CLINICAL APPROACH TO DISORDERS OF SEX DEVELOPMENT

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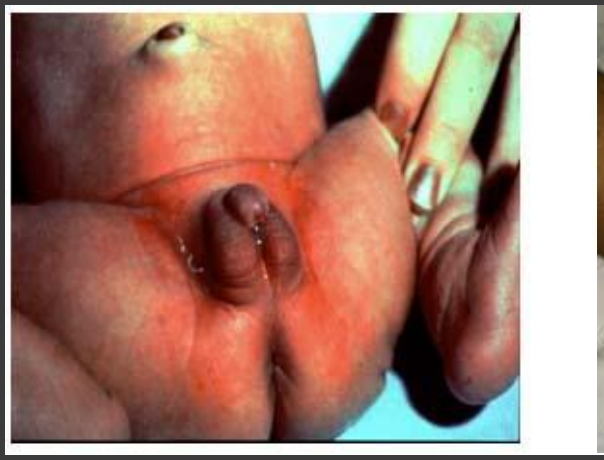
Introduction

- Sex assignment at birth is instantaneous in the majority of infants
- Sexual ambiguity/ intersex is a very sensitive issue
- Avoid undue delay in sex assignment

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Embryological, genetic & hormonal background

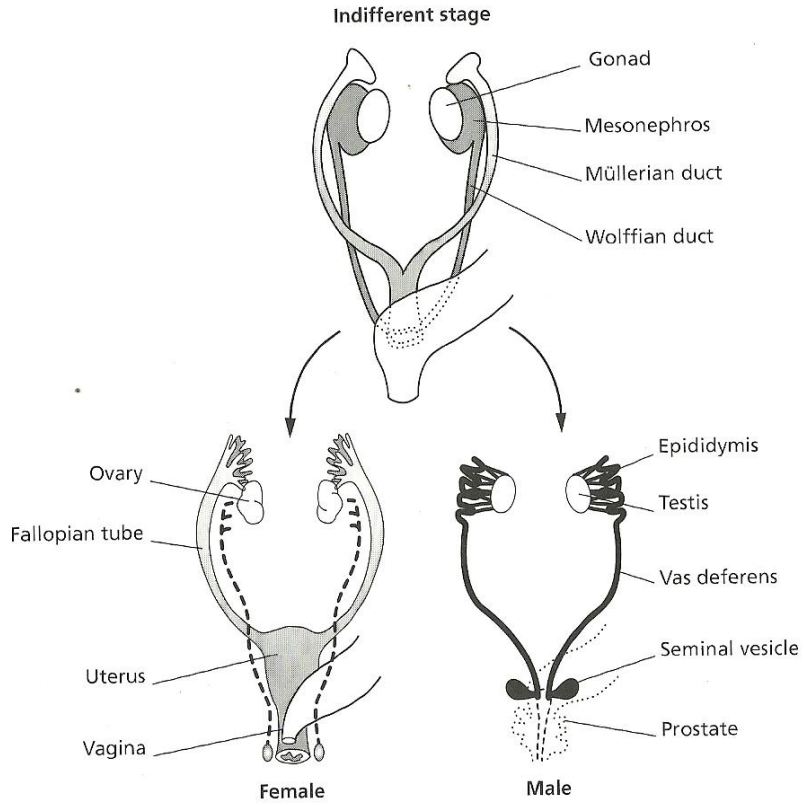
- Reproductive development is a highly integrated process
- Starts around 5 weeks of gestation and is complete 14, 15 years later when fertility is achieved at puberty
- Sexual abnormalities may present at different ages

Reproductive development

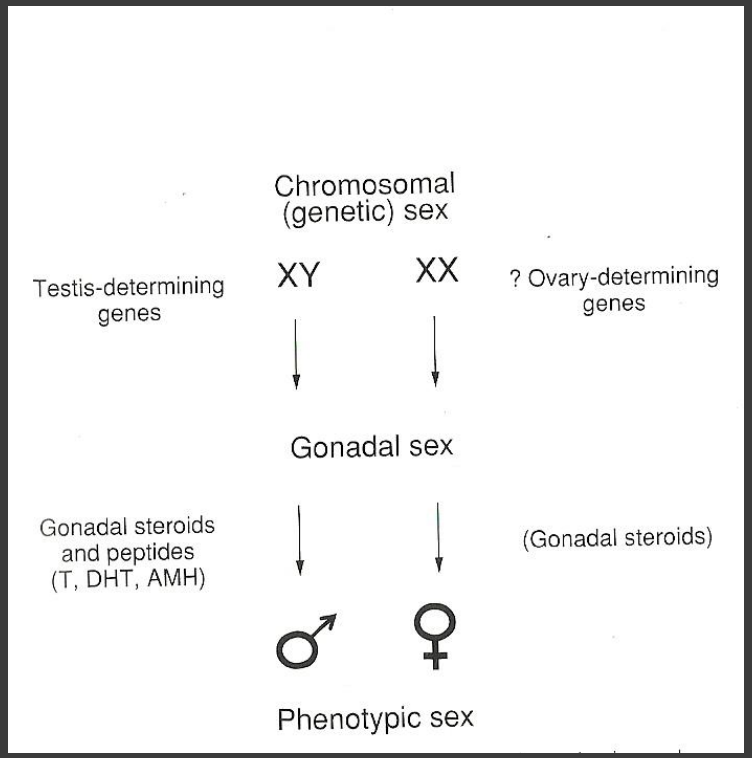
- Achieved in 4 stages:
  - Sex determination and differentiation(5weeks)
  - Development of the fetal hypothalamic, gonadotrope axis(from 6 weeks gestation)
  - Postnatal reproductive and endocrine events from birth to 6 months
  - Puberty

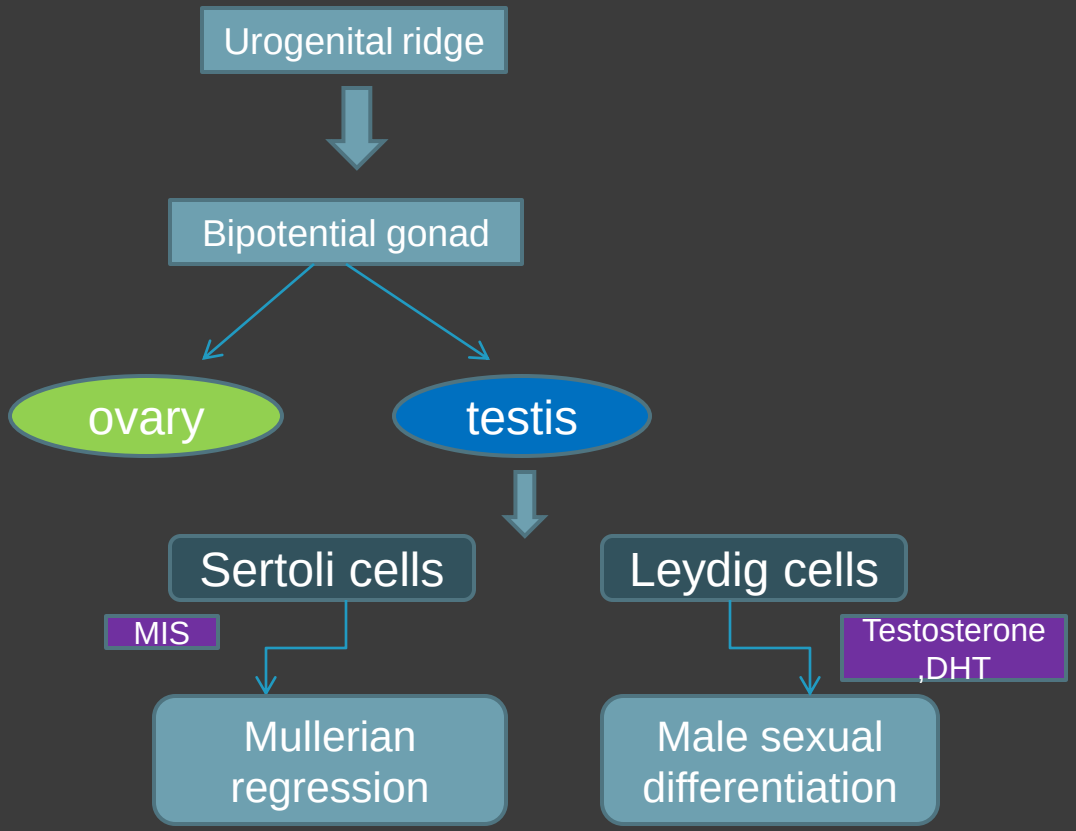
Sex determination & sexual differentiation

- Phenotypic sex determination begins with chromosomal sex and follows a cascade
- Presence of Testis-determining factor on Y chromosome(SRY) guides the indifferent gonad to develop into a testis
- Absence/alteration of this region causes indifferent gonad to develop into an ovary
- Stabilization/ regression of internal ducts


Indifferent stage
Gonad
Mesonephros
Müllerian duct
Wolffian duct
Ovary
Fallopian tube
Uterus
Vagina
Female
Epididymis
Testis
Vas deferens
Seminal vesicle
Prostate
Male

Sex determination & sexual differentiation





Differentiation of internal & external genitalia

- When testicular tissue is absent, the fetus completes internal sex duct development and external phenotypic development of a female

- When testicular tissue is present, testosterone and MIS are produced which guides development of male internal duct development and external male phenotype

Ambiguous genitalia a simple classification

Table 9.1. Causes of ambiguous genitalia: a functional classification.

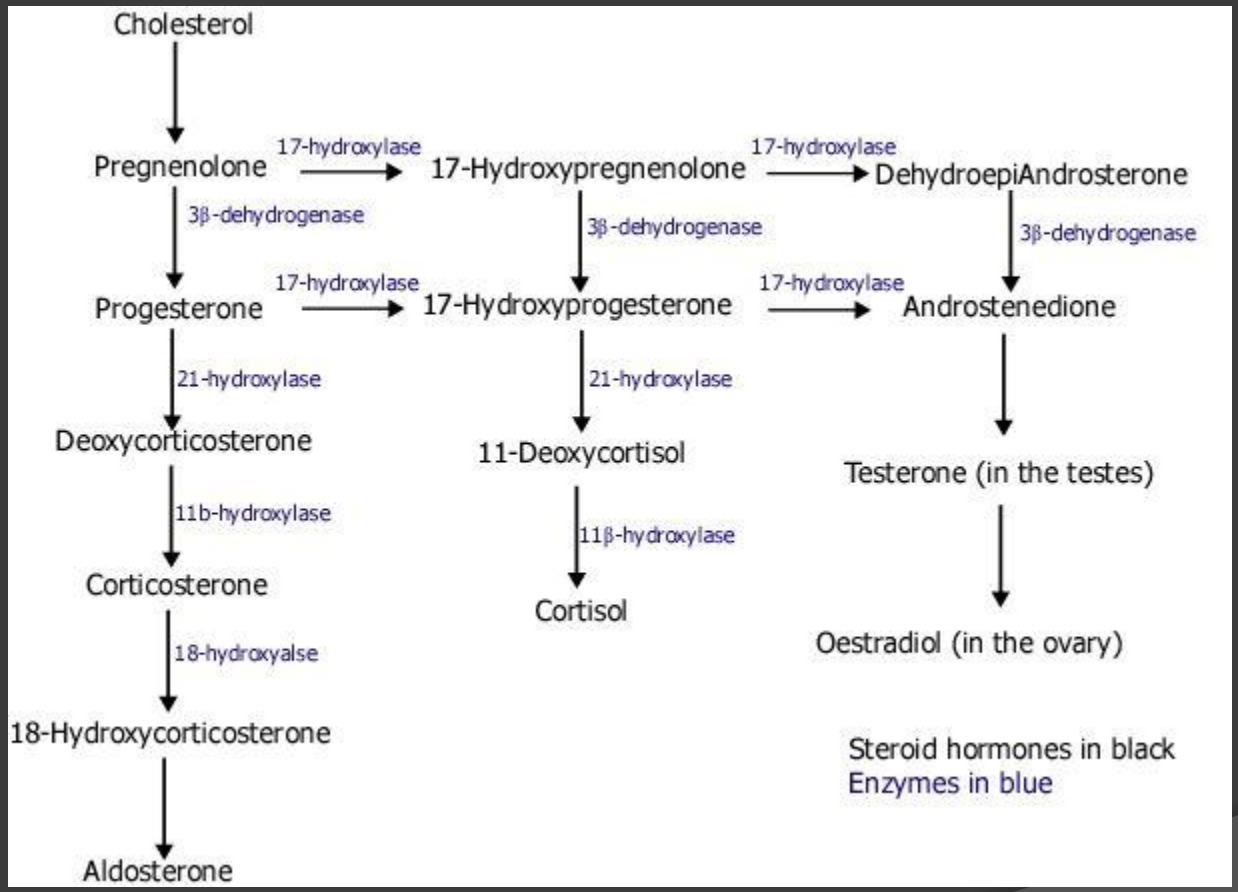
Type/cause	Illustrative examples
Masculinized female	
Fetal androgens	CAH, placental aromatase deficiency
Maternal androgens	Ovarian and adrenal tumors
Undermasculinized male	
Abnormal testis determination	Partial (XY) and mixed (XO/XY) gonadal dysgenesis
Androgen biosynthetic defects	LH receptor-inactivating mutations 17βOH-dehydrogenase deficiency 5α-reductase deficiency
Resistance to androgens	Androgen insensitivity syndrome variants
True hermaphroditism	
Presence of testicular and ovarian tissue	Karyotypes XX, XY, XX/XY
Syndromal	Denys–Drash, Frasier Smith–Lemli–Opitz

Masculinization of a female infant

- Congenital adrenal hyperplasia
- Fetal/ maternal androgens

- CAH is the commonest cause
- A straight forward diagnosis to establish
- Autosomal recessive enzymatic defects at different steps of adrenal hormone synthesis
- Most result in cortisol defficiency → stimulates pituitary to produce more POMC & ACTH.
- Also stimulates adrenal hypertrophy & hyperplasia

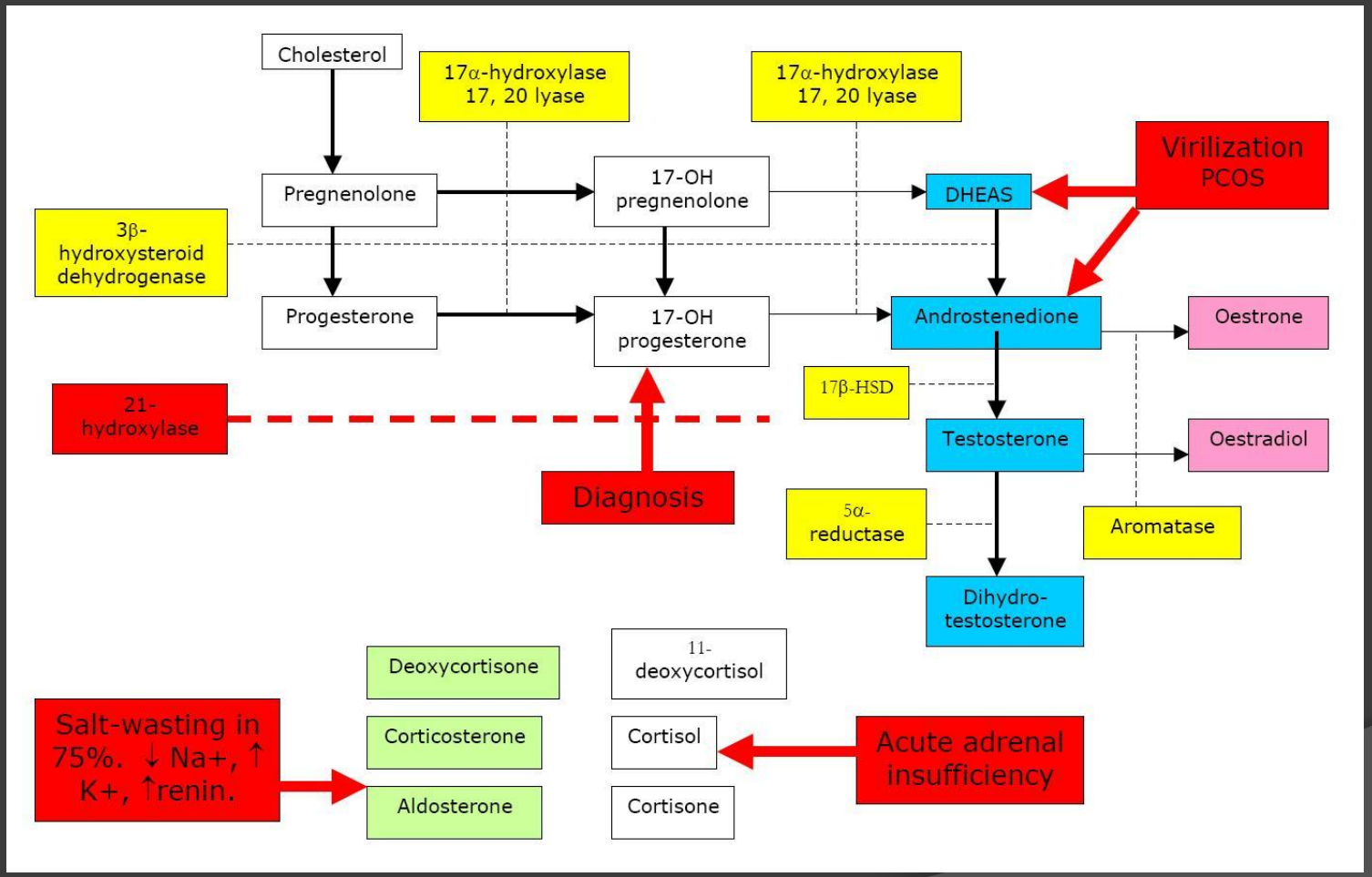
Congenital adrenal hyperplasia



21 Hydroxylase deficiency

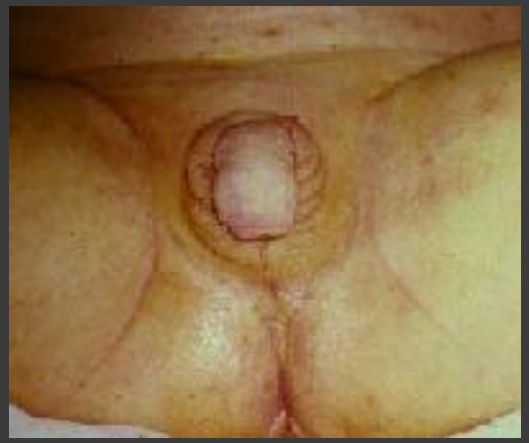
- Accounts for about 95% cases of CAH
- Enzyme deficiency causes inability to convert 17OHP → 11 Deoxycortisol → Cortisol deficiency
- 3 clinical forms
  - Salt wasting (classic)
  - Simple virilizing
  - Non classic

21 Hydroxylase deficiency



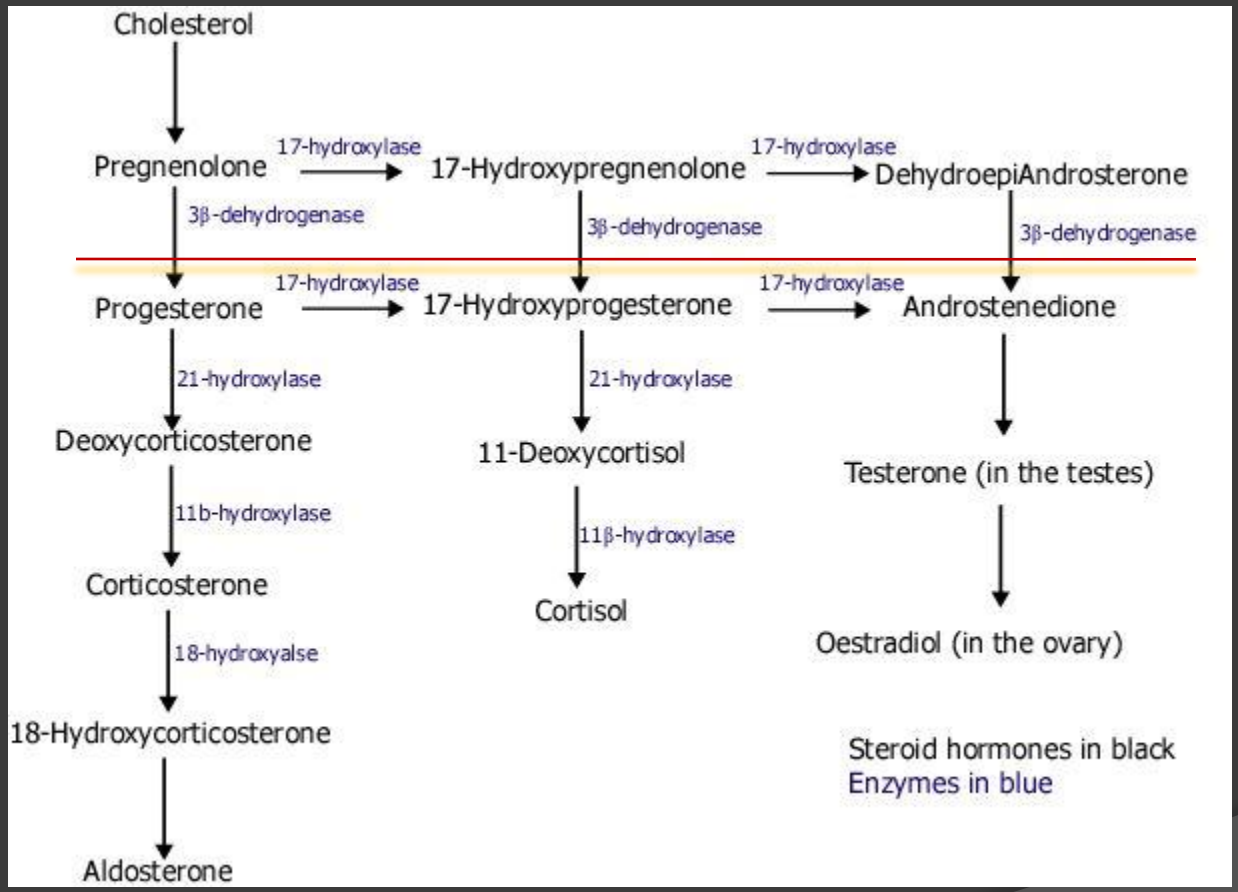
21 Hydroxylase deficiency

- Salt wasting type:
  - Complete absence of the enzyme eliminates both glucocorticoid & mineralocorticoid synthesis
  - Virilization of the female fetus range from mild clitoromegaly, labioscrotal fusion and traversing of the urethra along the enalarged clitoris
  - Male infants generally appear normal
- Simple virilizing:
  - Virilized female infants with no salt wasting
  - Precocious puberty in males
- Non classic:
  - Mild form of CAH
  - Females present in adult hood with hirsutism, menstrual irregularities, reduced fertility
  - There may be no phenotypic manifestations at all



3 beta hydroxysteroid dehydrogenase deficiency

- A rare cause of glucocorticoid, mineralocorticoid & androgen deficiency
- Genetic female: clitoromegaly, mild virilization due to overproduction of DHEA
- Genetic male: small phallus with severe hypospadias due to inadequate androgens
- Clinical presentation- male & female genital ambiguity, salt wasting


Cholesterol
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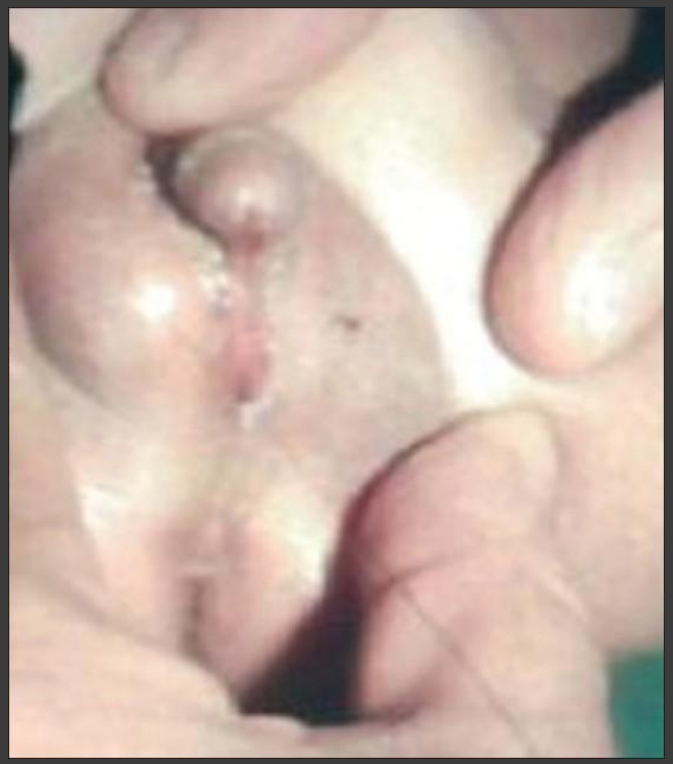
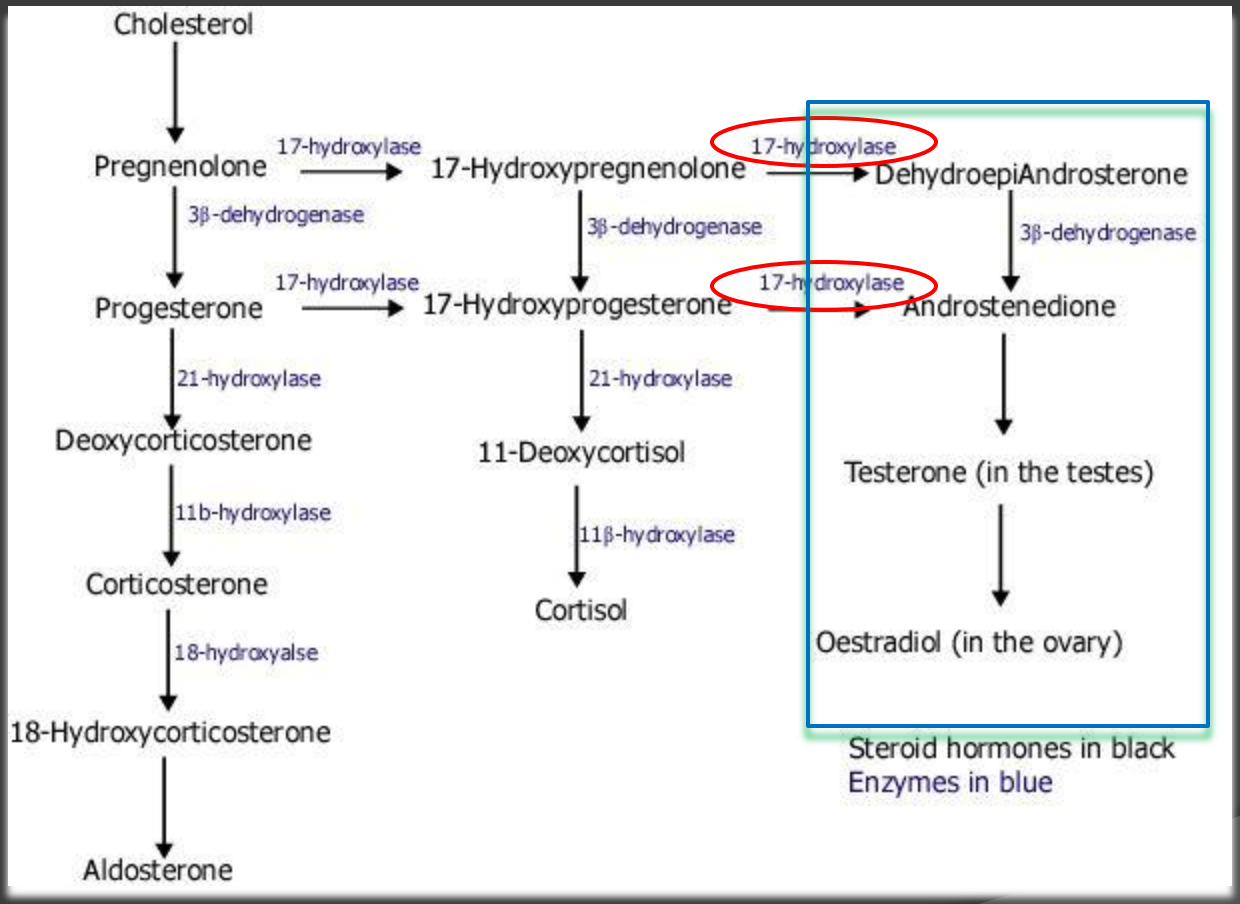
17-hydroxylase
17-Hydroxypregnenolone
17-hydroxylase
DehydroepiAndrosterone
3β-dehydrogenase
3β-dehydrogenase
3β-dehydrogenase
Progesterone
17-hydroxylase
17-Hydroxyprogesterone
17-hydroxylase
Androstenedione
21-hydroxylase
21-hydroxylase
Deoxycorticosterone
11-Deoxycortisol
Testerone (in the testes)
11b-hydroxylase
11β-hydroxylase
Corticosterone
Cortisol
Oestradiol (in the ovary)
18-hydroxyalse
18-Hydroxycorticosterone
Steroid hormones in black
Enzymes in blue
Aldosterone



17 alpha hydroxylase/ 17,20 lyase deficiency

- Rare
- Reduced synthesis of androgens
- Mild symptoms of glucocorticoid and mineralocorticoid deficiency
- Typical presentation:
  - Teenage female with sexual infantilism, failing to undergo puberty. Phenotypically normal at birth
  - Males have absent or incomplete development of external genitalia
- Over production of DOC causes Na retention, hypertension, hypokalaemia, suppress plasma renin activity & Aldosterone secretion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Aldosterone
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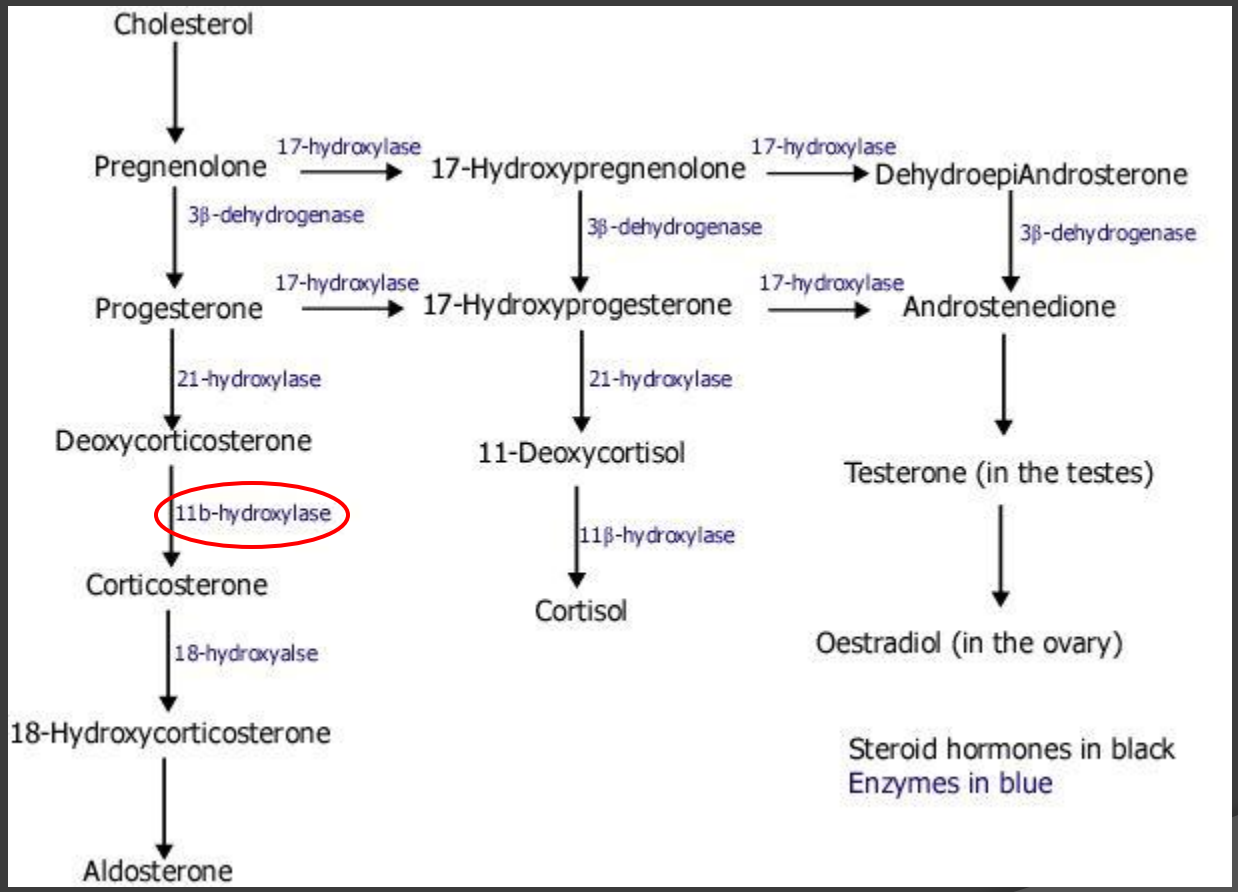
Enzymes in blue

11 beta hydroxylase deficiency

- Rare
- Enzyme deficiency leads to inability to convert DOC to Aldosterone
- High concentrations of DOC causes hypertension
- Sexual ambiguity is seen in female babies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Lipoid adrenal hyperplasia (congenital adrenal hypoplasia)

- Most severe disorder of steroid hormone synthesis
- The lesion prevents conversion of cholesterol to pregnenolone
- Absence of all steroids
- Male pseudohermaphroditism
- Salt wasting

Maternal androgens

- Foetus is generally protected from maternal androgens by placental aromatase
- Causes virilization of the female infant in the presence of placental aromatase deficiency

The undermasculinized male

- 3 broad categories
  - Defects in testis determination
  - Defects in androgen biosynthesis
  - Defects in androgen action

Defects in testis determination

- Complete or partial gonadal dysgenesis is the end result
- Normal development and function of sertoli & leydig cells are essential for hormone mediated sex differentiation of internal & external genitalia in the male
- Streak gonads are completely undifferentiated
- When both gonads are streak, phenotype is female – “ complete sex reversal with no ambiguity”

Defects in testis determination

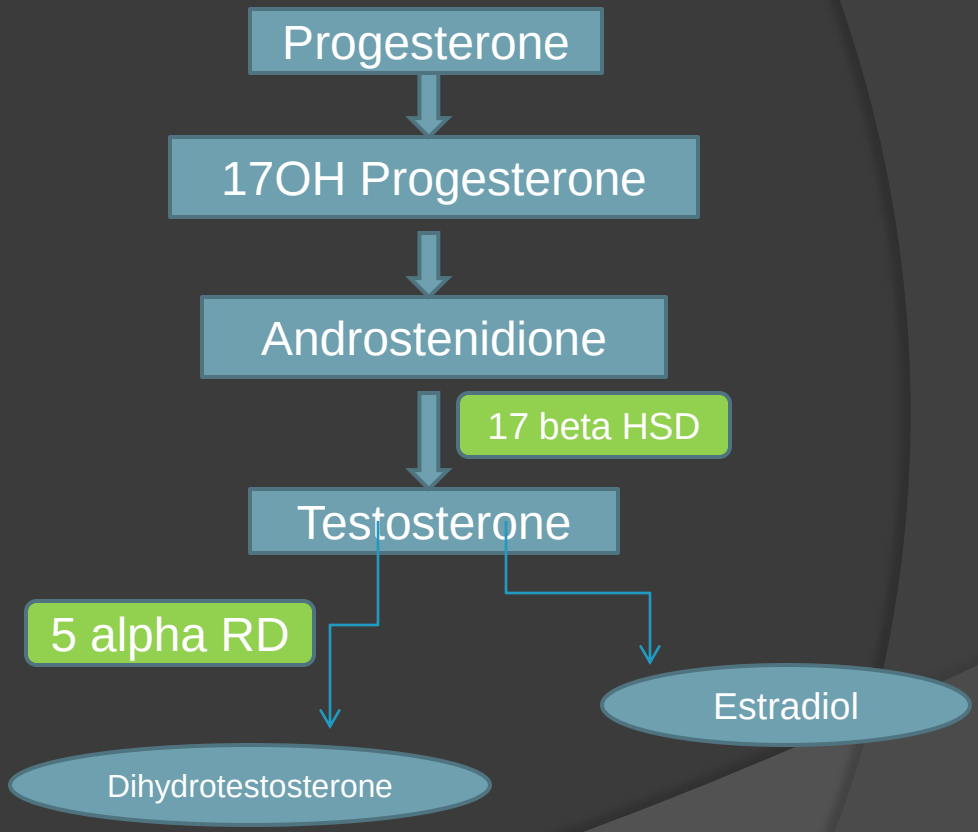
- Partial forms of gonadal dygenesis causes sexual ambiguity
- Mixed gonadal dysgenesis – 45X/46XY mosaicism. The degree of sex reversal is determined by the proportion of X and XY cell lines
- Syndromes with gonadal dysgenesis –
  - Denys Drash, Frasier

Defects in androgen biosynthesis

- Fetal leydig cell androgen synthesis is dependent on placental hCG initially and LH thereafter
- Mutations in LHR gene causes severe under masculinization
- Investigations will show
  - Low Testosterone, high LH
  - No Testosterone response to hCG stimulation
  - Histology – absent leydig cells

Enzyme deficiencies in Testosterone synthesis

- 17 beta hydroxysteroid dehydrogenase deficiency
  - Ambiguity range from complete sex reversal to varying degrees of hypospadias
  - Low Testosterone , normal AMH
  - hCG stimulation
    - Testos: Androstenidione ratio<0.8
- 5 alpha Reductase deficiency
  - Fusion of labio scrotal folds is dependent on DHT. Testosterone has a mild effect. Causes partial fusion
  - Testosterone, Androstenidione, ratio are all normal



Defects in androgen action

- 46XY with normal Androgen levels defines tissue specific resistance to the action of androgens
- Total resistance causes Complete Androgen Insensitivity Syndrome with complete XY sex reversal(CAIS/ Testicular Feminization)
- Some response to hormones results in Partial Androgen Insensitivity Syndrome(PAIS-manifest as mild clitoromagaly, true ambiguity, hypospadias or impaired fertility in an otherwise normal male

Androgen insensitivity

elevated LH & Testosterone levels, androgens are aromatized to estrogens causing breast development

- CAIS
  - Normal female phenotype at puberty
  - Scanty pubic & axillary hair
  - Primary amenorrhoea
  - Inguinal herniae in infancy
- PAIS
  - More male phenotype
  - Gynecomastia at puberty
  - Breast cancer common

Ovotesticular DSD (true hermaphroditism)

- Presence of both testicular and ovarian tissue which are well differentiated
- 46XX is the most frequent karyotype, majority having normal external male genitalia. Testis are small & firm, height below average, gynaecomastia is common.
- Majority are SRY gene positive due to X-Y chromosomal interchange during paternal meiosis

Sex chromosome abnormalities

- Klinefelters syndrome(47XXY)
  - affects around 1:600 males
  - Primary hypogonadism with small testis
  - Fibrosis of seminiferous tubules causing infertilty
  - Tall stature with long legs
  - Behavioural & psychological problems
  - Gynecomastia at puberty

Investigations

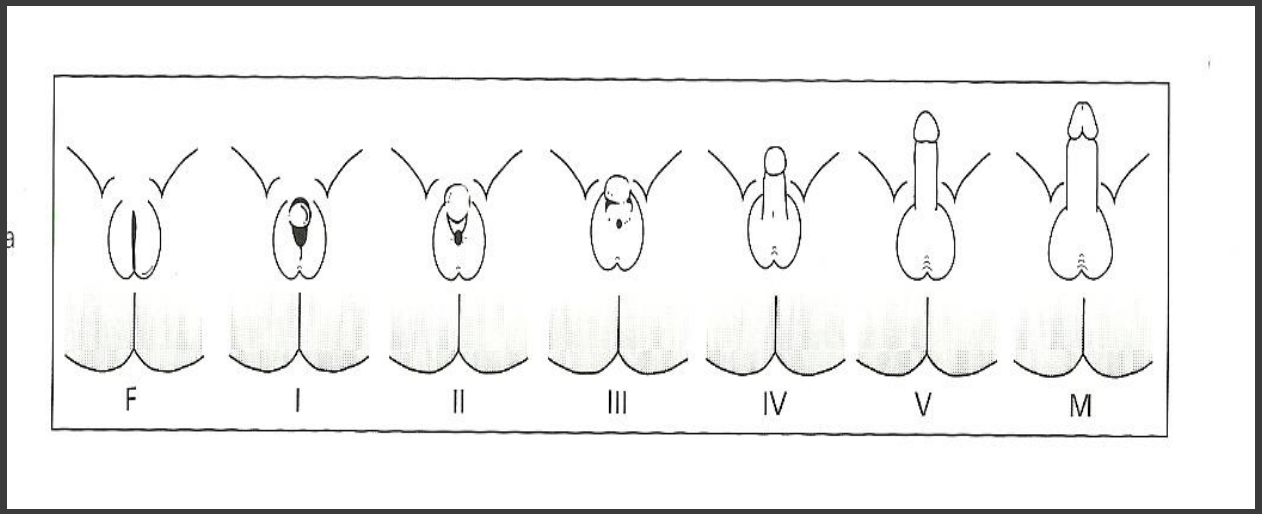
- The aim is to arrive at a functional diagnosis to allow early sex assignment
- Local protocols should be determined by the available facilities & practice
- Clinical assessment

Idealized male: XY karyotype with penile length 2.5-4.5 cm, normal position of the urethral meatus, testes in the scrotum

Idealized female: XX karyotype with clitoral size 0.5- 0.85 cm, normal female reproductive tract

Clinical assessment

- Family history, prenatal exposure to reproductive teratogens
- Examination of the ext. genitalia should record the following:
  - Phallus – size, chordee, micropenis/ clitoromegaly
  - Site of urethral opening
  - External orifices in the perineum
  - Development of labioscrotal folds – bifid scrotum/ fused labia, rugosity, pigmentation
  - Whether gonads are palpable & position
- Prader score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I
II
III
IV
V
M

Laboratory investigations

- Genetic sex: FISH analysis for Barr bodies
- Karyotype to confirm FISH results, analysis of a sufficient no. of mitoses to exclude mosaicism
- Karyotype 46XX→ 17OHP>300nmol/L with uterus in USS confirms 21 hydroxylase deficiency
- Ancillary biochemical tests to identify salt loosers
- Synacthen(ACTH) stimulation test in premature infants and when rarer CAH is suspected

Laboratory investigations

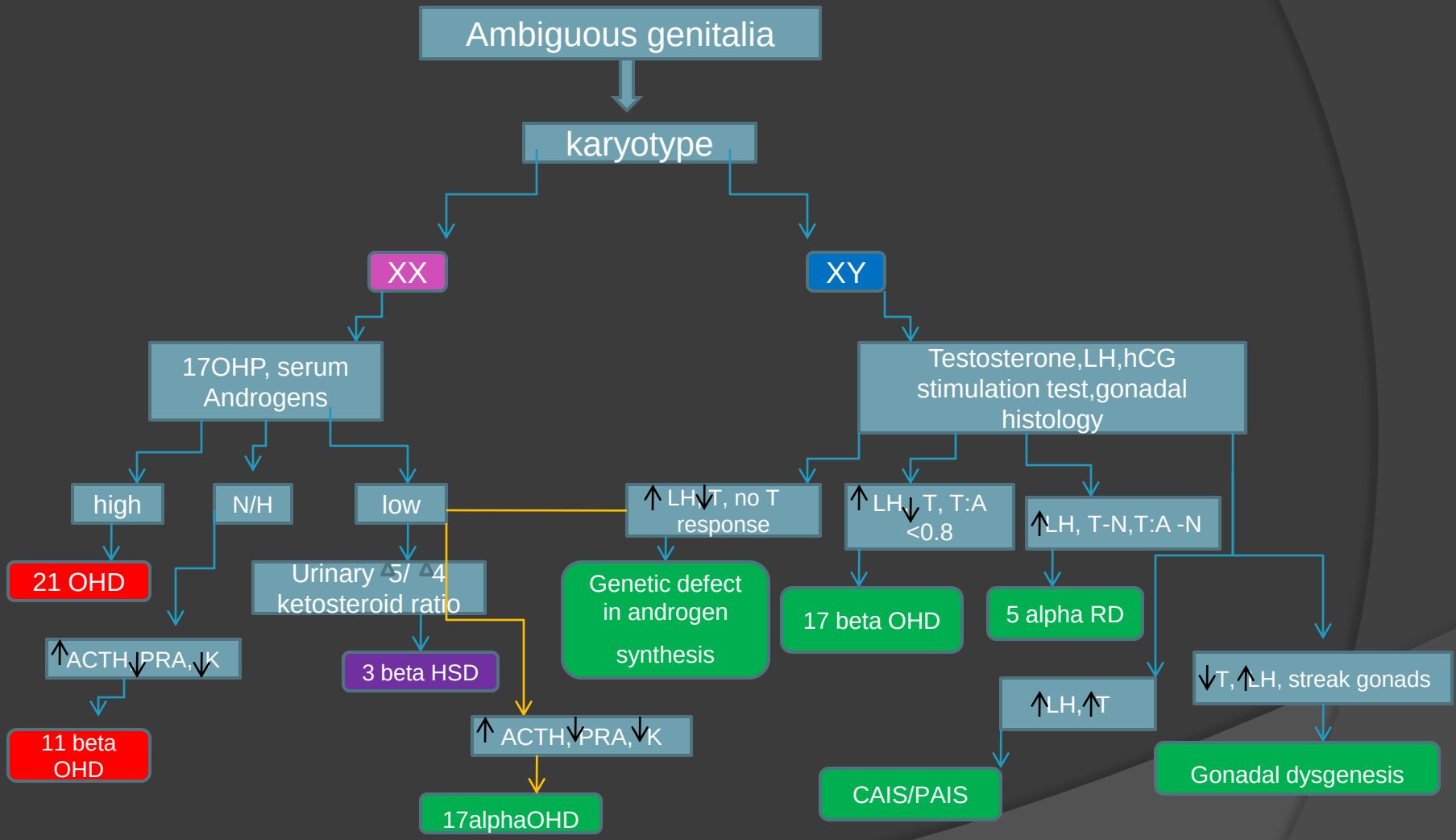
- Measurement of urinary steroid metabolites by gas chromatography
- Establishing location & function of testes in the XY or XY/XO infant with hCG stimulation test. Can be coupled with imaging & laparoscopy to identify the gonadal site and histology. Pre & post hCG blood samples analyzed for Testosterone, Androstenidione & DHT. Concomitant 24 hr urinary steroid analysis can be performed
- Testosterone : Androstenidione ratio
  - > 0.8 – Androgen insensitivity
  - Normal – 5 alpha reductase deficiency
  - <0.8 – 17 beta hydroxysteroid dehydrogenase deficiency

Laboratory investigations

- Sertoli cell function – measuring AMH, Inhibin B. both proteins are elevated during infancy. AMH levels fall during puberty in response to Testosterone
  - Androgen insensitivity – ↑ AMH
  - Gonadal dysgenesis – ↓ AMH
  - Anorchia – AMH undetectable
- Imaging with US and MRI to delineate the internal genital anatomy
- Histology to provide exact details of gonads by laparoscopy

Clinical presentation	Laboratory findings	Likely diagnosis
Masculinization of female infant, salt wasting	↑17-OHP before & after ACTH, ↑serum Androgens,↑urine 17-ketosteroids, suppression of androgens with glucocort treatment,↑ ACTH & PRA	21-OHD
Male & female pseudohermaphroditism, salt wasting	↑ACTH, PRA,↑▲5/▲4 steroids, ↑▲5 steroids before & after ACTH , ↓17-OHP	3 Beta -HSD
Masculinization of female infant,postnatal virilization in males & females	↑11-deoxycortisol before & after ACTH, ↑ACTH &↓PRA, hypokalaemia, ↑serum Androgens & 17 ketosteroids, suppression of androgens with glucocort treatment	11 Beta OHD
Male pseudohermaphroditism, female sex infantilism, hypertension	↑DOC, low 17 alpha hydroxylated steeroids and poor response to ACTH, poor response to hCG, hypokalaemia, ↑ACTH &↓PRA	17 Alpha-OHD

Summary of clinical evaluation



Thank you