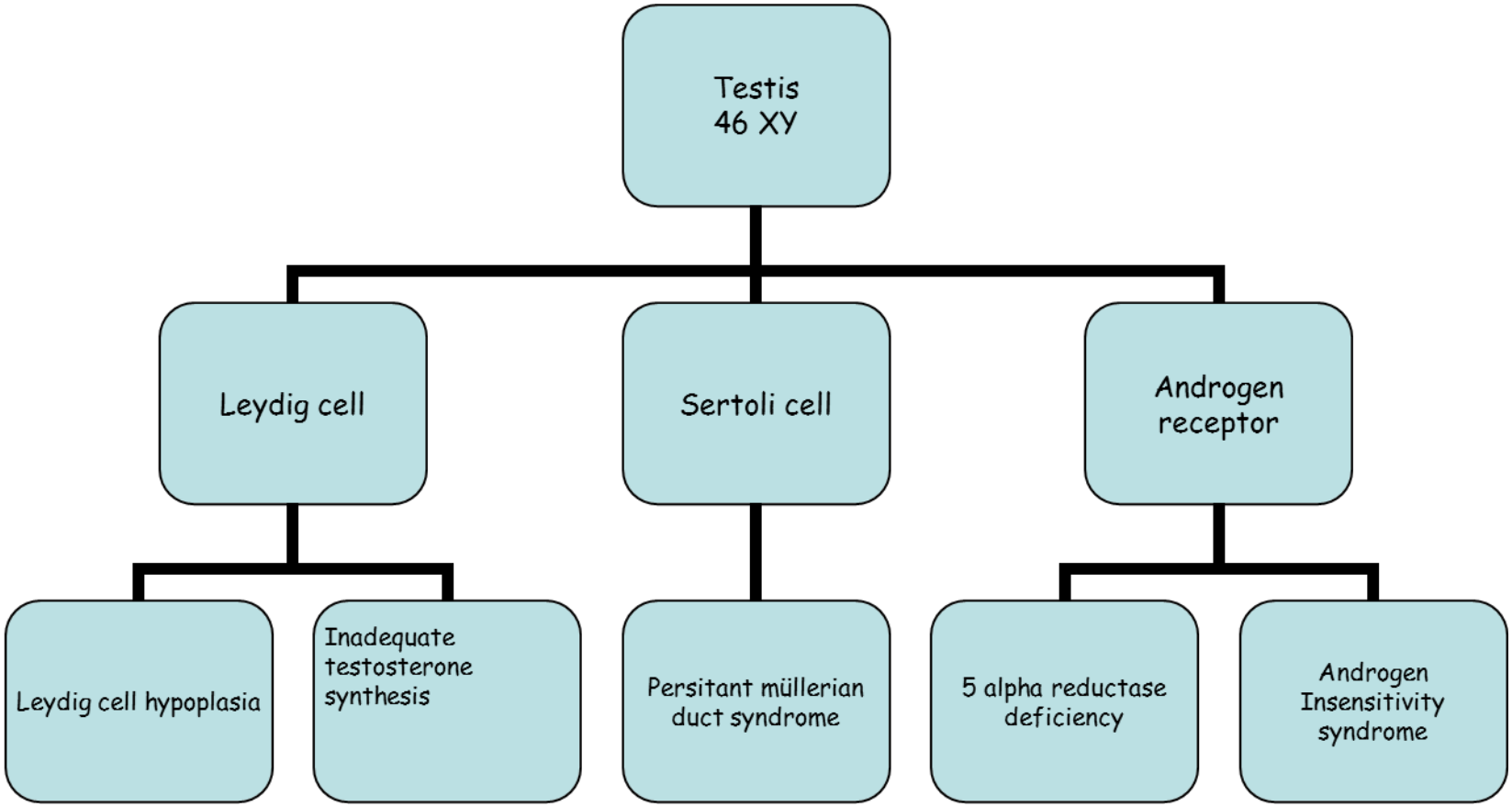
Ambiguous genitalia and gonadal status



Ovaries only



Testis only

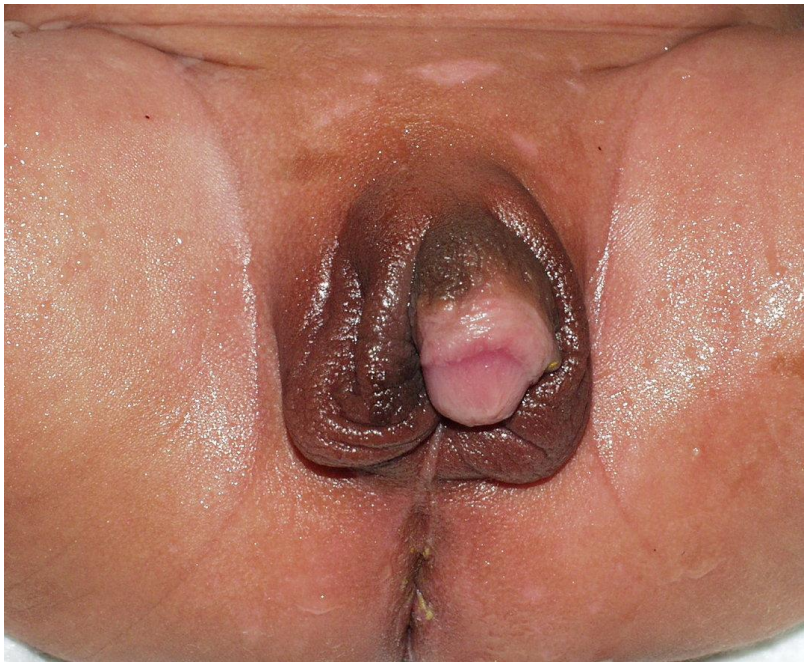

Testis
46 XY
Leydig cell
Sertoli cell
Androgen receptor
Leydig cell hypoplasia
Inadequate testosterone synthesis
Persitant müllerian duct syndrome
5 alpha reductase deficiency
Androgen Insensitivity syndrome

Conditions with dysgenetic gonads

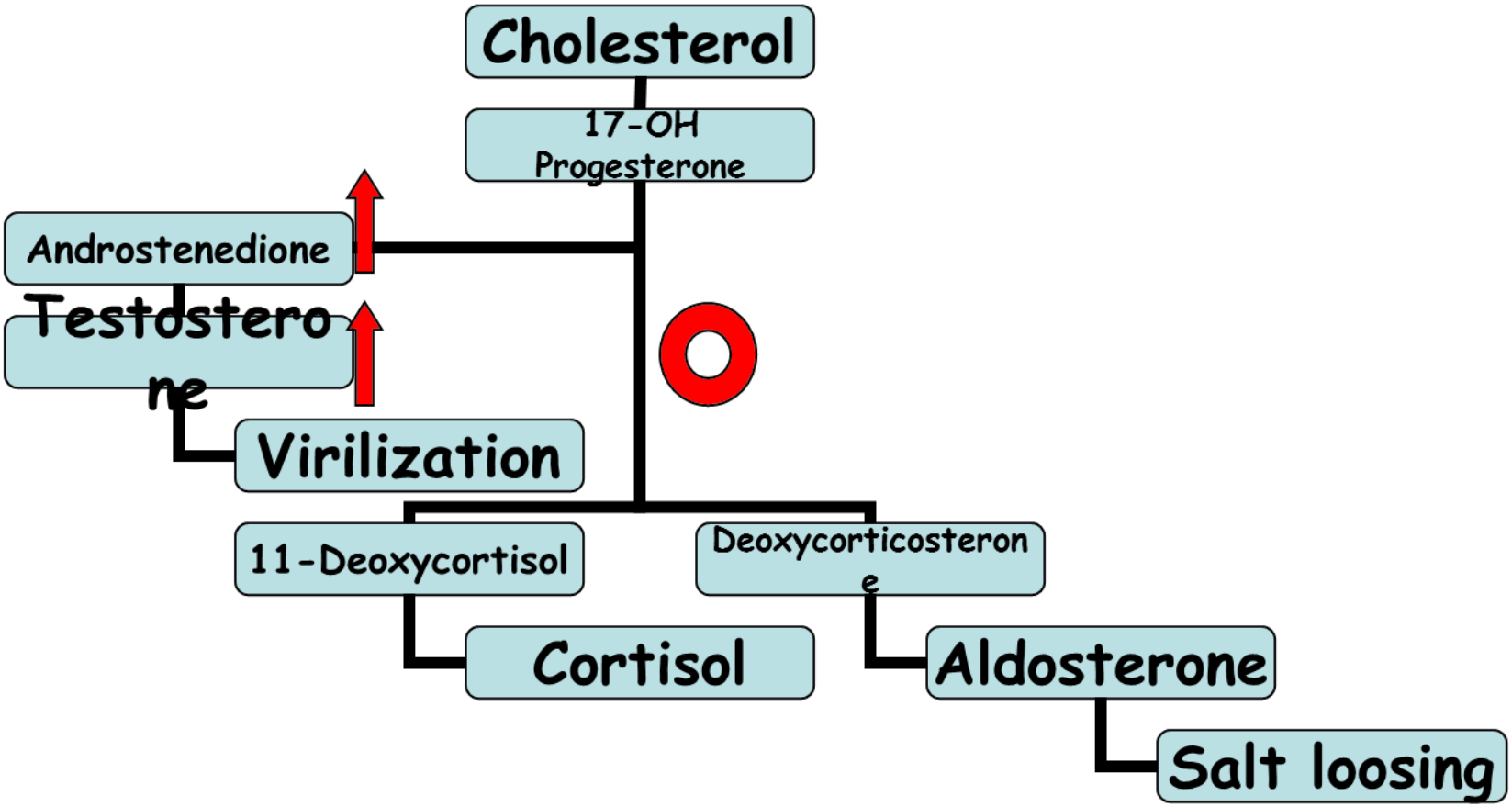
- Testis + streak
  - Mixed gonadal dysgenesis
- Streak + streak
  - Pure gonadal dysgenesis

Ambigious genitalia: virilized female

- Hypertrophy of the clitoris
- Absence of minor labiae
- Confluence of uro genital tract

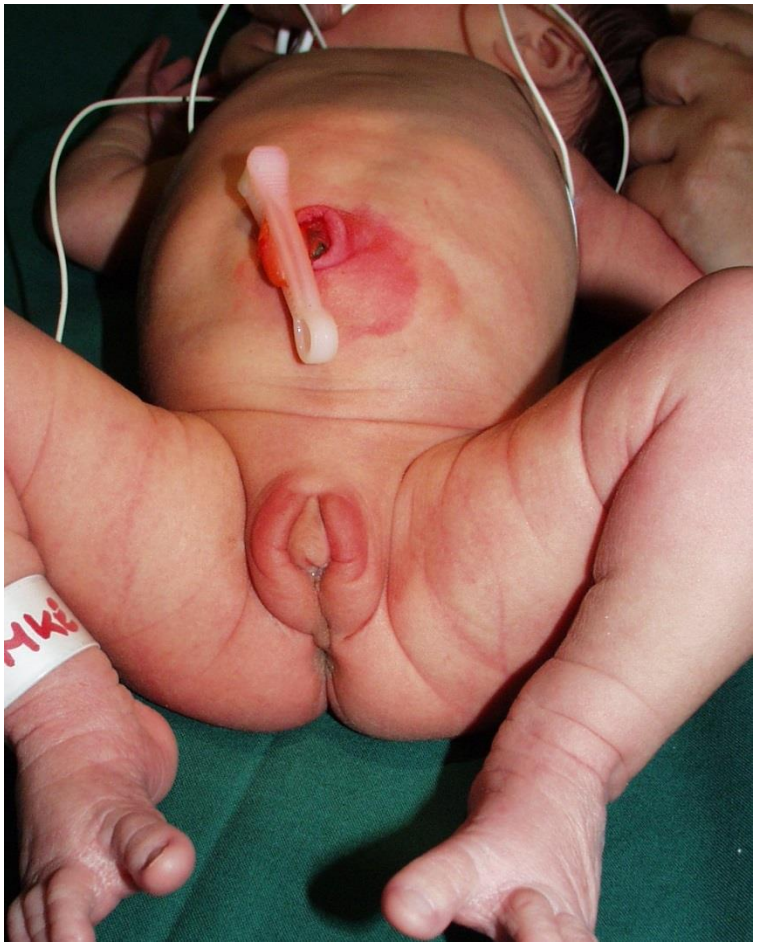


Ambigious genitalia: virilized female omw Fetale androgenen



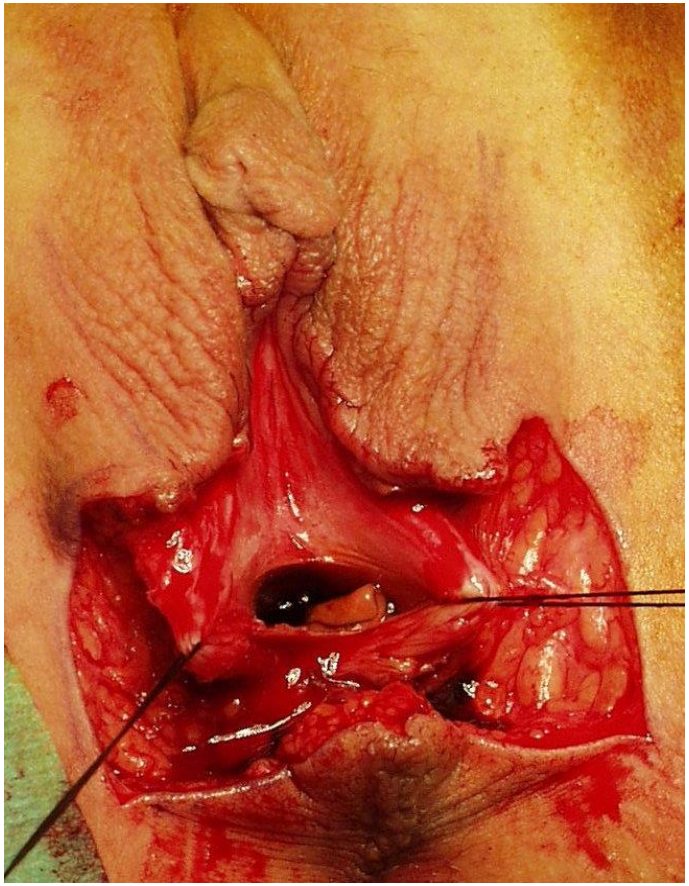
Maternal androgens

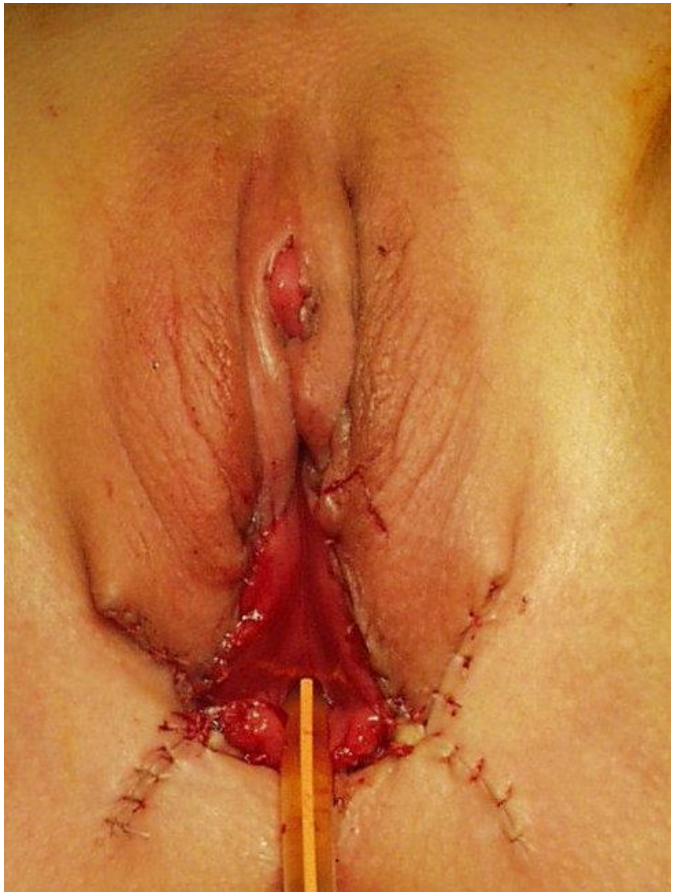
- Any maternal source of elevated androgens can induce virilization of the female foetus
  - luteoma of pregnancy, hilar-cell tumour, masculinizing ovarian stromal cell tumour,



Maternal androgens

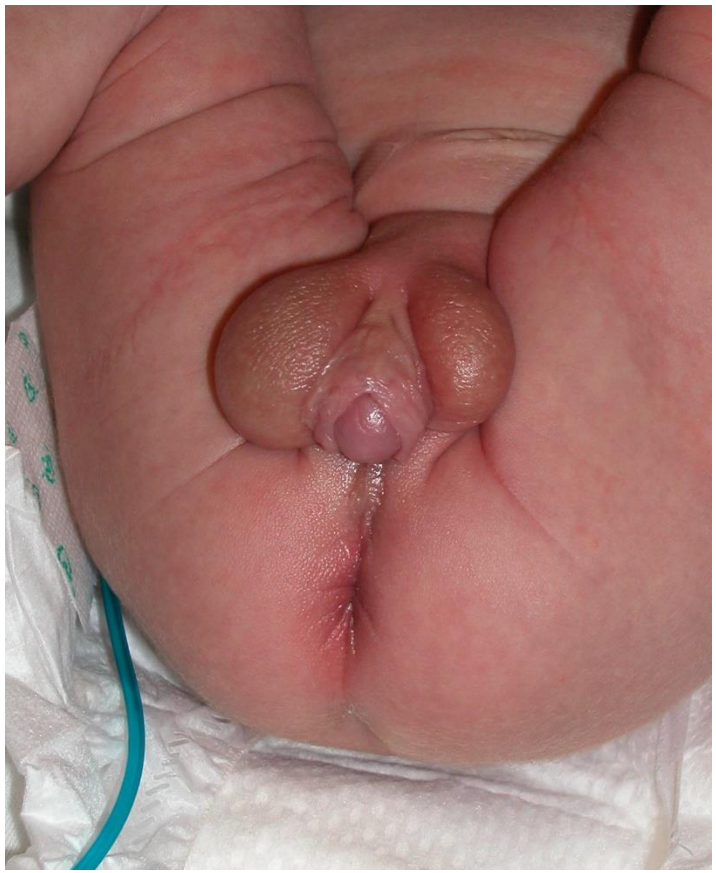
46 XX virilized female

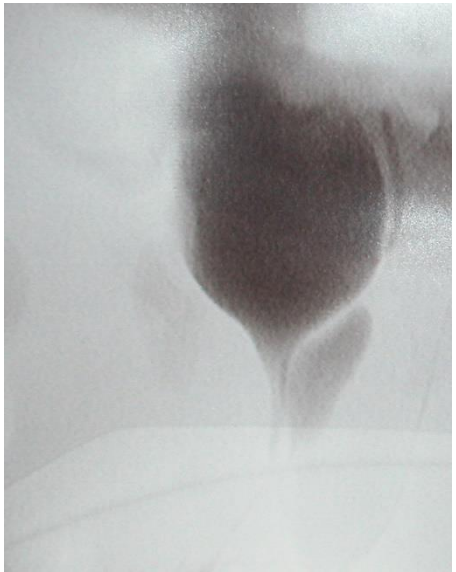




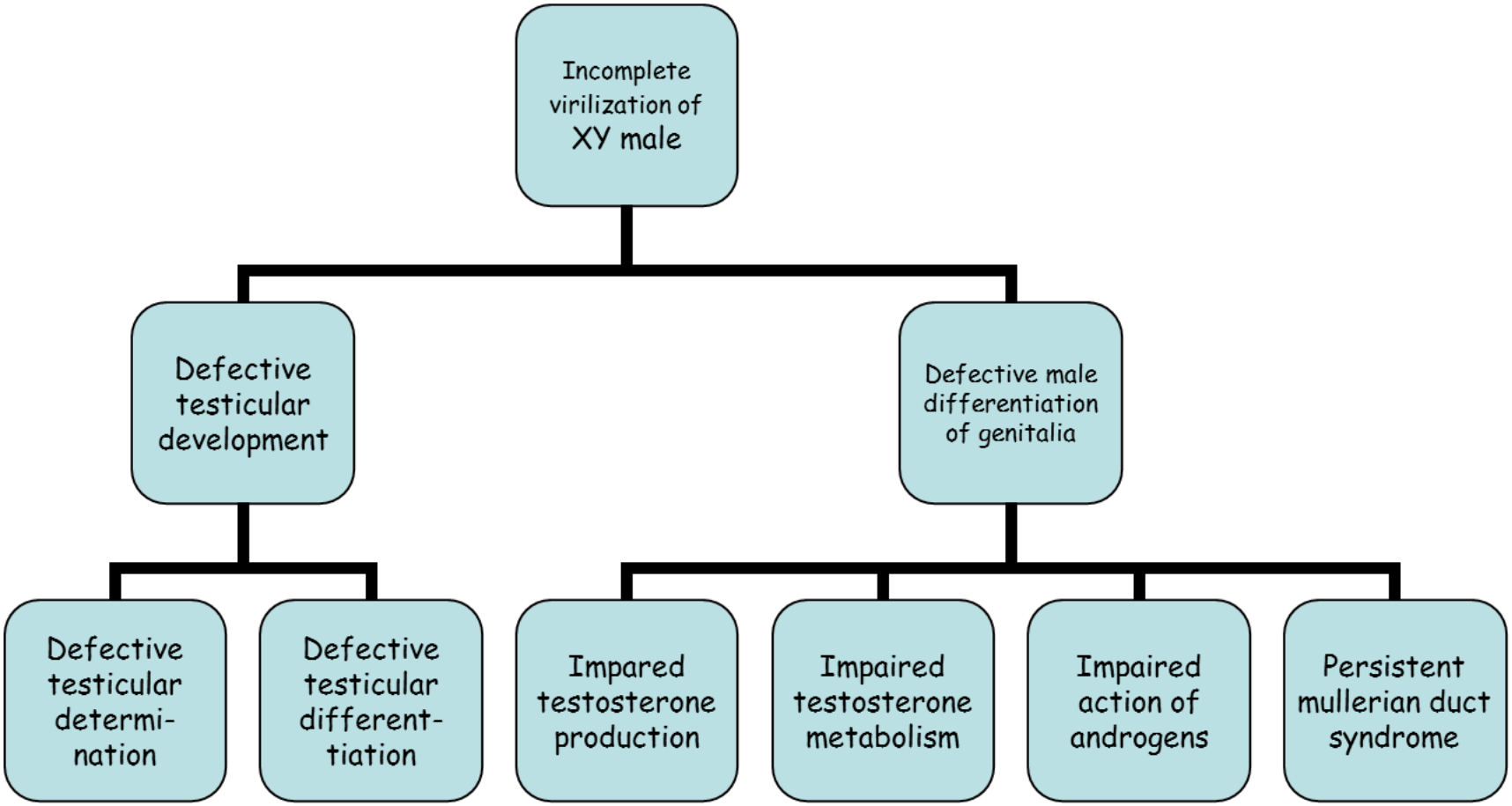
Ambigious genitalia: undervirilized male

- Hypospadias
- Labioscrotal folds
- Blind ending vagina
- Utricular cyst





Ambigious genitalia: undervirilized male

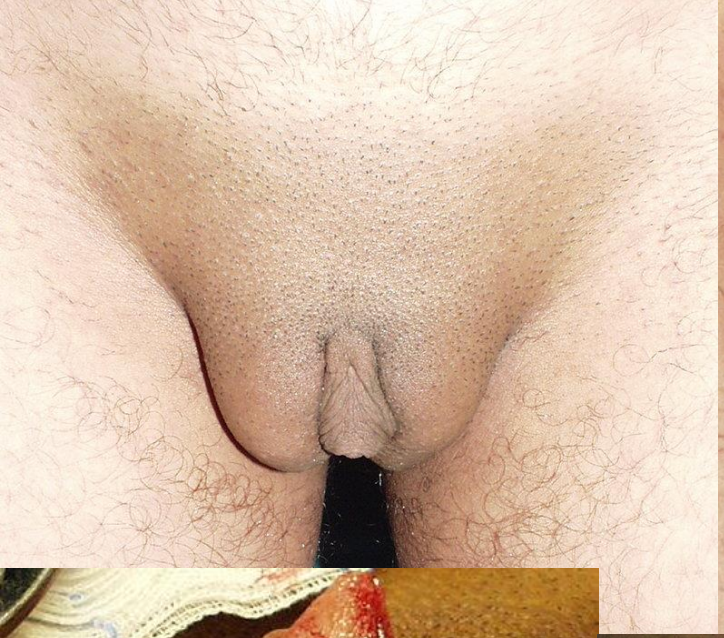
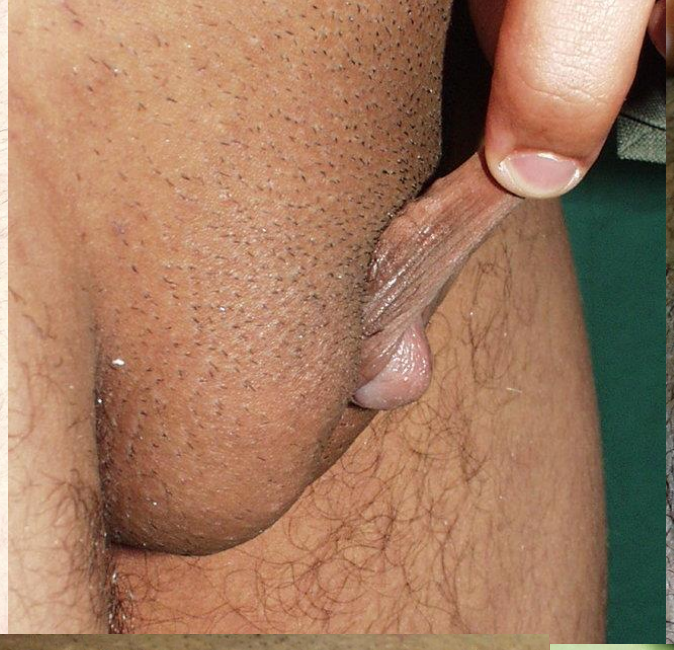
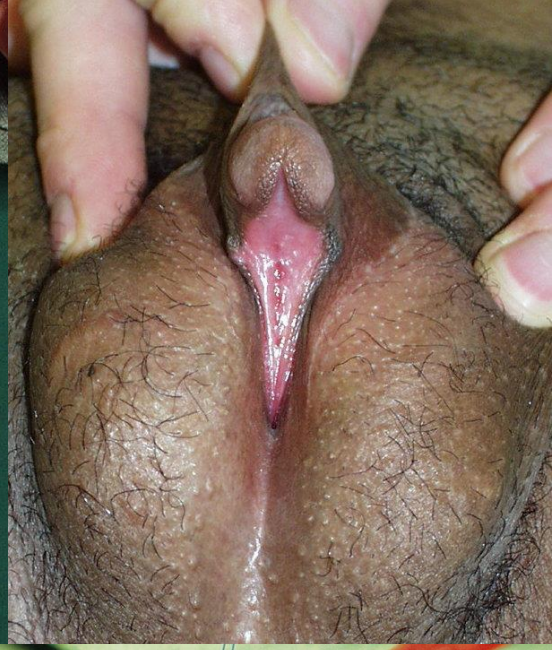
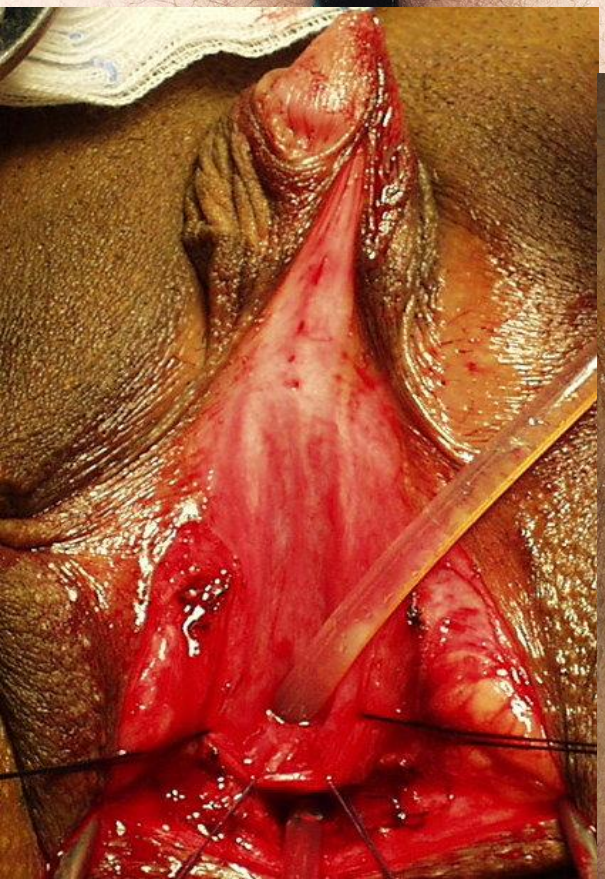
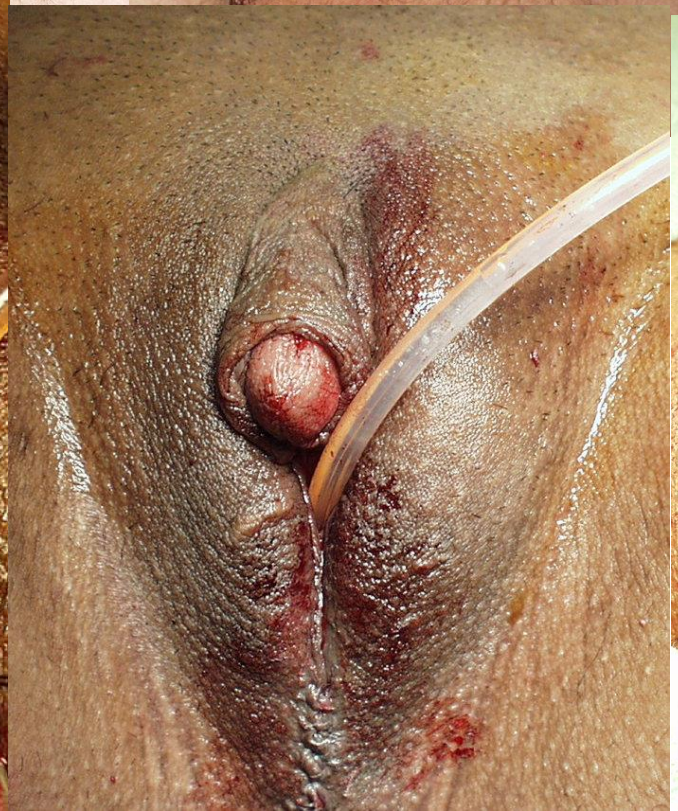
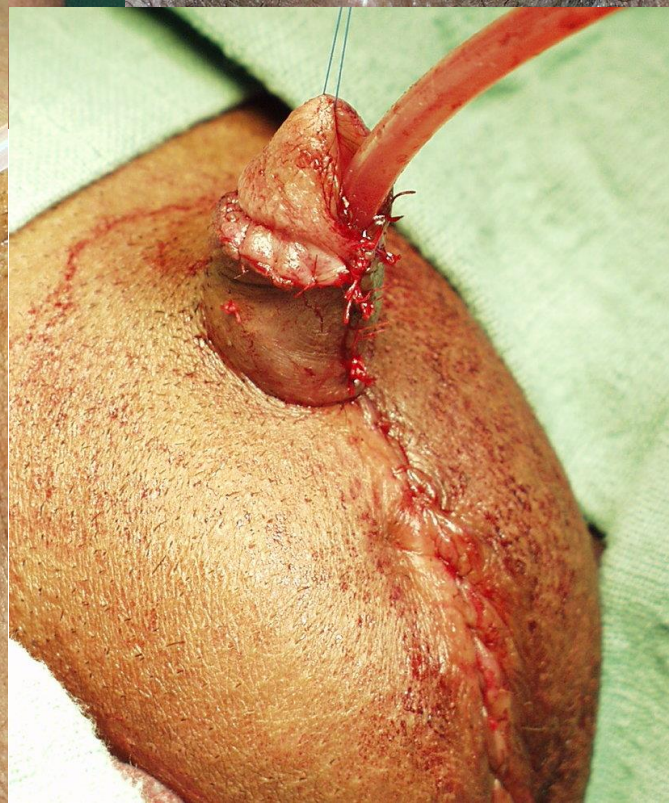


Leydig cell dysfunction: impaired testosterone synthesis

- From cholesterol to testosterone takes 5 enzymic steps. Defects of each of the enzymes involved has been described.
- Substrate to product ratio (after HcG stimulation).

Impaired testosterone metabolism: 5 alpha reductase deficiency

- Deficiency in production of dihydrotestosterone
- Rare Western Europe, common among communities in the Dominican Republic , Papua New Guinea, the Middle East and South America.
- Severe hypospadias, small vaginal opening
- Testis in the inguinal area.
- The male sex of rearing is preferred

Androgen insensitivity syndrome

- Complete (CAIS)
  - Unambiguous female
  - No internal female structures
  - Female gender
  - Remove gonads
- Partial (PAIS)
  - wide spectrum of undervirilized conditions ranging from mild hypospadias till slight clitoral hypertrophy with a normal vaginal opening.

Persistent müllerian duct syndrome

- No ambiguity of external genitalia
- 46 XY
- Local defect in production or action of MIS
- ‘hernia uteri inguinalis’
- Often associated with cryptorchidism
- In orchidopexy leave distal end of fallopian tube connected with spermatic cord

Disorders with dysgenetic gonads

- Pure gonadal dysgenesis
  - Unambiguous female
  - 45 XO Turner
  - 46 XX
  - 46 XY Swyer
- Mixed gonadal dysgenesis
  - Ambiguous genitalia
  - 1 testis & 1 streak gonad
  - Internal female/streak, male /testis
  - 46 XX / 45 XO

Ovotesticular DSD “True hermaphroditism”

- Rare in Europe and North America
- 46 XX, 46 XY, 46 XX-46XY
- Testis + Ovary (Ovotestis)
- From slightly virilized female to obviously male
- Sex assignment is difficult and outcome unpredictable

Investigation and management

- General concepts of care
- The multidisciplinary team
- Clinical evaluation
- Diagnostic evaluation
- Gender assignment in newborns
- Surgical management
- Sex steroid replacement
- Psychosocial management

General concepts of care

- First expert opinion before gender assignment
- Management in centre with multidisciplinary team
- All individuals should receive a gender
- Open communication with patients and families
- Respect for patient and family concerns

Multidisciplinary team

- Paeditric subspecialist in
  - Endocrinology
  - Surgery
  - Urology
  - Psychology
  - Psychiatry
  - Neonatology
  - Genetics
- Gynaecologist
- Endocrinologist
- Social work
- Nursing
- Medical ethics

Clinical evaluation

- Suggestive for DSD
  - Genital ambiguity
  - Enlarged clitoris, fused labia, inguinal labial mass
  - Bilateral undescended testes, micropenis, hypospadias with undescended testis
  - + family history (CAIS)
  - Discordance between, genital appearance and karyotype

Clinical evaluation

- Key points:
  - 2 gonaden palpeerbaar : 46 XY
  - Geen gonaad: 46 XX and URGENT !
  - 1 gonaad: mix van 46 XX, 46 XY, 45 XO,..
  - Testis ? Endocrine investigation

Clinical evaluation

- Late presentation
  - Unrecognized ambiguity
  - Inguinal hernia in female
  - Delayed or incomplete puberty
  - Virilization in female
  - Primary amenorrhea
  - Male breast development
  - Cyclic hematuria in males

Diagnostic evaluation

- Karyotyping with X and Y-specific probe detection
- Imaging
- 17-OH-progesterone, testoterone, gonadotropins, AMH, serum electrolytes, urinanalysis
- HcG and ACTH stimulation tests, biopsies, gene analysis
- Laparoscopy

Diagnostic evaluation

- Molecular diagnosis in 20% of DSD case
- Majority of 46XX virilized infants have CAH
- Only 50 % of 46 XY children with DSD will receive a diagnosis

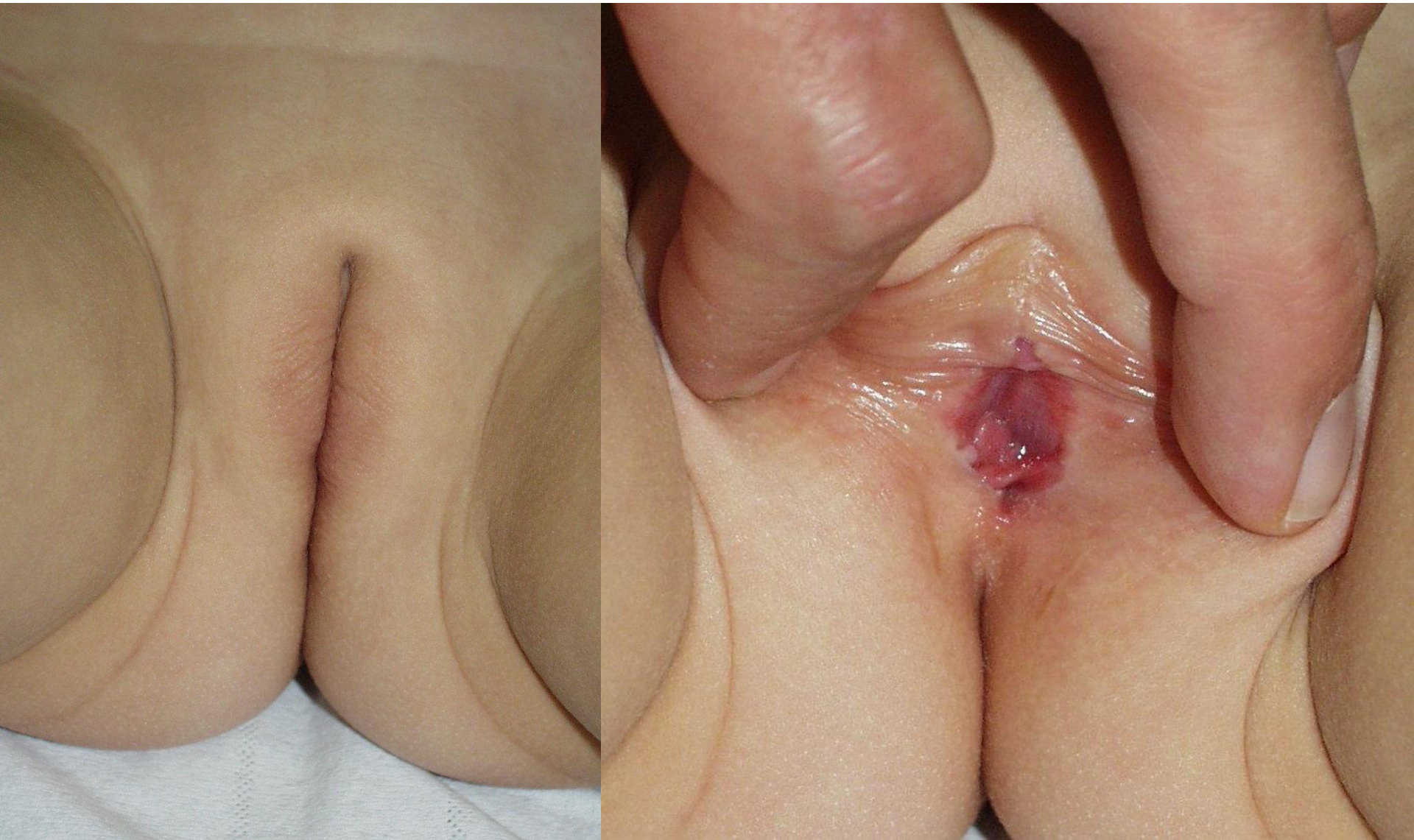
Treatment

- In ambiguous genitalia surgery and hormonal therapy if indicated are the treatment modalities
- Timing?
- A lot of controversy
- Psychological counseling of patients and parents
- Inform the patients

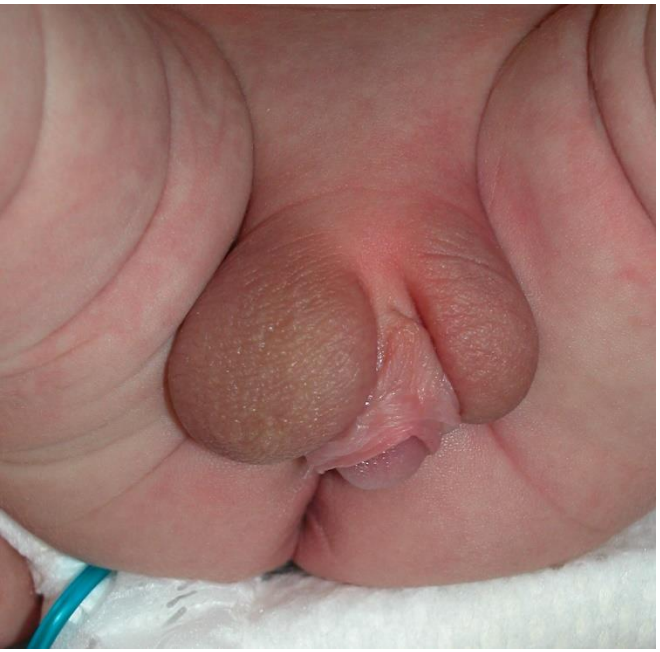
Surgical management

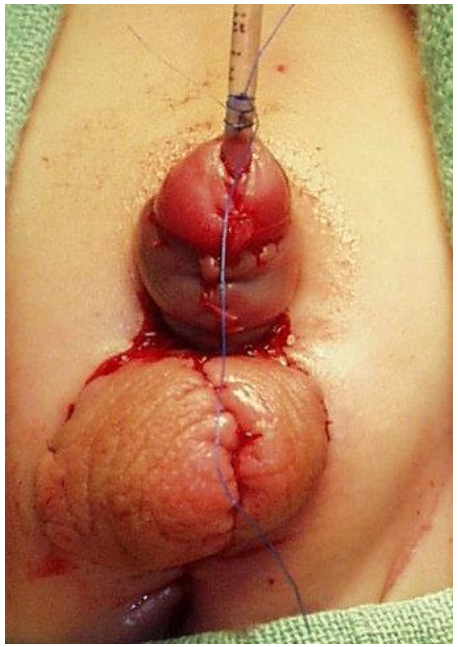
- No early surgery for mild deformities
- No evidence to abandon the early separation of vagina and urethra
- Absent vagina, vaginoplasty in adolescence
- Hypospadiasrepair
- Phalloplasty
- Gonadectomy

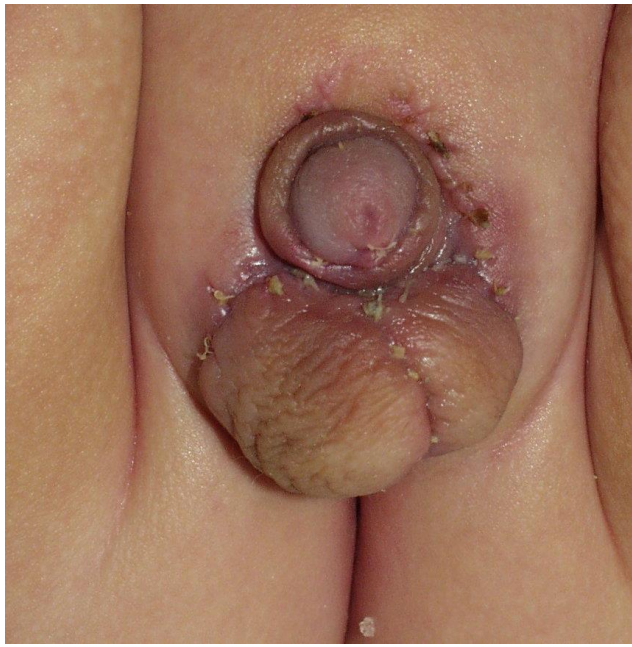
Feminising



Masculinising







Psychosocial management

- Mental health staff with expertise
- Psychological assessment of gender
- Disclosure
- Quality of life issues
- Sex therapy

What did we do at the end of last century?

- Multidisciplinary approach to the problem
- Decision on gender (not urgent in Belgium registration can be delayed till 6 months)
- Genderconfirming surgery early in life
  - Feminizing surgery: clitororeduction and vaginoplasty
  - Masculinizing surgery: hypospadias repair, repair of penoscrotal transposition and orchidopexy or removal of gonad(s)

What is the problem with early genderconfirming surgery?

Gender Neutral Surgery

- Is an oxymoron
- Surgery related to gender is never neutral
- Surgery in DSD
  - Masculinizing of undervirilized male genital
  - Feminising of overvirilized female genital

United Nations A/HRC/22/53

General Assembly

Distr.: General
1 February 2013

Original: English

Human Rights Council
Twenty-second session
Agenda item 3
Promotion and protection of all human rights, civil, political, economic, social and cultural rights, including the right to development

Report of the Special Rapporteur on torture and other cruel, inhuman or degrading treatment or punishment, Juan E. Méndez

http://www.ohchr.org/Documents/HRBodies/HRCouncil/RegularSession/Session22/A.HRC.22.53_English.pdf

Journal of Pediatric Urology (2014) 10, 8—10

ELSEVIER

Journal of Pediatric urology

EDITORIAL

The ESPU/SPU standpoint on the surgical management of Disorders of Sex Development (DSD)

SPU / ESPU

- Not limited to cosmetic surgery
  - Fluid retention, dysmenorrhea, sexual dysfunction
  - Poor penile development
  - Enlarged clitoris with painful erections
  - Gonadal cancers early in life
  - LUTD
  - ……..

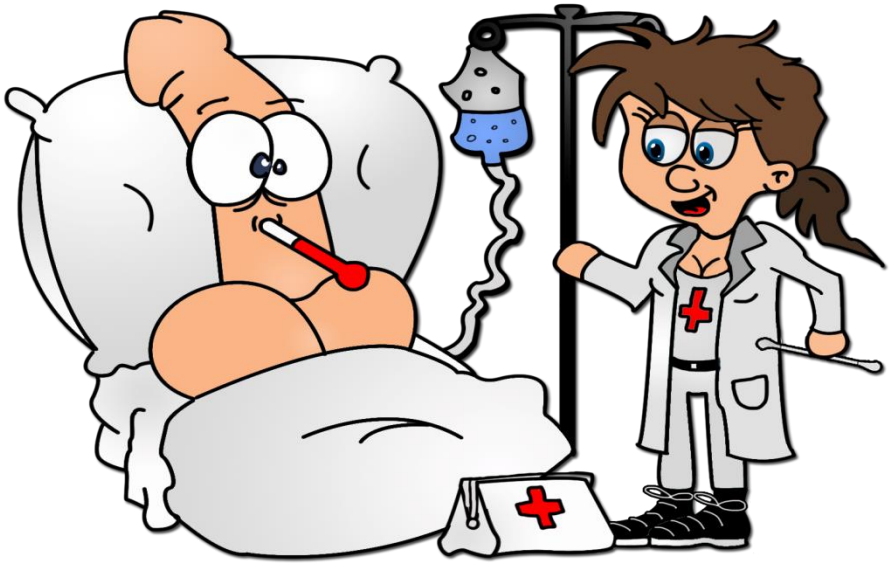
SPU / ESPU

- Aims of surgical and medical treatment
  - Avoid hazards related to altered anatomy
    - UTI
    - Painful erections
    - Continence problems
    - Malignancy risks
    - ……
  - Meeting parents' expectations
  - Help the individual to achieve future sexual function consistent with their gender identity
- Current dilemma
  - Reported long term outcomes are poor
  - Surgery is irreversible
  - Absence of informed consent

How to conclude?

- Discussion is essential, we must listen and answer….
- Prospective scientific approach to each specific DSD condition with outcomes research is mandatory
- Discriminate severe and mild conditions and identify medical risks related to no surgery
- Take the whole concept in the arguments to perform surgery
  - Genitals/gonads/hormones/LUT
- Multidisciplinary approach involving the parents in the discussion and talk about genderneutral options with the parents

Variaties in GeslachtsOntwikkeling



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