Anomalies of genital organs in newborn.

sex determining features

genetical

gonadal

genital

somatical

phenotypic

psychosexual

the genetical sex = chromosomal

46 XX

46XY

the gonadal sex
= a kind of gonad

ovary

testis

the genital sex

Internal and external genitalia

the somatic sex

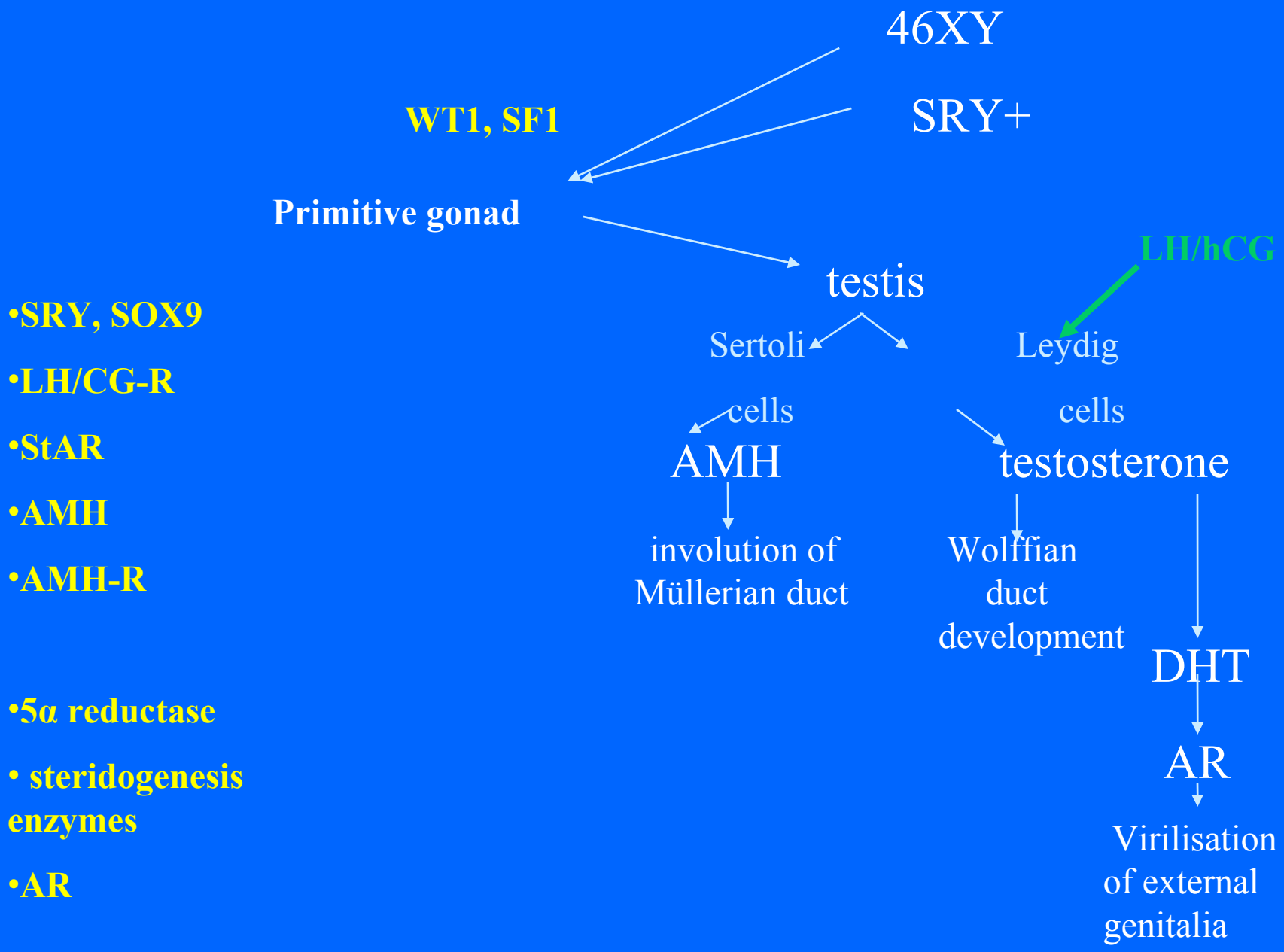
Secondary sex characteristics apearing at the puberty

the phenotypical sex

External and internal genitalia and secondary sex characteristics

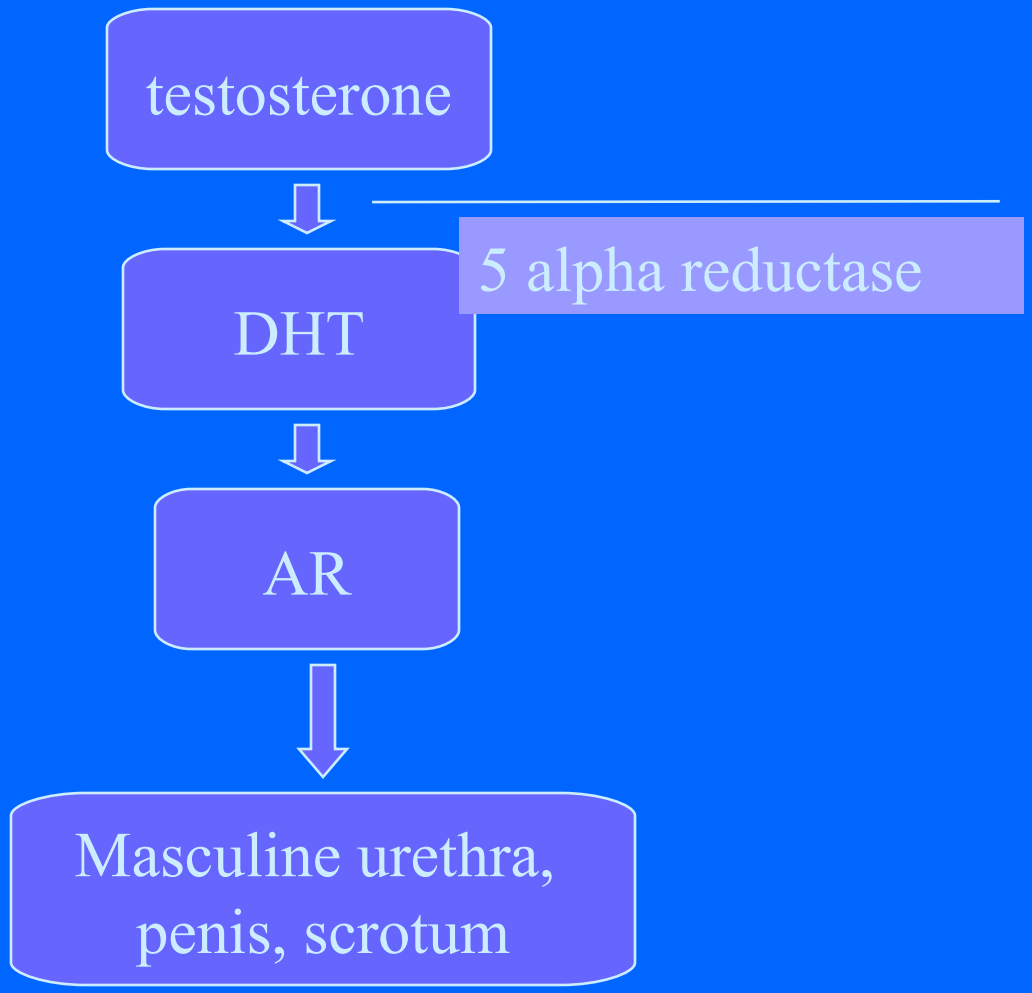
the psychosexual sex

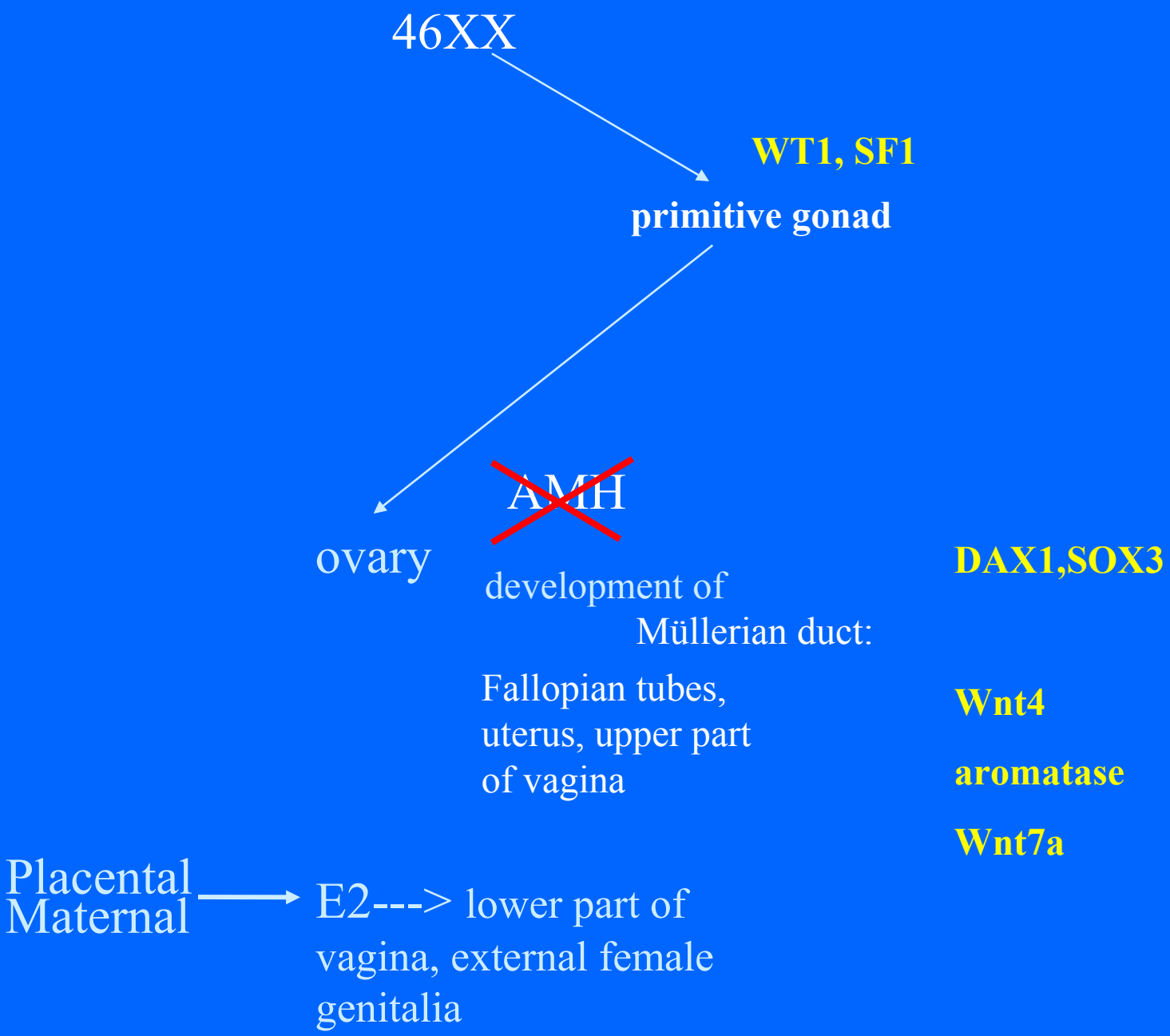
Sex gender, sexual behaviour


46XY
SRY+
WT1, SF1
Primitive gonad
testis
LH/hCG
Sertoli
cells
Leydig
cells
AMH
testosterone
involution of
Müllerian duct
Wolffian
duct
development
DHT
AR
Virilisation
of external
genitalia
•SRY, SOX9
•LH/CG-R
•StAR
•AMH
•AMH-R
•5α reductase
• steridogenesis
enzymes
•AR

Differentiation of external genitalia in male

8-14 Hbd




46XX
WT1, SF1
primitive gonad
AMH
ovary
development of
Müllerian duct:
Fallopian tubes,
uterus, upper part
of vagina
DAX1,SOX3
Wnt4
aromatase
Wnt7a
Placental
Maternal
E2---> lower part of
vagina, external female
genitalia

Basic steps in sex development

1. genetic sex determination- *genetic information determines that undifferentiated gonad differentiates into a testis or an ovary*

2. sex phenotype- *an active process of male sex differentiation: inhibition the müllerian ducts by AMH, stabilization of wolffian ducts (in absence of testis – female genitalia)*

3. external genitalia- *in male virilization by DHT*

In female- due to maternal and placental estrogens.

Conclusion: In absence of testis the genital primordia are irreversibly developing as female genitalia.

Classification of intersex disorders

I. Defective development of the primordial gonad and the bipotential reproductive system

defects of SF-1; WT1

II. Abnormal gonadal determination

gonadal dysgenesis;

true hermaphroditism (bisexual gonad)

III. Male pseudohermaphroditism(MPH)

Leydig cells disorders, testosterone, androgen receptors

IV. Female pseudohermaphroditism (FPH)

fetal: CAH, aromatase deficiency, maternal hyperandrogenism

Proposed revised nomenclature

Previous:	Proposed:
Intersex; hermaphroditism	– disorders of sex development
True hermaphrodite	- ovotesticular DSD
Male pseudohermaphrodite	- 46,XY DSD
Female pseudohermaphrodite	– 46,XX DSD

An example of a DSD classification

Sex chromosome DSD

- Turner sy
- Klinefelter sy
- 45,X/46,XY DSD
- 46,XX/46,XY DSD

46,XY DSD

- Disorders of gonadal (testicular) development
- Disorders of androgen synthesis
- other

46,XX DSD

- Disorders of gonadal (ovarian) development
- Androgen excess
- other

Defective development of the primordial gonad and the bipotential reproductive system

defects of SF-1

- gonadal and adrenal steroidogenesis disorders

defects of WT1

- dysgenetic gonads, degenerative renal diseases, Wilms' tumour

Abnormal gonadal determination

gonadal dysgenesis

- gonadal dysgenesis in XY, Klinefelter's syndrome, Turner's syndrome, gonadal dysgenesis in XX

true hermaphroditism (bisexual gonad)

- ovarian and testicular tissue in the same or opposite gonads

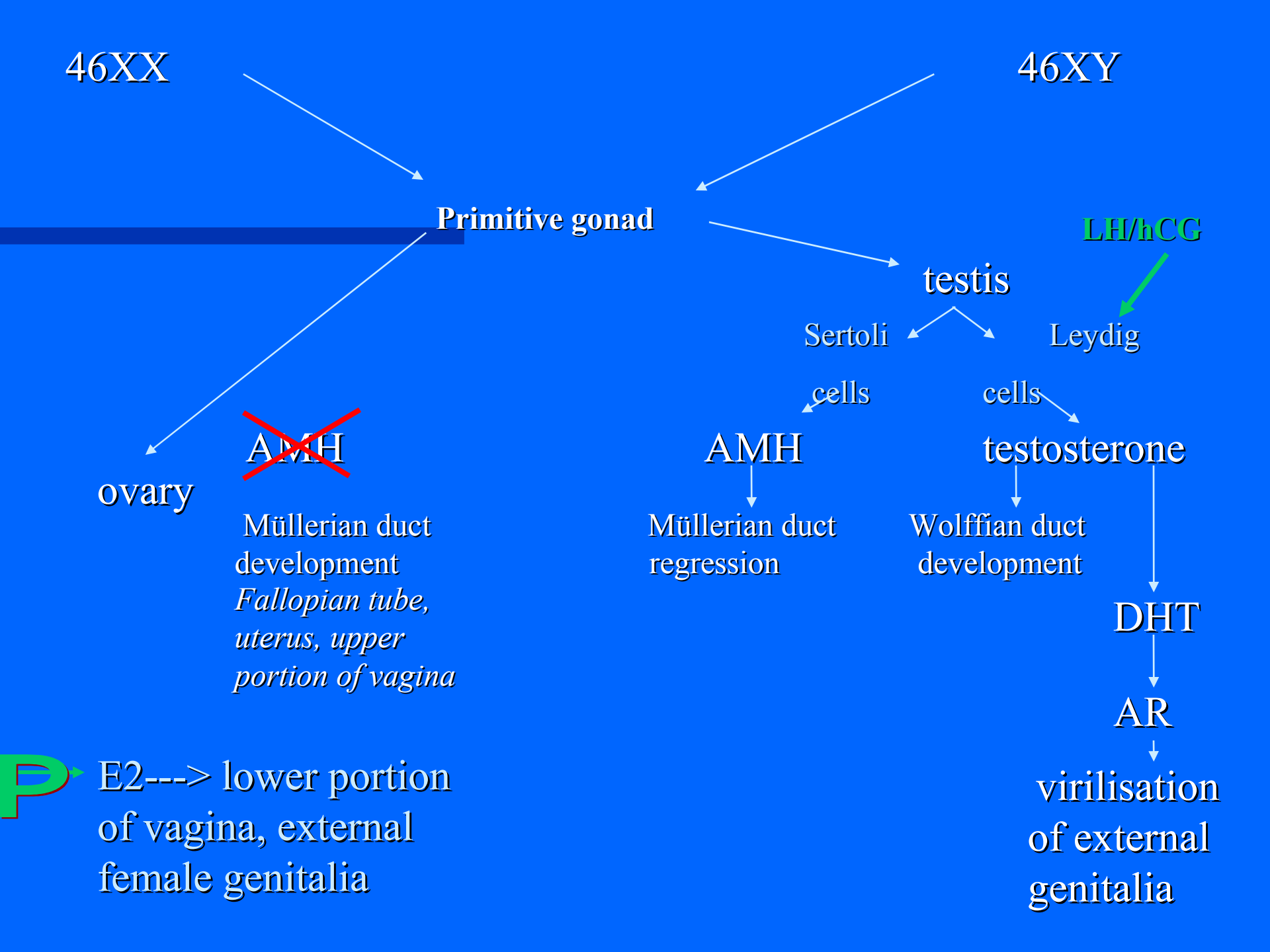
Male pseudohermaphroditism (MPH)

= incomplete masculinisation of XY male

Leydig cells/ LH/ LH-receptor disorders

errors of testosterone biosynthesis and metabolism (DHT)

androgen receptors insensitivity (complete/incomplete)


46XX
46XY
Primitive gonad
LH/hCG
testis
Sertoli cells
Leydig cells
AMH
testosterone
ovary
AMH
Müllerian duct development
Fallopian tube, uterus, upper portion of vagina
Müllerian duct regression
Wolffian duct development
DHT
AR
virilisation of external genitalia
E2---> lower portion of vagina, external female genitalia

An example of a DSD classification

Sex chromosome DSD

Turner sy

Klinefelter sy

45,X/46,XY DSD

46,XX/46,XY DSD

46,XY DSD

Disorders of gonadal (testicular) development

Disorders of androgen synthesis

other

46,XX DSD

Disorders of gonadal (ovarian) development

Androgen excess

other

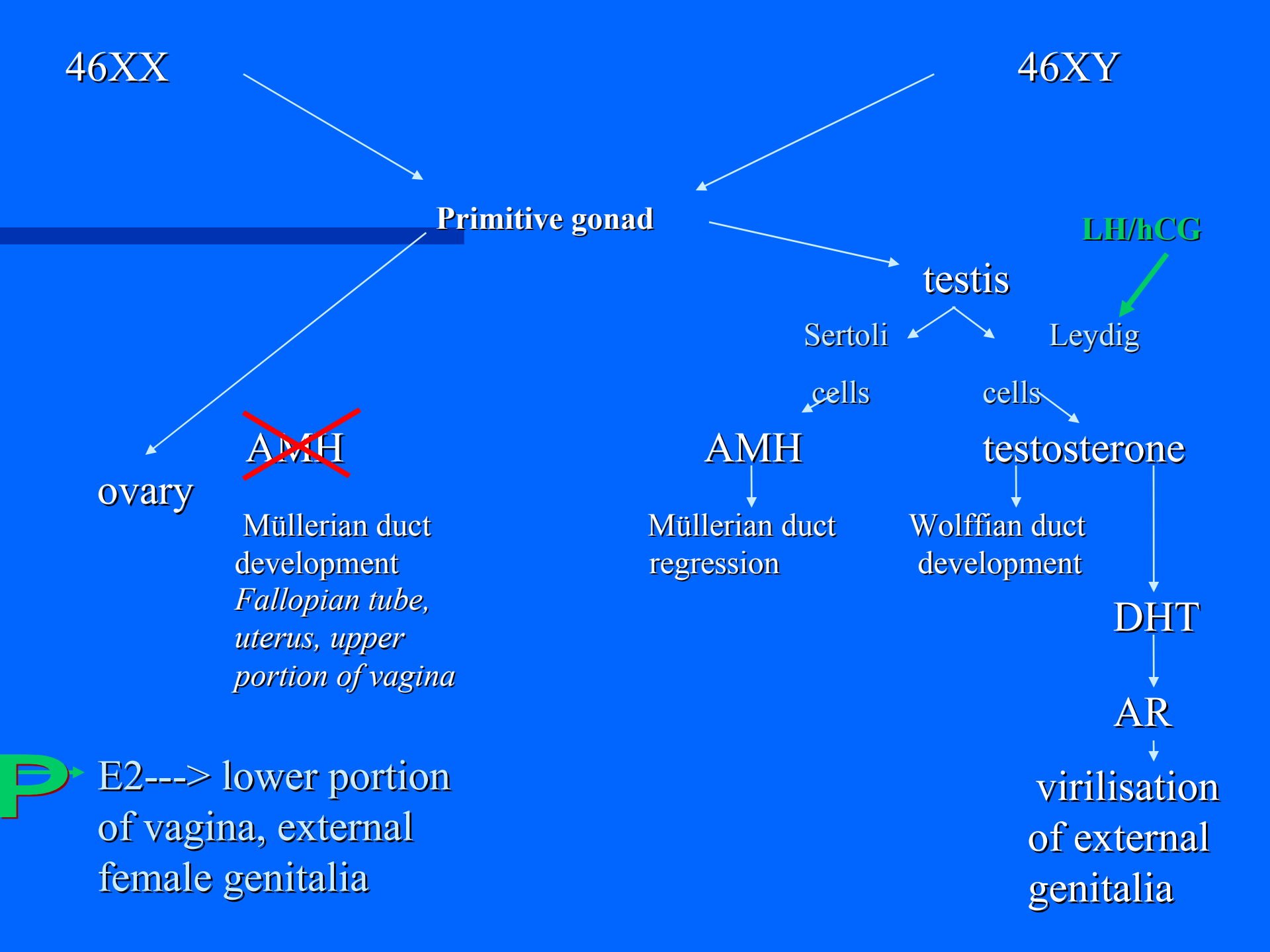
Female pseudohermaphroditism (FPH)

= virilisation of XX female

fetal: CAH,

aromatase deficiency,

maternal hyperandrogenism


46XX
46XY
Primitive gonad
LH/hCG
testis
Sertoli cells
Leydig cells
AMH
testosterone
ovary
AMH
Müllerian duct development
Fallopian tube, uterus, upper portion of vagina
Müllerian duct regression
Wolffian duct development
DHT
AR
virilisation of external genitalia
E2---> lower portion of vagina, external female genitalia

An example of a DSD classification

Sex chromosome DSD

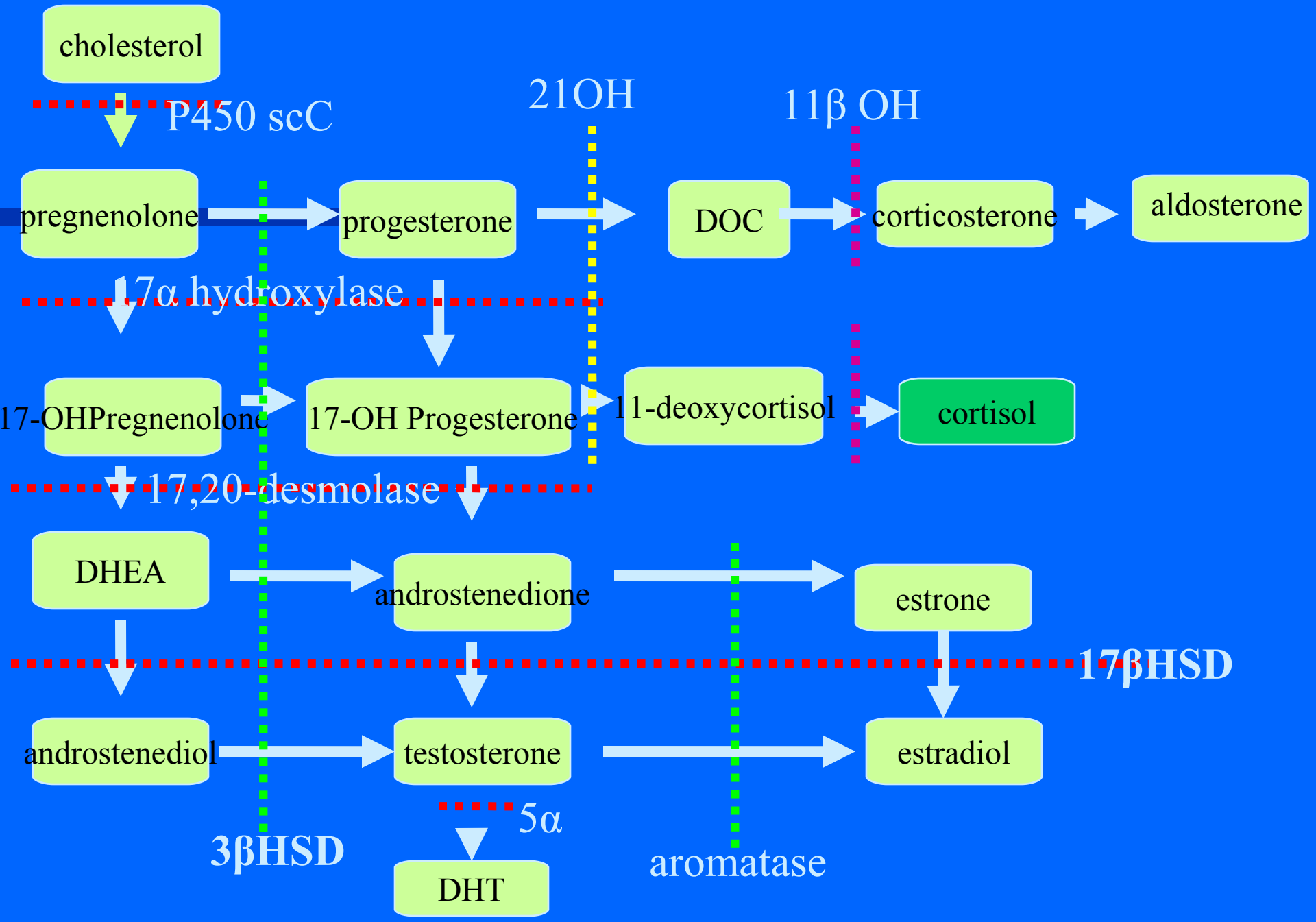
- Turner sy
- Klinefelter sy
- 45,X/46,XY DSD
- 46,XX/46,XY DSD

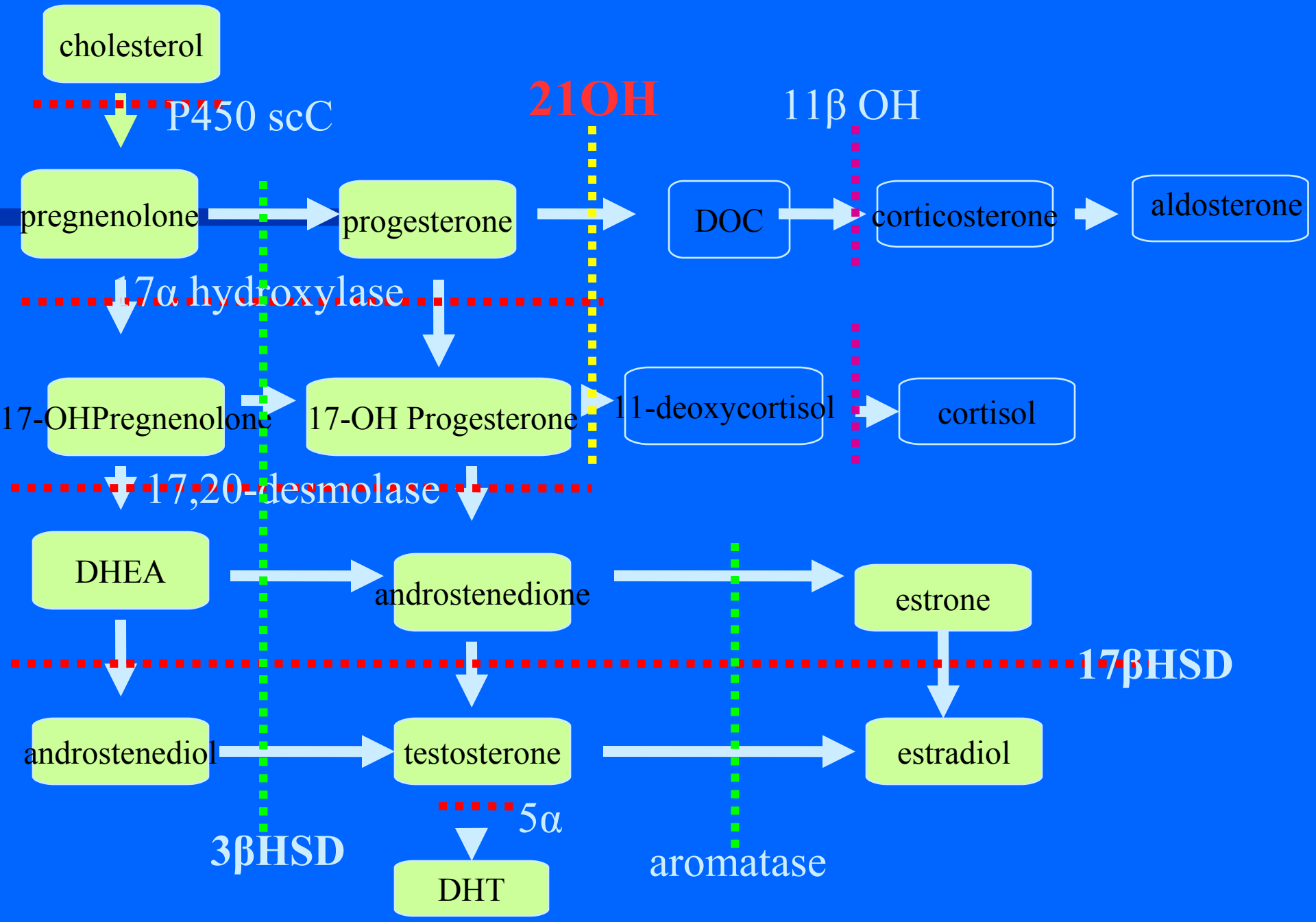
46,XY DSD

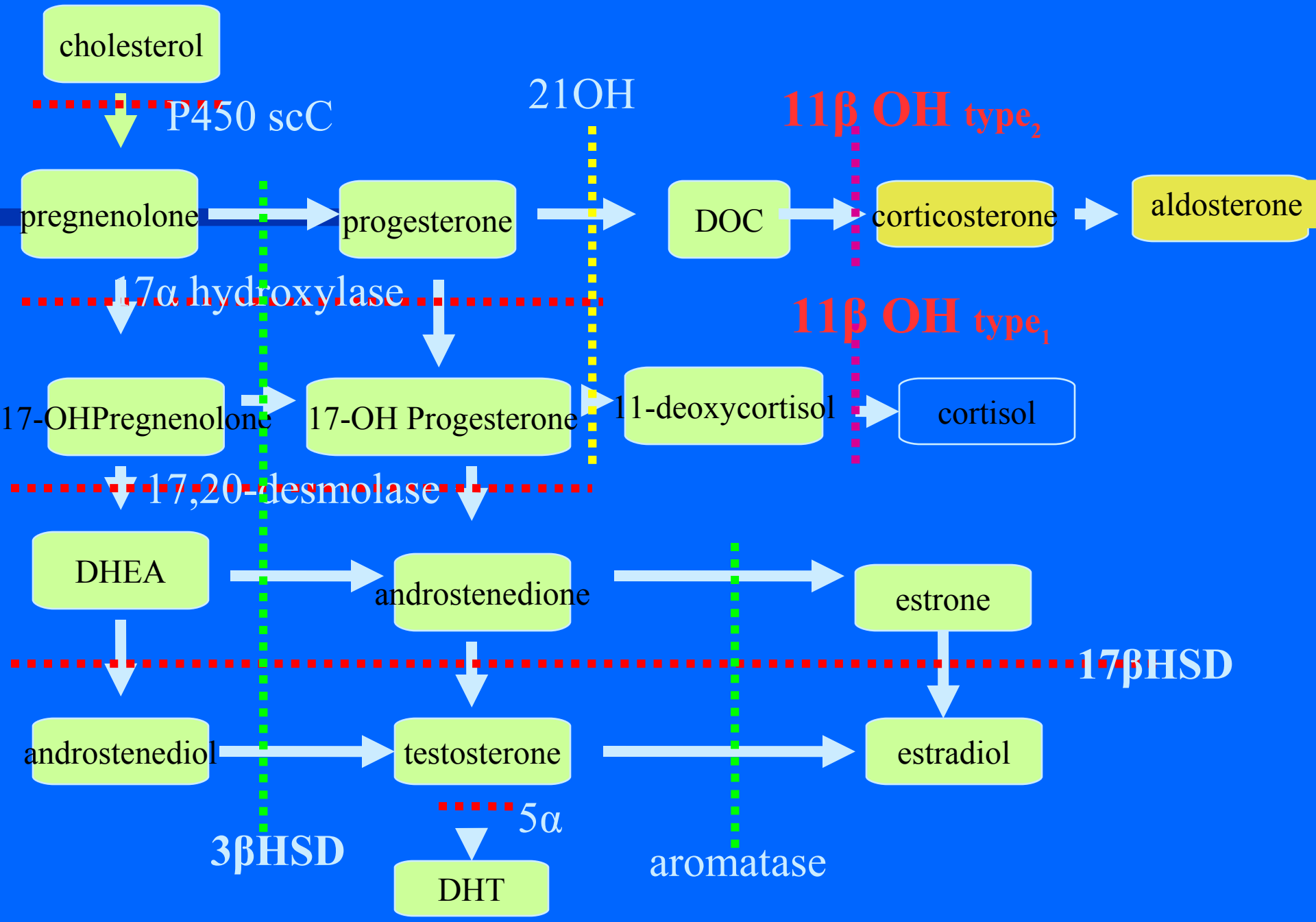
- Disorders of gonadal (testicular) development
- Disorders of androgen synthesis
- other

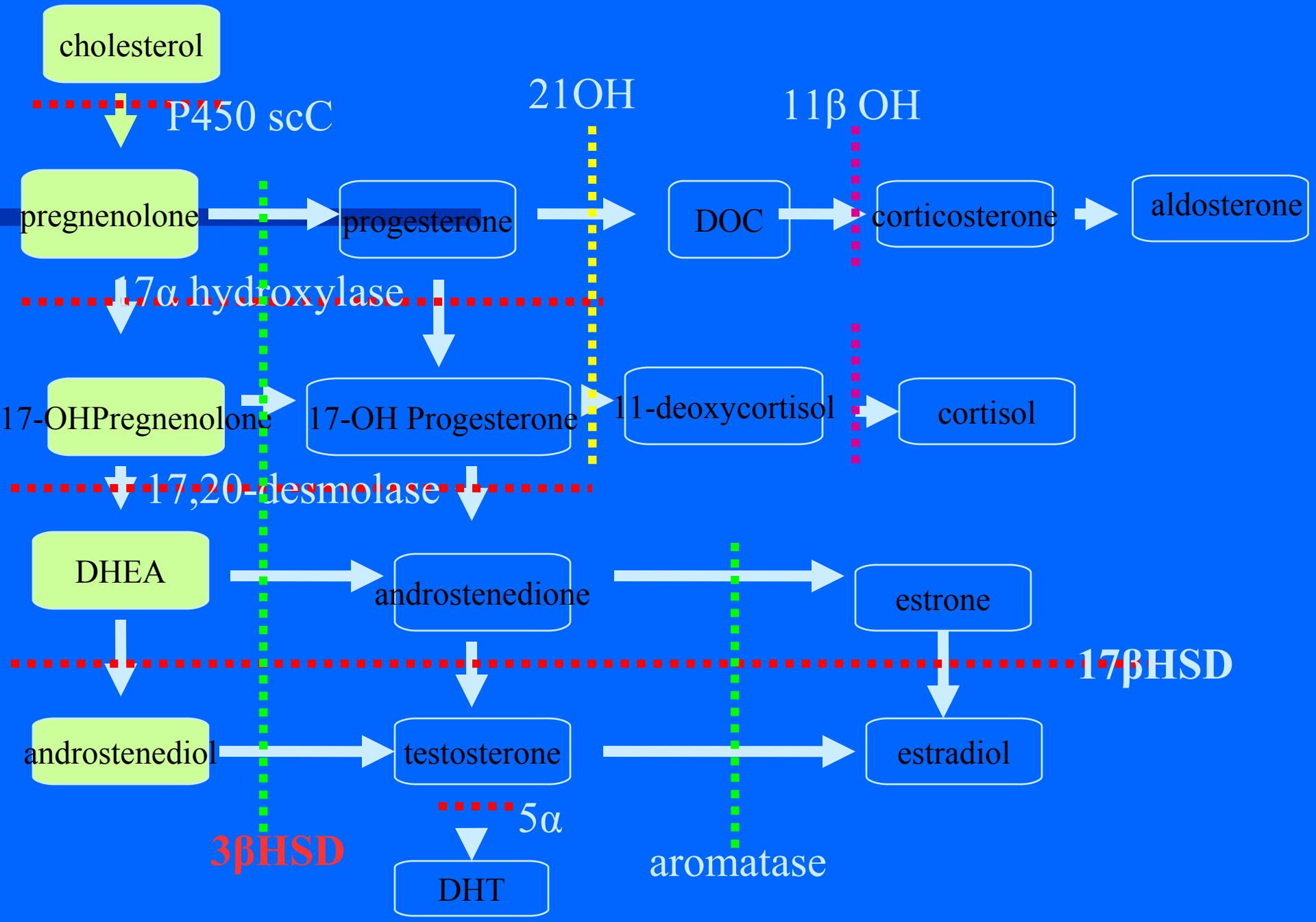
46,XX DSD

- Disorders of gonadal (ovarian) development
- Androgen excess
- other


cholesterol
P450 scC
21OH
11β OH
pregnenolone
progesterone
DOC
corticosterone
aldosterone
17α hydroxylase
17-OHPregnenolone
17-OH Progesterone
11-deoxycortisol
cortisol
17,20-desmolase
DHEA
androstenedione
estrone
17βHSD
androstenediol
testosterone
estradiol
5α
3βHSD
aromatase
DHT


cholesterol
P450 scC
21OH
11β OH
pregnenolone
progesterone
DOC
corticosterone
aldosterone
17α hydroxylase
17-OHPregnenolone
17-OH Progesterone
11-deoxycortisol
cortisol
17,20-desmolase
DHEA
androstenedione
estrone
17βHSD
androstenediol
testosterone
estradiol
5α
3βHSD
aromatase
DHT


cholesterol
P450 scC
21OH
11β OH type2
pregnenolone
progesterone
DOC
corticosterone
aldosterone
17α hydroxylase
11β OH type1
17-OHPregnenolone
17-OH Progesterone
11-deoxycortisol
cortisol
17,20-desmolase
DHEA
androstenedione
estrone
17βHSD
androstenediol
testosterone
estradiol
5α
3βHSD
aromatase
DHT


cholesterol
P450 scC
21OH
11β OH
pregnenolone
progesterone
DOC
corticosterone
aldosterone
17α hydroxylase
17-OHPregnenolone
17-OH Progesterone
11-deoxycortisol
cortisol
17,20-desmolase
DHEA
androstenedione
estrone
17βHSD
androstenediol
testosterone
estradiol
5α
3βHSD
aromatase
DHT

Abnormal genitalia in newborn

1 :4500 live births

Causes of abnormal genitalia in newborn

Female pseudohermaphroditism (FPH)-/ 46,XX DSD/ due to congenital adrenal hyperplasia (~80%)

Male pseudohermaphroditism, /46,XY DSD /

Gonadal dysgenesis

True hermaphroditism

Androgen insensitivity syndrome

FPH due to maternal hyperandrogenism

Investigation

Karyotype:

-chromosome number and morphology

Molecular genetics:

-SRY gene, other genes

Hormonal evaluation: adrenal function

testicular function

Anatomy of genitourinary tract

(USG, CT, MRI)

Histologic examination of the gonads

The aims of the aetiologic diagnosis

- to establish the genetic sex
- to evaluate the anatomic status of urogenital sinus, internal genitalia and gonads
- to recognize an enzymatic defect
- to assess Leydig cell and LH function
- to estimate tissue sensitivity to androgens
- to exclude iatrogenic causes

First steps of diagnostics

Delay birth registration. Information for parents.

Thorough clinical examination: external genitalia, gonads presence, pigmentation, **symptoms of salt loss**, other somatic anomalies

Family investigation: parents history, familial pedigree

Next step: The presence of palpable gonads

Gonads not palpable:

The first priority- to exclude FPH due to CAH

90-95% of CAH is 21 OH deficiency

Laboratory findings in 21OH deficiency:

- extremely high levels of 17 alpha hydroxyprogesterone
- high levels of ACTH
- high plasma renin activity (PRA)
- characteristic steroids profile in 24h urinary collection
- salt loss: hyponatremia, hyperkaliemia, hypoglicemia, metabolic acidosis

Gonads are palpated in the inguinal canal or scrotum/ labia

Palpable gonads are most likely testes.

Diagnostics: gonadal dysgenesis or MPH

Laboratory: Karyotype, SRY evaluation,

Steroid hormones in basal conditions: testosterone and its precursors

LH-RH test combined with steroid hormones determination

hCG stimulation test

Anatomic studies: genitography, urethrography, endoscopy, usg

Isolated forms of genital malformation

- Hypospadias
- Cryptorchidism
- Micropenis

Decision for sex of rearing

- **accurate diagnosis based on lab tests**
- **anatomy of external and internal genitalia and reconstruction possibilities**
- **hypothalamic sex differentiation**
- **Prognosis of sex hormones release at puberty**

Treatment

The replacement of deficient hormones:

cortisol/ mineralocorticoids/ testosterone

Surgical restoration (usually after 2nd y.)

- genitalia appropriate for sex of rearing
- removal of gonads and internal organs discordant for the sex of rearing
- removal of dysgenetic gonads in patients with Y chromosome

Psychological support of the family