

***AMBIGUOUS GENITALIA &
CONGENITAL ADRENALHYPERPLASIA***

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AMBIGUOUS GENITALIA

- Children born with ambiguous genitalia may be subdivided in to three groups**
 - a) The virilized female**
 - b) The undervirilized male &**
 - c) The child with abnormal gonadal differentiation**
- This distinction is useful clinically but is not an absolute guide to aetiology, which can only be determined by endocrine investigations and karyotype & sometime requires full assessment of internal pelvic structures.**

**Virilized female/XX
No gonads palpable**



**CONGENITAL ADRENAL
HYPERPLASIA**

**Undervirilized male/XY
Two symmetrical palpable
gonads**



**INCOMPLETE FEMINIZATION
SYNDROME
(receptor defect)
5alpha reductase deficiency
Inborn error of testosterone
synthesis**

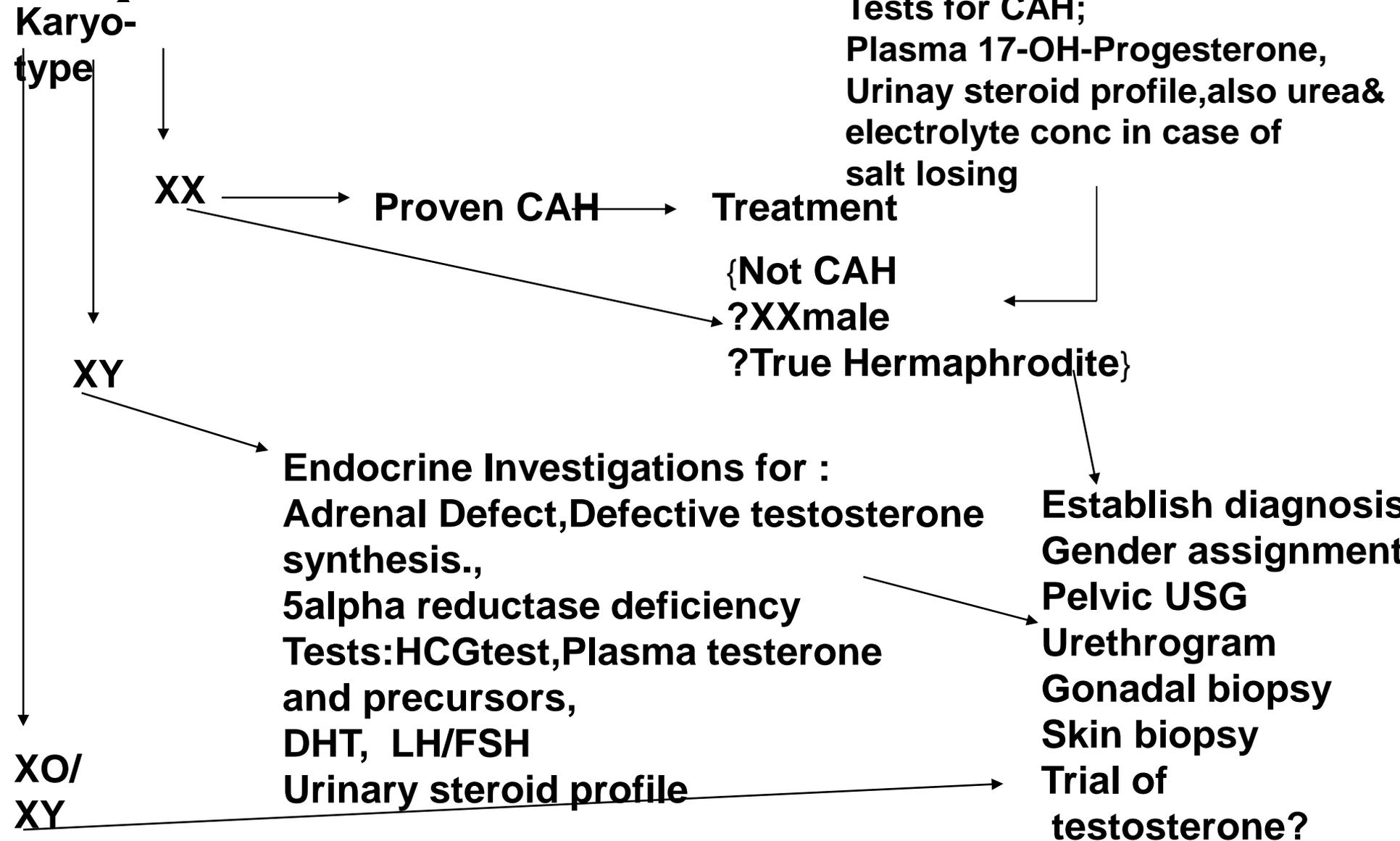
**Abnormal gonadal
differentiation
single or two asymmetrical
palpable gonads**



**TRUE HERMAPHRODITE
(usually XX)
MIXED GONADAL DYSGENESIS
(XO/XY)**

Categories of ambiguous genitalia

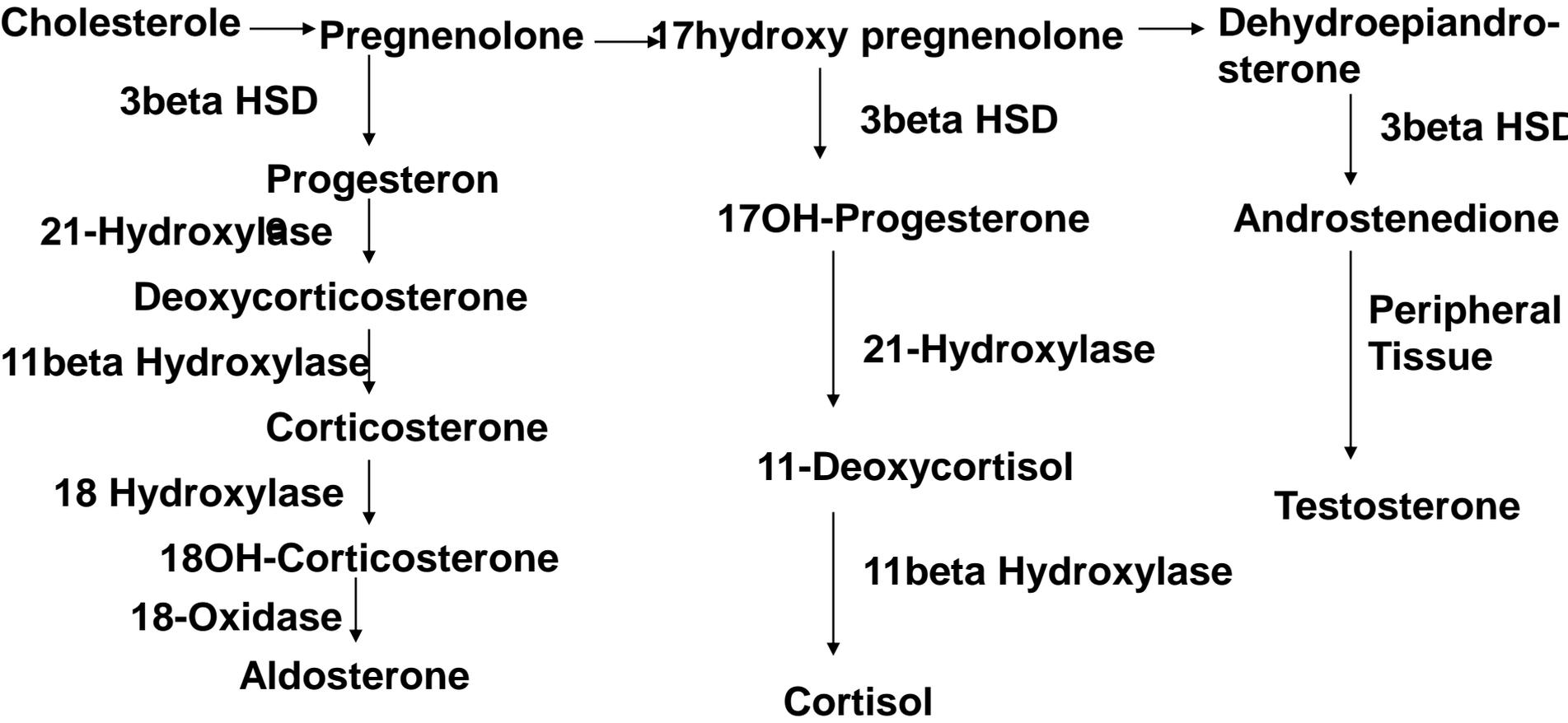
Management of Baby with Ambiguous Genitalia



Desmolase

17-alpha hydroxylase

C-17Lyase



Depending upon the enzymatic deficiency there can be

- 1. 21-Hydroxylase deficiency**
- 2. 11 β -Hydroxylase deficiency**
- 3. 3 β -Hydroxysteroid dehydrogenase deficiency,**
- 4. 17 α -Hydroxylase deficiency**

CONGENITAL ADRENAL HYPERPLASIA

- **Congenital adrenal hyperplasia (CAH) is a family of autosomal recessive disorders of cortisol biosynthesis .**
- **Cortisol deficiency increases secretion of corticotropin (ACTH), which in turn leads to adrenocortical hyperplasia and overproduction of intermediate metabolites.**
- **Depending on the enzymatic step that is deficient, there may be signs, symptoms, and laboratory findings of**
 - **mineralocorticoid deficiency or excess;**
 - **incomplete virilization or**
 - **premature puberty in affected males; and**
 - **virilization or sexual infantilism in affected females .**

Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency

➤ ETIOLOGY.

- **More than 90% of CAH cases are caused by 21-hydroxylase deficiency.**
- **This P450 enzyme (CYP21, P450c21) hydroxylates progesterone and 17-hydroxyprogesterone (17-OHP) to yield 11-deoxycorticosterone (DOC) and 11-deoxycortisol, respectively.**
- **These conversions are required for synthesis of aldosterone and cortisol, respectively.**

➤ TYPES

A. Classical 21-hydroxylase deficiency

In this type

- Both cortisol and aldosterone are deficient in the most severe, **“salt wasting”** form of the disease
- Slightly less severely affected patients are able to synthesize adequate amounts of aldosterone but have elevated levels of androgens of adrenal origin; this is termed **simple virilizing disease**.

B. Nonclassical 21-hydroxylase deficiency;

- These patients have relatively mildly elevated levels of androgens and may have signs of androgen excess after birth.

EPIDEMIOLOGY

- **Classical 21-hydroxylase deficiency**
 - ❑ occurs in about 1 in 15,000–20,000 births in most populations.
 - ❑ Approximately 70% of affected infants have the salt-losing form,
 - ❑ whereas 30% have the simple virilizing form of the disorder
- **Nonclassical disease**
 - ❑ has a prevalence of about 1 in 1,000 in the general population
 - ❑ occurs more frequently in specific ethnic groups such as Ashkenazi Jews, Hispanics, and Yugoslavians.

AFFECTED CHROMOSOME

6p21.3

AFFECTED GENES

- More than 90% of mutations causing 21-hydroxylase deficiency are **recombinations** between CYP21 and CYP21P.
- Approximately 20% are deletions generated by **unequal meiotic crossing-over** between CYP21 and CYP21P,
- whereas the remainder are **nonreciprocal transfers** of deleterious mutations from CYP21P to CYP21, a phenomenon termed **gene conversion**

CLINICAL MANIFESTATIONS

- ❑ **The signs and symptoms of cortisol and aldosterone deficiency include progressive weight loss, anorexia, vomiting, dehydration, weakness, hypotension, hypoglycemia, hyponatremia, and hyperkalemia.**
- ❑ **These problems typically first develop in affected infants at approximately 2 wk of age**
- ❑ **Without treatment, shock, cardiac arrhythmias, and death may occur within days or weeks**

II. Prenatal Androgen Excess.

- This problem begins in affected fetuses by 8–10 wk of gestation
- Male infants appear normal at birth. Thus, the diagnosis may not be made in boys until signs of adrenal insufficiency develop
- In female infants it leads to abnormal genital development causing **Female pseudohermaphroditism**

- ❑ **Affected females, who are exposed in utero to high levels of androgens of adrenal origin, have masculinized external genitals .**
- ❑ **The severity of virilization is usually greatest in females with the salt-losing form of 21-hydroxylase deficiency.**
- ❑ **The internal genital organs are normal, because affected females have normal ovaries and not testes and thus do not secrete anti-müllerian hormone**

III. Postnatal Androgen Excess

- **Untreated or inadequately treated children of both sexes develop additional signs of androgen excess after birth..**
- **Signs of androgen excess**
 - **Include 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** Muscular development may be excessive. Pubic and axillary hair may appear; and acne and a deep voice may develop.
 - **In affected boys ;the penis, scrotum, and prostate may become enlarged; however, the testes are usually prepubertal in size so that they appear relatively small in contrast to the enlarged penis. Occasionally, ectopic adrenocortical cells in the testes of patients become hyperplastic similarly to the adrenal glands, producing testicular adrenal rest tumors.**

- In affected females The clitoris may become further enlarged. Although the internal genital structures are female, breast development and menstruation may not occur unless the excessive production of androgens is suppressed by adequate treatment.
- Similar but usually milder signs of androgen excess may occur in **nonclassical 21-hydroxylase deficiency**. In this, 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**.

LABORATORY FINDINGS

- Patients with salt-losing disease typically have hyponatremia, hyperkalemia, metabolic acidosis, and often hypoglycemia, but these abnormalities can take 1–2 wk or longer to develop after birth.
- Blood levels of 17-hydroxyprogesterone are markedly elevated. However, levels of this hormone are high during the first 2–3 days of life, even in unaffected infants especially if they are sick or premature.
- After infancy, once the circadian rhythm of cortisol is established, 17-hydroxyprogesterone levels vary in the same circadian pattern, being highest in the morning and lowest at night.
- Blood levels of cortisol are usually low in patients with the salt-losing type of disease. They are often normal in patients with simple virilizing disease but inappropriately low in relation to the ACTH and 17-hydroxyprogesterone levels.

- In addition to 17-hydroxyprogesterone, levels of androstenedione and testosterone are elevated in affected females;
- Testosterone is not elevated in affected males because normal infant males have high testosterone levels compared with those seen later in childhood.
- Levels of urinary 17-ketosteroids and pregnanetriol are elevated.
- Corticotropin (ACTH) levels are elevated but have no diagnostic utility over 17-hydroxyprogesterone levels.
- Plasma levels of renin are elevated, and serum aldosterone is inappropriately low for the renin level. However, renin levels are normally high in the first few days of life.

- Diagnosis of 21-hydroxylase deficiency is most reliably established**
- by measuring 17-hydroxyprogesterone before and 30 or 60 min after an intravenous bolus of 0.125–0.25 mg of cosyntropin (ACTH 1–24).**
- Nomograms exist that readily distinguish normals and patients with nonclassical and classical 21- hydroxylase deficiency.**

□ PRENATAL DIAGNOSIS.

- **Prenatal diagnosis of 21-hydroxylase is possible late in the first trimester by analysis of DNA obtained by chorionic villus sampling or during the second trimester by amniocentesis.**
- **This is usually done when the parents already have an affected child.**

□ **NEWBORN SCREENING.**

- **Because 21-hydroxylase deficiency is often undiagnosed in affected males until they have severe adrenal insufficiency, many countries have instituted newborn screening programs. These programs analyze 17-hydroxyprogesterone levels .**
- **The nonclassical form of the disease is not reliably detected by newborn screening,**

EVALUATION OF A CHILD WITH AMBIGUOUS GENITALIA

- **History.**
 - Acute episodes of vomitings and collapse in neonate especially during 2nd or 3rd week of life
 - Failure to thrive inspite of adequate caloric intake.
 - Consanguineous marriage.
 - Drug intake during pregnancy eg progesterone, Danazole.
 - Severe hirsutism or neoplastic disease of the mother.

Examination

- **Weight, Length, Head circumference.**
- **Heart rate,-respiratory rate ,blood pressure and hydration status**
- **Dysmorphic features**
- **Genital examination to define the anatomy of the genitals, locate the urethral meatus, palpate the scrotum or labia and the inguinal regions for testes (palpable gonads almost always indicate the presence of testicular tissue and thus that the infant is a genetic male),**

Investigations

- **A rapid karyotype (such as fluorescence in situ hybridization of interphase nuclei for X and Y chromosomes) can quickly determine the genetic sex of the infant.**
- **Buccal smear for bar bodies.**
- **Serum electrolytes(Hyponatremia & Hyperkalemia)**
- **Ultrasonography is helpful in demonstrating the presence or absence of a uterus and can often locate the gonads**

- **Hormonal studies**
- **17-hydroxyprogesterone are markedly elevated, Elevated progesterone levels**
- **Increased plasma renin activity/Aldosterone ratio.**
- **Elevated ACTH levels**
- **Low or undetectable serum cortisol**
- **Increased urinary 17ketosteroids**
- **Injection of contrast medium into the urogenital sinus of female pseudohermaphrodites demonstrates a vagina and uterus, and most surgeons utilize this information to formulate a plan for surgical management.**

TREATMENT

□ **Glucocorticoid Replacement.**

- **Cortisol deficiency is treated with glucocorticoids.**
- **Larger glucocorticoid doses are needed , typically 15–20 mg/m²/24 hr of hydrocortisone daily administered orally in 3 divided doses.**
- **Affected infants usually require dosing at the high end of this range.**
- **Double or triple doses are indicated during periods of stress, such as infection or surgery.**

- **Glucocorticoid treatment must be continued indefinitely in all patients with classical 21-hydroxylase deficiency but may not be necessary in patients with nonclassical disease unless signs of androgen excess are present.**
- **The efficacy of treatment is monitored by measuring 17-hydroxy-progesterone and androstenedione concentration in plasma**
- **Over treatment with glucocorticoids results in obesity and growth retardation. Under treatment results in progressive virilization and bone age advancement.**

□ **Mineralocorticoid Replacement.**

- **Patients with salt-wasting disease (i.e., aldosterone deficiency) require mineralocorticoid replacement with fludrocortisone.**
- **Infants may have very high mineralocorticoid requirements in the first few months of life, usually 0.1–0.3 mg daily in 2 divided doses but occasionally up to 0.4 mg daily, and often require sodium supplementation (sodium chloride, 1–3 g) in addition to the mineralocorticoid.**
- **Older infants and children are usually maintained with 0.05–0.1 mg daily of fludrocortisone.**

- **Therapy is evaluated by monitoring of vital signs; tachycardia and hypertension are signs of overtreatment with mineralocorticoids.**
- **Serum electrolytes should be measured frequently in early infancy as therapy is adjusted.**
- **Plasma renin activity is a useful way to determine adequacy of therapy; it should be maintained in or near the normal range but not suppressed.**

- ❑ **Surgical Management** Vaginoplasty and Clitoral recession in female pseudo-hermaphroditism.
- ❑ **Psychosocial support** to patient and family.
- ❑ **Genetic counseling.**
- ❑ **Prenatal treatment** includes treatment of mothers at risk with **dexamethasone 20 µg/kg prepregnancy maternal weight daily in 2 or 3 divided doses** .This suppresses secretion of steroids by the fetal adrenal, including secretion of adrenal androgens. If started by 6 wk of gestation, it ameliorates virilization of the external genitals in affected females. Chorionic villus biopsy is then performed to determine the sex and genotype of the fetus; therapy is continued only if the fetus is an affected female.

THANK YOU