CONGENITAL ADRENAL HYPERPLASIA (CAH)

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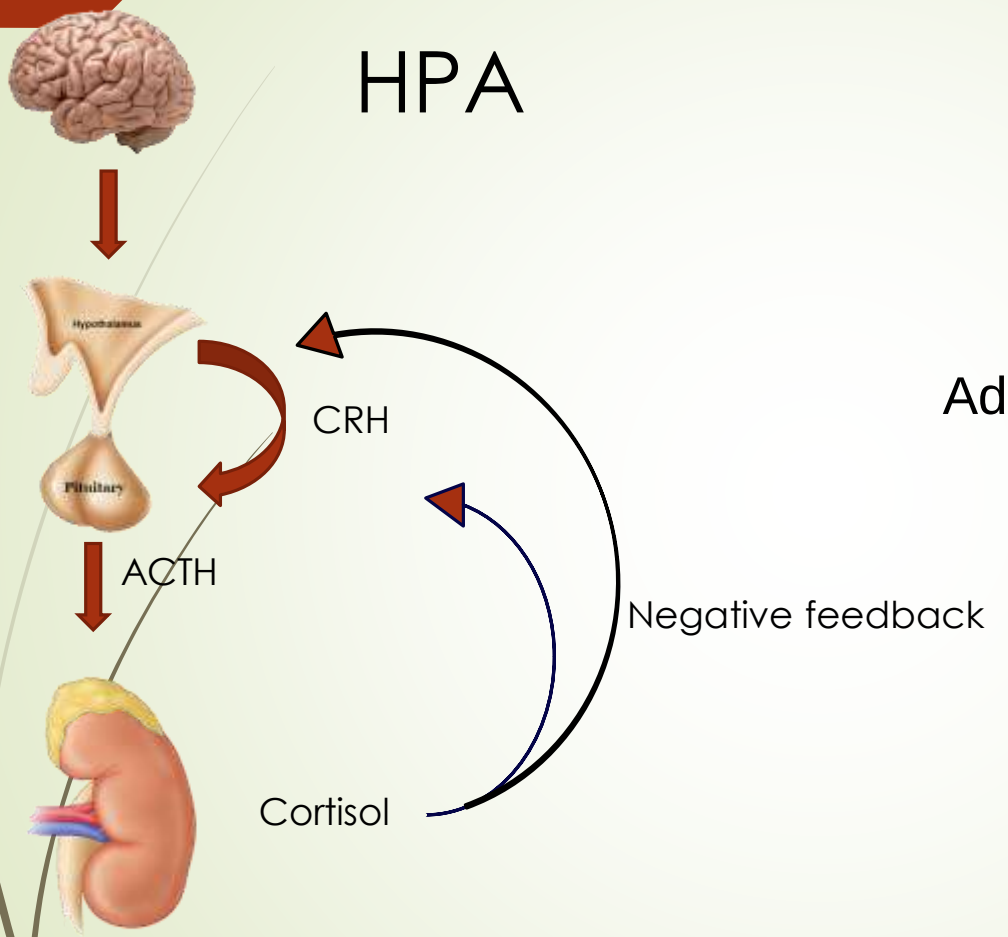
HPA



No cortisol

⬇

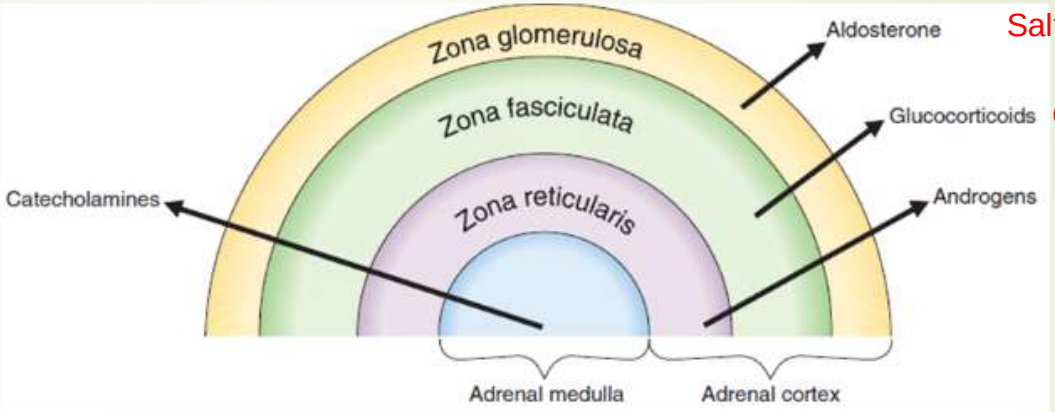
no negative feedback

High ACTH

⬇

Adrenal gland hyperplasia.

G F R



Salt regulation

Glucose regulation

Sex hormones

Aldosterone deficiency	Cortisol deficiency	High testosterone
Hyponatremia Hyperkalemia Acidosis	Hypoglycemia Increased ACTH	Female → virilization Male → - May be asymptomatic . - precocious puberty. - testicular adrenal rest tumor

❑ Aldosterone deficiency :

1- hyponatremia →dehydration , vomiting , shock and death.

2- hyperkalemia → arrhythmia .

3- acidosis .

❑ Cortisol deficiency :

1- hypoglycemia (no glycogenolysis) .

2- increase ACTH →hyper stimulation and hyperplasia of the adrenal gland.

- High testosterone :

1- Female → virilization

2- Male →

- May be asymptomatic .
- precocious puberty.
- testicular adrenal rest tumor .

Congenital Adrenal Hyperplasia

- The most common cause of adrenocortical insufficiency in newborns.
- Autosomal recessive trait.
- Boys and girls can be affected.

- **Impaired cortisol synthesis due to a deficiency in one of the enzymatic steps required for cortisol production.**

- inability to produce one or more of these hormones (Cortisol, Aldosterone or both), which in turn will result in the overproduction of another type .

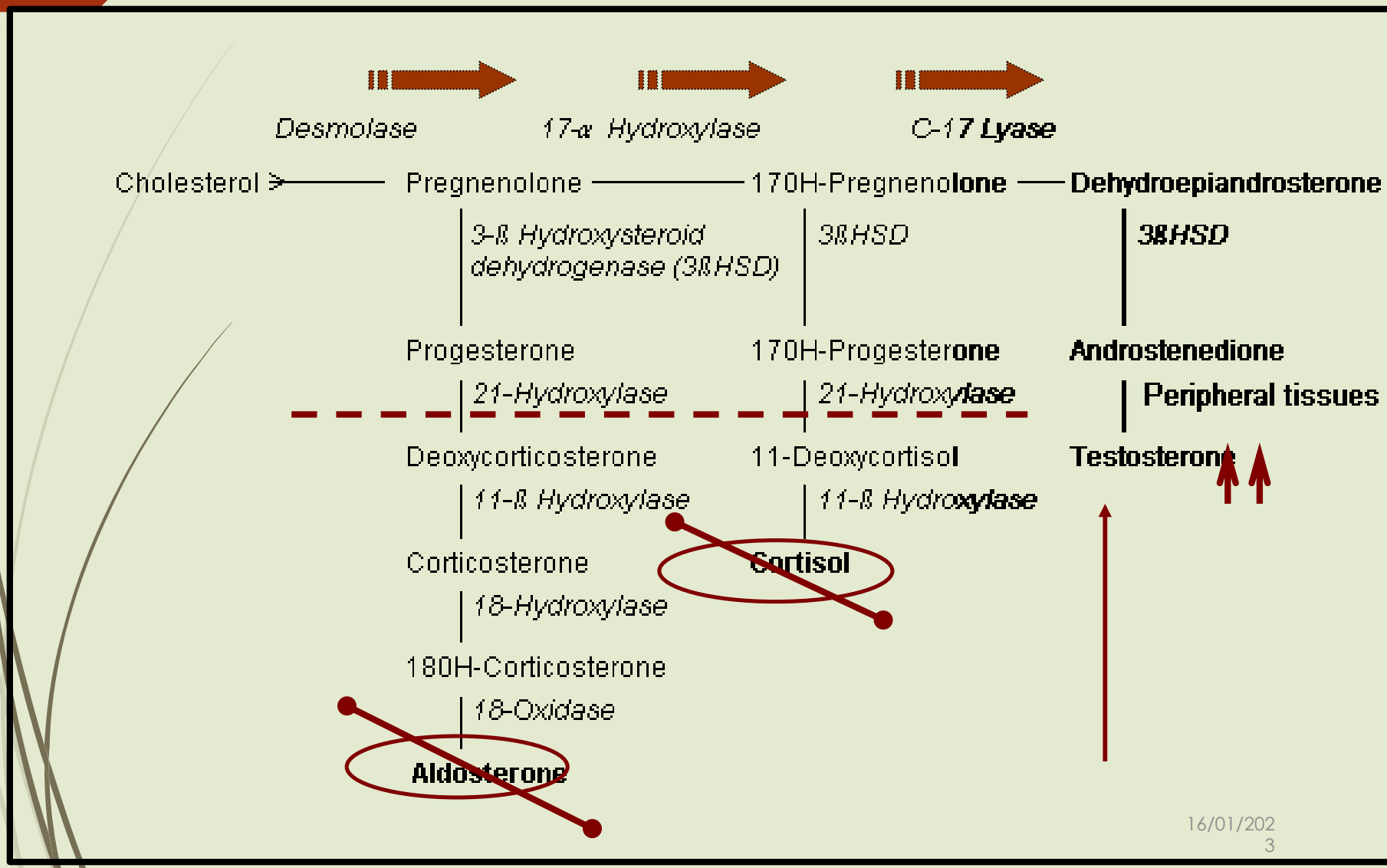
Etiology

- results from loss of function mutations in specific adrenocortical enzymes responsible for the synthesis of cortisol.
- 21-Hydroxylase deficiency is one of the most common defects of adrenal steroidogenesis. More than 90 % of cases.
- Steroid 11β-hydroxylase deficiency (11β-OHD) is the second most common form of CAH form 5 %.
- 17-Hydroxylase Deficiency .
- Very rare one 3-beta–hydroxysteroid dehydrogenase 2 def.

21-Hydroxylase Deficiency

- Most common type, accounts for >90% of cases.
- Gene is located on the short arm of chromosome 6 near the C4 locus in close association with HLA genes.
- More than 90% of mutations causing 21-hydroxylase deficiency are recombinations between *CYP21* and *CYP21P*
- Disease severity correlates with the mutations carried by an affected individual; for example, patients with salt-wasting disease usually carry mutations on both alleles that completely destroy enzymatic activity.

21-Hydroxylase deficiency



21-Hydroxylase Deficiency

- **2 forms:**

1. **Classic early virilization type with or without salt-losing crisis.**
2. **Non-classic type with late-onset virilization.**

- **Approximately 70% of affected infants have the salt-losing form, whereas 30% have the simple virilizing form of the disorder.**

- **Male babies with non salt-losing non-classic type remains asymptomatic till late childhood when they may show signs of sexual precocity.**

21-Hydroxylase Deficiency; epidemiology, Pathogenesis & clinical manifestations:

- **Classical CAD incidence is 1:15000 live birth.**

- **Non classical CAD incidence is 1:1000 in general population .**

- **It is characterized by reduced production of cortisol and aldosterone and increased production of progesterone; 17-OH-progesterone, and sex steroids.**

21-Hydroxylase deficiency: clinical manifestations

Hyperplasia

Salt losing

- Decreased secretion of aldosterone results in salt loss with hyponatremia and hyperkalemia; plasma renin activity is therefore elevated.

- In partial enzyme deficiencies, the aldosterone deficiency is not expressed, and patients remain normonatremic and normokalemic.

Clinical manifestations of salt wasting :

- Progressive weight loss (poor feeding) , anorexia , vomiting , dehydration , failure to thrive .
- Weakness , hypoglycemia , hypotension .
- hyponatremia , hyperkalemic metabolic acidosis progressing to adrenal crisis .

- These problems typically develop in affected infants at approximately 1-4 weeks of age.
- Without treatment, azotemia , vascular collapse , shock, cardiac arrhythmias, and death (adrenal crisis) may occur within days or weeks.

Effects of Cortisol Deficiency

- ***GI***: loss of appetite, nausea, vomiting, abdominal pain, weight loss
- ***Mental***: lethargy, apathy, confusion, psychosis
- ***Energy metabolism***: impaired glucose formation leading to hypoglycemia
- ***Heart/kidney***: impaired water excretion, reduced blood-pressure-raising effect of epinephrine, hypotension
- ***Pituitary***: unrestrained production of ACTH and related proteins resulting in increased pigmentation of skin and mucous membranes
- *Impaired tolerance to* ***stress***

Prenatal Androgen Excess

- This problem begins in affected fetuses by 8-10 wk of gestation and leads to abnormal genital development in females.
- Affected females, who are exposed in utero to high levels of androgens of adrenal origin, have masculinized virilized external genitalia with variable degrees.
- From enlargement of the clitoris with or without partial fusion of the labioscrotal folds, to the appearance of a penile urethra.
- The vagina usually has a common opening with the urethra (urogenital sinus).

- The internal genital organs are normal.
- Prenatal exposure of the brain to high levels of androgens may influence subsequent sexually dimorphic behaviors in affected females.
- Male infants appear normal at birth. Thus, the diagnosis may not be made in boys until signs of adrenal insufficiency develop.

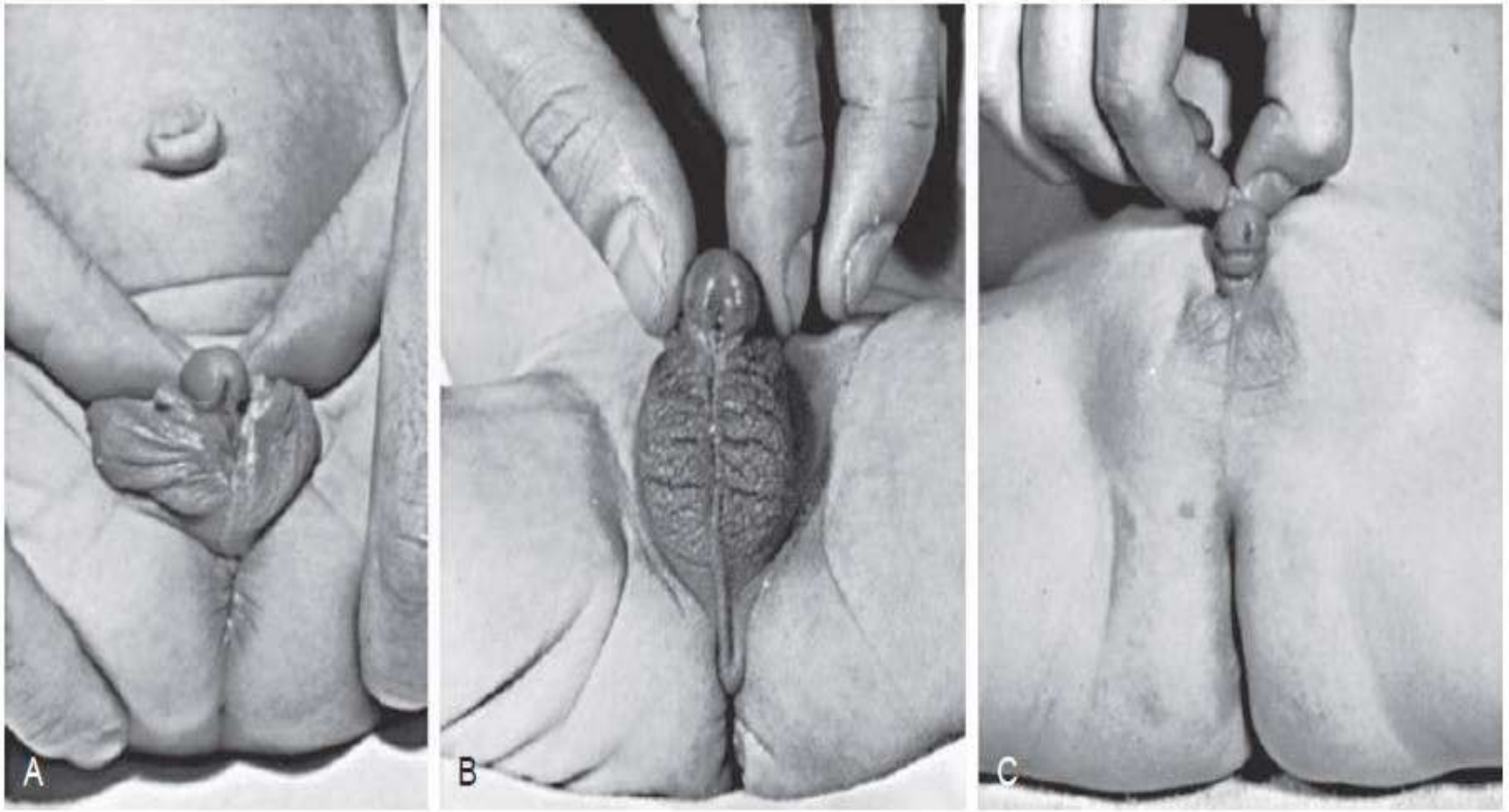


Figure 576-2 Three virilized females with untreated congenital adrenal hyperplasia. All were erroneously assigned male sex at birth, and each had a normal female sex-chromosome complement. Infants **A** and **B** had the salt-wasting form and received the diagnosis early in infancy. Infant **C** was referred at 1 yr of age because of bilateral cryptorchidism. Notice the completely penile urethra; such complete masculinization in females with adrenal hyperplasia is rare; most of these infants have the salt-wasting form.

Prader Virilization Scores

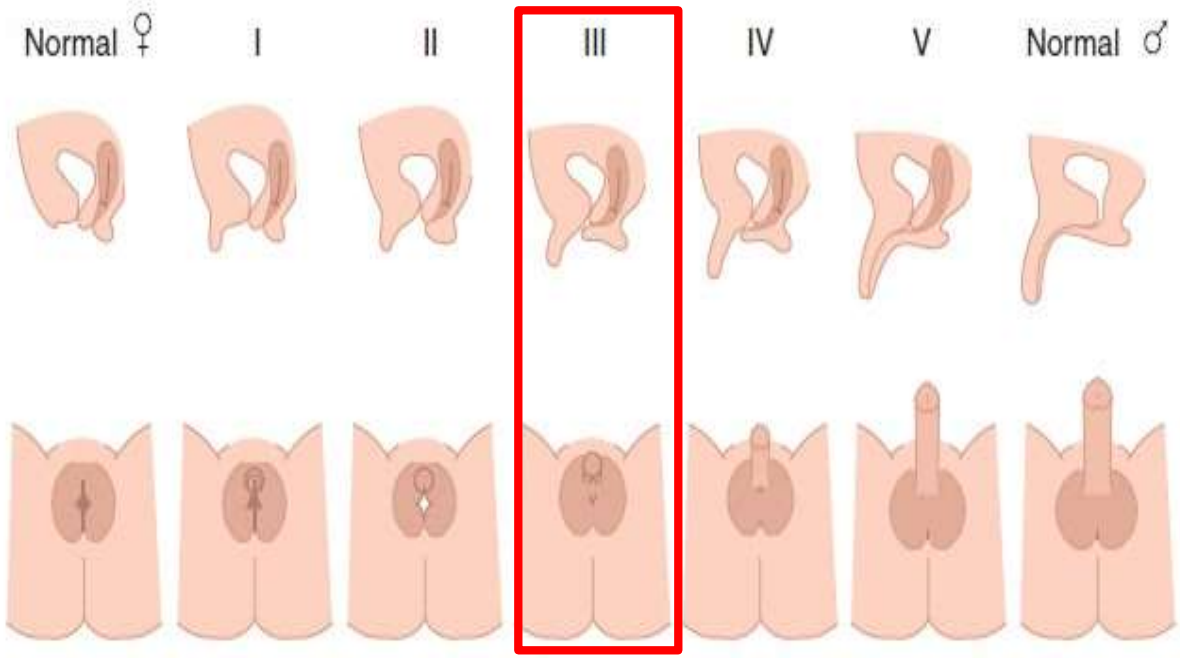


FIGURE 8-1 ■ Shows lateral and *en face* views of external genitalia of the fully differentiated female on the left, increasing amounts of virilization (excessive for a female and inadequate for a male) going from left to right, with complete male differentiation on the right.[3]

Kappy M, GEFFNER M, Allen D (eds). Pediatric Practice: Endocrinology. McGraw-Hill, 2009

Postnatal Androgen Excess

- **Untreated or inadequately treated children of both sexes develop additional signs of androgen excess after birth include:**

1. rapid somatic growth and accelerated skeletal maturation. Thus, affected patients are tall in childhood but premature closure of the epiphyses causes growth to stop relatively early, and adult stature is stunted.
2. Muscular development may be excessive.
3. Pubic and axillary hair may appear; and acne and a deep voice may develop.

4. The penis, scrotum, and prostate may become enlarged in affected boys; however, the testes are usually prepubertal in size so that they appear relatively small in contrast to the enlarged penis.

5. Both male and female patients are fertile but have reduced fertility rates.

Postnatal Non-classical 21-hydroxylase deficiency

- **In this attenuated** form, cortisol and aldosterone levels are normal and affected females have normal genitals at birth.
- Males and females may present with **precocious pubarche** and early development of pubic and axillary hair.
- Hirsutism, acne, menstrual disorders, and infertility may develop later in life.
- However, many females and males are **completely asymptomatic.**

CAH due to 21-OH deficiency

	Classic salt wasting		Classic simple virilizing		Nonclassic	
	Males	Females	Males	Females	Males	Females
Age at dx	Birth-6mo	Birth-1mo	2-4 yr	Birth-2yr	Child to adult	
External genitalia	Normal	Ambiguous	Normal	Ambiguous	Normal	Usually normal; may have clitoromegaly
Aldosterone	Low		Normal		Normal	
Cortisol	Low		Low		Normal	
17-OHP	Basal>20,000 ng/dL		Basal> 10,000 – 20,000 ng/dL		ACTH stimulated 1,500 – 10,000 ng/dL	
% of normal 21-OH activity	0		1-2		20-50	

Pediatrics Endocrinology, Mechanisms, Manifestations and Management, Ora H. Pescovitz, Erica A. Eugster, 2004 by Lippincott Williams & Wilkins.

11β-Hydroxylase Deficiency (11β-OH)

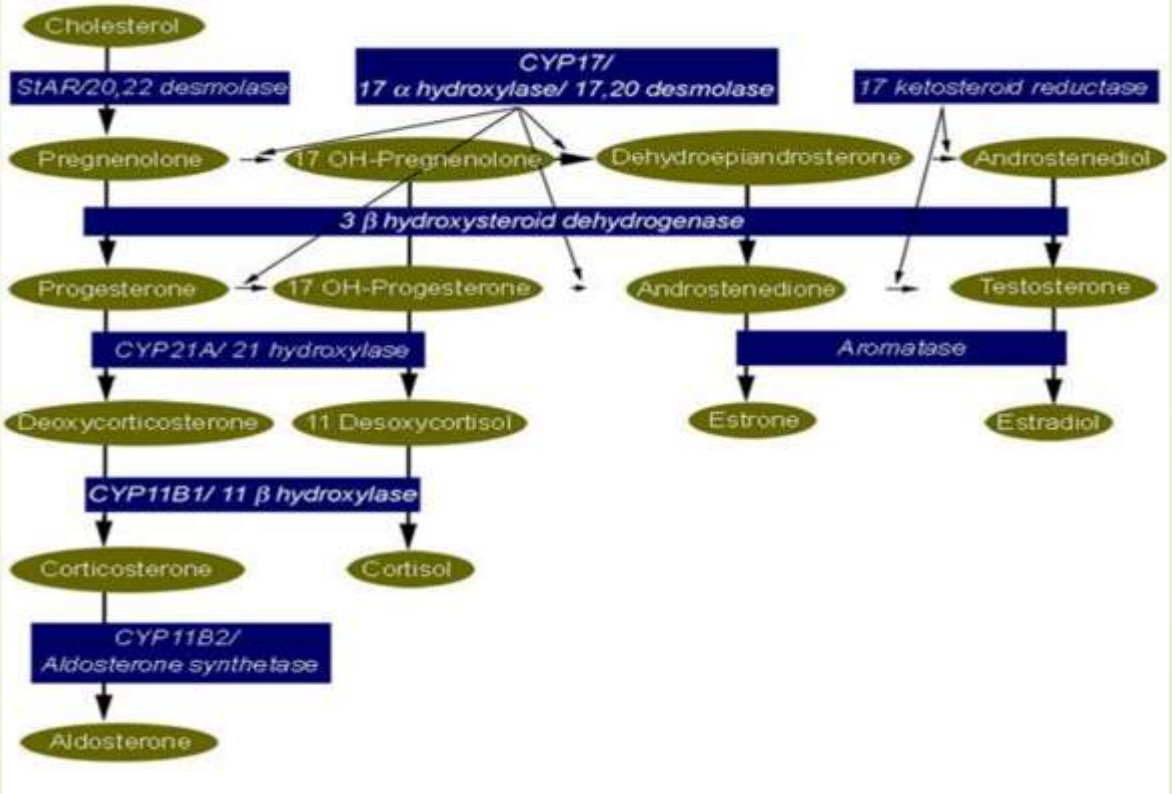
ETIOLOGY

Deficiency of 11β-hydroxylase is due to a mutation in the *CYP11B1 gene located on chromosome 8*. More than 30 different mutations in *CYP11B1 have been identified*.

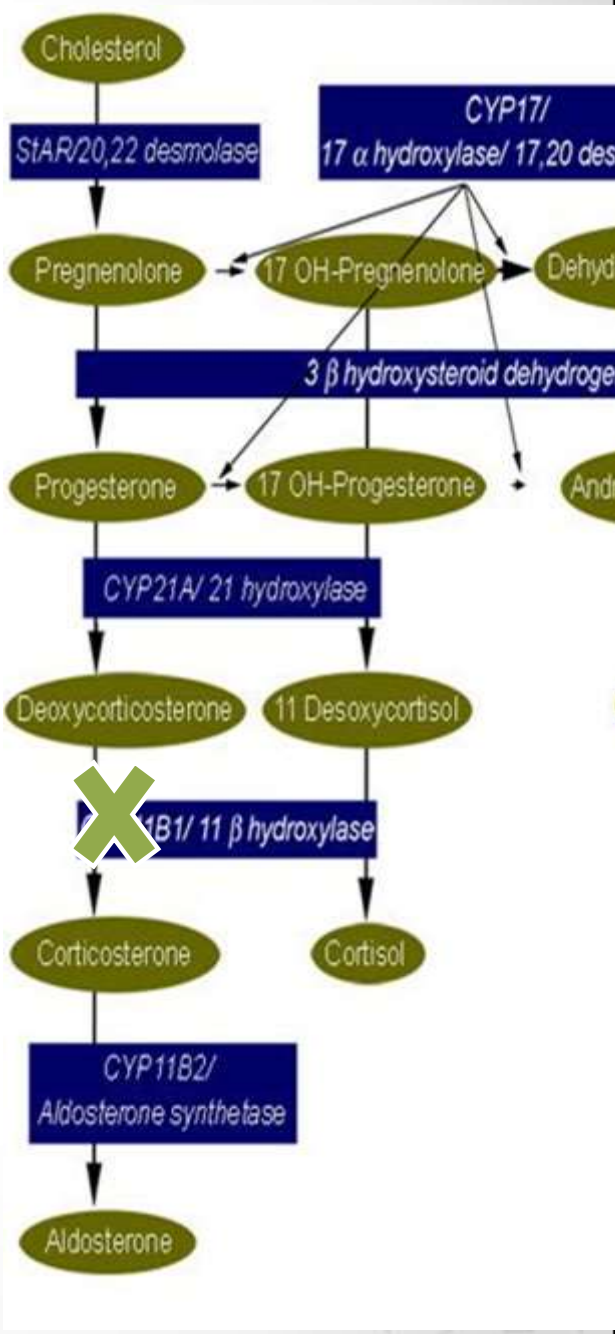
11-deoxycortisol (S) and will be accumulated and shunted into androgen biosynthesis in the same manner as occurs in 21-hydroxylase deficiency.

The adjacent *CYP11B2 gene encoding* aldosterone synthase is generally unaffected in this disorder, so patients are able to synthesize aldosterone normally.

Account 5 % of adrenal hyperplasia

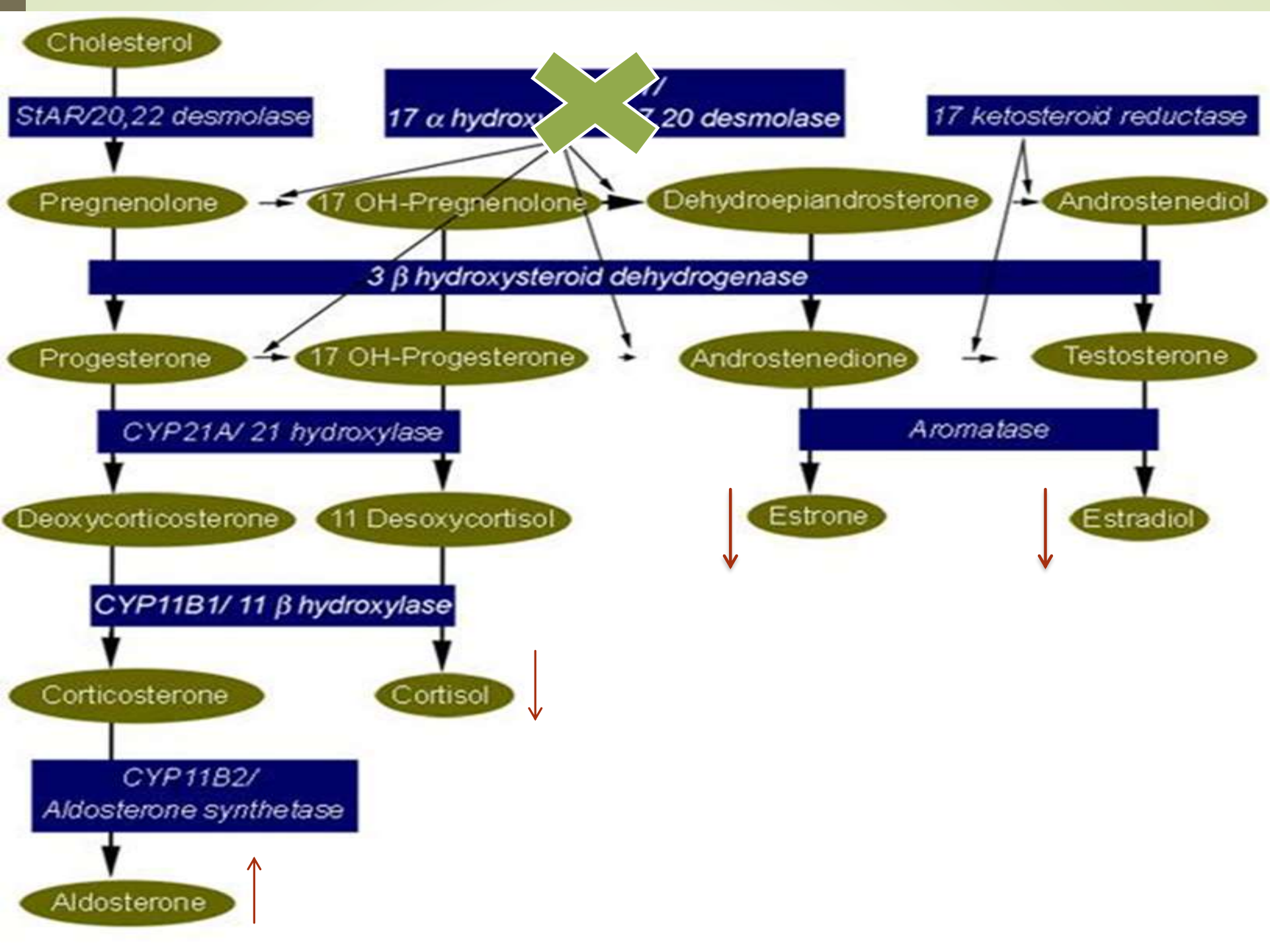

Cholesterol
StAR/20,22 desmolase
CYP17/
17 α hydroxylase/ 17,20 desmolase
17 ketosteroid reductase
Pregnenolone
17 OH-Pregnenolone
Dehydroepiandrosterone
Androstenediol
3 β hydroxysteroid dehydrogenase
Progesterone
17 OH-Progesterone
Androstenedione
Testosterone
CYP21A/ 21 hydroxylase
Aromatase
Deoxycorticosterone
11 Desoxycortisol
Estrone
Estradiol
CYP11B1/ 11 β hydroxylase
Corticosterone
Cortisol
CYP11B2/
Aldosterone synthetase
Aldosterone

- Approximately 65% of patients become **hypertensive, although this can take several years to develop.** Due to elevated levels of deoxycorticosterone (DOC), which has mineralocorticoid activity.
- hypokalemia



17-Hydroxylase Deficiency

- Less than 1% of CAH cases are caused by 17-hydroxylase deficiency.
- the enzyme is expressed in both the adrenal cortex and the gonads and encoded by a gene on chromosome 10. Most mutations affect both the hydroxylase and lyase activities, but rare mutations can affect either activity alone
- patients with 17-hydroxylase deficiency **are unable to synthesize sex hormones.** Affected **males are incompletely virilized and present as phenotypic females (but** gonads are usually palpable in the inguinal region or the labia) or with sexual ambiguity.
- Affected females usually present with **failure of sexual development at the** expected time of **puberty.**
- **HTN and hypokalemia**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20 desmolase
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Pregnenolone
17 OH-Pregnenolone
Dehydroepiandrosterone
Androstenediol
3 β hydroxysteroid dehydrogenase
Progesterone
17 OH-Progesterone
Androstenedione
Testosterone
CYP21A/ 21 hydroxylase
Aromatase
Deoxycorticosterone
11 Desoxycortisol
Estrone
Estradiol
CYP11B1/ 11 β hydroxylase
Corticosterone
Cortisol
CYP11B2/
Aldosterone synthetase
Aldosterone

Initial Laboratory Evaluation

- **Glucose**
- **electrolytes**
- **blood gas**
- **Cortisol** ↓ N (in simple virilizing)
- **ACTH** ↑
- **17-OHP** ↑
- **Androstenedione and Testosterone** ↑
- *Renin* ↑ **and aldosterone** ↓
- **Pelvic ultrasonography**
- **Karyotype**

Laboratory evaluation

- Increased 17-OH progesterone .

- **Definitive test** : measure 17-OH progesterone before & after intravenous bolus of ACTH .

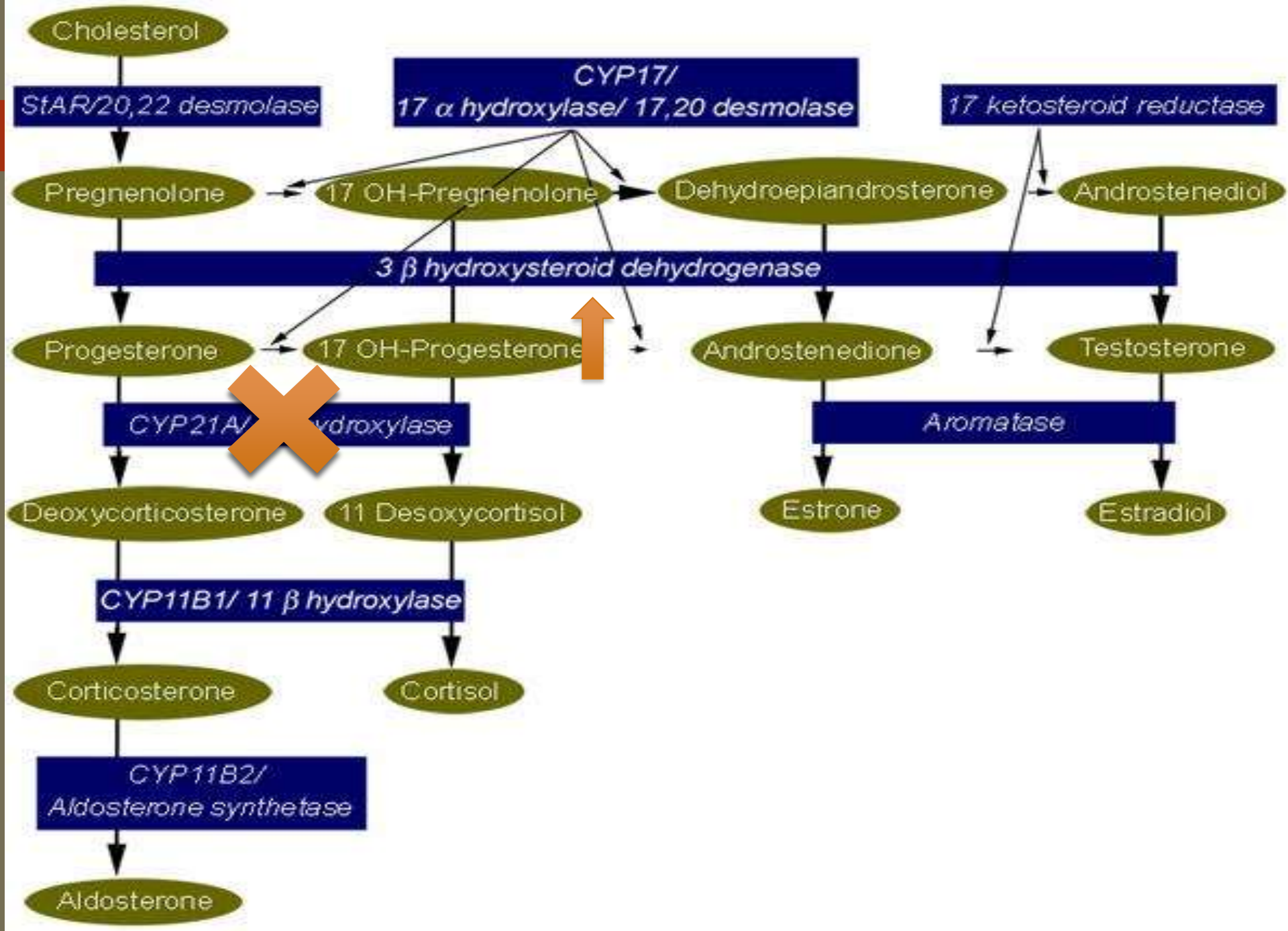
Laboratory evaluation

- Increased 17-OH progesterone .
- Low serum sodium & glucose , high serum potassium , acidosis .
- Low cortisol , high ACTH, increased androstenedione , and testesterone .
- Increased plasma renin , decrease aldosterone .

Investigations

In 21-hydroxylase deficiency, the levels of circulating17OH-progesterone are raised, but this may only be demonstrated after ACTH administration in late onset cases.

Definitive test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Pregnenolone
17 OH-Pregnenolone
Dehydroepiandrosterone
Androstenediol
3 β hydroxysteroid dehydrogenase
Progesterone
17 OH-Progesterone
Androstenedione
Testosterone
CYP21A/
ydroxylase
Aromatase
Deoxycorticosterone
11 Desoxycortisol
Estrone
Estradiol
CYP11B1/ 11 β hydroxylase
Corticosterone
Cortisol
CYP11B2/
Aldosterone synthetase
Aldosterone

Treatment

- The aim is to replace deficient corticosteroids and to suppress ACTH-driven adrenal androgen production.
- To treat congenital adrenal hyperplasia, it's best to get a referral to a specialist in childhood hormonal issues (pediatric endocrinologist).

Replacement hormone medication

- Hydrocortisone to replace cortisol (given orally)
- Fludrocortisone to replace aldosterone (given orally)

Monitoring

Regular assessment of height, weight, and physical examination.

Laboratory evaluation; 17-OHP, androstenedione, and testosterone

PRA can be used to monitor the effectiveness of mineralocorticoid and sodium replacement.

- Steroid-type replacement medications may cause side effects, particularly if the doses are high and are used long term.

- So the child should be monitored for theses side effects, such as the loss of bone mass and impaired growth.

- Girls with classic CAH need a careful balance of the right amount of hydrocortisone medications to suppress androgens, allowing for normal height and minimizing masculine characteristics.

- **Growth hormone and drugs that delay pubertal progression are considered experimental and further studies must be undertaken.**
- **Patients and parents should receive instructions about stress dose coverage, and every patient should wear a medical alert bracelet or necklace and carry the emergency medical information card that is supplied with it.**

Genitalia Surgery

Affected female infants may require surgical reconstruction, with reduction clitoroplasty and construction of a vaginal opening.

Treatment in stress:

- For mild-to-moderate stress, such as fever doubling or tripling the usual maintenance dose of oral hydrocortisone.
- Emergency injectable hydrocortisone must be available in case of vomiting.
- For severe stress and major surgery, administration of hydrocortisone (100 mg/m2 per day), divided in three to four IV doses for at least 24 hours peri- and postoperatively before tapering over several days to a maintenance dose.

Prenatal management

- Powerful corticosteroid drug, such as dexamethasone, before 7^{th}-8^{th} weeks of gestation.
- Corticosteroids can cross the placenta and suppress the activity of the fetus's own adrenal glands. By reducing the secretion of male hormones (androgens), this approach may allow female genitals to develop normally and reduce the masculine features.

- Measuring 17OH-progesterone in heelprick blood spot samples in the first week of life can avoid salt-wasting crises in infancy.

- Antenatal Diagnosis;

This is done genetically in siblings of affected children, by amniocentesis or chorionic villus sampling.

This allows prevention of development of symptoms in female by suppressing ACTH levels.

Prognosis

- Many children with congenital adrenal hyperplasia can successfully manage the condition by **staying on their replacement hormone medications.** They grow up to lead lives in good health and with a normal life expectancy.
- However, they may be shorter than their parents. And both men and women may have fertility problems in adulthood

- Girls who have corrective genital surgery may need further cosmetic surgery later in life.
- When they become sexually active, they're more likely than are women who have not had genital surgery to experience sexual problems such as pain during intercourse.

Prevention

Genetic counseling

The disorder can be diagnosed in fetuses, and prompt treatment, most often beginning in the first before 7th or 8th week of gestation, can reduce or even eliminate symptoms after birth.

Thank you