Disorders of Genitalia, Hypospadias, Undescended Testes, Differences of Sexual Differentiation

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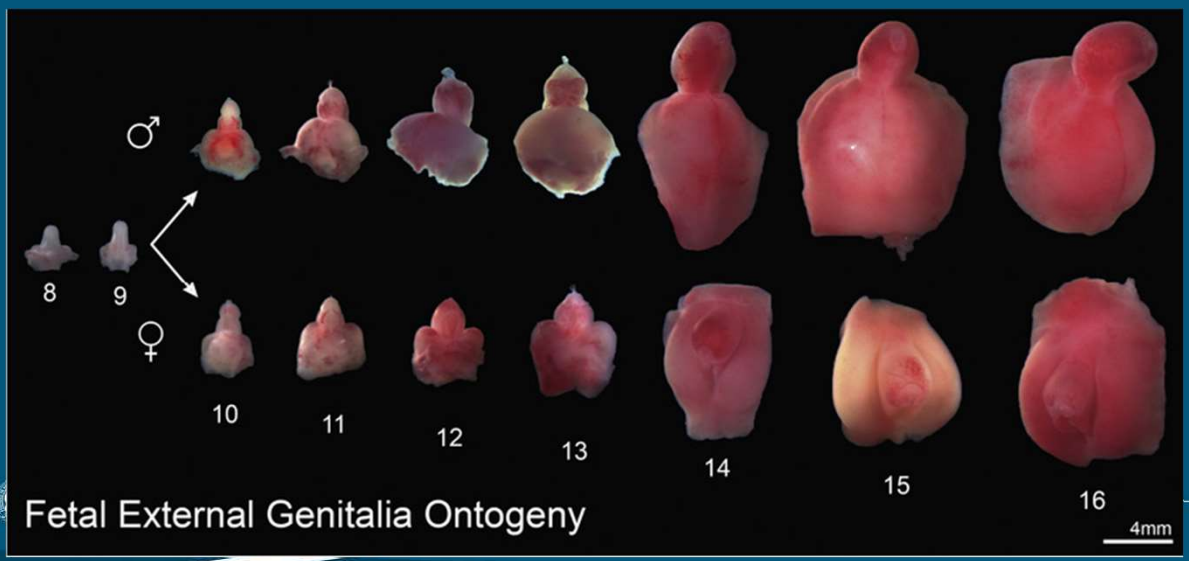
Embryology review…



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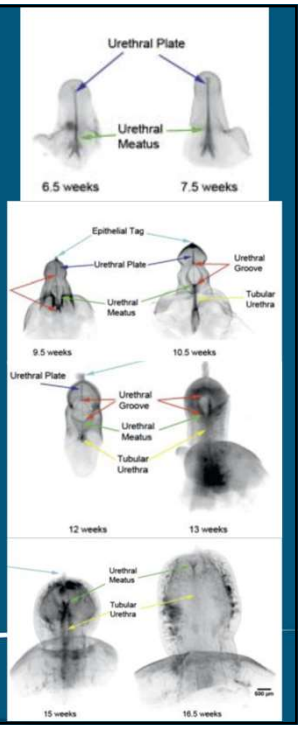
Embryology Key Points: Male

- At 8-9 weeks genitalia is undifferentiated -> done by 20 weeks
- ***SRY region -> gonads to become testes***
- ~9 weeks Leydig cells form and make testosterone (T)
- 5α-reductase in UGS and genital tubercle -> T to DHT
- T and DHT -> masculinization of external genitalia
- Urethral plate widens to form urethral groove ("opening zipper")
- Urethral groove fuses to form urethra ("closing zipper")
  - 6.5 weeks meatus scrotal -> 16.5 weeks glandular
- Curvature of penis straightens by 20 weeks



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J Urol. 2015 Apr;193(4):1353-59.

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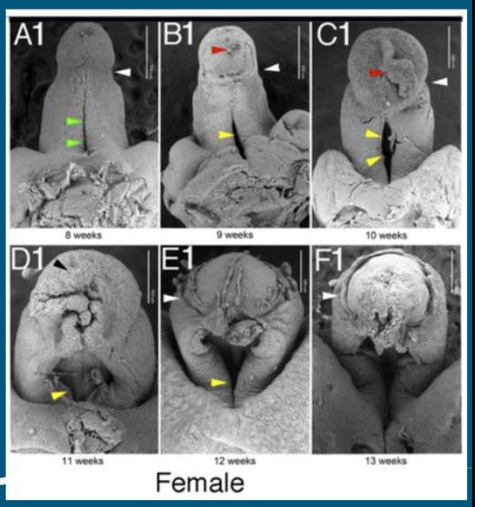
Embrology Key Points: Female

- Vestibular plate widens to form vestibular groove: "opening zipper"
  - Analogous to urethral plate/groove
- The vestibular groove does not tubularize
- Clitoris does not increase in size as much
- Curvature persists
- Nerves located dorsal lateral along corpora



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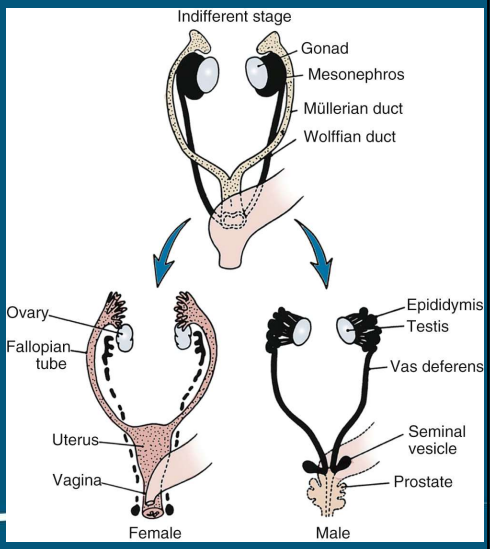
Differentiation. 2018 Sep-Oct;103:74-85.

4

Internal Anatomy Embryology

- In testes, Sertoli cell develop ~ 6 weeks
  - Anti-mullerian hormone (AMH) starts ~ 7-8 weeks
- AMH -> regression of mullerian structures
- ***If no AMH, then mullerian structures develop***
  - ***Fallopian tubes, uterus, cervix, upper 2/3 vagina***
- Gonads arise from germ cells at gonadal ridges
  - 8-9 weeks undifferentiated
  - ***SRY –> testes***
  - Testes descent depends on androgens



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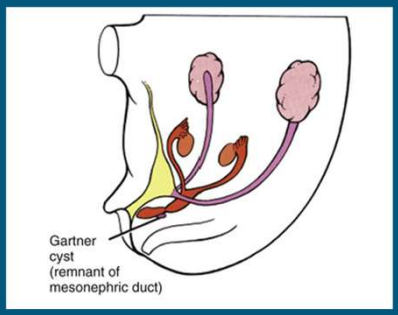
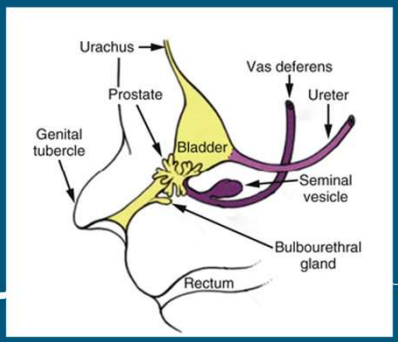
Internal Anatomy Embrology

- Androgens drive masculization of the Wolffian ducts (mesonephric ducts)
  - Epididymis, vas, seminal vesicles in males
  - Also gives rise to ureteral bud!
  - No androgens -> Regress in females
- Prostate and most of bladder develops from urogenital sinus
  - Endoderm in origin just like urethra
- Prostate is outgrowth of epithelial buds from the urogenital sinus





Differentiation. 2018, 103:24-45.

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Physiologic Phimosis

- Normal in infants
- Usually resolves in childhood
  - 25% age 1; 50-75% age 3, 90% age 5
- 1% get UTI
- Some risk of balanoposthitis
  - Tx: hygiene, antifungal, antibacterial
- Pain with phimosis resolution
- Smegma referrals…
- ***Treatment***
  - ***Gentle retraction with steroid cream***

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Pathologic Phimosis

- Balanitis xerotica obliterans
  - AKA: Lichen sclerosis
- Etiology? Repeated inflammation? Others?
- ***Problems: damage to glans, meatal stenosis, urethral stricture, penile cancer***
- Obvious -> circumcision
- Unclear? -> Trial of steroid cream

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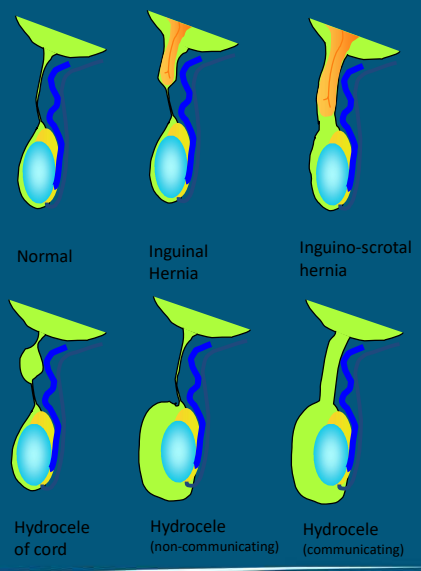
Hernia/Hydrocele

- Non communicating vs communicating
  - Age, history, exam
- Bowel herniation
  - Risk of incarceration/strangulation
  - Surgery recommended
  - Timing for surgery?
  - 5-10% contralateral recurrence - diagnostic laparoscopy?
- Surgery low risk, outpatient



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Testis Torsion

- History: acute severe abd or scrotal pain, nausea
- Exam: pubertal, hard high testis
- Evaluation: Doppler US or OR?
- Treatment: surgery ASAP
  - ***No transfers of teenagers***
- ***Perinatal = extravaginal, high loss***

Torsion of appendix testis

- History: slower onset, can be severe pain
- Exam: prepubertal, swollen, tender, red, blue dot?
- Evaluation: Doppler ultrasound
  - "epididymitis"; UA normal
- Treatment: supportive, ***no ABX***

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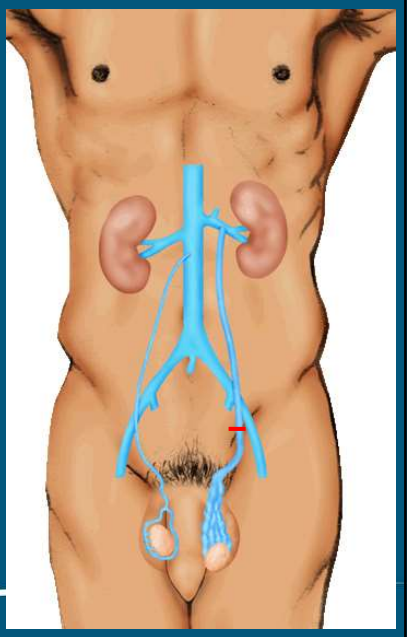
Adolescent Varicocele

- ~15%, 95% left sided; grade 3
- ***Most with varicoceles not infertile***
- Exam lying down and standing. Why?
- Isolated right sided varicocele?
  - AUA guidelines -> no imaging
- Pain, bother, 15-20% smaller, abnormal semen analysis used as indications
- ***Surgery not proven to help paternity***



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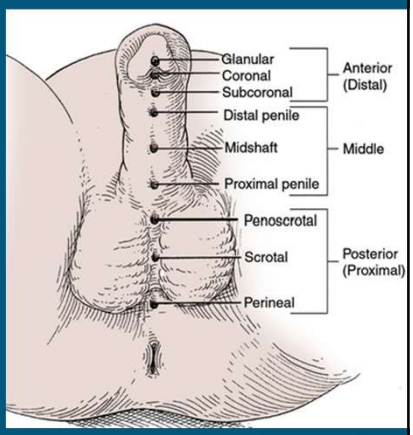
Hypospadias

- ~1 in 150 to 300 births
- ***Theory: "arrest in development"***
  - Incomplete "closing zipper" -> hypospadiac meatus
  - Persistent curvature/chordee
  - Incomplete ventral foreskin
- Associated with IUGR, twin, prematurity
- Most cases isolated
  - Some with mutations (WAGR, Denys Drash)
- Wide spectrum of severity
  - ~10% proximal or severe



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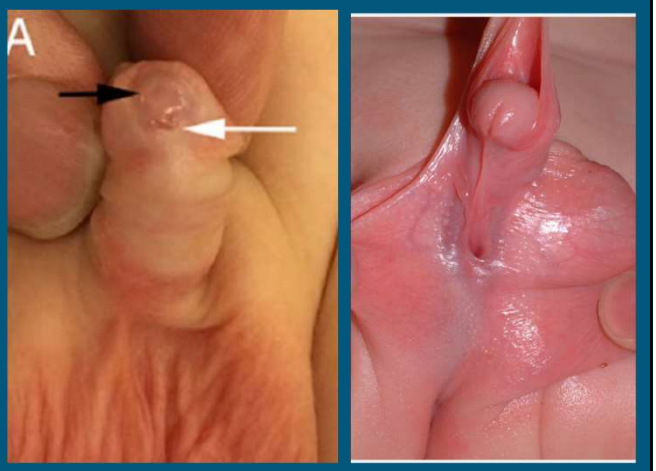
Hypospadias: Natural History depends on severity

- Infertility
  - Unlikely in mild cases
- Bother from chordee
  - Less likely if < 30 degrees
- Difficulty standing to void
  - Unlikely in mild cases
- Cosmetic concerns
  - Some adults with mild hypospadias unaware



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Androl Urol. 2014 Dec;3(4):347-58.
Clinical Pediatrics. 2017. Vol 56; 409-418

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Hypospadias Surgery Goals

- Correct chordee
  - Important step -> staged repair for severe chordee
- Meatus on glans with vertical slit appearance
  - Urethroplasty/meatoplasty
- Cover urethroplasty to help prevent fistula
  - Coverage with dartos/tunica vaginalis flap
- Glans connected over urethra = glansplasty
  - Sometimes not done in severe cases (functional is goal)
- Arrange skin for circumcised appearance (skin coverage)
  - Some will offer foreskin reconstruction for mild cases

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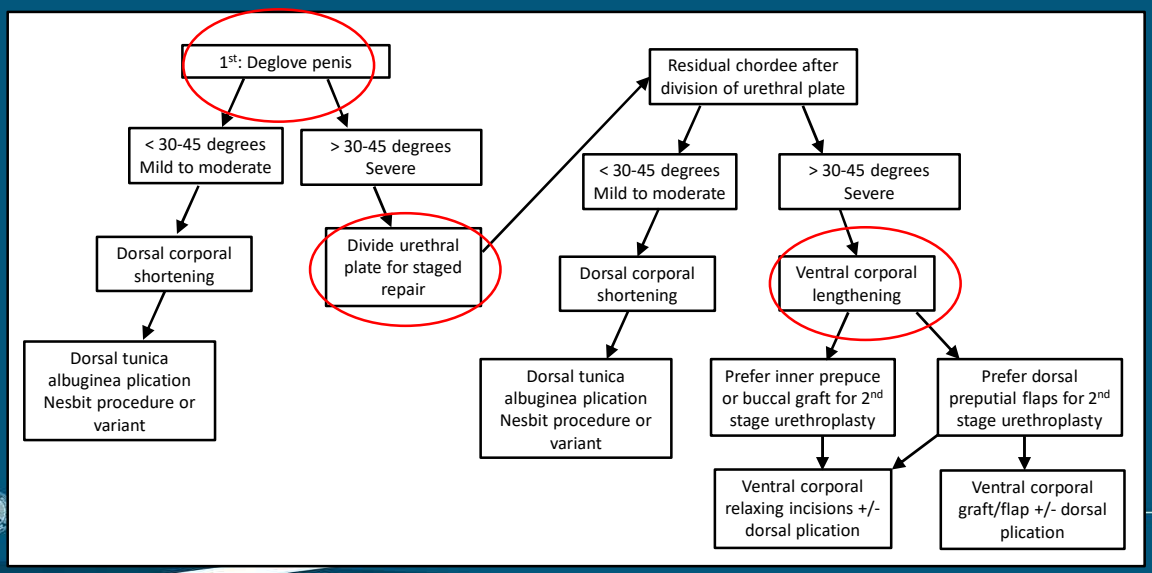
Chordee correction: Stepwise Approach



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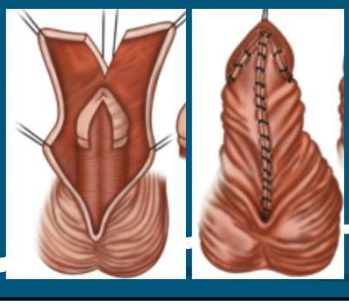
Staged repair options

After urethral plate divided

Inner prepuce or buccal graft

Tunica vaginalis flap

Inner prepuce flap: Byars flap



- ***High complication rate with proximal hypospadias repairs***
  - Fistula
  - Dehiscence
  - Stricture
  - Meatal stenosis
  - Diverticulum
  - Recurrent/persistent chordee

BJU International. 2012. 110:460
Hypospadiology. 187-199
Hypospadias Surgery. 619-629

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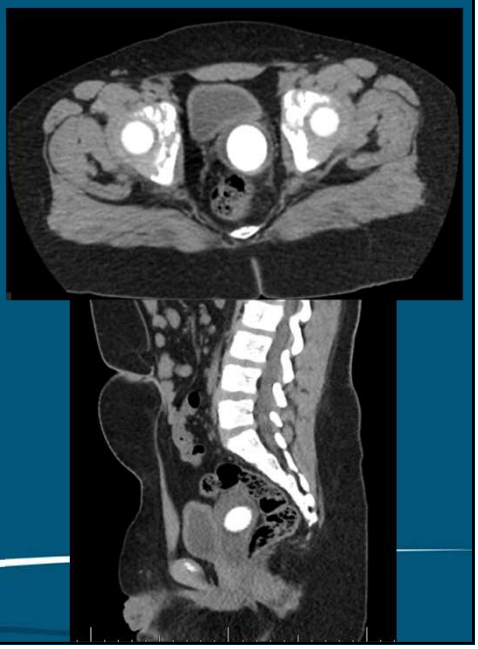
Hypospadias and Prostatic Utricle

- Remnant of mullerian ducts
  - Analogous to upper vagina
- Arises off posterior urethra in prostate
- ***Severe hypospadias or DSD typical***
- Usually asymptomatic
  - Difficulty with catheter placement
  - UTIs
  - Post void dribbling
  - Stones (in large ones)
- Can be removed surgically (open vs robotic)



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Undescended Testes

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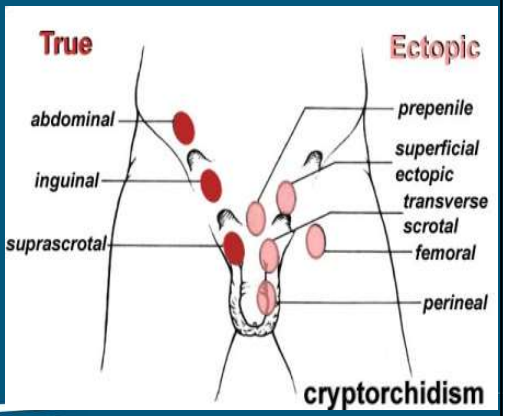
Undescended testes/Cryptorchidism

- About 2-3% at birth, 2/3 descend by 6 months
- Prematurity, IUGR, SGA associated
- Palpable – ~85%
- Non-palpable – ~15%
  - 20% abdominal, 30% intracannicular, 50% atrophic
- Ectopic – 10%
- Most sporadic, but can be part of syndrome



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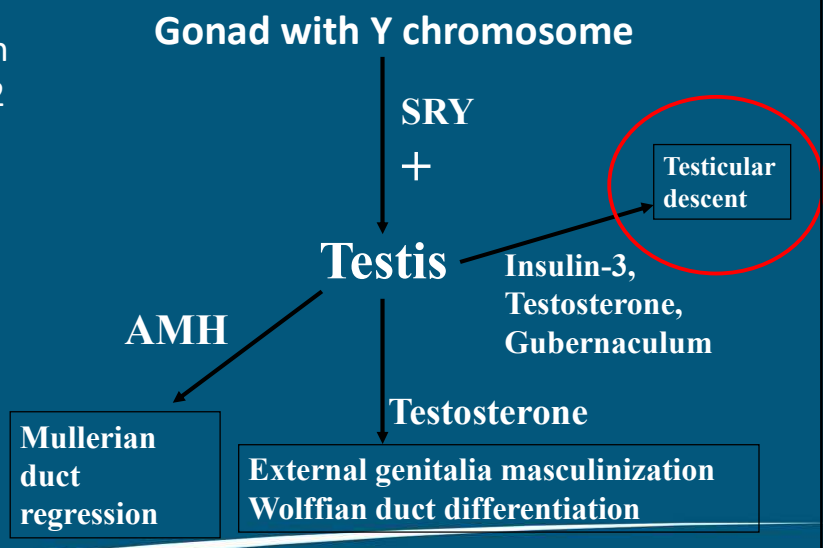
Undescended Testes: Embryology

- Trans-abdominal migration to internal ring by week 12
  - Insulin 3
  - Gubernacular swelling
- Transinguinal descent to the scrotum between weeks 22-30
  - ***Testosterone***
  - ***Gubernacular contraction***



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Undescended Testes: Definitions

- **Normal scrotal position**
  - Midpoint of testis at or below the midscrotum
- **Undescended/cryptorchidism**
  - Absence of one or both testis in normal scrotal position
- **Agenesis**
  - Testis never present, can be associated with ipsilateral mullerian duct persistence
- **Acquired cryptorchidism or "ascended" testis**
  - Documented normal scrotal position previously, no history of surgery. 1-7% with peak age 8.
- **Secondary cryptorchidism**
  - Supra-scrotal testis after inguinal hernia repair or orchiopexy
- **Retractile testis**
  - Easily retract above scrotum, but can be brought to normal position.

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Why is Orchiopexy Recommended?

- No spontaneous descent after 6 months
- ***Optimize fertility potential***
  - Reduced germ cells seen after 12 months of age
  - Unilateral UDT paternity essentially normal (90% vs 94% without)
  - Bilateral UDT paternity rate decreased, but optimized with surgery (~60%)
- ***Testis cancer risk: risk ratios 2-20***
  - Prepubertal orchiopexy decreases risk by 50%
- Inguinal hernia
- Cosmetic concerns
- Increased risk of testis torsion

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AUA Guidelines: Diagnosis

- ***No ultrasound*** or other imaging prior to referral
- Refer infants with UDT by 6 months
- Bilateral nonpalpable testes -> possible DSD?
- Increasing severity of hypospadias with UDT -> DSD concern
- If bilateral non-palpable and no CAH
  - Can check AMH levels/HCG stimulation test for anorchia
- Retractile testes should be assessed annually

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AUA GUIDELINES

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AUA Guidelines: Treatment

- ***Hormonal therapy not recommend***
  - low response and lack of long-term efficacy
- If no descent by 6 months, ***surgery within 1 year***
- Orchiectomy is acceptable if normal contralateral testes and:
  - short vessels/vas; dysmorhpic or hypoplastic testis; postpubertal age
- Status of the testicular vessels guides next steps
- Counsel patients/families regarding long term risks
  - Infertility, cancer

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AUA GUIDELINES

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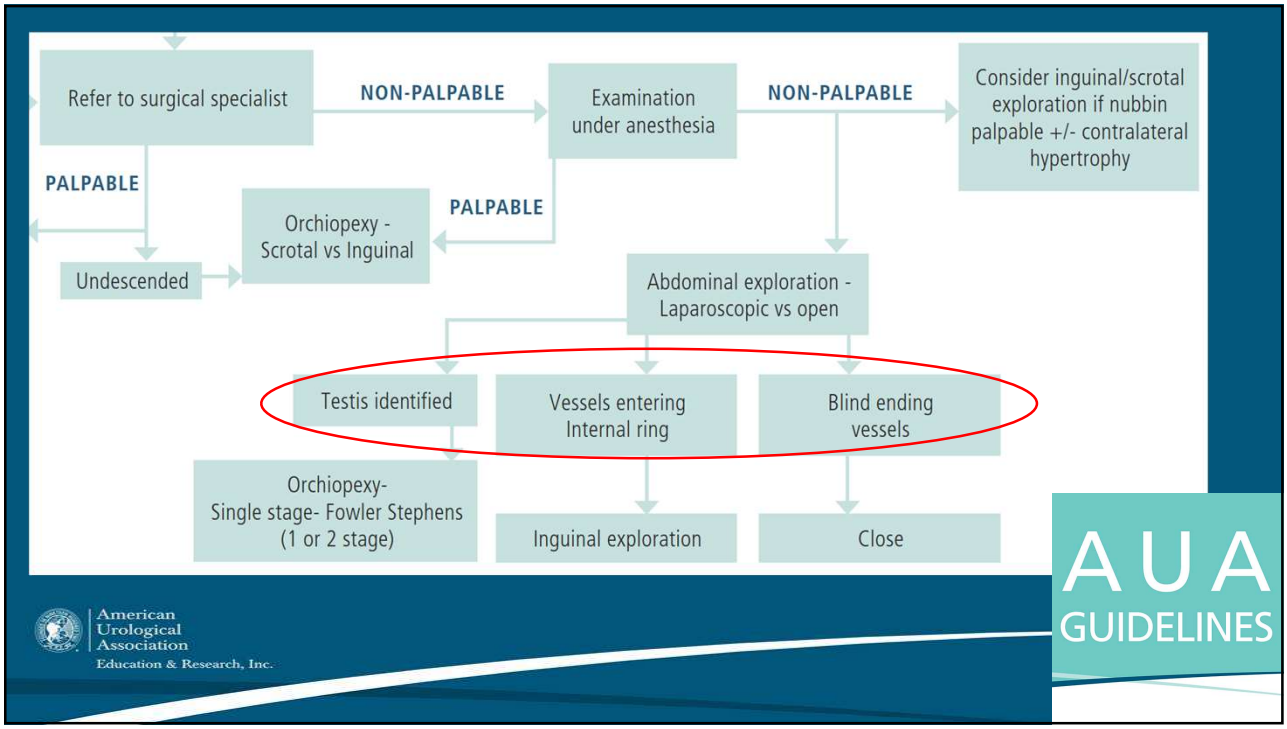

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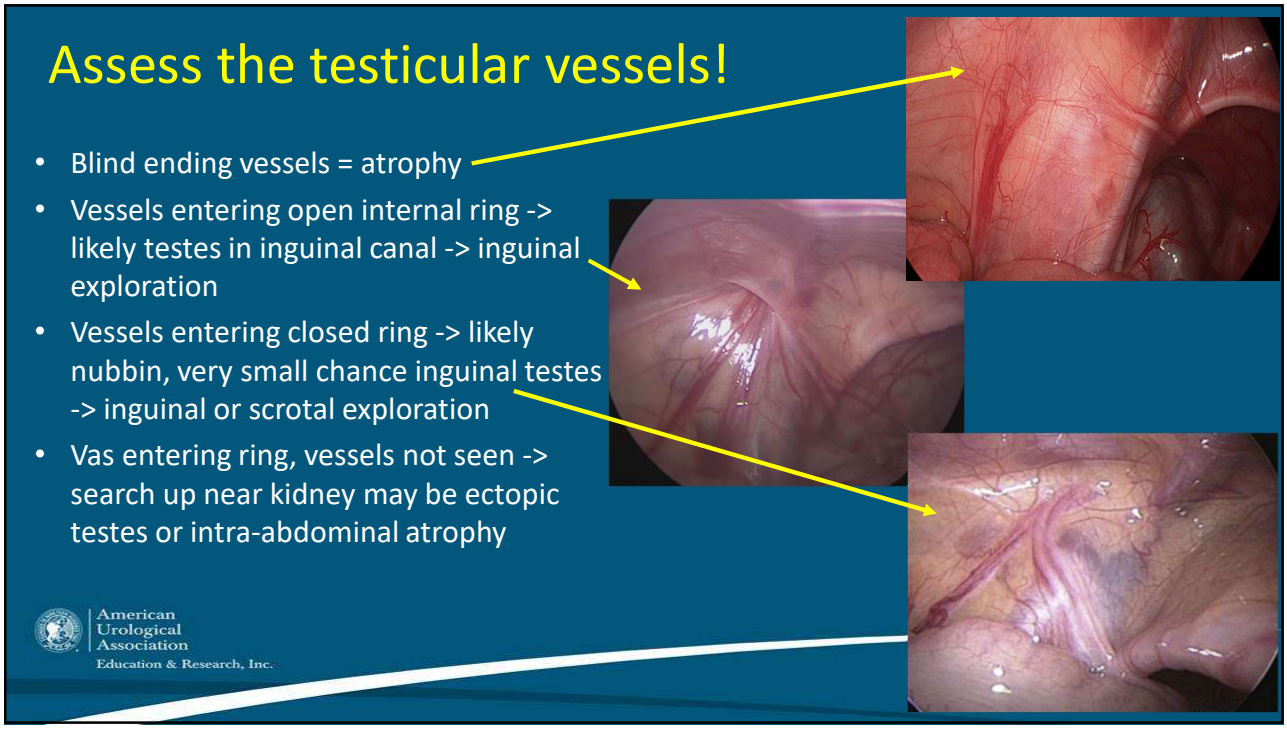

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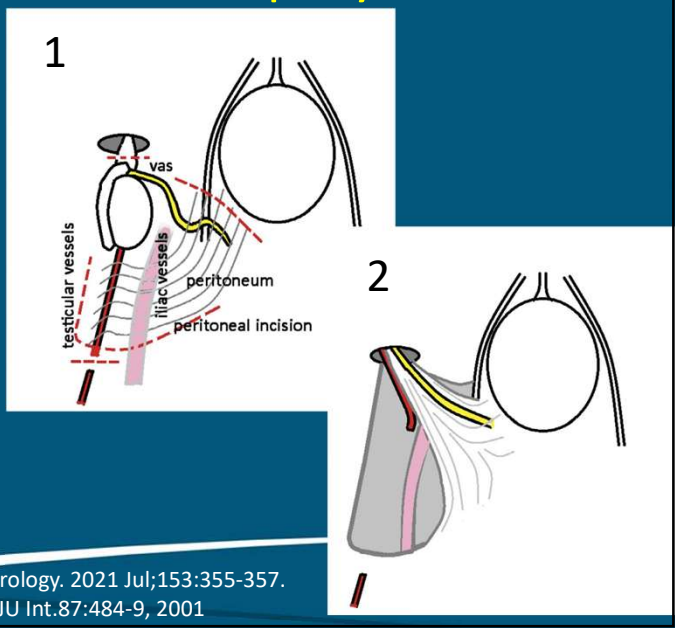
Fowler-Stephens Orchiopexy

- Laparoscopic
- High intra-abdominal testes
- Typically done in 2 stages
  - Survive: 88% vs 74% for 2 vs 1 stage
- 1. Divide main spermatic vessels
- 2. Bring testis to scrotum on vas and peritoneal stalk
- ***Primary laparoscopic without division of vessels often possible***
  - 93% survival



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Urology. 2021 Jul;153:355-357.
BJU Int.87:484-9, 2001

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DSD

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DSD: Takeaways

- Framework for differential diagnosis
  - ***Do not have to memorize it all!***
- Do not have to know details about reconstruction
  - Not all pediatric urologists do these cases
- Know approach to newborn with ambiguous genitalia
- There are a few classic diagnoses to know

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Framework for Differential Diagnosis

- Terms not to use
  - Hermaphrodite
  - male pseudohermaphrodite
  - Undervirilized male, etc

- Terms to use
  - 46 XY DSD
  - 46 XX DSD
  - Sex chromosome DSD
  - Gonadal dysgenesis
  - Ovotesticular DSD

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DSD: Framework for Differential Diagnosis

- For DSD – Framework based on
  - 1. ***karyotype (main way)***
  - 2. hypothalamic/pituitary/gonadal (HPG) axis
  - 3. hypothalamic/pituitary/adrenal (HPA) axis
- Understand this, you can make a differential diagnosis to pass any oral exam
- Learn a few outliers and subtle things – you're an expert

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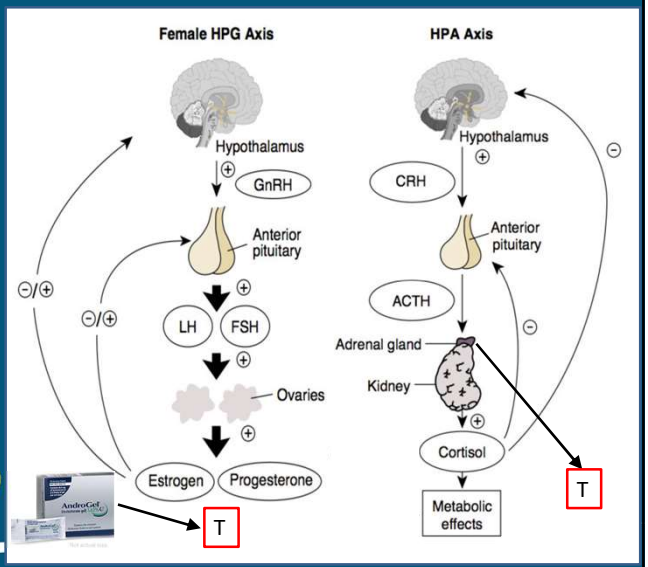
46 XX – Differential Easier

- Too much androgen – why?
  - ***Exogenous exposure?***
    - ***Exogenous T in pregnancy***
  - Too much GnRH?
    - Suppresses LH/FSH and estrogen
  - Too much LH/FSH?
    - Very rare tumors in adults
  - ***Adrenal gland makes too much androgen?***
    - ***Congenital adrenal hyperplasia***
  - Lack of cortisol receptor for feedback?
    - Chrousos syndrome – Very rare
  - FSH deficiency or receptor insensitivity
    - Rare, sexual infantilism at puberty
- ***Outlier***
  - ***SRY region translocation (46 XX sex reversal)***



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46 XX DSD Differential Diagnosis

- CAH
  - ***Over 95% of cases***
- Exogenous testosterone
  - Rare
- Rare XX sex reversal
  - Usually due to SRY translocation event
  - Outlier, experts know about this

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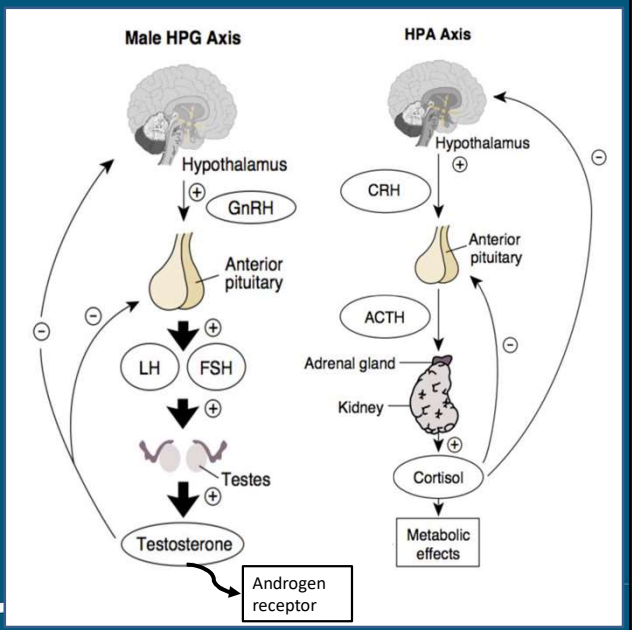
46 XY - Harder

- Too little androgen effect – why?
  - None or not enough GnRH
    - Yes, central hypogonadism
  - LH deficiency
    - Yes, but rare
  - LH receptor insensitivity/deficiency
    - Yes, but rare
  - No Leydig cell
    - Yes, rare - AKA Leydig cell hypoplasia
  - ***Testes don't make T right***
    - ***Gonadal dysgenesis***
    - ***Steroid synthesis mutations (CAH types)***
  - ***DHT synthesis from T (5α reductase def)***
  - ***Androgen receptor insensitivity/deficiency***



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46 XY DSD Differential Diagnosis

- All steps from pituitary to androgen receptor can lead to problems
- ***Most common are problems with testosterone production and androgen insensitivity***
  - ***46 XY gonadal dysgenesis***
  - ***Androgen insensitivity***
  - ***5-alpha reductase deficiency rare, but interesting***

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Sex Chromosome DSD and Ovotesticular DSD

- If the chromosomes are not normal, this is called ***sex chromosome DSD***
  - 45 XO/46 XY mosaicism, 47 XXY, 45 XO, etc
- If there are ovary and testis tissue, it is called ***ovotesticular DSD***
  - Specific DSD category

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- ***All forms of DSD fall into one of these***
  - ***–46 XX DSD***
  - ***–46 XY DSD***
  - ***–Sex chromosome DSD***
  - ***–Ovo-testicular DSD***

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Newborn with Ambiguous Genitalia

- History
  - Gestational, maternal T exposure, family history, consanguinity, pregnancy losses
- Physical Exam
  - Other abnormalities? Syndrome?
  - GU exam: ***gonads***, phallus, openings, virilization
- Labs
  - ***Karyotype – main way to categorize***
  - ***Electrolytes***
  - ***17-OHP – CAH most common***
  - T/LH/FSH – HPG axis
- Imaging
  - ***Pelvis US – Uterus present?***
  - ***Renal US – adrenal hyperplasia***
- Other labs?
  - 11-deocycortisol if 17-OHP elevated
  - AMH level – any testis present?
  - HCG stim test – testis function
- Additional genetic testing
  - More mutations being found
- Possibility of CAH makes evaluation emergent -> salt wasting
  - ***Bilateral non-palpable gonads***

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Specific Diagnoses to know

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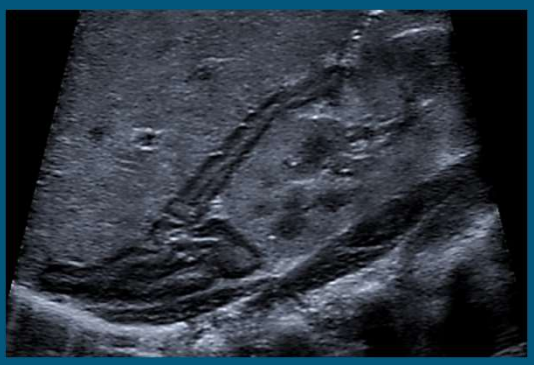
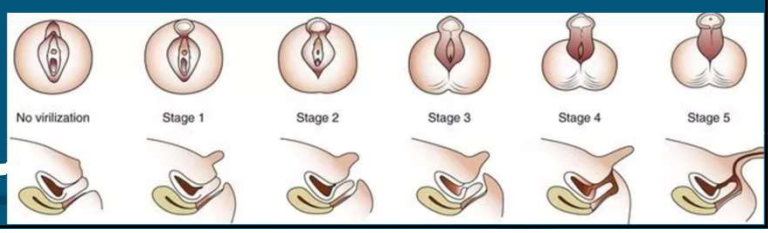
CAH – most common 46 XX DSD

- 21 hydroxylase deficiency most common
  - Diagnosis: elevated (17-OHP) levels
  - Internal anatomy = normal mullerian structures & ovaries
    - Due to no AMH
- External anatomy
  - Slightly virilized to fully formed penis with bilateral non-palpable gonads
  - Prader Scale
- RUS shows adrenal hyperplasia





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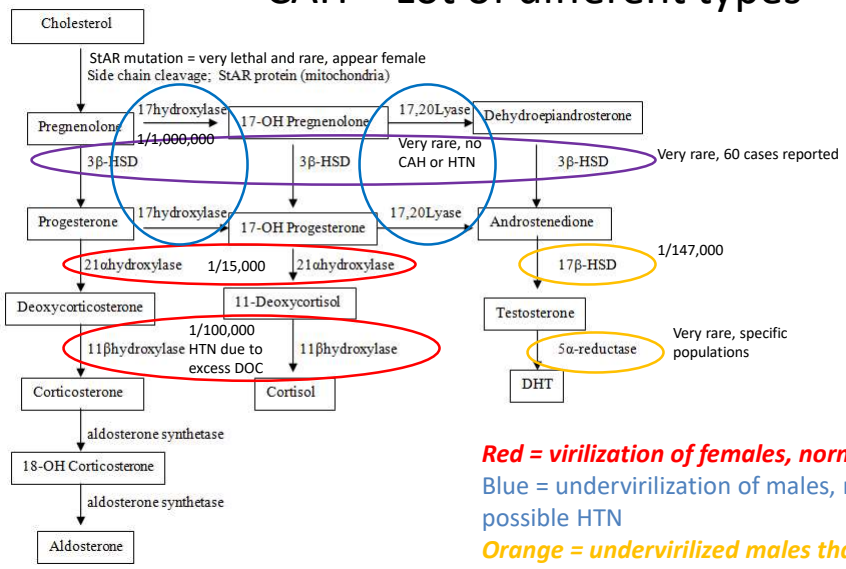
CAH – Lot of different types



Red = virilization of females, normal males

Blue = undervirilization of males, normal females, possible HTN

Orange = undervirilized males that can virilize some at puberty, normal females, no HTN

Purple = undervirilized males and virilized females

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CAH Medical Management

- Salt wasting crisis can be life threatening
  - Classic case is male at 1-2 weeks of life with failure to thrive, dehydration, hyponatremia, hyperkalemic acidosis
  - Tx: Mineralocorticoids, resuscitation, supportive care
- ***Glucocorticoids -> Prevent further virilization***
- ***Mineralocorticoids -> prevent salt wasting***
- Stress dose steroids with illness/surgery
- Monitor bone age; may need growth hormone for height

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CAH Surgical Management

- Exam under anesthesia, assess anatomy with genitogram
- Feminizing genitoplasty
  - Surgical correction of genitourinary sinus & vaginoplasty
  - Allow vaginal intercourse, possibly lower UTI risk
- Clitoroplasty
  - Reduction clitoroplasty, avoid damage to nerves dorsally
  - ***Controversial*** if should be done, many methods
- ***Timing is controversial***
  - Many advocate to wait until assent possible

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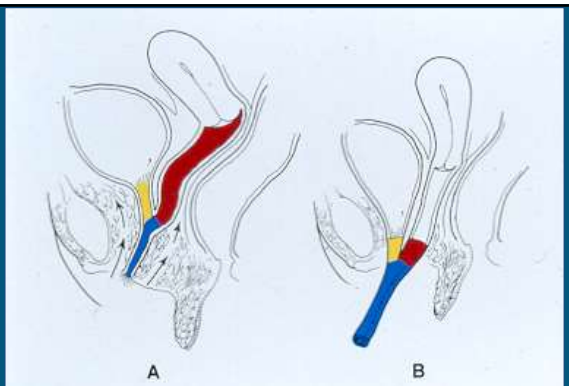
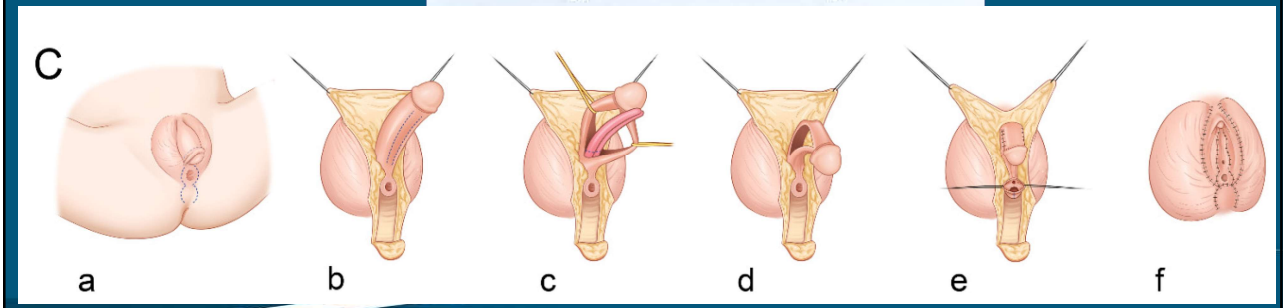
CAH surgical





Int. J. Environ. Res. Public Health **2021**, *18*(21), 11152

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Complete Androgen Insensivity Syndrome (CAIS)

- 46XY -> testes -> testosterone -> AR no good -> Female
- Presentation: prenatal testing, inguinal hernias in young girls, amenorrhea at puberty
- Internal anatomy: no Mullerian structures (AMH is present)
- Normal female external genitalia, minimal pubic hair
- Breast development occurs
  - Why? Excess testosterone aromatized to estrogen
- What to do with gonads?
  - Seek assent, 2-4% lifetime risk of cancer vs estrogen replacement
- Short vagina: dilation usually works, vaginoplasty
- Gender dysphoria rare, 80% will have AR mutation found

Hanne Gaby Odiele: Belgian model and intersex advocate

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Androgen Insensitivity is a Spectrum

- Partial androgen insensitivity (PAIS)
  - 46 XY DSD
  - Varying degrees of undervirilization
  - High dose T to increase penile size
  - Can be difficult to determine gender of rearing
- Breast development at puberty
  - Aromatization, often high T levels
- Outcomes
  - Males with small penises and dissatisfaction
  - Risk of gender dysphoria (esp raised female)
  - Individualize treatment plans

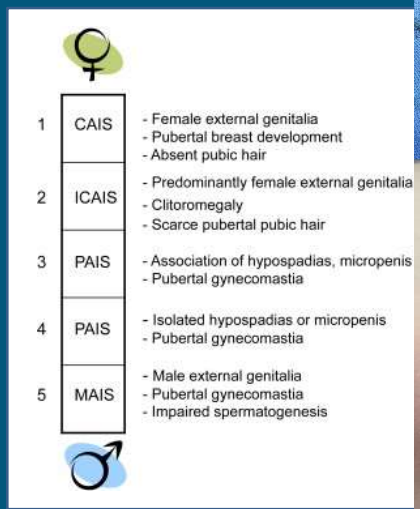

Photo courtesy of Andrew J. Kirsch, MD

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5-Alpha Reductase Deficiency: low DHT

- 46 XY DSD, autosomal recessive, rare
- Very undervirilized infants, bilateral UDT; can be missed and raised as female
- Puberty -> virilization, increase muscle mass
- Diagnosis
  - Elevated T:DHT ratio with HCG stim test or puberty (>20:1)
  - Genetic testing
- Risk of gender reversal if raised female

Photo courtesy of Andrew J. Kirsch, MD

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Demystifying Gonadal Dysgenesis

- Gonadal dysgenesis = Gonad formed abnormally
  - ***Usually due to genetic mutation***
- 46XX gonadal dysgenesis
  - Streak gonads -> Female with no puberty
- 46XY gonadal dysgenesis
  - "Partial" phenotype: some gonad function -> wide spectrum
  - "Complete" phenotype: no gonad function -> Female external
- Gonadal dysgenesis with 45 XO/46XY mosaicism
  - Phenotype range: female turner syndrome (45 XO) to male (46XY)

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46 XY Complete Gonadal Dysgenesis: Swyer Syndrome: bilateral streak gonads

- External phenotype: female
- Internal phenotype: mullerian structures are present
  - Bilateral streak gonads = no AMH
- Presentation: no puberty and amenorrhea
  - Can be diagnosed by prenatal testing
- Sometimes genetic cause found
- Can be fertile with hormones and egg donors (no ovaries)
- ***XY Streak -> High risk for gonodoblastoma -> bilateral gonadectomy***
- Rare gender dysphoria

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46 XY Partial Gonadal Dysgenesis

- Phenotype: Ambiguous genitalia with bilateral UDT
  - Wide spectrum of severity and gender of rearing can be difficult
  - ***Not one condition, but multiple mutations/causes***
- Often dysmorphic features, other anomalies
  - Named syndromes, or new mutation, or unknown
- What to do with gonads? Common sense approach.
  - Remove if intra-abdominal, streak appearing, and can't bring to scrotum
  - Orchiopexy for inguinal or lower testes that look "normal"
  - Biopsy at puberty or yearly ultrasounds? Controversial, no standard.
- Typical infertile and may need testosterone supplementation

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46 XY Partial Gonadal Dysgenesis: Syndromes

Table 2: 46 XY DSD Testicular Development Disorders and Associations

Product	Genetics	Target organs	Syndrome	Phenotype/Associations
WT1	11p13 Autosomal dominant	Kidney Gonad	Denys-Drash Syndrome Frasier Syndrome	Dysgenetic testes resulting in atypical genital with cryptorchidism Bilateral Wilms tumor Nephrotic syndrome — Early onset renal failure /mesangial sclerosis Streak gonads with high risk of gonadoblastoma Female to atypical (ambiguous) phenotype Renal failure, 2nd decade
SF1	9q33 NR5A1, nuclear receptor gene Autosomal dominant	Adrenal Gonad Hypothalamic-pituitary-gonad axis		Dysgenetic testis Variable atypical phenotype-Adrenal failure
SOX9	17q24 Autosomal dominant	Sertoli/AMH Gonad Chondrocytes	Campomelic dysplasia	Dysgenetic testis or sex reversal External spectrum: Male with UDT to atypical to female Shoulder girdle, spine, pelvic anomalies; bowed legs Cleft palate

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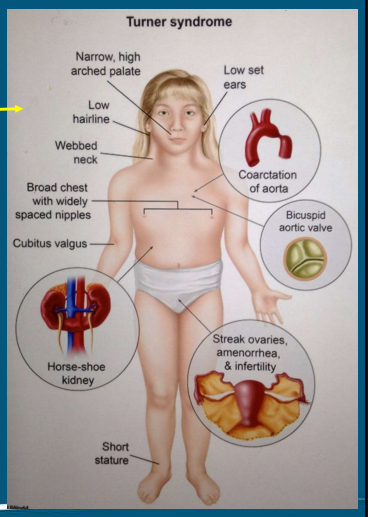
45 XO Gonadal Dysgenesis: Turner Syndrome

- A form of "sex-chromosome" DSD
  - Bilateral streak gonads/ovaries
- Typical phenotype
- Other organs: coarctation of aorta, horseshoe kidney
- Those with 45XO/46XX karyotype have fewer features
- Infertile, need growth hormone and estrogen
- 45XO/46XY karyotype should have gonads removed
  - Increased risk of gonadoblastoma with Y chromosome



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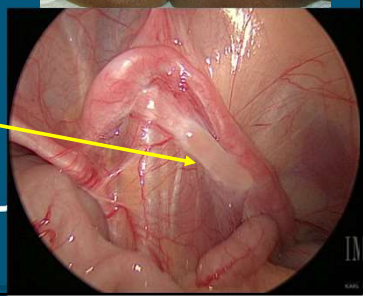
45XO/46XY & Mixed Gonadal Dysgenesis

- Phenotypes for 45XO/46XY?
  - Normal male (90-95%), but some decreased fertility (25%)
  - Female with turner syndrome -> remove streak gonads
  - ***1 scrotal gonad, 1 intra-abdominal streak with remnant mullerian, and hypospadias = "mixed gonadal dysgenesis"***
  - Even more severe under virilization -> potential female rearing
- ***Mixed gonadal dysgenesis is a descriptive term***
  - ***2nd most common DSD diagnosis***
  - Treatment: typically male rearing, remove streak & mullerian, hypospadias repair
  - Normal puberty usually, infertile typically, other Turner syndrome features such as short stature, remaining gonad may fail over time



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Tumor risk and gonadal dysgenesis

- Gonadoblastoma = benign tumor composed of gonadal elements (germ cell, sertoli cells, stromal cells).
- Dysgerminoma – tumor similar to seminoma, arises in gonadoblastoma
- ***Dysgenetic gonads with "Y" chromosome material have increased risk of gonadoblastoma and dysgerminoma***
- ***The more abnormal the gonad and higher it is, the higher the risk***

RISK GROUP	DISORDER	MALIGNANCY RISK (%)
High	GD*(+Y)† intra-abdominal	15-35
	PAIS nonscrotal	50
	Frasier	60
	Denys-Drash (+Y)	40
Intermediate	Turner (+Y)	12
	17β-hydroxysteroid	28
	GD (+Y)† scrotal	Unknown
	PAIS scrotal gonad	Unknown
Low	CAIS	2
	Ovotesticular **DSD**	3
	Turner (−Y)	1

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What Gonads Should Be Removed? In order of decreasing degree of certainty (my own).

- YES: 46 XY Complete gonadal dysgenesis (Swyer syndrome)
- YES: Turner syndrome with Y-chromosome (45XO/46XY)
- YES: Mixed gonadal dysgenesis – the streak gonad (45XO/46XY)
- YES: 46 XY partial gonadal dysgenesis – intra-abd streak (Denys/Drash)
- ?: PAIS – high non-scrotal, abnormal appearing, being raised female
- ?: Ovo-testicular DSD – remove part of gonad not consistent with sex of rearing. Consider delaying this until older childhood/assent.
- No?: CAIS – after puberty if patient wants them removed or at time of hernia repair if family wants you to.

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Ovotesticular DSD – Separate category

- More common with African descent
- ***Karyotype usually 46 XX without SRY***
- Presence of testis and ovary tissue
  - Any combo, most common ovary or testis on one side and ovo-testis on the other side
- Wide range of virilization
- Gender assignment, surgery, removal of discordant gonad tissue individualized.
  - Consider waiting for age of assent
  - Fertility possible for some if assigned female

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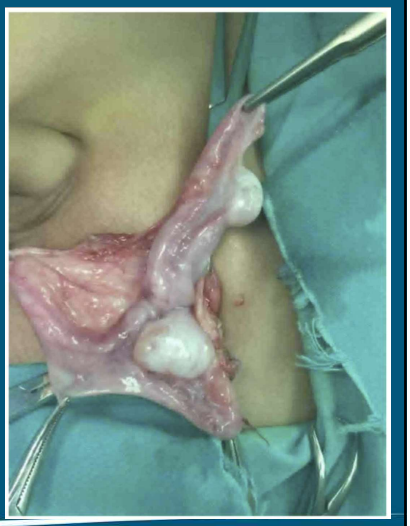
Persistent Mullerian Duct Syndrome

- A form of 46 XY DSD
- No AMH or no AMH receptor
  - Persistence of mullerian duct (uterus/fallopian tubes)
- Presentation
  - UDT/hernia usually. Both testes on same side (rare).
- Fertility
  - Rare (<10%); gonadal failure in 3rd – 4th decades
- Cancer risk: 3-8% mullerian structures; 33% testis if left intra-abdominal



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Exp Ther Med. 2017 Dec;14(6):5779-5784.

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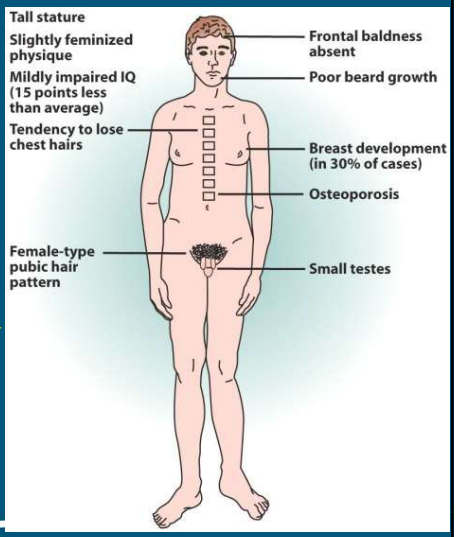
Klinefelter's Syndrome

- 47 XXY or variants (46XY/47XXY, 48XXXY, etc)
  - A "sex-chromosome" DSD
- Seminiferous tubules atrophy -> small testes < 3.5 cm
- Gonadal failure: low normal T, high LH/FSH, high estradiol at puberty
- Most azospermic, some mosaics can have sperm
  - Can present with infertility
- Typical phenotype
- Tx: T supplementation, breast reduction, can retrieve sperm with micro-TESE or in semen before T started



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46 XX Male: Rare

- Rare: 1/20,000 males
- 10% hypospadias, 100% infertile
- ***90% are SRY positive, translocation***
- ***Klinefelter-like: hypogonadism, azoospermia, low T with high LH/FSH, gynecomastia***
- Tx: individualized. Breast reduction, testosterone replacement

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Isolated Micropenis

- Endocrinology condition
- Evaluation
  - Karyotype, T, LH/FSH, pituitary imaging
- Etiology
  - central hypogonadism due to pituitary gland problem
  - ***Kallmann syndrome - anosmia***
  - idiopathic
- Treatment
  - T or HCG supplementation; male sex of rearing

Age	Mean	Mean -2.5 SD
Newborns		
Preterm newborns (30 weeks)	2.5±0.4	1.5
Preterm newborns (34 weeks)	3.0±0.4	2.0
Term newborns	3.5±0.4	2.5
Infants and children		
0-5 months	3.9±0.8	1.9
6-12 months	4.3±0.8	2.3

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Thank you!

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