EVALUATION & MANAGEMENT OF INFANT WITH DSD

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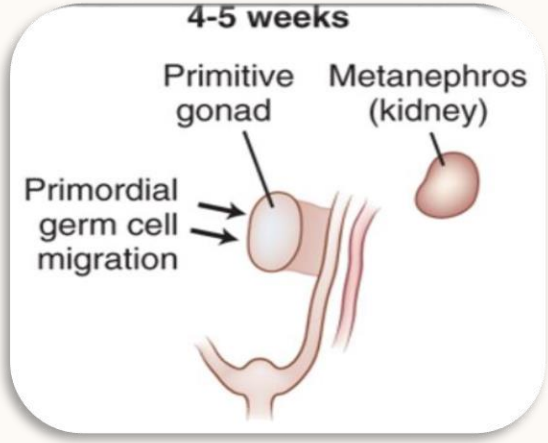
INTRODUCTION

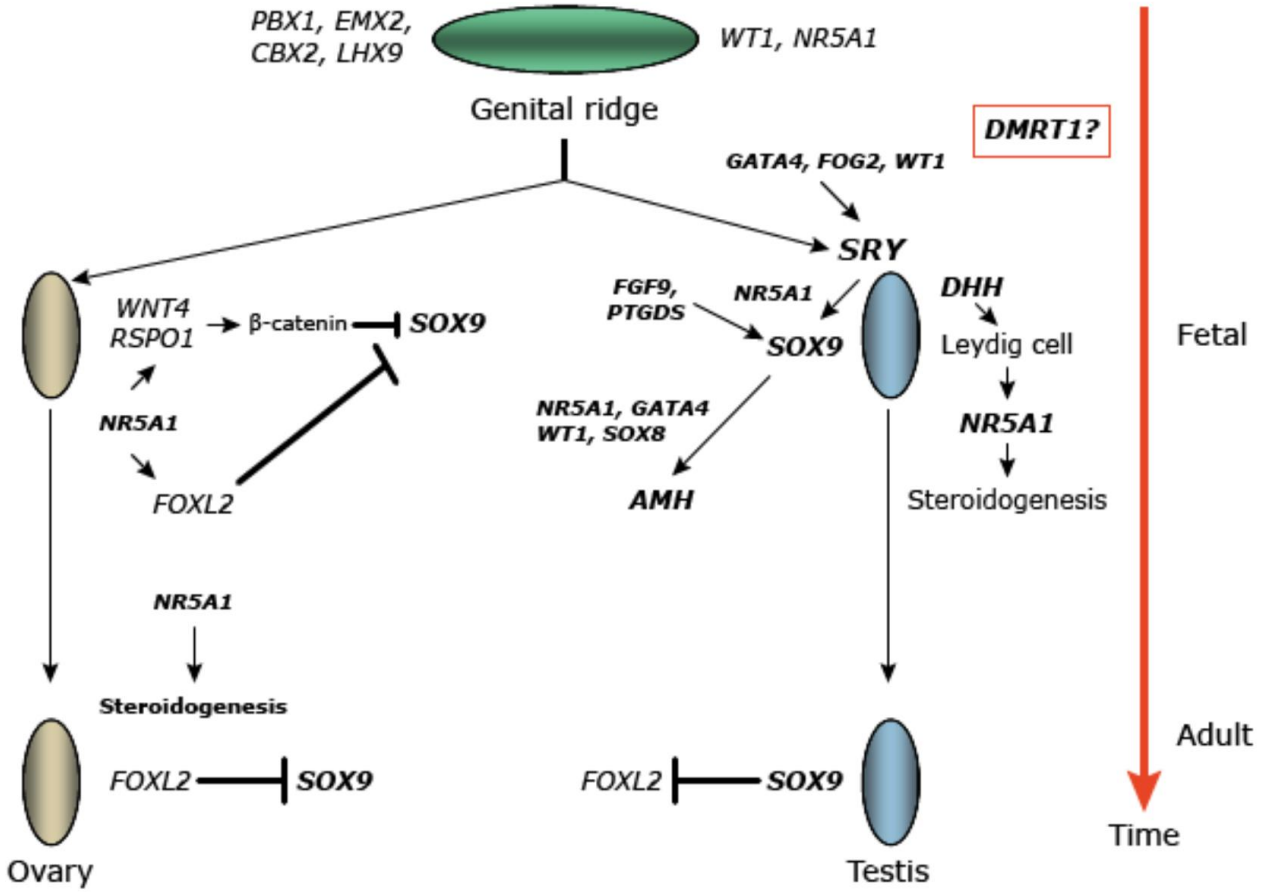
- Infants born with genitals that do not appear typically male or female, or that have an appearance discordant with the chromosomal sex , are classified as having a disorder of sex development .

TYPICAL SEX DEVELOPMENT

- The ovaries and testes derive from a primitive bipotential gonad.
- In typical XY individuals, expression of the *SRY* gene activates pathways that cause the gonads to differentiate as testes.
- In typical XX individuals, the absence of *SRY* causes the gonads to differentiate into ovaries.



Molecular and genetic events in mammalian sex determination and differentiation



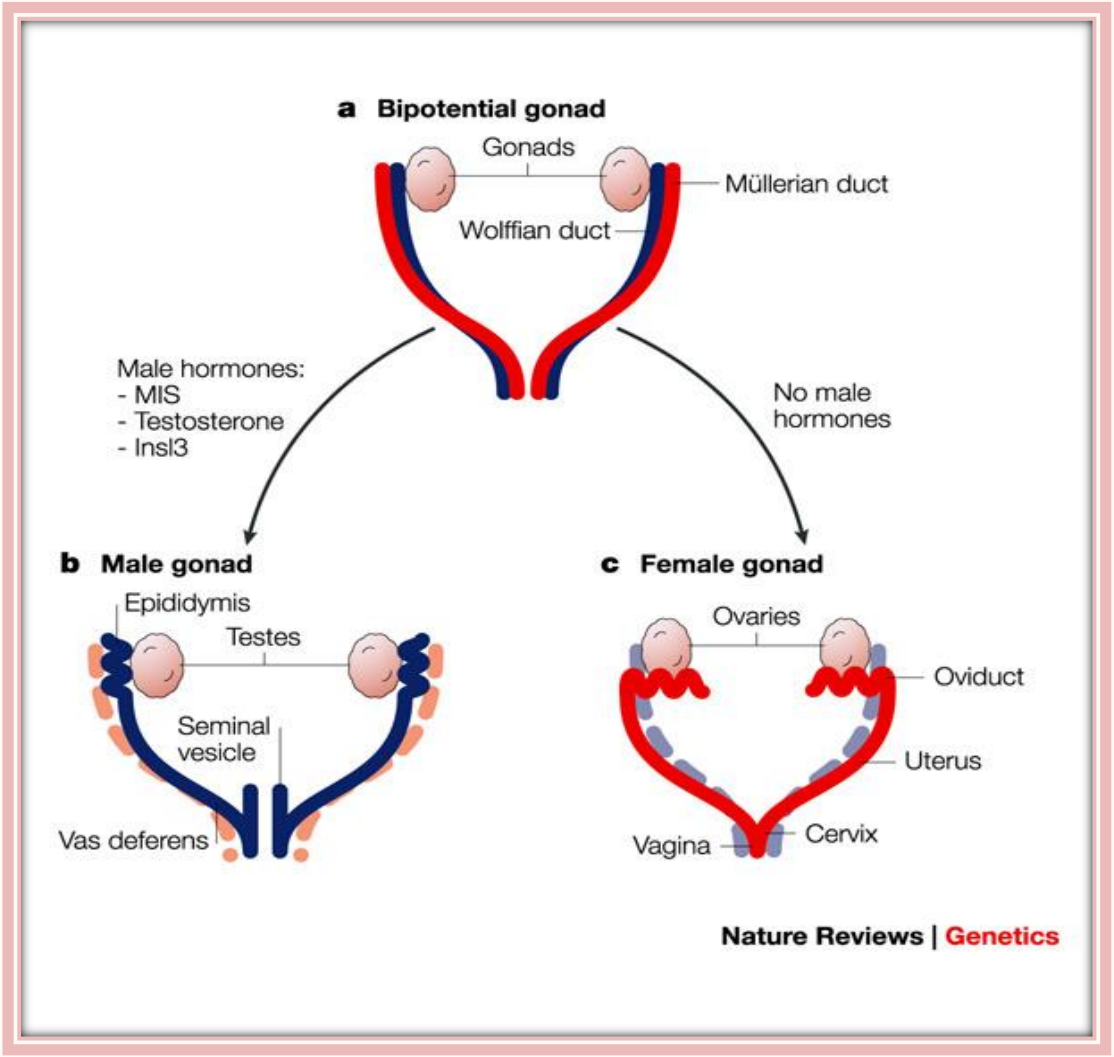
TYPICAL SEX DEVELOPMENT

TESTIS

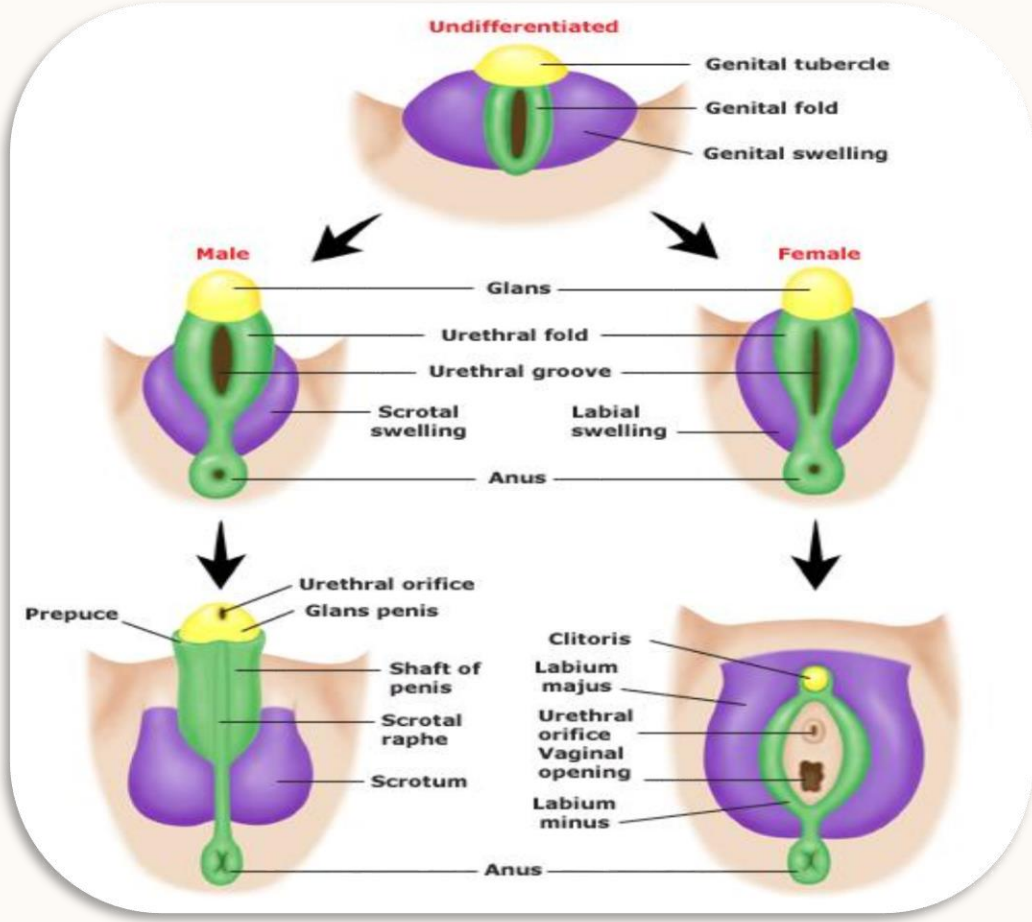
- **Leydig cells :**
- Testosterone, which is converted to DHT by the enzyme 5-alpha-reductase type 2
- INSL3
- **Sertoli cells :**
- AMH

OVARY

- Ovary **does not** produce significant amounts of testosterone, INSL3, or AMH.


a Bipotential gonad
Gonads
Müllerian duct
Wolffian duct
Male hormones:
- MIS
- Testosterone
- Insl3
No male hormones
b Male gonad
Epididymis
Testes
Seminal vesicle
Vas deferens
c Female gonad
Ovaries
Oviduct
Uterus
Vagina
Cervix
Nature Reviews | Genetics

TYPICAL SEX DEVELOPMENT



CLASSIFICATION DISORDERS OF SEX DEVELOPMENT

XX DSD

XY DSD

Sex chromosome DSD

CAUSES OF XX DSD

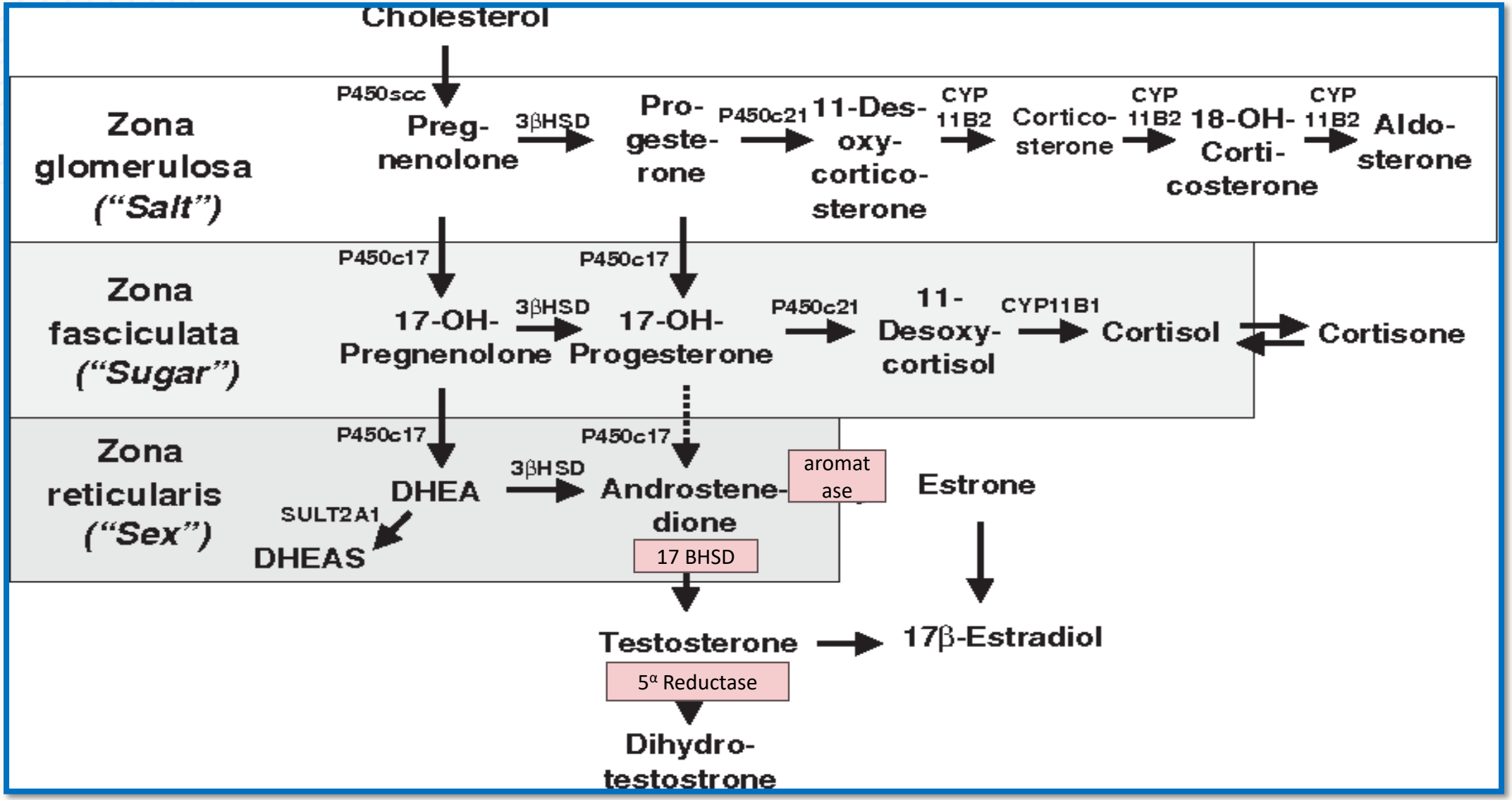
DSD in an individual with an XX complement of sex chromosomes is caused by atypically high levels of androgen, which can be due to :

- Overproduction of androgens by the adrenal cortex
- Overproduction by the gonads
- Ectopic or exogenous source of androgens

CAUSES OF XX DSD

ADRENAL OVERPRODUCTION OF ANDROGENS

1. **Congenital adrenal hyperplasia**
2. **Glucocorticoid resistance**


Cholesterol
P450scc
Zona glomerulosa ("Salt")
Preg-nenolone
3βHSD
Pro-geste-rone
P450c21
11-Des-oxy-cortico-sterone
CYP 11B2
Cortico-sterone
CYP 11B2
18-OH-Corti-costerone
CYP 11B2
Aldo-sterone
Zona fasciculata ("Sugar")
P450c17
17-OH-Pregnenolone
3βHSD
17-OH-Progesterone
P450c21
11-Desoxy-cortisol
CYP11B1
Cortisol
Cortisone
Zona reticularis ("Sex")
P450c17
DHEA
3βHSD
Androstene-dione
aromat ase
Estrone
SULT2A1
DHEAS
17 BHSD
Testosterone
17β-Estradiol
5α Reductase
Dihydro-testostrone

CAUSES OF XX DSD

ADRENAL OVERPRODUCTION OF ANDROGENS

1. **Congenital adrenal hyperplasia**

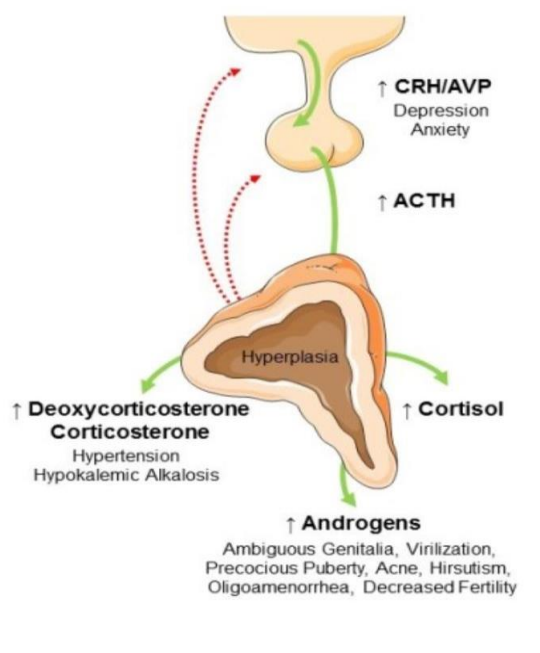
- 21-hydroxylase defect
- 11-hydroxylase defect
- 3β-hydroxysteroid dehydrogenase defect
- P450 Oxidoreductase deficiency

CAUSES OF XX DSD

ADRENAL OVERPRODUCTION OF ANDROGENS

2. Glucocorticoid resistance

- Impaired response to cortisol results in loss of negative feedback and high levels of ACTH, resulting in adrenal overproduction of mineralocorticoids and androgens .



CAUSES OF XX DSD

GONADAL OVERPRODUCTION OF ANDROGENS

1. **XX testicular or ovotesticular DSD**
2. **Aromatase deficiency**

CAUSES OF XX DSD

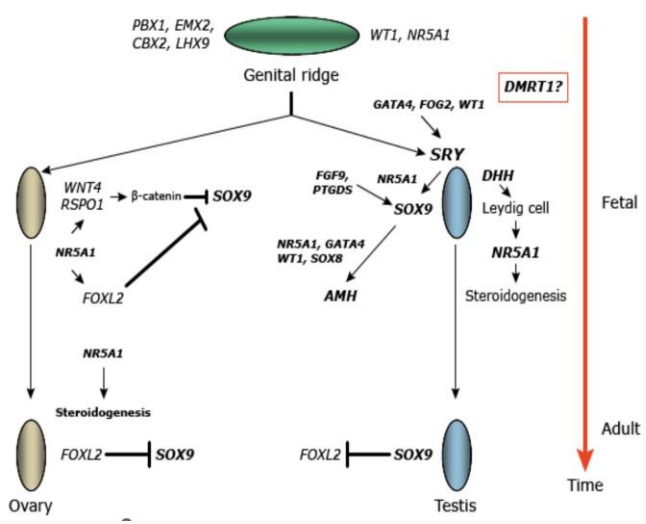
GONADAL OVERPRODUCTION OF ANDROGENS

1. **XX testicular or ovotesticular differences of sex development**

- Is a term for conditions in which the gonads develop along the testicular rather than the ovarian pathway.

CAUSES OF XX TESTICULAR OR OVOTESTICULAR DSD

- **Presence of *SRY***
- **Mutations in *NR5A1*** (*SF1*)
- **Duplication of *SOX9***
- **Inappropriate expression of *SOX3***



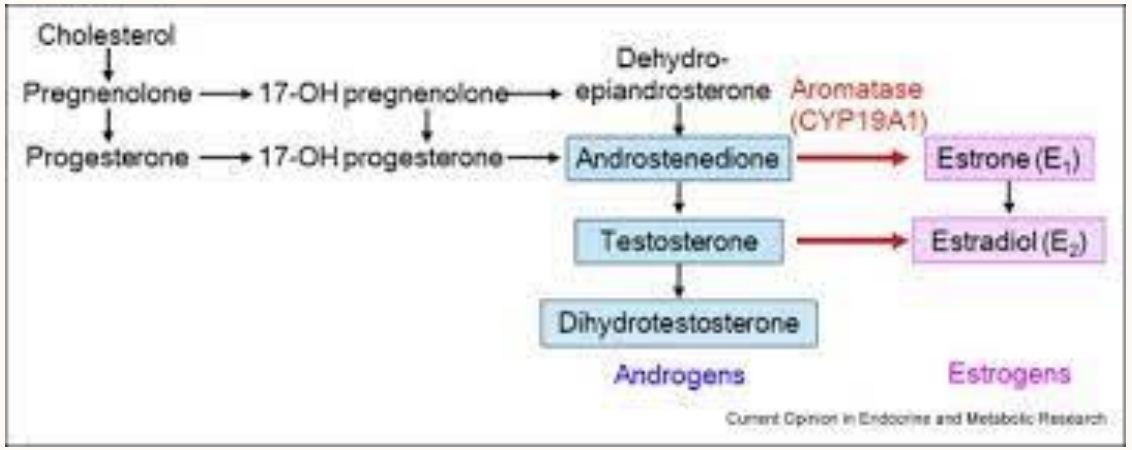
- **Loss-of-function mutations in genes that repress testicular pathways**
- •*WNT4*
- •*RSPO1*

CAUSES OF XX DSD

GONADAL OVERPRODUCTION OF ANDROGENS

2. Aromatase deficiency

- Defect conversion of androgens to estrogens.
- Androgens from the fetus can cross the placenta and also cause maternal virilization.



CAUSES OF XX DSD

ECTOPIC OR EXOGENOUS SOURCE OF ANDROGENS

❑ **Gestational hyperandrogenism**

- Maternal luteoma or theca lutein cysts
- Exogenous progestin or androgen exposure

CAUSES OF XY DSD

- XY DSDs occur because of atypically low levels of DHT action. This can be caused by :

➢ Global defect in testicular function due to gonadal dysgenesis

➢ Specific defect in DHT production

➢ Inability to respond to DHT and other androgens

CAUSES OF XY DSD

GLOBAL DEFECTS IN TESTICULAR FUNCTION

- **XY gonadal dysgenesis** :

✓ Complete XY gonadal dysgenesis (Swyer syndrome) : typical female external genital , intact müllerian structures, and streak gonads .

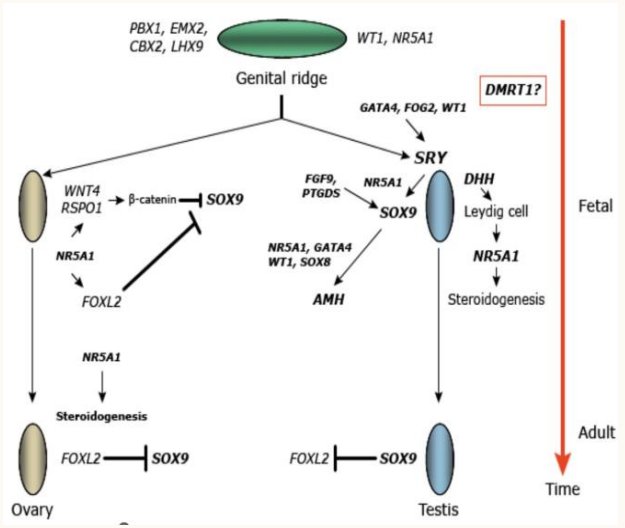
✓ Partial XY gonadal dysgenesis : wide range of testicular function and wide range of phenotypes (isolated infertility without undervirilization, hypospadias, frankly atypical genital appearance, to near-complete undervirilization with clitoromegaly. The müllerian structures may be normal, hypoplastic, or absent.)

CAUSES OF XY GONADAL DYSGENESIS

- **Mutations in *NR5A1*** (SF1 : gonads and adrenal)
- **Mutations in *SRY***
- **Mutations in *WT1*** (Renal and gonadal)
- **Loss-of-function mutations in genes essential for testicular development**

MAP3K1, *CBX2*, *DHH*, *DHX37*, *DMRT1*, *FGF9*, *FOG*, *GATA4*, *SOX9*, and *ZFPM2*

- **Gain-of-function mutations in *NR0B1*** (*DAX1*)



CAUSES OF XY DSD

TESTICULAR DYSFUNCTION WITHOUT ATYPICAL GENITALIA

❖ **Persistent müllerian duct syndrome :**

- Mutations in the *AMH* gene or in the AMH receptor gene .
- The disorder is characterized by normal external male genitalia, variable testicular descent, and presence of müllerian structures (such as a uterus).

CAUSES OF XY DSD

TESTICULAR DYSFUNCTION WITHOUT ATYPICAL GENITALIA

❖ **Testicular regression syndrome** (congenital anorchia or vanishing testes syndrome):

- Loss of testicular function late in fetal life results in anorchia but typical male genital appearance and absence of müllerian ducts .
- The cause is unclear but is thought to be due to bilateral fetal/infant testicular **torsion** in some cases.
- **Mutations in the *DHX37*** gene have been described.

CAUSES OF XY DSD

DISORDERS WITH ABNORMAL ANDROGEN SYNTHESIS

- **Leydig cell hypoplasia (LH/CG receptor defects)**

- XY patients have female external genital but lack a uterus and fallopian tubes; the epididymis and vas deferens may be present .
- Laboratory evaluation reveals low testosterone concentrations despite elevated concentration of LH, and patients are unresponsive to exogenous hCG.

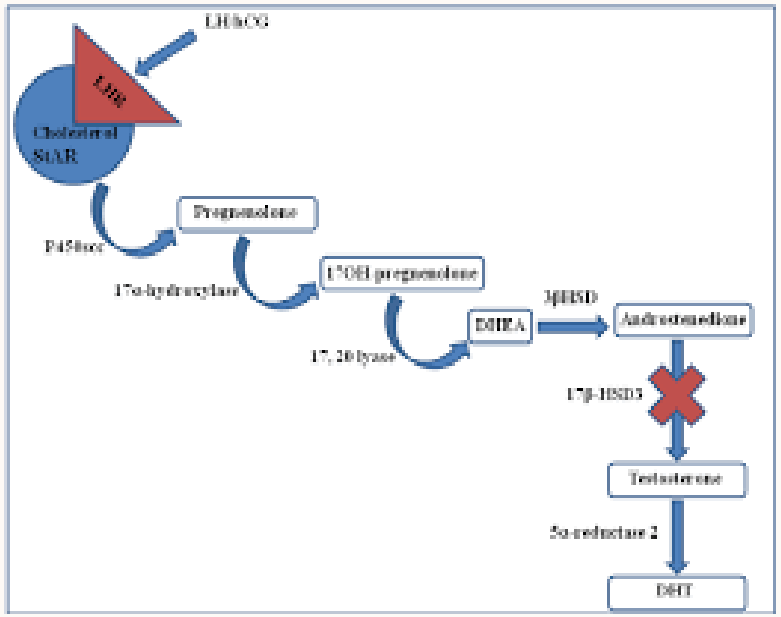
- **Smith-Lemli-Opitz syndrome**

- Affected individuals can exhibit growth and developmental delays, microcephaly, characteristic facial features, cleft palate, syndactyly and/or polydactyly,

CAUSES OF XY DSD

DISORDERS WITH ABNORMAL ANDROGEN SYNTHESIS

- **17-beta-hydroxysteroid dehydrogenase type 3 deficiency**
- Defective conversion of androstenedione to testosterone.
- Ratio of testosterone to androstenedione <0.8.



CAUSES OF XY DSD

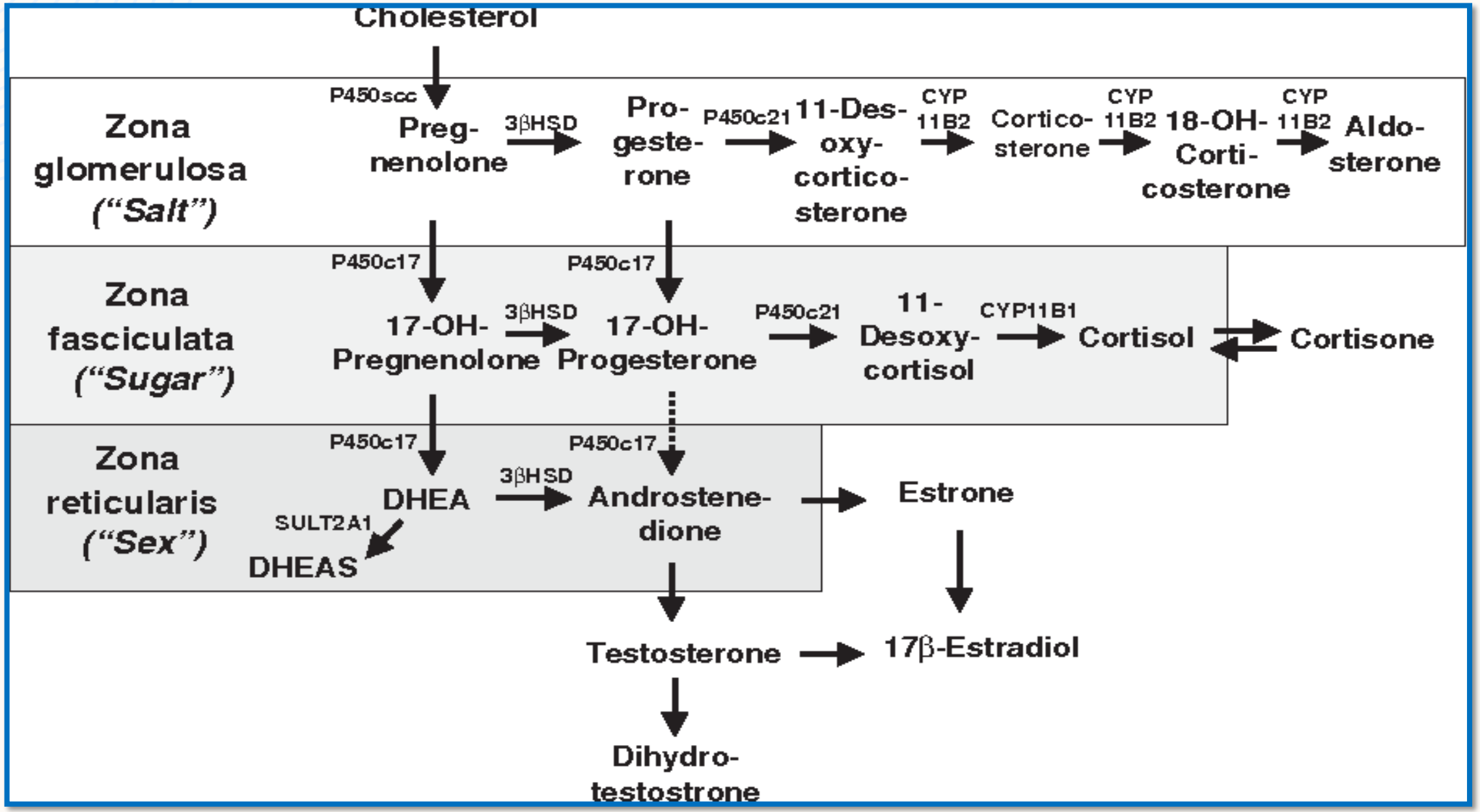
DISORDERS WITH ABNORMAL ANDROGEN SYNTHESIS

- **5-alpha-reductase type 2 deficiency**
- Defective conversion of testosterone to DHT.
- Ratio of testosterone: dihydrotestosterone >10:1.

CAUSES OF XY DSD

DISORDERS WITH ABNORMAL ANDROGEN SYNTHESIS

- **Forms of congenital adrenal hyperplasia**
- **3-beta-hydroxysteroid dehydrogenase type 2 deficiency (3-beta-HSD)**
- **17-alpha-hydroxylase deficiency**
- **P450 oxidoreductase (POR) deficiency**
- **Lipoid CAH**
- **P450 side-chain cleavage enzyme deficiency**


Cholesterol
P450scc
Zona glomerulosa ("Salt")
Preg-nenolone
3βHSD
Pro-geste-rone
P450c21
11-Des-oxy-cortico-sterone
CYP 11B2
Cortico-sterone
CYP 11B2
18-OH-Corti-costerone
CYP 11B2
Aldo-sterone
P450c17
P450c17
Zona fasciculata ("Sugar")
17-OH-Pregnenolone
3βHSD
17-OH-Progesterone
P450c21
11-Desoxy-cortisol
CYP11B1
Cortisol
Cortisone
P450c17
P450c17
Zona reticularis ("Sex")
DHEA
3βHSD
Androstene-dione
Estrone
SULT2A1
DHEAS
Testosterone
17β-Estradiol
Dihydro-testostrone

CAUSES OF XY DSD

DISORDERS WITH ANDROGEN INSENSIVITY

➢ **Androgen insensitivity**

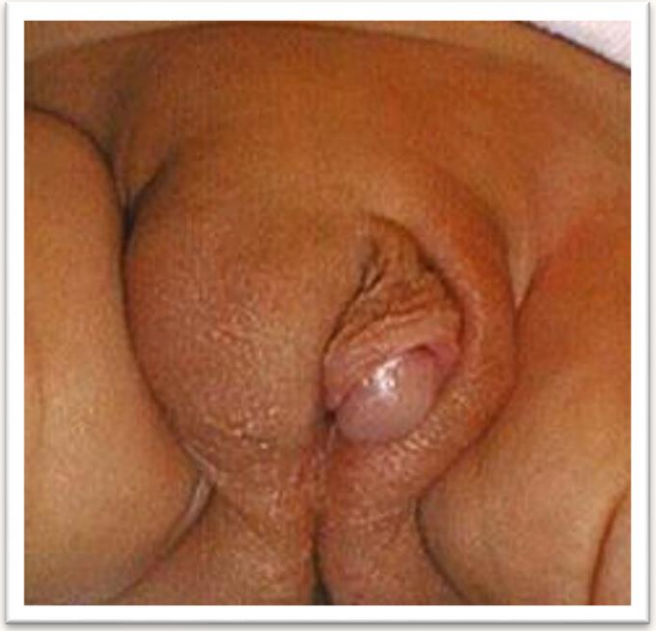
- In an individual with XY DSD, normal or elevated serum testosterone production at baseline or after hCG stimulation suggests androgen insensitivity syndrome .
- **Partial AIS** :
- From mild virilization, to more atypical genital appearance, to typical male genital appearance with infertility.
- **Complete AIS** : typical female external genital appearance.

SEX CHROMOSOME DSD

- This subtype of DSD is defined by presence of a sex chromosome complement other than XX or XY.
- 45,X (Turner syndrome)
- 47,XXY (Klinefelter syndrome)
- 45,X/46,XY (Mixed gonadal dysgenesis)
- 46,XX/46,XY

45,X/46,XY (MIXED GONADAL DYSGENESIS)

Poorly developed testicle and Wolffian structures on one side (usually the right) and a gonadal streak and müllerian structures (often incompletely developed) on the other, potentially producing asymmetric genital anatomy.



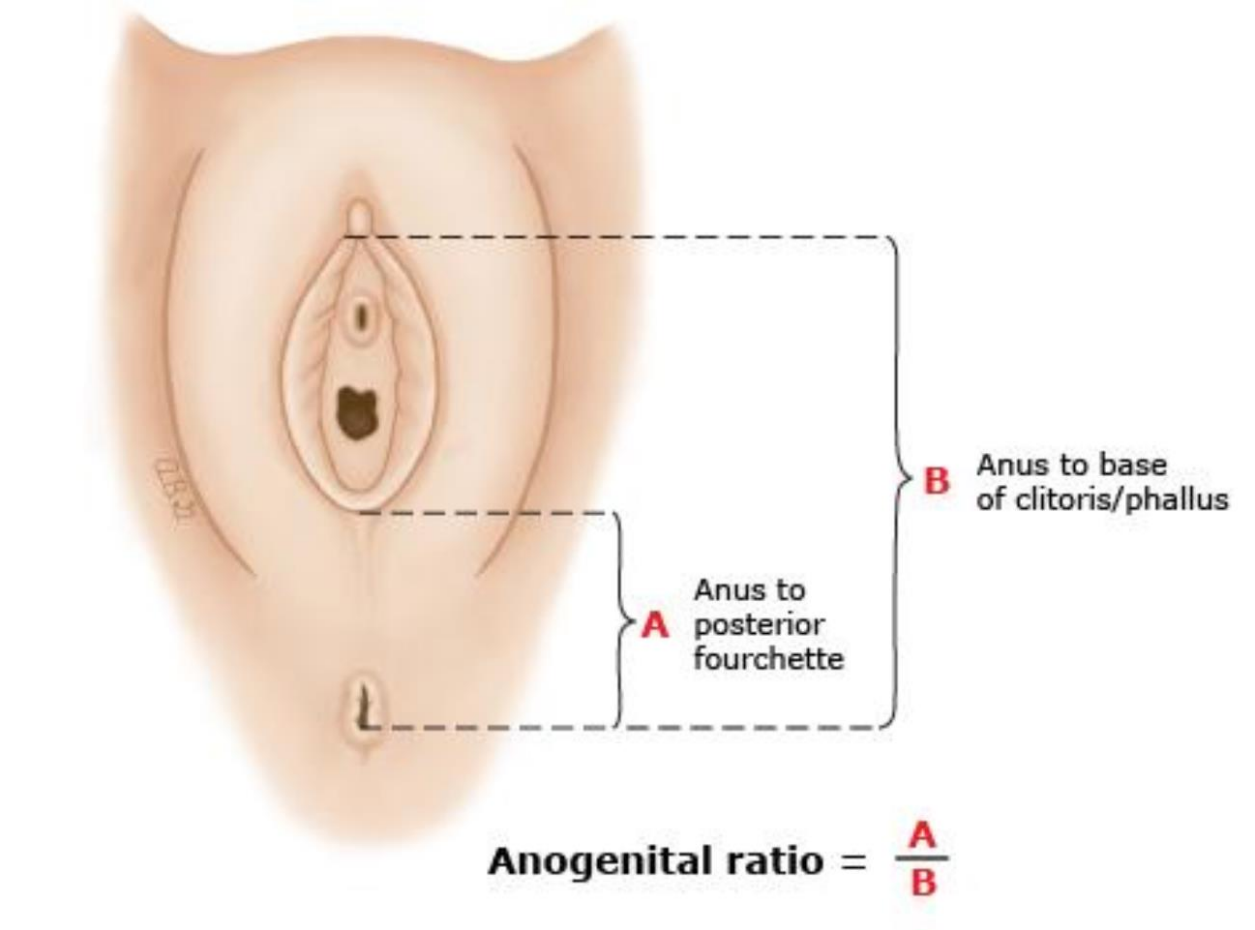
INDICATIONS FOR EVALUATION

INDICATIONS FOR EVALUATION

- ❑ Male genital appearance with :
- ✓ Bilaterally nonpalpable gonads
- ✓ Severe hypospadias (scrotal or perineal)
- ✓ Any degree of hypospadias accompanied by unilateral or bilateral cryptorchidism and/or micropenis (stretched penile length < 2.5 cm in a full-term infant)
- ✓ Genital appearance discordant with the sex chromosomes

INDICATIONS FOR EVALUATION

- ❑ Female genital appearance with:
- ✓ Clitoromegaly (width >6 mm or length >9 mm)
- ✓ Posterior labial fusion (Anogenital ratio >0.5 ; single opening)
- ✓ Gonads palpable in the labioscrotal folds or the inguinal region
- ✓ Genital appearance discordant with the sex chromosomes


B
Anus to base of clitoris/phallus
A
Anus to posterior fourchette
Anogenital ratio = A/B

DSD EVALUATION NOT REQUIRED

- **Male-appearing genitals with standard hypospadias** (ectopic meatus on the glans, penile shaft and/or penoscrotal junction, with a normal-sized phallus and glans and penile curvature that is no more than mild to moderate, if both gonads are palpable)
- **Male-appearing genitals with isolated micropenis** (though such infants should be evaluated for hypogonadotropic hypogonadism/hypopituitarism).
- **Female-appearing genitals with an atypical clitoral hood** but no clitoromegaly.

DIAGNOSTIC APPROACH

DIAGNOSTIC APPROACH

❑ 1.HISTORY

- **Prenatal exposure to androgens or endocrine disrupters**

  (danazol, testosterone, spironolactone, finasteride)

- **Maternal virilization in pregnancy**

  (placental aromatase deficiency or a maternal androgen-secreting tumor)

- **Women who have been unable to bear children and/or have amenorrhea**

  (androgen insensitivity)

- **History of consanguinity**

  (CAH or disorders of androgen biosynthesis)

DIAGNOSTIC APPROACH

❑ 2.PHYSICAL EXAMINATION

- Inspection and palpation of the genitalia
- Palpation of labioscrotal folds and inguinal regions for gonads
- Documentation of number of urogenital openings
- Measurements of the phallus/clitoris and anogenital ratio

OTHER PHYSICAL FEATURES

- **Elevated blood pressure**

  11-beta-hydroxylase deficiency and 17-hydroxylase deficiency

- **Gastrointestinal anomalies**

  Disorder of cloacal differentiation

- **Microcephaly, micrognathia, low-set and posteriorly rotated ears, and syndactyly and/or polydactyly**

  Smith-Lemli-Opitz syndrome

- **Craniofacial and limb abnormalities (Antley-Bixler syndrome)**

  P450 oxidoreductase deficiency

INITIAL LABORATORY TESTING

Initial laboratory testing
Expedited determination of sex chromosomes (karyotype or other method).
Adrenal steroids – 17-OHP (essential; this test is part of newborn screening in the United States). Tests for uncommon causes of CAH (17-hydroxypregnenolone, cortisol, 11-deoxycortisol) are sometimes done at this point but may be deferred to minimize blood loss.
Gonadal function – FSH, LH, testosterone*, dihydrotestosterone, AMH.
Electrolytes (baseline; follow every 24 to 48 hours until CAH is confirmed or excluded).
Abdominal and pelvic ultrasound to assess for gonads, uterus, and vagina.

INITIAL LABORATORY TESTING

❖ **Sex chromosome analysis** : is a critical element of diagnosis and should be performed as soon as possible in any infant with atypical genital appearance.

- **Interpretation** – The results of the karyotype permit classification of the infant into one of three diagnostic categories :

➢ XX DSD

➢ XY DSD

➢ Sex chromosome DSD

INITIAL LABORATORY TESTING

❖ **17-hydroxyprogesterone**

- **Indications** – 17-OHP should be measured in all infants with bilateral nonpalpable gonads presenting with atypical genital appearance and typical male genital appearance .
- Measurement of 17-OHP should be done after 48 hours of life to avoid the birth-associated surge in adrenal hormones.

Table 1. Serum 17-OHP Levels by Gestational Age

Gestational age(wks)	No.	17-OHP(ng/ml)
≥32	34	24.7±13.8
33-34	35	18.8±11.2
35-36	44	15.0±10.2
37-38	202	12.1± 7.6
39-40	307	11.8± 8.0
41-42	115	10.5± 7.4

Table 2. Serum 17-OHP Levels by Birth Weight

Weight(gm)	No.	17-OHP(ng/ml)
<1,500	17	26.7±11.7
1,501-2,000	33	18.0±13.9
2,001-2,500	63	17.9±10.5
2,501-3,000	131	12.1± 7.9
3,001-3,500	274	11.5± 8.1
>3,500	193	11.4± 7.5

INITIAL LABORATORY TESTING

- **DHEAS** , **Androstenedione** , **Cortisol** , **ACTH**
- 17-hydroxypregnenolone , 11-deoxycortisol

INITIAL LABORATORY TESTING

❖ **Electrolytes**

●**Indications** – In any infant for whom CAH is considered possible, serum electrolytes should be measured at the time of presentation and then repeated every 24 to 48 hours until CAH is excluded.

●**Interpretation** – Salt wasting is suggested by the findings of hyponatremia, hyperkalemia, and non gap metabolic acidosis.

INITIAL LABORATORY TESTING

❖ **Testosterone**

- Levels of testosterone begin to rise by approximately one week of age in full-term infants ("mini-puberty" of infancy) .
- In boys, serum testosterone usually peaks between one to three months and male mini-puberty ends by approximately six months of age.
- In girls, mini-puberty ends by around two years of age.
- Premature infants may take longer to enter the "mini-puberty" phase.

INITIAL LABORATORY TESTING

- **DHT**
  - **Ratio of Testosterone to DHT < 10**

INITIAL LABORATORY TESTING

❖ **LH**

- > 0.3 mIU/mL demonstrates that the infant has entered "mini-puberty".

- **Low LH** can be seen in children who are :

➢ Not in mini-puberty (infant is younger than 14 days, testing should be repeated)

➢ Hypogonadotropic hypogonadism

INITIAL LABORATORY TESTING

- **Elevated LH** during the mini-puberty of infancy suggests:
  - Gonadal dysgenesis
  - Defects in testosterone, DHT , and/or estradiol synthesis
  - Androgen insensitivity

INITIAL LABORATORY TESTING

❖ **AMH**

- Is still produced after mini-puberty ends.
- In boys (>30 ng/mL) and girls (<10 ng/mL)

INITIAL LABORATORY TESTING

- **In a virilized XX infant or child**, an AMH level **above the female range** indicates the presence of Sertoli cells and, in turn, the presence of testicular tissue and therefore suggests an **XX testicular or ovotesticular DSD**.

INITIAL LABORATORY TESTING

- If AMH is **below the typical male range** in an **XY individual with atypical genital** appearance, this suggests a **global defect in testicular function**, ie, gonadal dysgenesis affecting both Leydig and Sertoli cells.

- If AMH is **within the typical male range** in an **XY individual with undervirilization**, this suggests an **isolated defect in androgen synthesis or action**.

INITIAL LABORATORY TESTING

❖ **Imaging**

- Ultrasonography of the abdomen and pelvis, and occasionally MRI or genitoscopy, is important to determine the presence of gonads, a uterus, and/or a vagina.

INTERPRETATION OF INITIAL FINDINGS

XX karyotype			
17-OHP	**AMH**	**Likely diagnosis**	**Comments**
Very elevated	Within female range	▪ CAH due to 21-hydroxylase deficiency	▪ Risk for adrenal crisis; treat immediately ▪ Gonads are not palpable
Elevated	Within female range	▪ CAH due to 21-hydroxylase deficiency ▪ Other form of XX CAH¶ ▪ Stress	▪ Risk for adrenal crisis ▪ Follow electrolytes ▪ Repeat 17-OHP if stress is present ▪ Interpret other adrenal steroids and/or ACTH stimulation test for definitive diagnosis
Normal	Within female range	▪ Gestational hyperandrogenism	▪ Maternal virilization during pregnancy
Normal	Elevated above female range	▪ Testicular or ovotesticular DSD	▪ Elevated testosterone and AMH (above female range) suggests that testicular tissue is present ▪ To determine cause, test for presence of *SRY*, sequence *NR5A1*, and consider next-generation sequencing ▪ May have palpable gonads

INTERPRETATION OF INITIAL FINDINGS

XY karyotype			
Ultrasound	**AMH**	**Likely diagnosis or category**	**Comments**
No uterus	Within male range	▪ Defect in androgen synthesis or action	▪ Testosterone:dihydrotestosterone (when expressed in same units) <10:1 (normal) • Elevated testosterone – Probable AIS • Normal testosterone – Likely AIS, possible 17-beta-HSD or partial gonadal dysgenesis • Low testosterone – 3-beta-HSD2 or other forms of XY CAH[Δ] ▪ Testosterone:dihydrotestosterone >10:1 (elevated) • 5-alpha-reductase deficiency ▪ If LH is low, repeat after 2 weeks of age or consider hCG stimulation testing
Uterus present or absent	Below male range	▪ Gonadal dysgenesis (global impairment of testicular function)	▪ Genetic testing to determine cause: • *NR5A1* sequencing • Other mutations[◇]

SUBSEQUENT EVALUATION

- For selected patients, stimulation testing may be needed to establish or confirm a diagnosis and/or to identify associated issues.

SUBSEQUENT EVALUATION

❖ **ACTH stimulation test**

Syntetic ACTH (1-24) :

0.1 mg in newborn

0.15 mg in children < 2 years

0.25 mg in children > 2

0 – 60 min

Peak cortisol concentration <18 mcg/dL at 60 minutes indicates adrenal insufficiency.

17-hydroxyprogesterone: >10 ng/ml 60 minutes after administration indicates CAH .

SUBSEQUENT EVALUATION

- *Synacthen Depot*
- 0 – 1h – 5h
- 5-hour test: Plasma cortisol levels double in first hour then increase more gradually; normal values at 5 hours: 37 to 66 mcg/dL
- 17-hydroxyprogesterone: >10 ng/ml indicates CAH.

SUBSEQUENT EVALUATION

- Due to the presence of benzylalcohol, Synacthen Depot is contraindicated in premature babies and in neonates (less than 1 month)

➢ **1month to less than 2 years:** 0.25 mg

➢ **2 to less than 5 years:** 0.25 to 0.5 mg

➢ **5 to less than 12 years:** 1 mg

SUBSEQUENT EVALUATION

❖ **HCG stimulation test**

➢ hCG (1500 units/m^2 SC) is administered on day 1 and repeated on day 3.

SUBSEQUENT EVALUATION

❖ **Identifying ovarian tissue**

- Inhibin A is secreted by the ovary but not the testis.

❖ **Genetic testing**

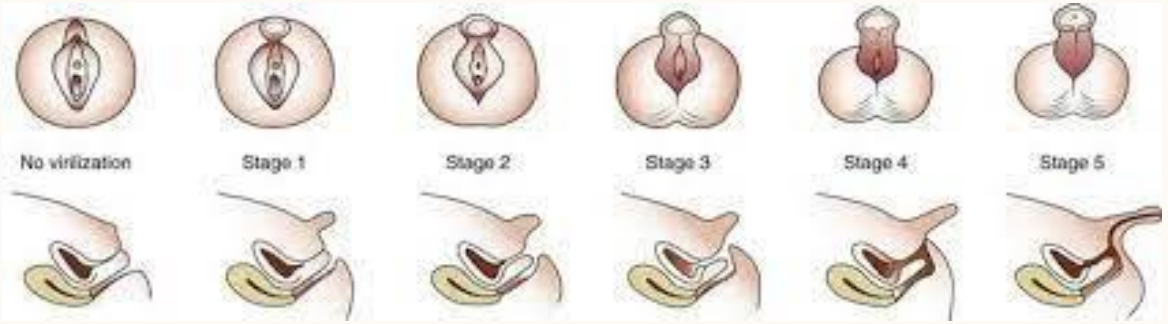
MANAGEMENT OF INFANTS WITH CLINICALLY SIGNIFICANT DSD

INITIAL STABILIZATION

- **Risk of adrenal crisis**
- **Is it a boy or a girl?**
- **Specific DSD diagnosis**
- **Care setting**

APPROACH TO 46,XX CONGENITAL ADRENAL HYPERPLASIA

- Mild or moderate virilization (II – IV)
- Severe virilization



- Early surgical intervention
- Late surgical intervention

APPROACH TO MIXED GONADAL DYSGENESIS

- Most individuals with 45,X/46,XY mosaicism will have a male gender identity.
- Increased risk of gonadal malignancy (>30 %)
- Removal of the streak gonad should be performed within the first decade of life .
- A biopsy of the scrotal testis is recommended after puberty.

APPROACH TO 46,XY 17-BETA-HSD AND 5-ALPHA-REDUCTASE DEFICIENCIES

- They usually develop male gender identity .
- Risk for gonadal malignancy is intermediate.
- Active surveillance permits retention of the testes in these 46,XY individuals, while monitoring for malignancy.

APPROACH TO PARTIAL ANDROGEN INSENSITIVITY SYNDROME

- One approach is to make suggestions concerning sex of rearing based upon the response of the phallus to testosterone therapy.
- Risk for gonadal tumors is minimal until late puberty.

APPROACH TO OVOTESTICULAR DSD

- Surgical decisions for patients remain complex .
- The risk for gonadal tumors is low (2.6 %)

LONG-TERM MANAGEMENT

- **Psychosexual**
- **Medical**
  - ✓ Malignancy in gonadal tissue
  - ✓ Sex steroid exposure
  - ✓ Bone mineral density

THANK YOU