INTERSEXES - PART 2
**Ambiguous genitalia**

- **Girls with classic 21-hydroxylase deficiency:**
  - exposed to high level of adrenal androgen level (GA 7 wks)

- **Girls with ambiguous genitalia:**
  - a large clitoris
  - rugated and partially fused labia majora
  - uterus, fallopian tubes, and ovaries: normal

- **Boys:**
  - no overt signs of the disease
  - except variable and subtle hyperpigmentation
  - and penile enlargement
Unclassified Ambiguous Genitalia

- **Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome**
- Congenital absence of the uterus and vagina
- Presents → primary amenorrhea
- Upper urinary tract anomalies occur in 33% includes renal agenesis, pelvic kidney, and horseshoe kidney
- Atypical form of MRKH in 10%
  - asymmetrical uterine remnants and/or aplasia of one or both fallopian tubes
  - endometrial tissue or variable development of the uterus with hematometra → cyclic abdominal pain
- Ultrasound and MRI may define müllerian anatomy accurately in MRKH and distinguish between typical and atypical forms of the disorder
- Surgical creation of a neovagina to allow for sexual function and drainage of menstrual fluid if necessary
Drugs with Androgenic side effects ingested during pregnancy

- Testosterone
- Synthetic progestins
- Danocrine
- Diazoxide
- Minoxidil
- Pheneretoin sodium
- Streptomycin
- Penicillamine
Female Pseudohermaphroditism: Maternal Hormones & Tumors

- Androgen or progestational agent affects the female fetus
  - Function of the strength of the agent, its maternal dosage, and timing and duration of administration
    - Masculinization occurred in 2% of female infants whose mothers were treated with progestins during pregnancy to prevent abortion (Ishizura et al, 1962)
- Rarely, maternal ovarian or adrenal tumor has virilizing effects on a female fetus
  - arrhenoblastoma
  - hilar cell tumor
  - lipoid cell tumor
  - ovarian stromal cell tumor
  - luteoma of pregnancy
  - adrenocortical carcinoma and adenoma
  - Krukenberg's tumor
- Management is confined to external genital reconstruction
Incompletely Masculized Males
Male pseudohermaphroditism (XY- FEMALE)

**Failure to utilize testosterone**
- Androgen receptor deficiency
  * Complete androgen Insensitivity (TFS)
  * Incomplete androgen Insensitivity
- 5-alpha reductase deficiency

**Failure to produce testosterone**
- Defects in testicular steroidogenesis
- Gonadotropin-resistant testes (LH receptor mutation)
- Congenital lipoid adrenal hyperplasia
- Defective synthesis, secretion, or response to anti-mullerian hormone
Male

Cholesterol
  StAR
  P450 scc

\[\Delta^5\]
  Pregnenolone \[\xrightarrow{17\alpha-OH}\] 17-OH Pregnenolone
  3\beta-HSD

\[\Delta^4\]
  Progesterone \[\xrightarrow{17\alpha-OH}\] 17-OH Progesterone
  21-OH

Desoxycorticosterone
  11\beta-OH

Corticosterone
  18-OH

18-OH Corticosterone
  18-oxidase

\[\text{Aldosterone}\]

\[\text{Testosterone}\]

\[\text{Estrone}\]

\[\text{Androstenedione}\]

\[\text{Dehydroepiandrosterone}\]

\[\text{17\beta-HSD}\]

\[\text{Aromatase}\]

\[\text{5\alpha-reductase}\]

\[\text{Dihydrotestosterone}\]

\[\text{Estradiol}\]
**Male Pseudohermaphroditism**

- **Disorders of Testosterone Biosynthesis**
  - Defect in any of the five enzymes → incomplete (or absent) virilization of the male fetus during embryogenesis
  - Inheritance is autosomal recessive

- **Cholesterol Side Chain Cleavage Deficiency (StAR Deficiency)**
  - A defect in cholesterol transport prevents conversion of cholesterol to pregnenolone
  - 46,XY individuals have female or ambiguous external genitalia
    - a blind-ending vaginal pouch
    - intra-abdominal, inguinal, or labial testes
    - absence of müllerian structures & Wolffian ducts are present but rudimentary
    - severe adrenal insufficiency and salt wasting
  - Suspect this if → nonvirilized female external genitalia with:
    - cortisol and aldosterone deficiency
    - hyponatremia, hyperkalemia, and metabolic acidosis.
  - Abdominal CT scanning demonstrates large, lipid-laden adrenal glands
Male Pseudohermaphroditism

- **3β-Hydroxysteroid Dehydrogenase Deficiency**
  - incomplete masculinization with salt-wasting → impaired aldosterone and cortisol synthesis
  - a small phallus, hypospadias with labioscrotal fusion, a urogenital sinus, and a blind-ending vaginal pouch. Testes are often scrotal, and wolffian ducts develop normally
  - diagnosis: increased levels of 3β-hydroxysteroids (pregnenolone, 17-hydroxypregnenolone, and DHEA)

- **17α-Hydroxylase Deficiency**
  - conversion of pregnenolone and progesterone to 17-hydroxypregnenolone and 17-hydroxyprogesterone
  - impaired cortisol production → ACTH hypersecretion → increased DOC, corticosterone, and 18-hydroxycorticosterone in the adrenals (check levels)
  - These mineralocorticoids → salt and water retention, HTN, and hypokalemia
  - Fertility has not been reported and inadequate testosterone production makes androgen imprinting a less significant issue for these patients
    - Phenotype may dictate gender assignment
Male Pseudohermaphroditism

- **17,20-Lyase Deficiency**
  - cortisol and ACTH secretion are normal $\rightarrow$ aldosterone normal $\rightarrow$ no HTN
  - ambiguous rather than totally female genitalia at birth
    - suspect this dx if absent müllerian derivatives and no defect in glucocorticoid or mineralocorticoid synthesis.

- **17β-Hydroxysteroid Oxidoreductase Deficiency**
  - similar to 5α-reductase deficiency $\rightarrow$ normal female phenotype, no significant virilization
  - well-differentiated testes located intra-abdominally, inguinally, or in the labia and no müllerian structures.
  - At puberty $\rightarrow$ phallic growth and male secondary sexual characteristics
    - Androstenedione $\rightarrow$ increased to 10 to 15x normal
    - type III 17β-hydroxysteroid dehydrogenase isozyme mutation $\rightarrow$ male pseudohermaphroditism
Incompletely Masculinized Males

Incompletely masculinized males are male by genetic sex (XY) and possess testicles, but the external genitalia are not normally male. Male pseudohermaphrodites can arise in 1 of 4 ways:

1. Defective responses in androgen dependent tissues — Androgen Insensitivity Syndromes.

2. Abnormal androgen synthesis.


4. Absent or defective anti-müllerian hormone.

Syndromes of Androgen Insensitivity

Factors that influence the response to androgens in specific target cells include the following:

1. The intracellular concentration of androgen.

2. The relative binding affinity of these steroids to their nuclear androgen receptors.

3. The binding capacity of the receptor.

4. The nuclear content of androgen receptors.

5. The cellular concentrations of catabolic and/or synthetic enzymes (e.g., 5α-reductase, aromatase, 17β-hydroxysteroid dehydrogenase).

6. The adequacy of the nuclear (chromatin) acceptor site.

7. The adequacy of regulatory molecules (adapter proteins) controlling chromatin “read” of the androgen message.

8. RNA processing and translation.

Male Pseudohermaphroditism

- 46,XY individuals with differentiated testes who exhibit varying degrees of feminization phenotypically.
  - Inadequate secretion of testosterone by the testes at the necessary period in development
  - Inability of target tissue to respond to androgen appropriately
  - Impaired production or action of MIS
**Testicular feminization syndrome**

46-XY/SRY

TESTIS $\Rightarrow$ MIF

Testosterone

$5\alpha$-reductase

DHT

Absent androgen receptors

Female External Genitalia

Male Internal Genitalia

*Incomplete form $\Rightarrow$ Ambiguous genitalia*
What is AIS?

- A genetic condition where affected people have male chromosomes & male gonads with complete or partial feminization of the ext. genitals

- An inherited X-linked recessive disease with a mutation in the Androgen Receptor (AR) gene resulting in:

  - Functioning Y sex chromosome
  - Abnormality on X sex chromosome

Types

1. CAIS (completely insensitive to AR gene)
   - External female genitalia
   - Lacking female internal organs

2. PAIS (partially sensitive-varying degrees)
   - External genitalia appearance on a spectrum (male to female)

3. MAIS (mildly sensitive, rare)
   - Impaired sperm development and/or impaired masculinization

Also called Testicular Feminization
Androgen Receptor Gene

- AIS results from mutations in the androgen receptor gene, located on the long arm of the X chromosome (Xq11-q12)

- The AR gene provides instructions to make the protein called androgen receptor, which allows cells to respond to androgens, such as testosterone, and directs male sexual development

- Androgens also regulate hair growth and sex drive

- Mutations include complete or partial gene deletions, point mutations and small insertions or deletions
The Process of Sexual Development

- In AIS the chromosome sex and gonad sex do not agree with the phenotypic sex
- Phenotypic sex results from secretions of hormones from the testicles
- The two main hormones secreted from the testicles are testosterone and mullerian duct inhibitor
  - Testosterone is converted into dihydrotestosterone
  - Mullerian duct inhibitor suppresses the mullerian ducts and prevents the development of internal female sex organs in males
- Wolffian ducts help develop the rest of the internal male reproductive system and suppress the Mullerian ducts
  - Defective androgen receptors cause the wolffian ducts & genitals to be unable to respond to the androgens testosterone and dihydrotestosterone
AIS Fetus Development

- Each fetus has non-specific genitalia for the first 8 weeks after conception.
- When a Y-bearing sperm fertilizes an egg an XY embryo is produced and the male reproductive system begins to develop.
  - Normally the testes will develop first and the Mullerian ducts will be suppressed and testosterone will be produced.
- Due to the inefficient AR gene cells do not respond to testosterone and female genitalia begin to form.
- The amount of external feminization depends on the severity of the androgen receptor defect.
  - CAIS: complete female external genitalia
  - PAIS: partial female external genitalia
  - MAIS: Mild female external genitalia, essentially male.
Complete Androgen Insensitivity

- Testicular Feminization SD (female phenotype)

- 1 in 20-60,000 males, X-linked trait

- In utero loss of androgen, & MIS secretion means loss of internal genitalia

- 2% of males with an inguinal hernia have Complete androgen sensitivity

- Usually diagnosed c amenorrhea, absence of pubic hair or hormonal profile

- Gonadectomy and Oestrogen replacement therapy
Incomplete Androgen Insensitivity
(Reifenstein’s Syndrome)

- Incomplete male pseudohermaphroditism
- Ambiguous genitalia
- Normal testosterone, LH and testosterone/DHT ratio
- All intermediate type of androgen insensitivity
- Azoospermia or severe oligospermic infertility
  \(\rightarrow\) indication of androgen insensitivity
## The Androgen Insensitivity Syndromes

<table>
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<th>5α-redutase</th>
<th>Complete</th>
<th>Incomplete</th>
<th>Reifenstein</th>
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<td>Female Clitomegaly</td>
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<td>Female</td>
<td>Female</td>
<td>Gynecomastia</td>
<td>Gynecomastia</td>
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</tbody>
</table>
Testing for AIS

- Tests
  - During Pregnancy
    - Chorionic Villus Sampling (9-12 weeks)
    - Ultrasound and Amniocentesis (after 16 weeks)
  - After Birth
    - Presence of XY Chromosomes
      - Buccal Mouth Smear
      - Blood Test
    - Pelvic Ultrasound
    - Histological Examination of Testes
Treatments

- Surgery
  - Orchidectomy or gonadectomy
    - Removal of the testes
  - Vaginal lengthening
  - Genital plastic surgery
    - Reconstructive surgery on the female genitalia if masculinization occurs
    - Phalloplasty
    - Vaginoplasty
    - Pressure dilation
    - Clitorectomy
5-alpha-reductase deficiency

46-XY/SRY

Testis $\Rightarrow$ MIF

Testosterone

$\downarrow$ 5-\alpha-reductase

$\downarrow$ DHT

Female or Ambiguous external Genitalia

Male Internal Genitalia
5-alpha reductase deficiency

- Normal internal genitalia:
  - testes secrete T, MIH causes Mullerian ducts to degenerate

- Lack of DHT leads to inadequate masculinization of external genitalia at birth:
  - Testes in labia or inguinal canal
  - Urogenital sinus: urethra & blind vagina
  - Prostate gland: small or absent

- At puberty, lots of T
  - testes descend, scrotum darkens, phallus enlarges, muscular & deep voice
Testosterone Biosynthesis

- 5 enzymes involved in the conversion of cholesterol to testosterone

- 3 in the adrenal & testis
  - Cholesterol side change cleavage
  - $3\beta$ OH steroid Dehydrogenase
  - $17\alpha$ Hydroxylase

- 2 in the testis only
  - $17,20$ Lyase Deficiency
  - $17\beta$ OH steroid Dehydrogenase
Testicular enzymatic failure

46-XY/SRY

Testis ⇔ MIF (defects in testosterone Synthesis)

↑ testosterone precursors
↓ DHT

Ambiguous External Genitalia
Male Internal Genitalia

Autosomal recessive enzyme deficiency:
-20-22 desmolase
-3-β-ol-dehydrogenase
-17-β-hydroxylase
-17,20-desmolase
17-β-OH steroid dehydrogenase
Pathways of steroid biosynthesis in the adrenal cortex
Male Pseudohermaphroditism

- **Leydig Cell Aplasia (Luteinizing Hormone Receptor Abnormality)**
  - 46,XY male karyotype, normal-appearing female phenotype
  - Typically, testes are palpable in the inguinal canals or labia majora
  - no rise in testosterone after HCG stimulation
  - spectrum $\rightarrow$ absent Leydig cells to Leydig cells with abnormal LH receptor
  - autosomal recessive trait
  - DDx = androgen insensitivity syndrome or a terminal defect in androgen synthesis.
  - testis histology = absent of Leydig cells in intratubular spaces, normal Sertoli cells
Leydig Cell hypoplasia / LH receptor mutation

- 46 XY karyotype but female phenotype
- Palpable testes but ↑ LH and ↓ Testosterone
- No stimulation of testosterone with hCG
- No Mullerian structures / short vagina
- Histology demonstrates no Leydig cells
Leydig-cell agenesis

46-XY/SRY

TESTIS ⇔ MIF
( partial/ complete absence Of leydig-cells)

No or ↓ testosterone
No or ↓ DHT

Female or ambiguous external Genitalia

± Male Internal Genitalia
Congenital Lipoid Adrenal Hyperplasia

A. Normal
- Corticotropin
- Low-density lipoprotein
- ATP
- cAMP
- Steroid
- Lysosome
- Lipid droplet
- StAR
- Mitochondrion
- StAR-independent cholesterol flow
- Nucleus
- Endoplasmic reticulum

B. Early Congenital Lipoid Adrenal Hyperplasia
- Corticotropin
- Low-density lipoprotein
- ATP
- cAMP
- Steroid
- Lysosome
- Lipid droplet
- StAR
- StAR-independent cholesterol flow
- Nucleus
- Endoplasmic reticulum

C. Late Congenital Lipoid Adrenal Hyperplasia
- Corticotropin
- Low-density lipoprotein
- ATP
- cAMP
- Steroid
- Lipid droplet
- Nucleus
- Endoplasmic reticulum
CHOLESTEROL

PREGNENOLONE → 17-HYDROXYPREGNENOLONE → DEHYDROEPIANDROSTERONE

PROGESTERONE → 17-HYDROXYPROGESTERONE → ANDROSTENEDIONE

CORTICOSTERONE → 11-DEOXYCORTISOL → CORTISOL

18-HYDROXYCORTICOSTERONE → ALDOSTERONE

Target Cell

Steroidogenic Acute Regulatory Protein (StAR)

CYP17

HSD3B2

CYP21

DOC

CYP11B2

CYP11B2

CYP11B2

CYP11B2

CYP19

HSD17B3

HSD17B1

ESTRONE

TESTOSTERONE

OSTERONE

ESTRADIOL

OVARY

TESTIS

HSD17B1

DHT

SRD5A2

ADRENAL CORTEX
Hernia Uterine Inguinale (persistent mullerian structures)

- Normal phallus, uterus and tubes in the inguinal hernia sac
- Poor sperm and hormone production
- Gonad cancer risk
- Can be familial
- Presumed failure of AMH function
- Fertility – rarely preserved
- AR pattern
Androgen Receptor & Post-Receptor Defects

- Most common definable cause of male pseudohermaphroditism
- All are 46,XY karyotype and have testes
- Three classifications exist that describe the spectrum of phenotypes

**Complete androgen insensitivity**
- female-appearing external genitalia, and absence of müllerian derivatives
  - Blind ending vagina, reduced pubic hair
  - 1 in 20,000 to 1 in 60,000 males
    - 2% of female with hernia → so vaginoscopy prudent
    - X-linked trait, chromosome Xq11–12, point mutation
  - unequivocal female gender identity → androgen resistance of brain tissue
    - No reported female → male gender conversion at puberty
  - gonadectomy is key → wait until after puberty
    - 2% to 5% risk of seminoma or gonadoblastoma
    - Testis produces estradiol → feminization
Androgen Receptor & Post-Receptor Defects

- Partial androgen insensitivity (Reifenstein's syndrome)
  - ambiguity of the external genitalia to varying degrees
    - male with perineoscrotal hypospadias, cryptorchidism, rudimentary Wolffian duct structures, gynecomastia, and infertility
    - the phenotypic spectrum can range from hypospadias and a pseudovagina to gynecomastia and azoospermia
  - etiology:
    - (1) a reduced number of normally functioning androgen receptors
    - (2) a normal receptor number but decreased binding affinity
  - gender assignment is often dictated by phenotype and degree of virilization

- Infertile male syndrome
  - normal male phenotype but are azoospermic or severely oligospermic
  - normal to elevated serum testosterone
  - normal to elevated LH
  - decreased androgen receptor binding to DHT in genital skin fibroblasts
5α-Reductase Deficiency

(Williams Textbook of Endocrinology, 10th ed, 2003)
Androgen Receptor & Post-Receptor Defects

- 5α-reductase deficiency
- Secondary to mutations in the type II gene
- Phenotype may vary from penoscrotal hypospadias to, more commonly, markedly ambiguous genitalia
- Elevated mean plasma testosterone, but low DHT levels
- DHT appears to be critical for the development of normal external genitalia in utero
- Testosterone alone appears sufficient for wolffian duct development
- Male gender assignment is generally favored, bearing in mind that the studies strongly supporting male gender identity in this disorder

urogenital sinus with separate urethral and vaginal openings, and posterior labioscrotal fusion

clitoromegaly with marked labioscrotal fusion and small vaginal introitus
Androgen Receptor & Post-Receptor Defects

- **Persistent Müllerian Duct Syndrome (PMDS)**
- 46,XY karyotype and normal male external genitalia but internal müllerian duct structures
- Phenotypic males with:
  - unilateral or bilateral undescended testes
  - bilateral fallopian tubes
  - uterus
  - upper vagina draining into a prostatic utricle
- Discovered when müllerian tissue is found during inguinal herniorrhaphy or orchidopexy
  - 60% to 70% with bilateral intra-abdominal testes in a position analogous to ovaries
  - 20% to 30% in which one testis is found in a hernia sac or scrotum in association with a contralateral inguinal hernia (the classic presentation of hernia uteri inguinale)
  - 10% in which both testes are located in the same hernia sac (as a result of transverse testicular ectopia) along with the fallopian tubes and uterus
  - **PMDS is believed to be etiologically important in transverse testicular ectopia, occurring in 30% to 50% of cases**
- Decreased secretion of MIS and others have an abnormality of the MIS receptor
- All patients are phenotypic males who require orchidopexy
  - vasa deferentia are in close proximity to the uterus and proximal vagina → preserve fertility
  - malignancy of retained müllerian structures has not been reported
Diagnosis of XY Female

Testosterone concentration

Low

Concentration of Testosterone precursors

High

Testicular enzyme Failure

Low

Absent testes or Absent leydig-cell

Surgical exploration

Low

5α-reductase Deficiency

Normal

Male level

DHT

Normal

Testicular Feminization Syndrome
Disorders of Gonadal Development
Disorders of Gonadal Differentiation and Development
Klinefelter's syndrome

(Williams Textbook of Endocrinology, 10th ed, 2003)
Seminiferous Tubule Dysgenesis (Klinefelter's syndrome)

- Syndrome characterized by eunuchoidism, gynecomastia, azoospermia, increased gonadotropin levels, and small, firm testes, 47,XXY karyotype
  - nondisjunction during meiosis
  - 1 of 1000 liveborn males
  - associated with 48,XXYY; 49,XXXXY; 48,XXXY; 49,XXXXXY; 46,XY/47XXY
- Gynecomastia can be quite marked at pubertal development
  - 8 X risk for breast carcinoma compared with normal males
- Seminiferous tubules degenerate and are replaced with hyaline
  - Fertility, with the benefit of ICSI, has been reported in one patient
  - decreased androgens prevents normal secondary sexual development
    - poor muscle development, the fat distribution is more female than male.
    - Normal amounts of pubic and axillary hair, but facial hair is sparse.
    - Patients tend to be taller than average, due to disproportionately long legs
- Predisposed to malignant neoplasms of extragonadal germ cell origin.
- Androgen supplementation to improve libido & reduction mammoplasty
  - surveillance for breast carcinoma
46,XX maleness

- Occurs in 1 of every 20,000 males
- Testicular development in subjects who have two X chromosomes and lack a normal Y chromosome.
- Most of these subjects have normal male external genitalia, but 10% have hypospadias and all are infertile
  - 80% are Sry positive and rest are Sry negative
  - Sry-positive group rarely have genital abnormalities, but they have phenotypic features of Klinefelter's syndrome
- Shorter (mean height, 168 cm) and have more normal skeletal proportions than Klinefelter’s patients
- Due to translocation of Y chromosomal material, including SRY, to the X chromosome
- Infertile → lack of germ cell elements
Swyer’s syndrome
(Bilateral dysgenesis of the testes)

46, XY

No SRY OR its receptors

STREAK GONADS
- NO MIF
(Uterus +)
- NO SEX

Female
external
Genitalia

Female
Internal
Genitalia
Testicular regression syndrome
Congenital Anorchia

46-XY/SRY

Testis ⇔ MIF (self destruction)

± testosterone
± DHT

Male
Infantile
External
genitalia

± Male
Internal
genitalia
TRUE HERMAPHRODITISM IS RARE

- True hermaphroditism:
  - Co-existence of ovarian and testicular tissue either in the same or opposite gonads
  - **Phenotype is variable** - 60% are 46 XX; 20% are 46XY or 45 X/46XY and rest are mosaics/chimeras

Gonads:
- ovary one side and testis on the other side of the abdomen
- bilateral ovotestis

Karyotype:
46,XX most common(70%); XY and XX/XY

Internal genitalia:
Both mullerian and wolffian derivates

Gonadal biopsy is required for confirming diagnosis
Gonadal Dysgenesis
Turners Syndrome (45 X0)

- Presence of one functioning X Chromosome
- 1 in 2500 females. Mosaicism 45 X/46 XX (10%) or 45 X/46 XY (3%)
- Oocytes degenerate leaving streak gonads (in broad lig.) at birth
- Reduced Oestrogen, Raised FSH/LH. No pubertal development

Management includes:
- Growth Hormone to Children & estrogens at puberty
- Up to one third may have functioning ovaries
  - so pregnancy is possible
- Remove Streak gonads in Mosaic patients

Features:
1. Female Phenotype
2. Short Stature
3. No Secondary Sexual Characteristics
4. Somatic Abnormalities
   - Webbed Neck
   - Broad Chest
   - Short Ring finger

Renal Anomalies:
90% Multiple Renal Arteries
20% Renal agenesis/Duplication
15% Malrotation
10% Horseshoe kidney

Occult Y Ch. Material:
Predisposed to Virilisation
and Gonadoblastoma (30%)
and other GCT (50%).
Short stature
Mental retardation
X-linked ichthyosis
Kallmann's syndrome

Xp
- Pseudoautosomal region
- Genes responsible for Turner Syndrome and short stature
- Androgen receptor

Gene(s) that affect ovarian function (and some stigmata of Turner Syndrome)

Yp
- Pseudoautosomal region
- SRY Sex determining region
- Genes that prevent short stature & stigmata of Turner Syndrome
- Centromere
- Genes that affect spermatogenesis and the predisposition to gonadoblastoma in dysgenetic gonads
- Heterochromatin region (genetically inactive)

Xq

Yq
Turner syndrome

Karyotype 45,X (60%)
(45,X/46,XX, structural abnormalities of X chromosome)

Short stature (final height 142-147 cm)
Gonadal dysgenesis - streak gonad & sexual infantilism
Skletal abnormalities & dysmorphic face
Cardiac and kidney malformation
Autoimmune ds: Hashimoto’s thyroditis, Addison’s ds
Mild insulin resistance & hearing loss
Lymphedema
Essential hypertension
No mental defect
Impairment of cognitive function: mathematical ability↓
Visual–motor coordination, spatial-temporal processing↓

H. Tuner, 1938
Turner syndrome – work up

- IVP or renal USG
- Echocardiography
- Audiometry
- TFT (annually) & Ab (at least one)
- Lipid profile & glucose metabolism (annually)
- Annual pelvic examination & appropriate screening for gonadal neoplasm as an adnexal mass
- Expert consultation to pursue further analysis with X- and Y-specific DNA probes
Turner’s Syndrome (45,XO)

- No oocytes remain in the ovaries, which become streaks
  - Fertility = 60% pregnancy rate w/ART
  - Ovum donation for those with bilateral streaks
- 1 in 2500 live births
- 60% are 45,XO and 40% are mosaics
- Y chromosomal material → masculinization & gonadoblastoma (30%)
- 33% - 60% have structural or positional abnormalities of the kidney
  - horseshoe kidney = 10%,
  - duplication or renal agenesis = 20%
  - malrotation = 15%
  - multiple renal arteries = 90%
- Four classic features:
  - female phenotype
  - short stature
  - lack of secondary sexual characteristics
  - a variety of somatic abnormalities:
    - peripheral edema at birth, short 4th metacarpal
    - hypoplastic nails, multiple pigmented nevi
    - coarctation of the aorta, and renal anomalies
46,XX pure gonadal dysgenesis

- normal female external genitalia
- normal müllerian ducts with absence of wolffian duct structures
- a normal height
- bilateral streak gonads
- sexual infantilism
- normal 46,XX karyotype

- streak gonads $\rightarrow$ elevated serum gonadotropins
- Management of 46,XX "pure" gonadal dysgenesis:
  - cyclic hormone replacement with estrogen and progesterone.
  - growth is basically normal so GH is not needed
- possibly autosomal recessive trait
Pure Gonadal Dysgenesis

- All subjects with female genitalia, normal mullerian structure & streak gonads (with either 46,XX or 46,XY karyotypes)

- None of Turner phenotype anomalies
46,XY Gonadal Dysgenesis

- **Etiology**: a short arm Y chromosome deletion involving SRY. Most with the pure gonadal dysgenesis form without Turner SD.

- The propensity to tumor development: 20~30% incidence. Patients with mosaic patterns → reduced risk of tumor (10%).

- **Gonadoblastoma** (m/c), dysgerminoma & embryonic carcinoma.

- Intraabdominal testes should be removed as early as possible.
Gonadal Dysgenesis

- **Multiple X female (47,XXX)**
  - Normal development & reproductive function
  - Mental retardation - frequent
  - Secondary amenorrhea & eunuchoidism
Mixed Gonadal Dysgenesis

- Karyotype 46XY / 45X0
- Combined features of Turner’s SD & male pseudohermaphroditism
- Short stature
- Streak gonad on one side with a testis on the other side
- Unicornuate uterus & fallopian tube-side of streak gonad
- Considerable variation in the sexual phenotype
Mixed Gonadal Dysgenesis

- Mosaicism: 45 XO/ 46 XY
- Second most common cause for Ambiguous genitalia
- Mostly phenotypic females, but entire spectrum covered
- Due to lack of MIS production in unilateral dysgenetic testis with ipsilateral fallopian tube
- Management includes Gender assignment (2/3 female), Appropriate gonadectomy & screen for Wilm’s tumor

Features:
- Unilateral testis (undescended)
- Contralateral Streak Gonad
- Persistent Mullerian Structures
- Some masculinisation
- Mostly females with;
  - Enlarged phallus
  - Labioscrotal folds
  - Uterus /vagina & tubes

Increased risk of:
- Gonadoblastoma (20%)
  - testis > streak gonad
- Wilm’s tumor
- Denys-Drash Syndrome
  - Nephropathy /CRF
  - Genital Abnormalities
  - Wilms tumour
  - XX/XY mosaicism
- May need prophylactic bilateral nephrectomy
Mixed gonadal dysgenesis (MGD)

- Characterized by a unilateral testis, often intra-abdominal
- Contralateral streak gonad
- Persistent müllerian structures with varying inadequate masculinization
- Most are 45,XO/46,XY, the most common form of Y chromosome mosaicism
- Second most common cause of ambiguous genitalia after CAH
- Dysgenetic or streak gonad is associated with ipsilateral müllerian derivatives (uterus, fallopian tube)
- Well-differentiated testis with functional Sertoli and Leydig cells will have ipsilateral wolffian but no müllerian ducts
  - no germ cells so infertility is the rule
- Increased risk of developing gonadoblastoma or dysgerminoma of 15% to 20%
  - Also increased risk for Wilm’s tumor and association with Denys-Drash
- Endocrine function of testis is normal post-pubertally
  - fetal testis dysfunction may account for ambiguous genitalia
- 90% to 95% of 45,X/46,XY mosaicism have normal-appearing male genitalia
DYSEMBROGENESIS
Genital ambiguity with associated anomalies

- Can occur in both genitic males and genitic females
- Most common genital malformation:
  - Penoscrotal transposition
  - Agenesis of phallus in a genitic male
- Coexistence of other caudal or urologic abnormalities should strongly suggest dysembryogenisis
Dysgenetic Male Pseudohermaphroditism

- Two dysgenetic testes rather than one dysgenetic testis and a streak gonad as in MGD
- Typically are 45,X/46,XY or 46,XY
- Present with a spectrum of external genital abnormalities
- Dysgenetic testis is composed of immature hypoplastic seminiferous tubules and persistent stroma resembling that seen in the streak gonad
- Incidence of gonadoblastoma or dysgerminoma is 46% by 40 years
- At risk for Denys-Drash
46,XY Complete Gonadal Dysgenesis

Characterized by:
- normal female genitalia
- well-developed müllerian structures
- bilateral streak gonads
- nonmosaic karyotype

Ambiguity of genitalia is not an issue

Sexual infantilism is the primary clinical problem
- present in their teens with delayed puberty

An abnormality of the Sry gene function, or loss of another gene downstream from Sry that is necessary for SRY protein action

LH elevated → clitoromegaly

30% risk of germ cell tumor development by age 30 years
- gonadoblastoma is most common
- embryonal carcinoma, endodermal sinus tumor, choriocarcinoma, and immature teratoma have also been reported

Management → removal of both streak gonads and proper cyclic hormone replacement with estrogen and progesterone
Embryonic Testicular Regression and Bilateral Vanishing Testes Syndromes

- 46,XY karyotype and absent testes but clear evidence of testicular function during embryogenesis
- "embryonic testicular regression" = loss of testicular tissue within the first trimester and is associated with ambiguity of external genitalia
- "bilateral vanishing testes syndrome" refers to individuals in whom male sexual differentiation of ducts and genitalia took place but loss of testicular tissue occurred subsequently in utero
- Diagnosis can be made on the basis of a 46,XY karyotype and castrate levels of testosterone despite persistently elevated serum LH and FSH
  - bilateral vanishing testes syndrome, agonadal XY phenotypic males with fully developed wolffian structures, but an empty scrotum, absent prostate, and microphallus
  - intermediate point presentation is the 46,XY patient with absent gonads and internal ductal structures but with ambiguous genitalia \( \rightarrow \) incomplete elaboration of androgen
  - most severe form, agonadism is discovered in a 46,XY phenotypic female with no internal genital structures; \( \rightarrow \) the testis has elaborated MIS but vanishes at 60-70 days before elaboration of androgen
True Hermaphroditism

- Individuals who have both testicular tissue with well-developed seminiferous tubules and ovarian tissue with primordial follicles, which may take the form of one ovary and one testis or, more commonly, one or two ovotestes.

- External genitalia and internal duct structures of true hermaphrodites display gradations between male and female.

(Williams Textbook of Endocrinology, 10th ed, 2003)
True Hermaphroditism

- In most patients, the external genitalia are ambiguous but masculinized to variable degrees, and 75% are raised as male.
- Internal ductal development are influenced by ipsilateral gonad:
  - Fallopian tubes are consistently present on the side of the ovary.
  - A vas deferens is always present adjacent to a testis.
  - Fallopian tube is present with 66% of ovotestes, vas or both in 33%.
  - Most have urogenital sinus and uterus.
- 80% of those raised as male have hypospadias and chordee.
- Ovaries usually on left in normal position, testis usually on right and located anywhere along path of descent.
- 60% of gonads palpable in canal or labia are ovotestes.
True Hermaphroditism

- Ovarian portion of the ovotestis is frequently normal, whereas the testicular portion is typically dysgenetic.
- 66% of patients are 46 XX.
- Gonadal tumors is approximately 10% in 46,XY true hermaphroditism and 4% in 46,XX true hermaphroditism.
- Most important aspect of management in true hermaphroditism is gender assignment.
- Sex assignment should be based on the functional potential of external genitalia, internal ducts, and gonads, according to the findings at laparoscopy or laparotomy.
- Unlike patients with most other forms of gonadal dysgenesis, true hermaphrodites have the potential for fertility if raised as female with the appropriate ductal structures.
- Males, remove ovaries and/or ovotestis and mullerian duct structures consider gonadectomy.
- Females remove all testicular and wolffian structures.
TRUE HERMAPHRODITISM

- Gonads:
  - ovary one side and testis on the other or
  - bilateral ovotestis

- Karyotype:
  46,XX most common (57%); XY (13%) and XX/XY (30%)

- Internal genitalia:
  Both mullerian and wolffian derivates

- Phenotype is variable

- Gonadal biopsy is required for confirming diagnosis
CLINICAL PRESENTATION OF INTERSEXUALITY

- **AT BIRTH**
  - Ambiguous genitalia
- **DURING CHILDHOOD**
  - Heterosexual features
- **AT ADOLESCENCE**
  - Delayed or Heterosexual Puberty
The external genital organs look unusual, making it impossible to identify the sex of the newborn from its outward appearance.

Any one of the following:

- A small, hypospadiac phallus and unilaterally undescended gonad.
- An enlarged phallus with bilaterally impalpable gonads.
- An enlarged phallus and a vagina in the same infant.
MANAGEMENT OF NEWBORN WITH AMBIGUOUS GENITIALIA

GENERAL GUIDELINES

- Medical and social emergency
- Avoid immediate declaration of sex
- Proper counselling of the parents
- Team management; obstetrician, neonatologist, pediatric endocrinologist, genetist and paediatric surgeon.
MANAGEMENT OF NEWBORN WITH AMBIGUOUS GENITALIA

DIAGNOSIS

- History: pregnancy; family
- Detailed examination: abdomen; pelvis; external genitalia; urethral and anal openings.

*Federman’s rule: a palpable gonad below the inguinal ligament is testes until proven otherwise*
MANAGEMENT OF NEWBORN WITH AMBIGUOUS GENITALIA

**Investigations**

- Rule out congenital adrenal hyperplasia: Serum electrolytes; 17-OHP level and urinary levels of 17-ketosteroids
- Karyotype (buccal smear; blood)
- Pelvic US and sometimes MRI or Genitogram
- Skin biopsy; fibroblast culture to measure 5alpha-reductase activity or dihydrotestosterone binding
- Laparoscopy
- Gonadal biopsy (laparotomy)
A PROTOCOL FOR INVESTIGATION OF A NEWBORN WITH AMBIGUOUS GENITALIA

Karyotype all

Palpable gonad

YES

Biochemical profile
US / MRI /
? genitogram
? Gonadal biopsy

NO

CAH Sreen

Positive

- US / MRI
-? Genitogram

Negative
Sex assignment

General guidelines

• Sex assignment should be decided after detailed assessment, investigations and accurate diagnosis

• Complete gender assignment by age 18 months
Sex assignment

• **Male gender assignment**:  
  - stretched phallus > 2 cm  
  - erectile tissue  
  - lack of severe hypospadias

• **Female gender assignment**:  
  - inadequate phallus  
  - cervix and uterus present

_In difficult cases; sex assignment should be to the sex which can be surgically made to be adequate for coitus_
SURGICAL CONSIDERATIONS

- Phallic / clitoral reduction if the assigned sex is female, before 3 years of age
- Removal of intra-abdominal gonads / streaks in newborns carrying Y chromosome
- Vaginal construction / repair is better performed around puberty
Before surgery  

After surgery
Concluding remarks on Management of newborn with genital ambiguity

- The causes of ambiguous genitalia are many and complex, so it is important to approach the treatment of children with this disorder in a systematic fashion.
- Evaluation should be done expeditiously, and parents should be kept informed during the evaluation to help them understand the embryologic anomaly that led to their child's genital ambiguity.
- Endocrine supplementation should be instituted when necessary, and a pediatric surgeon should be actively involved in assigning the child's sex of rearing as well as performing any necessary reconstructive surgery.
## INTERSEXUALITY PRESENTING AT ADOLESCENCE

<table>
<thead>
<tr>
<th>Primary amenorrhea</th>
<th>Ambiguous genitalia</th>
</tr>
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<tbody>
<tr>
<td>- Complete androgen insesitivity (TFS)</td>
<td>- Neglected congenital adrenal hyperplasia</td>
</tr>
<tr>
<td>- Congenital anorchia ( early testicular regression syndrome)</td>
<td>- Mixed gonadal dysgenesis</td>
</tr>
<tr>
<td>- Complete leydig-cell agenesis</td>
<td>- Partial androgen resistance</td>
</tr>
<tr>
<td>- Some forms of enzymatic testicular failure</td>
<td>- Congenital anorchia ( Late )</td>
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<tr>
<td></td>
<td>- Testicular enzymatic failure</td>
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<td>- Leydig cell agenesis</td>
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<td>( incomplete)</td>
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<td></td>
<td>- True hermaphrotidism</td>
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</tbody>
</table>
Cortisol replacement therapy and corrective surgery in CAH
Corrective surgery in drug induced cliteromegally
In almost all other instances (XY- FEMALE), whatever the diagnosis is to maintain the gender role as female
In some cases of enzymatic testicular defects or 5α-reductase deficiency: Some may seek to change the gender role
INTERSEXUALITY PRESENTING AT ADOLESCENCE
Surgical aspects of management

- Clitoral reduction
- Removal of gonads in the presence of Y chromosome
- Vaginal repair and construction
GONADECTOMY
VAGINAL CREATION
Vaginal dilatation
McIndoe Vaginoplasty
William’s vulvo-vaginoplasty
Colovaginoplasty
Transsexualism

- Transsexualism occurs when a person strongly believes that he or she belong to the opposite sex.
- This is typically a lifelong feeling and results in varied degrees of physical/external changes.
- These patients should be referred to the psychiatrist.
Concluding remarks
Management of adolescent with intersex

- By following an approach that is based on a few embryological; physiological and anatomical principles—and with a minimum of tests—the clinician can arrive at a prompt and accurate diagnosis in patients with intersexuality.
- If such a patient is managed correctly, she or he may live a happy, well-adjusted life and may even be fertile.
- If the patient is managed incorrectly, she or he may be doomed to live as a sexual freak in loneliness and frustration.
- Gynecologists, endocrinologists, plastic surgeons, urologists and psychiatrists should be actively involved in the management of these patients.
What should you do at the birth of a baby?

- Careful evaluation of genitalia of all neonates (does not need to be overtly ambiguous for diagnostic evaluation)
- Defer gender assignment
- Discuss with parents: “The genitalia are unfinished in their development, and we will need a few days to perform some studies to determine which sex your baby was intended to be”
- Most of the diagnostic evaluation for gender assignment can be done within 3 days.
Diagnostic evaluation - 1

- History:
  - Maternal androgens, drugs, teratogens
  - Affected relatives, sibs who died in infancy (CAH?)
  - Consanguinity
Diagnostic evaluation - 2

- Physical examination:
  - Genitalia
  - Gonads
  - Rectal
  - Hyperpigmentation
  - Turner syndrome?
  - Dysmorphic features?
Diagnostic evaluation - 3

- Chromosomes:
  - Rapid test for X and Y chromosomes
  - Karyotype
  - Contact laboratory personally and ask for result ASAP
  - Buccal smears are no longer recommended
Diagnostic evaluation - 4

- **Anatomic evaluation**
  - **Ultrasound**
    - Uterus seen?
      - seen in 94% of normal females
      - If no uterus, suggests MIS production by testes
      - If uterus +, suggests bilateral ovaries or gonads that do not produce MIS
    - Intrapelvic gonads sometimes seen
  - **Endoscopy**
  - **Retrograde genitography**
    - Anatomy of urethra and vagina.
    - Presence of cervix confirms mullerian duct structures
Biochemical evaluation

If patient is:

- XX with mullerian ducts: 17 OHP, 11-deoxycortisol, 17OHPe, T
- XX without mullerian ducts: T, E2, LH, FSH
- XY with mullerian ducts: T, E2, LH, FSH
- XY without mullerian ducts: T, DHT, LH, FSH
Management

- **Gender Assignment:**
  - Usually made when chromosome status and mullerian duct status are known
  - Occasionally need to defer until biochemical results are known
  - Consultation with pediatric urologist and endocrinologist necessary
  - If bilateral ovaries are present, usually reared as female
  - Males with poor androgen insensitivity difficult to assign

- Psychological counseling to family (and later to patient)
Management

- Management of CAH if present
- Female: surgical correction of ambiguous genitalia (procedure depending on age)
- Male:
  - Testosterone for micropenis
  - Course of HCG followed by orchiopexy if necessary for cryptorchidism
  - No circ if hypospadias
  - Do not remove mullerian structures
  - Gonadectomy if streak or dysgenetic gonads with Y chromosome (risk of malignancy high from infancy)
Surgical Removal of Gonadal Tissue

- The gonadal tissue having any Y chromosome component in phenotypic females → removal as soon as the diagnosis is made to avoid the risk of malignant gonadal tumor (except complete androgen insensitivity)
  : Laparoscopy or laparotomy

- The uterus and tubes should be preserved for the possibility of pregnancy with donor oocytes
Hormone Treatment of Patients Without Ovaries

- Starting when the bone age is 12 with unopposed estrogen (0.3mg conjugated estrogens or 0.5mg estradiol daily)

- After 2 years, a sequential program is initiated with 0.625mg conjugated estrogens or 1.0mg conjugated estrogens + 5mg medroxyprogesterone acetate for 14 days (if a uterus is present)

- In patients with genetic shortness in stature (e.g. Turner SD) → Estrogens treatment is not started until bone age is 12 (to avoid epiphysial closure)
Stimulation of Growth

- Growth hormone treatment for short stature in turner SD: Optimal response → an early onset of Tx around age 6~7

- Now that the success of GH treatment is recognized & accepted, an argument can be made for chromosomal screening by molecular analysis of all growth-retarded girls
The Possibility of Pregnancy

- In women who have variants of gonadal dysgenesis and who menstruate, pregnancy can occur.

- 30% incidence of congenital anomalies in the offspring
  - amniocentesis or chorionic villus biopsy

- Donated oocytes yields excellent results

- *Fatal aortic events (aneurysm, dissection, or rupture)* can occur during pregnancy in patients with gonadal genesis. *A cardiology consultation with an echocardiogram is strongly advised.*
Noonan syndrome

- Both affected males and females have apparently normal chromosome complements and normal gonadal function.

- The phenotype appearance of Turner syndrome: short stature, webbed neck, shield chest & cardiac malformations (esp, pulmonic stenosis).

- The trait as autosomal-dominant with variable expression.
Medical and psychosocial emergency to be handled with great sensitivity toward the family

Goals:
- precise diagnosis of the intersex disorder
- assign a proper sex of rearing based on the diagnosis
- determine the status of the child's anatomy
- delineate the functionality of genitalia and reproductive tract

Valuable history points:
- infant death
- infertility
- amenorrhea
- hirsutism
- maternal medications (i.e. steroids, OCP), during pregnancy

Physical examination: the presence of one or two gonads
Distinctly palpable gonad along the pathway of descent is highly suggestive of a testis
EVALUATION AND MANAGEMENT OF THE NEWBORN WITH AMBIGUOUS GENITALIA

- Bilaterally impalpable testes or a unilaterally impalpable testis and hypospadias should be regarded as having an intersex disorder until proven otherwise, whether or not the genitalia appear ambiguous
  - Unilateral cryptorchid testis and hypospadius, intersex \( \rightarrow \) 30% overall (Kaefer et al, 1999)
    - 15% if the undescended testis was palpable and 50% if it was impalpable
  - Bilateral undescended testes and hypospadias, intersexuality \( \rightarrow \) 32%
    - only 16% if both gonads were palpable.
    - If one of two undescended testes was impalpable, the incidence of intersex tripled to 47%, comparable to the rate in those with a unilateral, impalpable, cryptorchid testis.
EVALUATION AND MANAGEMENT OF THE NEWBORN WITH AMBIGUOUS GENITALIA

- Posterior urethral meatal position is a strong predictor of intersex 65%, versus 5% to 8% with a midshaft to anteriorly located hypospadiac meatus
- Penile size should be assessed and an accurate measure of stretched penile length recorded.
- Precise means of assessing müllerian anatomy is by pelvic ultrasound
- Karyotype should be obtained
- Serum studies should be immediately sent to rule out a salt-wasting form of CAH.
- Serum electrolytes, testosterone and DHT should be measured early
MANAGEMENT OF NEWBORN WITH AMBIGUOUS GENITALIA

GENERAL GUIDELINES

- Medical and social emergency
- Avoid immediate declaration of sex
- Proper counselling of the parents
- Team management; obstetrician, neonatologist, pediatric endocrinologist, genetist and paediatric surgeon.
MANAGEMENT OF NEWBORN WITH AMBIGUOUS GENITALIA

DIAGNOSIS

- History: pregnancy; family
- Detailed examination:
  - Are gonads palpable?
  - What is the phallus length?
  - What is the position of the urethral meatus?
  - To what degree are the labioscrotal folds fused?
  - Is there a vagina, vaginal pouch, or urogenital sinus?
  - Dehydration, hypotension, hyperpigmentation in adrenal hyperplasia
MANAGEMENT OF NEWBORN WITH AMBIGUOUS GENITALIA

**Investigations**

- Pelvic US and sometimes MRI or Genitogram
- Karyotype
- Rule out Cong. Adrenal hyperplasia
  - Serum electrolytes; 17-OHP level, 11-DOC & urinary levels of 17-ketosteroids
- Serum androgen (androstenedione, testosterone, DEA, DEAS)
- Laparoscopy
- Gonadal biopsy (Laparotomy)
Gender Assignment

- Issues related to the diagnosis-specific potential for normal sexual functioning and fertility and the risk of gonadal malignancy should be addressed.
- In the setting of a 46,XX karyotype, gender assignment is usually appropriately female.
- If the karyotype is 46,XY, the issue is a more complex one and includes factors such as penile length and evidence of androgen insensitivity.
- The degree of masculinization of the external genitalia appears to vary with the amount of testicular tissue present.
  - Gender assignment depends on the functional potential of the gonadal tissue, reproductive tracts, and genitalia.
- Parameters of Optimal Gender Policy (Meyer-Bahlberg, 1998)
  - Reproductive potential (if attainable at all)
  - Good sexual function
  - Minimal medical procedures
  - An overall gender-appropriate appearance
  - A stable gender identity
  - Psychosocial well being
Assignment of Sex of Rearing

- Future fertility
  - Isolated hypospadia
  - Repaired isolated cryptorchidism
  - The uterine hernia syndrome

- The projected appearance of genitalia after puberty

- Penile adequacy for coital function
Sex assignment

**General guidelines**

- Sex assignment should be decided after detailed assessment, investigations and accurate diagnosis
- Complete gender assignment by age 18 months
DDx Algorithm

Ambiguous Genitalia

Gonads Palpable
- Müllerian Structures (MRI or ultrasound) Absent
  - 17-OH Progesterone Normal
    - Karyotype XY
      - Male Pseudohermaphroditism
    - Karyotype Poly X+Y
      - Variant of Seminiferous Tubule Dysgenesis
- Müllerian Structures (MRI or ultrasound) Present
  - 17-OH Progesterone Normal
    - Karyotype XY
      - Male Pseudohermaphroditism
    - Karyotype XO / XY
      - Dysgenetic Male Pseudohermaphroditism
      - Mixed Gonadal Dysgenesis
    - Karyotype XX / XY
      - True Hermaphroditism
  - Karyotype XY
    - Non Adrenal Female
      - Pseudohermaphroditism; Aromatase Deficiency

Gonads Not Palpable
- 17-OH Progesterone Elevated
  - Karyotype XX
    - Congenital Adrenal Hyperplasia (types I-IV)
  - Karyotype XO / XY
    - True Hermaphroditism
  - Karyotype XX, XY or XX / XY
    - Male Pseudohermaphroditism
- 17-OH Progesterone Normal
  - Karyotype XY
    - True Hermaphroditism
The End