Congenital adrenal hyperplasia (CAH)

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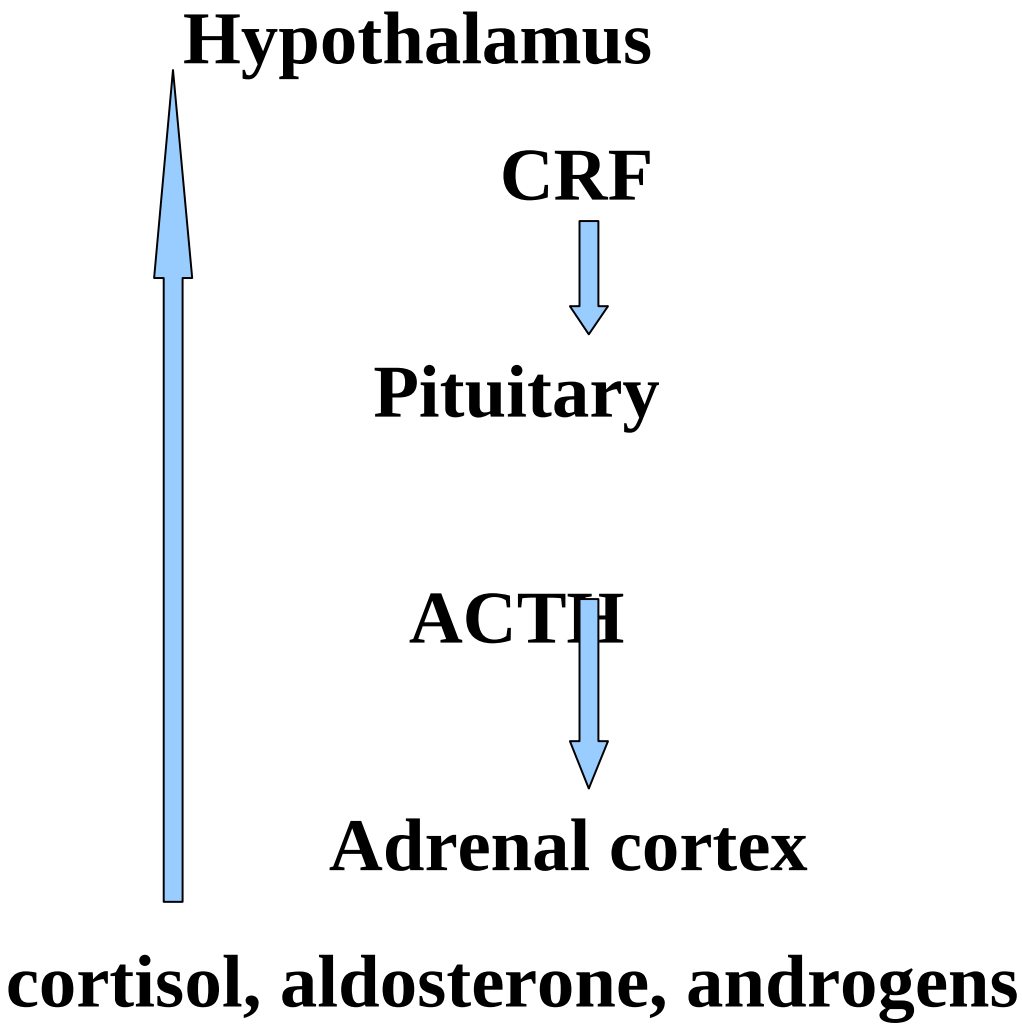
Congenital disorders of enzymes

of the steridogenesis leading to insufficient production of cortisol in adrenal cortex


Hypothalamus
CRF
Pituitary
ACTH
Adrenal cortex
cortisol, aldosterone, androgens

The consequences of the enzymes deficiency of the cortisol biosynthesis

Cortisol deficiency

Activation of the HPA axis

Hyperstimulation of adrenal cortex

Excess of the steroids produced without defect

Excess of steroids produced before the enzymatic block

Enzymes contributing in cortisol biosynthesis:

20,22 desmolase

3β hydroxysteroid dehydrogenase

17 α -hydroxylase

21 α -hydroxylase

11β- hydroxylase 1

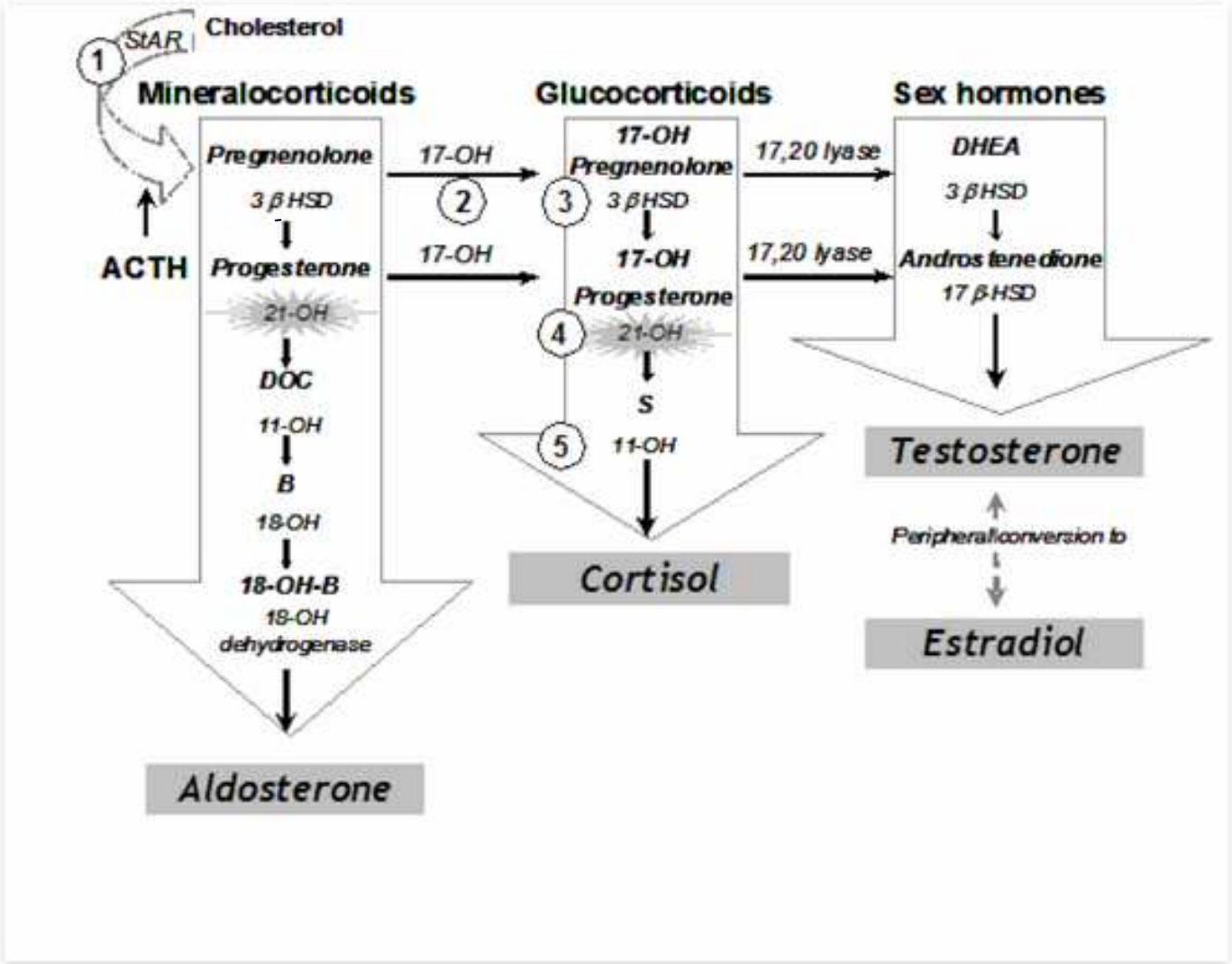


Figure 1 Adrenal steroidogenesis: Five enzymatic steps necessary for cortisol production are shown in numbers. 1= 20, 22 desmolase, 2= 17 hydroxylase (17-OH), 3=3ß-hydroxysteroid dehydrogenase (3ß HSD), 4=21 hydroxylase (21OHD), 5=11ß hydroxylase (11-OH) In the first step of adrenal stereoidgeneis, cholesterol enters mitochondria via a carrier protein called StAR. ACTH stimulates cholesterol cleavage, the rate limiting step of adrenal steroidogenesis.

21α -hydroxylase deficiency

The most common enzymatic block (95%)

The frequency 1:10 000- 1:15 000

Genes on chromosome 6: *CYP 21P*, *CYP21*

Prenatal diagnosis possible

Clinical features depend on the amount of functioning enzyme

Clinical types of 21α -hydroxylase deficiency

Classic CAH with salt loss (SW CAH, Salt Wasting CAH)

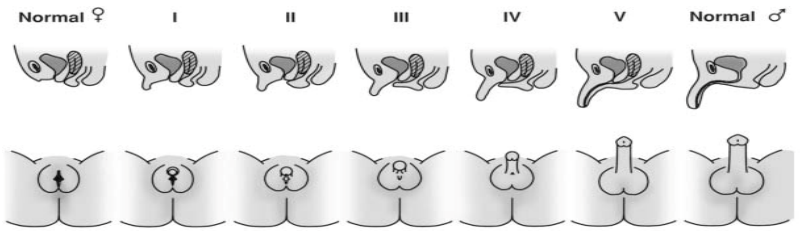
Classic CAH without salt loss

Nonclassic CAH (late onset CAH)

Classic form with salt wasting

Severe cortisol and aldosterone deficit

Virilisation of external genitalia in female (Prader scale I-V)



Hiperpigmentation of the skin in both sexes (POMC)

Salt loss syndrome from 2nd week of life: adrenal crisis

Adrenal crisis

Apetite loss

Vomits, diarrhea

Progressive body weight loss

Apathy

Symptomes of hypovolemia

Lab findings:

- -hyperkalemia with hyponatremia
- -hypochloremia
- -hypoglicemia
- -metabolic acidosis

Symptomes of adrenal androgens excess

FEMALE

- *abnormal external genitalia*
- *progressive androgenisation: precocious adrenarche*

  hypertrophy of clitoris, hirsutism
- *increased height velocity, abnormal body proportions*
- *precocious growth termination (advanced BA)*

MALE

- *normal development of external male genitalia*
- *precocious adrenarche,*
- *initiation of the puberty at the bone age 11-12 years*
- *increased growth velocity, abnormal body proportions*
- *precocious growth termination (advanced BA)*

Nonclassic form of CAH (late onset)

Frequency 1: 500- 1:1000 live birth

Partialy impaired activity of 21-OH

Slightly elevated androgenes

Hirsutism at the puberty

Menstrual disorders, PCOS

Infertility in both sexes

Hormonal diagnostics

Blood sampling:

-cortisol, 17 OHProgesterone, ACTH

- renine, aldosterone

- 11-deoxcortisol, androstenedione, DHEA, DHEAS

- in late onset CAH- 17 OHP after ACTH

Urine sampling:

- metabolites of 17OHP (pregnantriol)
- metabolites of androgens (17KS)
- metabolites of cortisol (17OHCS), free cortisol
- steroid profile in 24h urine collection

Neonatal screening

17OH Progesterone after 3th day of life (dry blood drop)

Positive results – confirmed by steroid profile in the blood (mass spectrometry)

Next diagnostics:

molecular analysis (gene CYP21)

Glicocorticoid substitution

Hydrocortisone in 3 doses:

infants ~25 mg/m^2/day (3-4doses)

children: 10-15 mg/m^2/day

After growth termination (bone age maturation):

Prednisolone 2-4 mg/m^2/day (in 2 doses)

or Dexamethasone 0,25-0,375 mg/m^2/day(1x)

stress doses: 2-3 times increased dose

Mineralocorticoids substitution:

Patients with classic SW CAH

fludrocortisone:

infants:

fludrocortisone 0,05-0,3mg/day

often additional suplementation of NaCl 1-3g/day

children after 12 months of age-

only fludrocortisone -

doses are dependent on renin value and BP

Substitution in pregnant women with CAH

Recommended Hydrocortisone or Prednisolone, (they do not pass the placenta)

Dexamethasone contraindicated

(except prenatal therapy)

Doses according to testosterone level in pregnant patient (Normal)

Delivery protected with Hydrocortisone i.v.

Cesarean section in patients after vaginoplasty

Diagnostics and prenatal treatment

The genetic examination of parents before the pregnancy

The evaluation of fetal DNA from chorionic biopsy

The evaluation of fetal karyotype

Prenatal treatment with dexamethasone

- Only in female fetuses with high risk of classic CAH

The aim- the prophilaxy of the virilisation of external genitalia

Start -early pregnancy,

not later than 9 weeks after LM

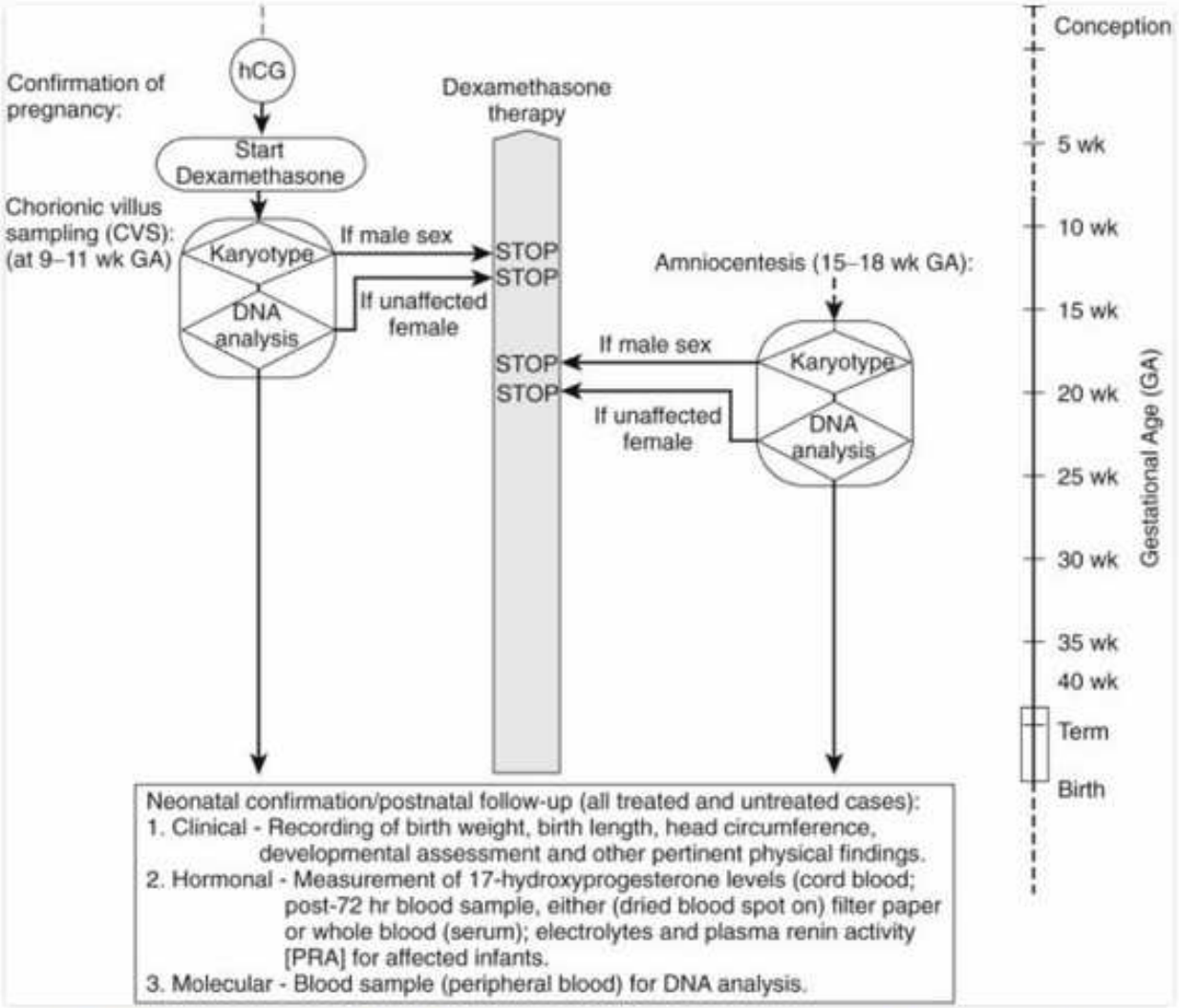


Figure 6 Algorithm of treatment, diagnosis and decision-making for prenatal treatment of fetuses at risk for 21-hydroxylase deficiency congenital adrenal hyperplasia. Mercado AB, Wilson RC, Cheng KC, Wei JQ, New MI 1995 Extensive personal experience: Prenatal treatment and diagnosis of congenital adrenal hyperplasia owing to steroid 21-hydroxylase deficiency. J Clin Endocrinol Metab 80:2014-2020. Permission obtained. [86]