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The University of Texas at Austin
Dell Medical School

# Infertility & Hypogonadism

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Disclosures:

Swiss Precision Diagnostics – Consultant

Marius Pharmaceuticals – Consultant

Boston Scientific – Consultant

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# Outline

- Physiology and Pathophysiology of Male Reproduction
- Evaluation of the Infertile Male
- Treatment of the Infertile Male (Surgical and Non-Surgical)
- Hypogonadism
- Testosterone Replacement

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# Physiology and Pathophysiology of Male Reproduction

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# Embryology

- Bipotential Gonad
- SRY gene causes cells of the genital ridge to differentiate into seminiferous tubules
- Sertoli cells secrete MIS which causes Mullerian ducts to regress (8-10 weeks)
  - Remnants of Mullerian ducts: appendix testis, prostatic utricle
- Leydig cells form in response to SRY protein and start secreting T → virilization of the Wolffian Ducts

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# Embryology

- Wolffian Ducts → Vas, SVs, Ejaculatory Ducts, Epididymis
  - Cranial portion of WD → appendix epididymis
- At 12 weeks gestation, continuity of male gonadal tract exists (seminiferous tubules → efferent ductules→ rete testes → epididymis…)
- Absence of SRY gene → ovarian follicles
- Phenotypic differentiation reliant on androgen production

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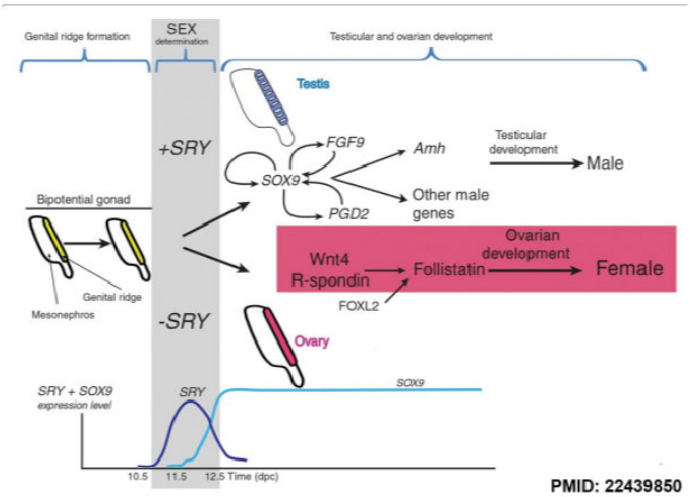
# Embryology




PMID: 22439850

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De Lau WB, Genome Biol. 2012

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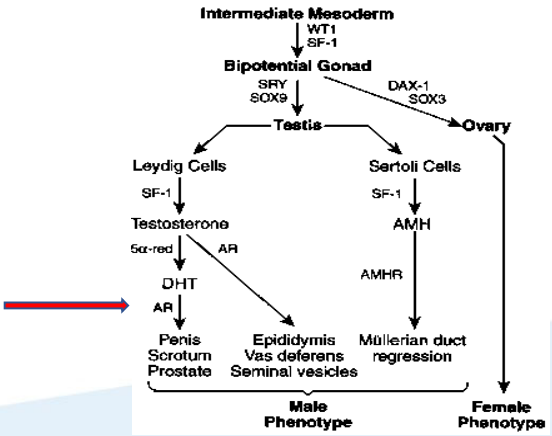
# Embryology




- DHT (Dihydrotestosterone) causes differentiation of penis, scrotum and prostate
- Testosterone causes differentiation of epididymis, vas deferens, seminal vesicles

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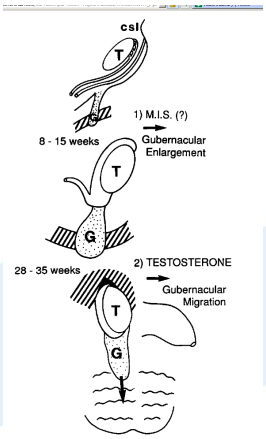
# Embryology – Testicular Descent

- Transabdominal Phase (approx. 12 weeks)
  - Depends on Leydig cell-derived insulin-like peptide
  - This phase is rarely disrupted
- Inguinoscrotal Phase (approx. 25 weeks)
  - Depends on androgens produced by Leydig Cells
  - Gubernaculum bulges beyond external inguinal ring and descends into scrotum, guiding testis
  - Processus vaginalis allows intraabdominal testis to exit the abdominal cavity

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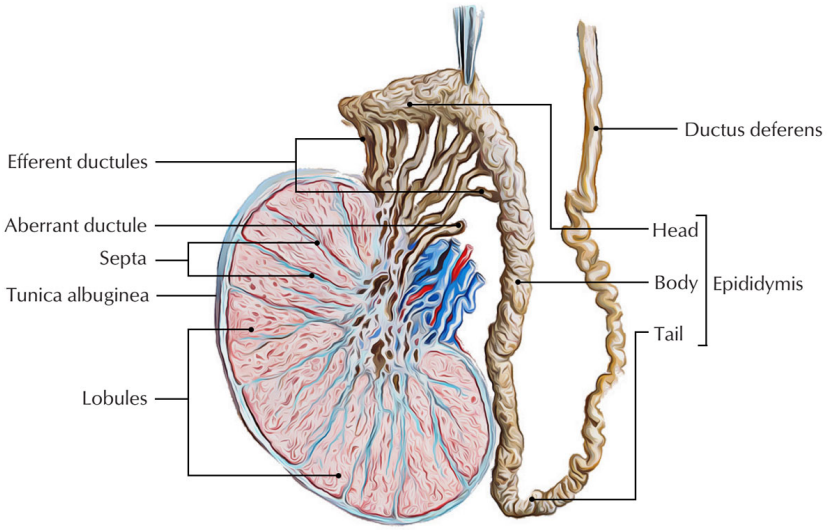
# Anatomy of the Testis

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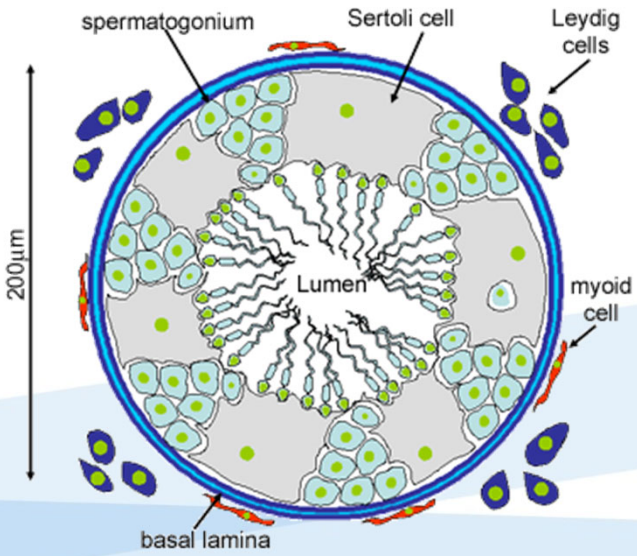
# Anatomy of the Testis

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# Hypothalamic-Pituitary-Gonadal Axis

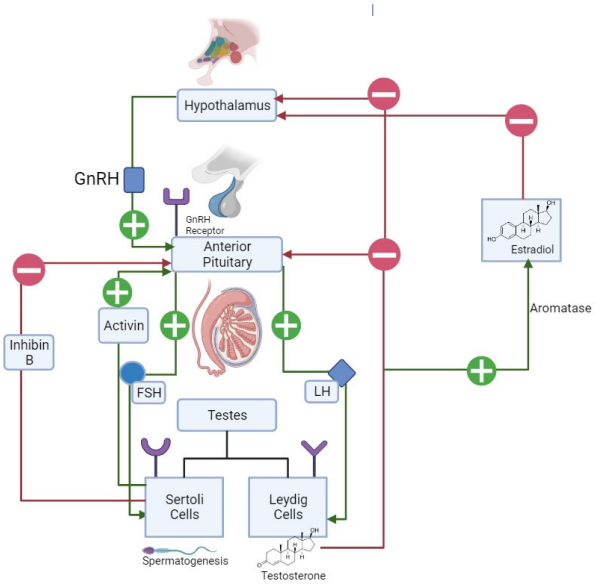


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Image by Noopur Naik, CCLCM MS2

# Spermatogenesis

- 74 day process occurs in a immuno-privileged site (blood-testis barrier: Sertoli cell tight junctions)
- Dependent on high levels of intra-testicular T and DHT
- Spermatogonial Stem Cells:
  - A (dark) spermatogonia – quiescent reserve
  - A (pale) spermatogonia – continuously self-renewing (mitosis)
  - B spermatogonia – immediate precursors to primary spermatocytes

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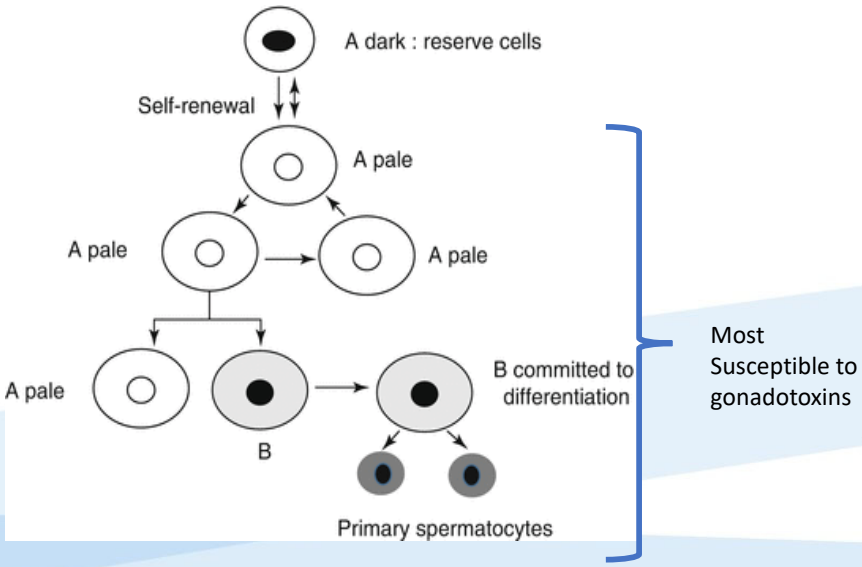
# Spermatogenesis

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# Pathophysiology of Male Reproduction

- Anatomic
- Environmental/Behavioral
- Iatrogenic
- Idiopathic
- Infections
- Syndromes

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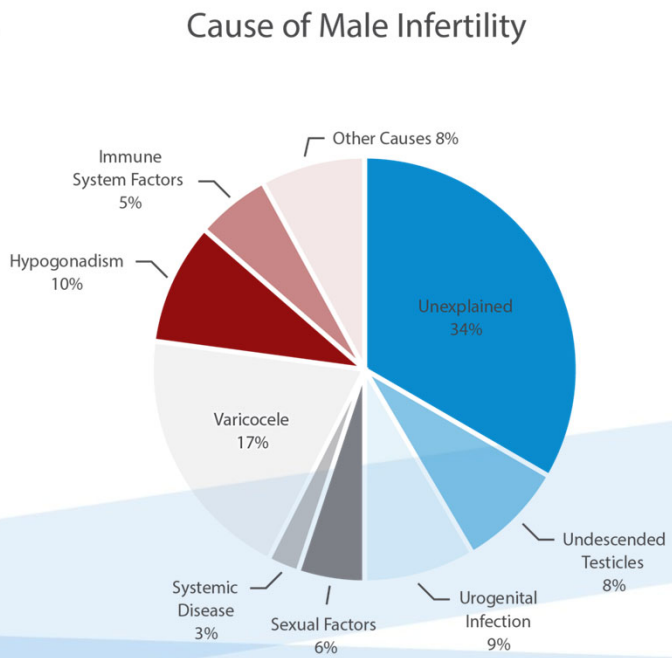
# Pathophysiology of Male Reproduction

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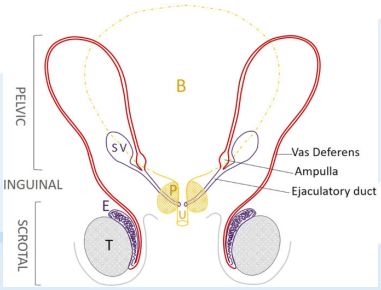
# Congenital Absence of the Vas Deferens

- Unilateral, Bilateral, Partial or Complete
- Epididymal hypoplasia
- Seminal vesical agenesis/hypoplasia
- Associated with renal anomalies (more common in CUABD)
- *Check Renal Ultrasound*

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# Congenital Absence of the Vas Deferens

- SVs → 60-70% semen volume
  alkaline
  coagulates
- Prostate → 30-40% semen volume
  acidic (PAP)
  liquifies
- Testes → <5% semen volume
  sperm, epididymal fluid

<u>Classic Semen Findings (Bilateral)</u>:
Low Volume, low pH, azoospermia

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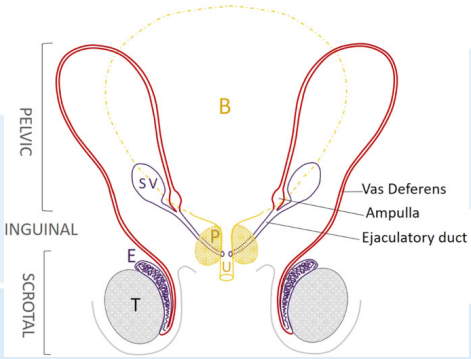
# Congenital Absence of the Vas Deferens

- CFTR mutations identified in 80-97% of men with CBAVD and 40% of men with CUAVD (Casals et al, 1995)
- Treat men with CBAVD as CF carriers independent of genetic findings

PHSYICAL EXAM IS KEY TO DIAGNOSIS

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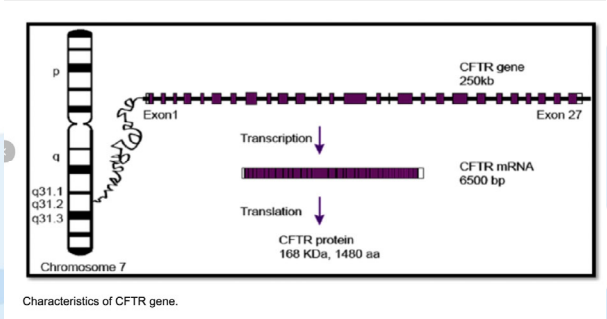
# Congenital Absence of the Vas Deferens

- "Clinicians should recommend Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) mutation carrier testing (including assessment of the 5T allele) in males with vasal agenesis or *idiopathic obstructive azoospermia*"




Characteristics of CFTR gene.

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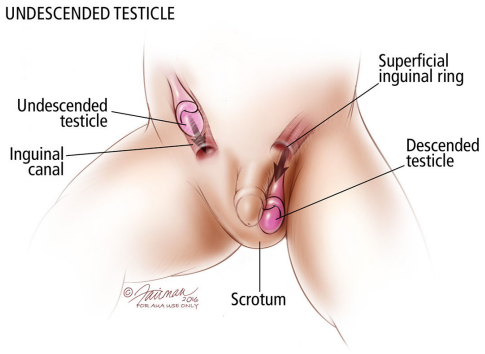
Brannigan RE, AUA/ASRM guideline (2024). J Urol.

# Cryptorchidism

- Estimates 1-9% of infants, 7-30% of premature infants – 1-7% by 12 months of age
- Associated with infertility by several mechanisms - likely a developmental etiology
- Bilateral cryptorchidism: 6-fold increased risk of infertility
- Hx of cryptorchidism in 20-27% of men with azoospermia (Fedder et al, 2004)
- 3-8% of men with OAT (Lee & Coughlin, 2001)

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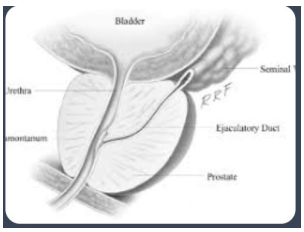
# Ejaculatory Duct Obstruction




- Partial or complete obstruction of the ejaculatory ducts
  - Obliteration
  - Narrowing
  - External compression (Mullerian, Wolffian, Utricle Cysts)
  - Stone
- Typical SA findings: low ejaculate volume, acidic pH (pH <7), fructose negative, azoospermia, severe oligoasthenospermia

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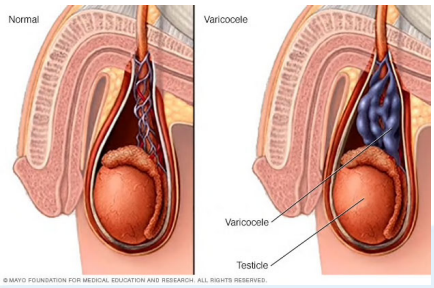
# Varicocele

- Abnormal dilatation of the spermatic cord veins
- Several mechanisms of fertility impairment
  - Hypoperfusion → Hypoxia
  - Heat Stress
  - Oxidative Stress
  - Hormonal
- Present in 15-25% of males, 35-60% of men with infertility
- Most common reversible cause of male factor infertility

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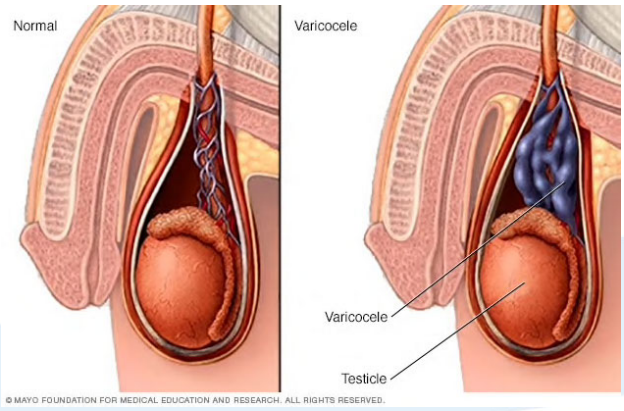
# Varicocele

- More common on the LEFT side due to right-angled insertion of the LEFT spermatic cord vein into the LEFT renal vein
- Nutcracker phenomenon: compression of LEFT renal vein between SMA and aorta
- Pathologic venous compression (RP tumor, etc)

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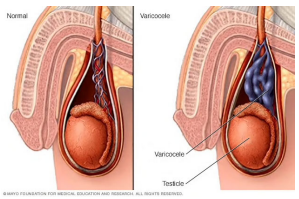
# Varicocele




| | Grade | Reflux | Varicosities | Testicular Hypotrophy |
|---|---|---|---|---|
| **Ultrasound** Sarteschi [38] | 1 | During Valsalva | None | No |
| | 2 | During Valsalva | Small | No |
| | 3 | Clearly during Valsalva | Overt | No |
| | 4 | Spontaneous reflux, increased with Valsalva or standing | Present in all positions | Common |
| | 5 | Spontaneous reflux at rest without increase during Valsalva | Venous dilatation in all positions | Yes |
| **Clinical** Dubin and Amelar [37] | Subclinical | Seen on imaging, but no varicocele on exam | | |
| | I | Small, palpable with valsalva | | |
| | II | Moderate, palpable when standing without valsalva | | |
| | III | Large, easily visible | | |

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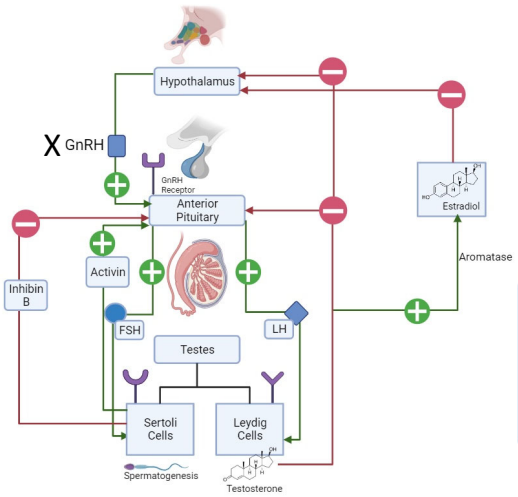
# Hyperprolactinemia

- Present in 1% of the general population
- Prolactinoma is the most common cause of hyperprolactinemia
- Prolactin *inhibits pulsatile GnRH secretion* therefore results in reduced LH, FSH, T

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Dabbous & Atkin, Arab J Urol 2018

# Hyperprolactinemia

- Elevation in prolactin on two occasions without clear benign cause should prompt MRI of the pituitary
- Prolactin to Testosterone ratio > 0.10 or Prolactin > 25 ng/mL predictive of positive MRI findings (Naelitz et al)
- Medical treatment with dopamine agonists (Cabergoline) for small adenomas, surgery for larger adenoma

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Naelitz et al, J Urol 2020

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# Iatrogenic

- Medications
  - Chemotherapy/Radiation: depends on agent, dose delivered, site, schedule
  - Mitotically/Meiotically active cells most sensitive
- Surgery
  - Iatrogenic injury to vas deferens (inguinal hernia repair), epididymis (spermatocele/hydrocele)
  - Testicular atrophy due to injury to testicular blood supply
  - Retroperitoneal/Pelvic surgery may result in anejaculation or retrograde ejaculation

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# Syndromes

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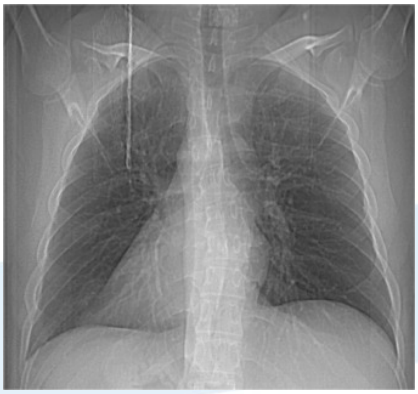
# Kartagener Syndrome

- Type of Primary Ciliary Dyskinesia
- Autosomal recessive ciliary disorder
- 1:30,000
- Associated with situs inversus, bronchiectasis sinusitis
- Diagnosis made with electron microscopy, genetics evaluation
- Treatment: ICSI



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# Hypogonadotropic Hypogonadism

- Absence of pubertal development, no secondary sexual characteristics, delayed growth spurt, low libido, sexual dysfunction, *anosmia*
- Secondary HH: pituitary tumor, infiltrative disease (i.e hemochromatosis, sarcoidosis, TB), exogenous androgen, chronic illness, head trauma
- Low LH, FSH, Testosterone
- Treatment:
  - Testosterone Replacement Therapy
  - GnRH
  - HCG & HMG (rFSH)
    - 84% of patients return of sperm to ejaculate by 18 months

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Stamou MI et al, Ped Repro Endo 2017
Warn DW et al, Fertil Steril 2009

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# Kallmann Syndrome

- Congenital Hypogonadotropic Hypogonadism (X-Linked Recessive)
- Absent GnRH production
- Genetically and Phenotypically heterogenous
- Associated with anosmia, cryptorchidism, microphallus, poorly developed secondary sexual characteristics

**Table 1 – Genes associated with Kallmann Syndrome and normosmic idiopathic hypogonadotropic hypogonadism and their characteristics.**

| Gene | Description | Chromosome | Function | Phenotype |
|---|---|---|---|---|
| *KAL1* | Kallmann 1 | chrXp22.31 | Neurodevelopmental | KS |
| *NSMF* | NMDA receptor synaptonuclear signaling and neuronal migration factor | chr9q34.3 | Neurodevelopmental | KS and nIHH |
| *FGFR1* | Fibroblast growth factor receptor 1 | chr8p11.23 | Neurodevelopmental | KS and nIHH |
| *FGF8* | Fibroblast growth factor 8 | chr10q24.32 | Neurodevelopmental | KS, nIHH and AHH |
| *FGF17* | Fibroblast growth factor 17 | chr8p21.3 | Neurodevelopmental | KS and nIHH |
| *IL17RD* | Interleukin 17 receptor D | chr3p14.3 | Neurodevelopmental | KS |
| *DUSP6* | Dual specificity phosphate 6 | chr12q21.33 | Neurodevelopmental | KS |
| *SPRY4* | Sprouty drosophila homolog of 4 | chr5q31.3 | Neurodevelopmental | KS and nIHH |
| *GLCE* | Glucuronic acid epierase | chr15q23 | Neurodevelopmental | KS and nIHH |
| *FLRT3* | Fibronectin like domain containing leucine rich transmembrane protein 3 | chr20p12.1 | Neurodevelopmental | KS and nIHH |
| *PROK2* | Prokineticin 2 | chr3p13 | Neurodevelopmental | KS and nIHH |
| *PROKR2* | Prokineticin receptor 2 | chr20p12.3 | Neurodevelopmental | KS, nIHH and AHH |
| *HS6ST1* | Heparin sulfate 6 O sulfutransferase | chr2q14.3 | Neurodevelopmental | KS and nIHH |
| *CHD7* | Chromodomain helicase DNA binding protein 7 | chr8q12.2 | Neurodevelopmental | KS and nIHH |
| *WDR11* | WD Repeat-Containing protein 11 | crh10q26.12 | Neurodevelopmental | KS and nIHH |
| *SEMA3A* | Semaphorin 3A | chr7q21.11 | Neurodevelopmental | KS |
| *SEMA3E* | Semapthorin 3E | chr7q21.11 | Neurodevelopmental | KS and nIHH |
| *TUBB3* | Tubulin beta 3 | chr16q24.3 | Neurodevelopmental | KS |
| *SOX10* | SRY box 10 | chr22q13.1 | Neurodevelopmental | KS |
| *OTUD4* | OUT domain containing protein 4 | chr4q31.21 | Neurodevelopmental | nIHH and ataxia |
| *FEZF1* | fez family zinc finger protein 1 | chr7q31.32 | Neurodevelopmental | KS |
| *RNF216* | Ring finger protein 216 | chr7p22.1 | Neurodevelopmental | nIHH and ataxia |
| *POLR3A* | Polymerase III RNA subunit A | chr10q22.3 | Neurodevelopmental | nIHH and ataxia |
| *POLR3B* | Polymerase III RNA subunit B | chr12q23.3 | Neurodevelopmental | nIHH and ataxia |
| *PNPLA6* | Patatin-like phospholipase domain-containing protein 6 | chr19p13.2 | Neurodevelopmental | nIHH and ataxia |
| *STUB1* | Stip1 homologous and U box containing protein 1 | chr16p13.3 | Neurodevelopmental | nIHH and ataxia |
| *DMXL2* | DMX like 2 | chr15q21.2 | Neuroendocrine | nIHH and polyendcrin3-polyneuropahty syndrome |
| *GNRH1* | GnRH 1 | chr8p21.2 | Neuroendocrine | nIHH |
| *GNRHR* | GnRH Receptor | chr4q13.2 | Neuroendocrine | nIHH and AHH |
| *KISS1* | Kisspeptin 1 | chr1q32.1 | Neuroendocrine | nIHH |
| *KISS1R* | Kisspeptin 1 receptor | chr19p13.3 | Neuroendocrine | nIHH |
| *TAC3* | Tachykinin 3 | chr12q13.3 | Neuroendocrine | nIHH |
| *TACR3* | Tachykinin receptor 3 | chr4q24 | Neuroendocrine | nIHH |
| *LEP* | Leptin | chr7q32.1 | Neuroendocrine | nIHH and obesity |
| *LEPR* | Leptin receptor | chr1p31.3 | Neuroendocrine | nIHH and obesity |
| *NR0B1* | Nuclear receptor subfamily 0, group B, member 1 | chrXp21.2 | Neuroendocrine | nIHH |

Known IGD genes and their characteristics including their description, chromosomal location, function and phenotype that are associated [illegible]. KS: Kallmann syndrome, nIHH: normosmic hypogonadotropic hypogonadism, AHH: adult-onset hypogonadotropic hypogonadism.

1.02 in

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Stamou MI et al, Ped Repro Endo 2017

# Non-Obstructive Azoospermia

- No sperm in the ejaculate due to *primary testicular failure*
  - Primary vs Secondary testicular failure
- Typical Findings: Elevated LH/FSH, Small Testis Volume
- Gold Standard Treatment: Microsurgical Testicular Sperm Extraction
- Also offered at some centers: FNA Mapping
- Limited data supporting use of EMT prior to mTESE in NOA

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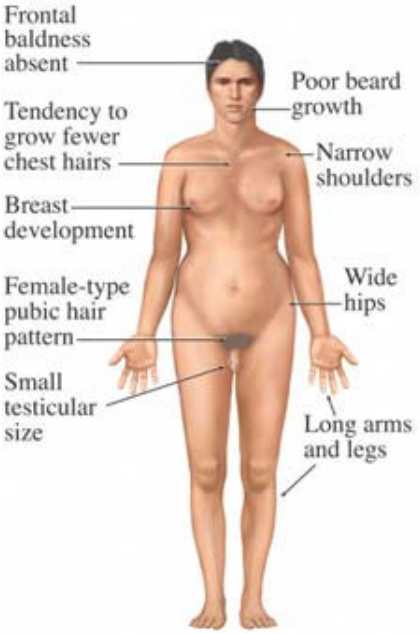
# Klinefelter's Syndrome

- Presence of extra X chromosome
- 1:500 to 1:1000 men
- 11% of NOA men
- Most common sex aneuploidy anomaly in men
- Results in substantial germ cell loss but there is significant phenotypic variance

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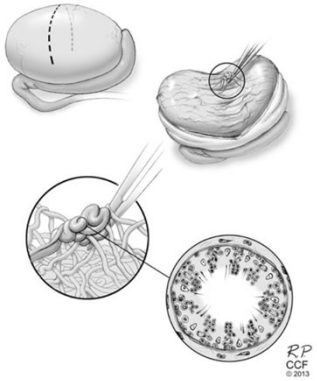
# Klinefelter's Syndrome

- Increased rates of Diabetes, lung disease/cancer, epilepsy, cerebrovascular disease, breast cancer, non-Hodgkins lymphoma
- Treatment:
  - Hypogonadism
  - Infertility
    - Surgical sperm retrieval rate ~44% (Corona et al, 2017)



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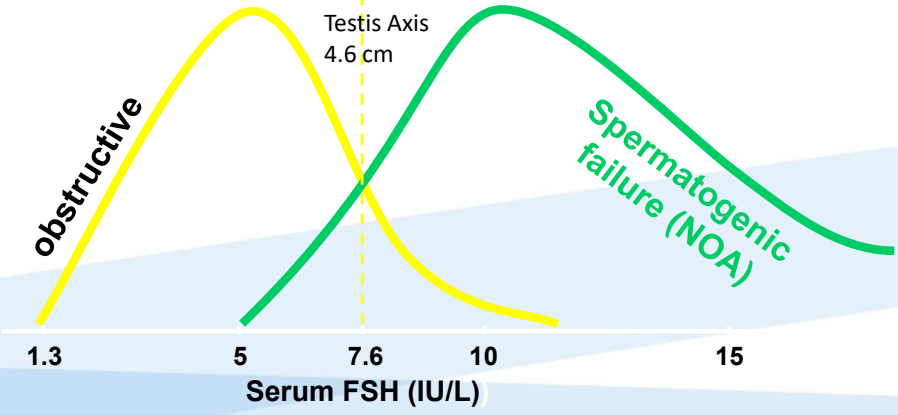
# Surgical Sperm Retrieval for NOA

Normal : obstruction  Elevated: spermatogenic failure

***FSH levels in azoospermic men undergoing testis biopsy***

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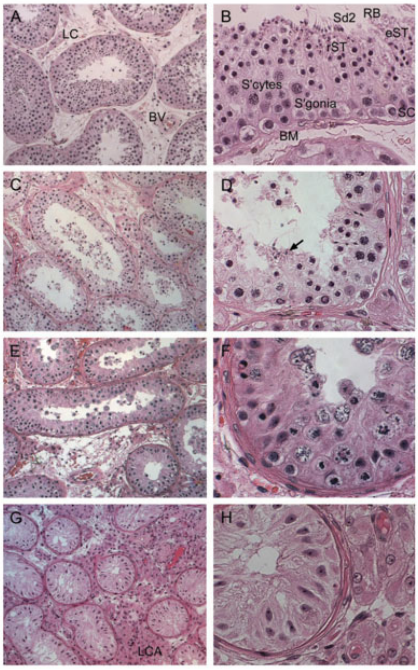
Schoor et al, J Urol 2002

# Pathology on Testis Biopsy

- Normal Spermatogenesis
- Hypospermatogenesis
- Maturation Arrest
- Sertoli Cell Only / Germ Cell Aplasia

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McLachlan RI, Human Reprod, 2007

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# Predictors of Surgical Sperm Retrieval

- FSH is not a predictor
- Testicular Volume is not a predictor
- Best predictor is histology on prior testis biopsy

| CONDITION | RETRIEVAL |
|---|---|
| Klinefelter syndrome | 68% |
| AZFc deletions | 70% |
| Sertoli cell only | 37% |
| Postchemotherapy | 53% |
| Cryptorchidism (postorchiopexy) | 74% |
| Maturation arrest | 40% |
| AZFa, AZFb deletions | 0% |

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# Evaluation of the Infertile Male

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# Indications for Evaluation

- Couples who fail to achieve a pregnancy after 12 months of regular, unprotected intercourse
- Earlier evaluation justified based on medical history of physical exam findings or female partner age > 35 years
- Evaluation justified if a man has a concern about their future fertility

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# Reproductive History

- Timing/Frequency of intercourse
- Duration of infertility, prior pregnancies
- Childhood illnesses (i.e. Mumps)
- Systemic medical conditions (i.e DM, upper respiratory infections)
- Prior surgeries
- Medications
- Sexual history
- Exposure to toxic chemicals, radiation, heat
- Family reproductive history
- Social History i.e illicit drug use, tobacco, ETOH

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# Physical Examination

- Location of urethral meatus
- Measurement of testes size
- Presence of vasa/epididymis
- Presence of absence of varicocele
- Secondary sex characteristics: body hair distribution, body habitus, breast development

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# Semen Analysis

- Cornerstone of male evaluation: “one or more” semen analyses

**TABLE 1**

**Lower limits of the accepted reference values for semen analysis.**

| Parameter | Reference value |
|---|---|
| On at least two occasions | |
| Ejaculate volume | 1.5 mL |
| pH | 7.2 |
| Sperm concentration | $15 \times 10^6$ spermatozoa/mL |
| Total sperm number | $39 \times 10^6$ spermatozoa/ejaculate |
| Percentage motility | 40% |
| Forward progression | 32% |
| Normal morphology | 4% normal |
| And | |
| Sperm agglutination | Absent |
| Viscosity | ≤2 cm thread after liquefaction |

*Note:* Data from World Health Organization, 2010 (10).

*Practice Committee. Evaluation of the infertile male. Fertil Steril 2015.*

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# Endocrine Evaluation

Indications (ASRM Committee Opinion & AUA Best Practice Statement & AUA Guidelines):

- Oligo or Azoospermia
- Impaired libido, ED
- Other clinical findings suggesting a specific endocrinopathy
- Failed ART Cycles, Recurrent Pregnancy Loss

Minimal Evaluation: FSH, T

Also commonly ordered: LH, prolactin, estradiol, TSH

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# Counseling

Indications (ASRM/AUA Guideline: Diagnosis and Treatment of Infertility in Men)

- Counsel infertile men of health risks associated with abnormal sperm production
- Infertile men with specific identifiable causes should be informed of relevant associated health conditions
- Couples with advanced paternal age (men over 40) - increased risk of adverse health outcomes for their offspring
- Discussed risk factors associated with male infertility, albeit weak data

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# Additional Testing

## Post Orgasmic Urinalysis

- Consider in setting of absent ejaculate, low volume ejaculate, high risk for retrograde ejaculation with oligospermia
- No defined cut off for normalcy in non-azoospermic patients

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# Additional Testing

## Ultrasonography of the Scrotum

- Not routinely recommended in work-up of infertile male
- Recommended in setting of difficult exam or concern for testicular mass

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Brannigan RE, AUA/ASRM guideline (2024). J Urol.

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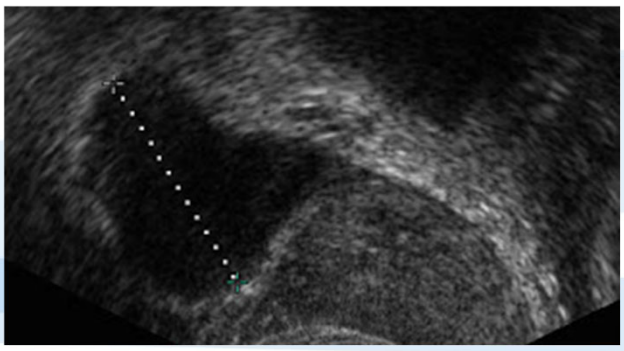
# Additional Testing

## Transrectal Ultrasound of the Prostate

- Assessment of ejaculatory duct obstruction
- "May recommend TRUS (or pelvic MRI) in males with SA suggesting of EDO i.e. acidic, azoospermic, low volume, normal T, palpable vasa"
- Seminal Vesicle AP diameter > 1.5 cm: consistent with EDO



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Brannigan RE, AUA/ASRM guideline (2024). J Urol.

# Additional Testing

- Antisperm Antibodies – consider in isolated asthenospermia, sperm agglutination
- DNA Fragmentation – insufficient evidence to support use during initial workup
  - Recommended for recurrent pregnancy
  - Can consider testicular sperm retrieval in patients with elevated DNA fragmentation
- Reactive Oxygen Species - insufficient evidence to support use
- Quantification of Leukocytes - evaluate for infection if elevated
- Sperm Viability Testing

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Brannigan RE, AUA/ASRM guideline (2024). J Urol.

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# Genetics

Karyotype

Indicated in men with NOA or conc less than 5M/ml "when accompanied by elevated FSH, testicular atrophy or diagnosis of impaired sperm production", *recurrent pregnancy loss*

Y-Chromosome Microdeletions

Indicated in men with NOA or conc less than 1M/ml "when accompanied by elevated FSH, testicular atrophy or diagnosis of impaired sperm production"

Cystic Fibrosis Gene mutations

Indicated in men with CBAVD, CUAVD, idiopathic obstructive azoospermia

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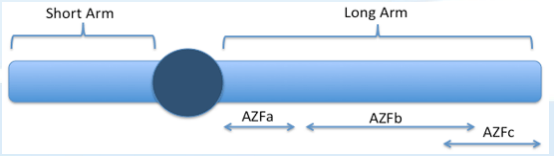
Brannigan RE, AUA/ASRM guideline (2024). J Urol.

# Y Microdeletion

- Occur in the AZF region of long arm of the Y chromosome
  - AZFa – poor prognosis
  - AZFb – poor prognosis
  - AZFc – can proceed to MTESE
- Sons of individuals with Y microdeletions will inherit the abnormality and have infertility

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# Treatment of the Infertile Male: Medical

- Clomiphene Citrate
- Anastrozole
- HCG/FSH
- Antioxidants (existing data inadequate to support use)

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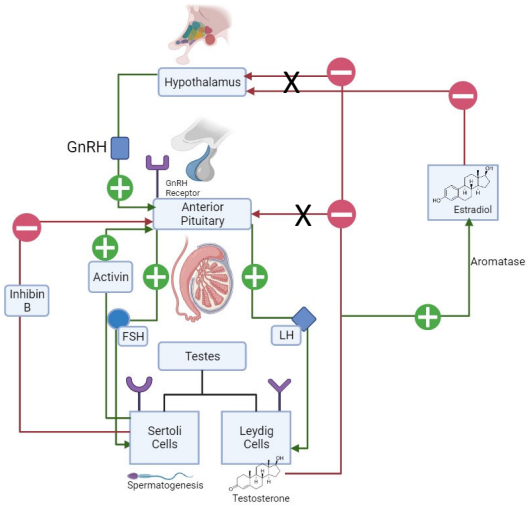
Brannigan RE, AUA/ASRM guideline (2024). J Urol.

# Clomiphene Citrate

- Selective Estrogen Receptor Modulator that blocks negative feedback at the level of the hypothalamus and the pituitary
- ↑ LH, FSH, T
- Bridges et al: meta-analysis revealed mean increase in concentration of 7.7M/ml

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Bridges et al, Urol Practice 2015

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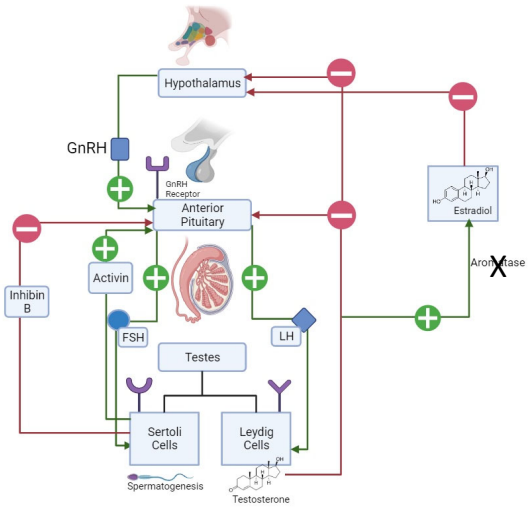
# Anastrozole

- ↓ estrogen production by reversible inhibition of aromatase
- Best used in men with T/E ratio of < 10:1
- Raman & Schlegel: 5.5M/ml to 15.6M/ml
- Others: Letrozole, Testolactone

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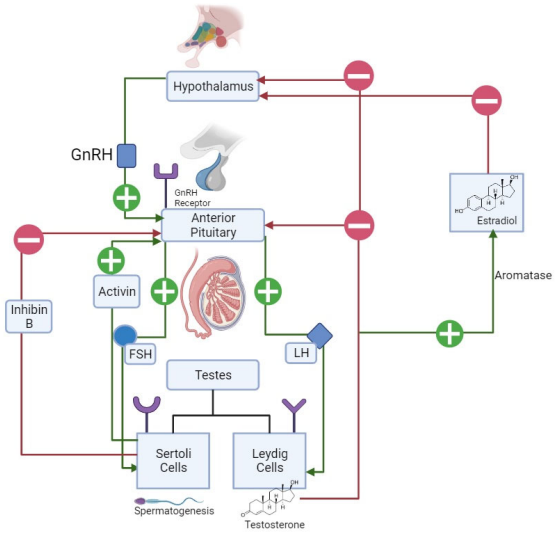
Raman DJ & Schlegel, J Urol 2002

# HCG

- LH analog derived from urine or recombinant sources
- Increases intra-testicular testosterone levels thereby improving spermatogenesis
- Only FDA approved treatment for male infertility

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Raman DJ & Schlegel, J Urol 2002

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# Gonadotropin Replacement in Hypogonadotropic Hypogonadism

- **First treat LH deficiency**: cheaper, occasionally is only agent required
  - Human chorionic gonadotropin (hCG) 1500–2000 IU 2–3X weekly for 18-24 weeks (hCG has biologically equivalent action to LH and centrally stimulates release of LH of FSH). Goal: T > 300
- **If necessary, add FSH** until pregnancy is achieved
  - Human menopausal gonadotropin (hMG) 75 IU 2-3X weekly (contains FSH+LH)
  - Recombinant FSH (rhFSH, ex. Gonal-F) 37.5-75 IU 2-3X weekly
- **Outcomes**
  - Increased testicular volume (average increase from 4 to 12 cc)
  - Induction of sperm production (goal > 5 million/ml)
  - Natural conception often possible

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# Ejaculatory Dysfunction

- Premature Ejaculation
  - SSRIs, topical lidocaine
- Retrograde Ejaculation
  - Alpha Agonists (Phenylephrine, Imipramine)
  - Alkalinize Urine with Sodium Bicarb and harvest sperm from urine for intrauterine insemination
- Anejaculation
  - Penile Vibratory Stimulation, Electroejaculation
  - Surgical sperm harvest

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Gilija I, Eur Urol 1994

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# Treatment of the Infertile Male: Surgical

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# Diagnostic Testicular Biopsy

- Should not be routinely performed to differentiate between azoospermia and non-obstructive azoospermia
- Can consider diagnostic testicular biopsy in men with normal testicular size, at least one palpable vasa, normal FSH

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Brannigan RE, AUA/ASRM guideline (2024). J Urol.

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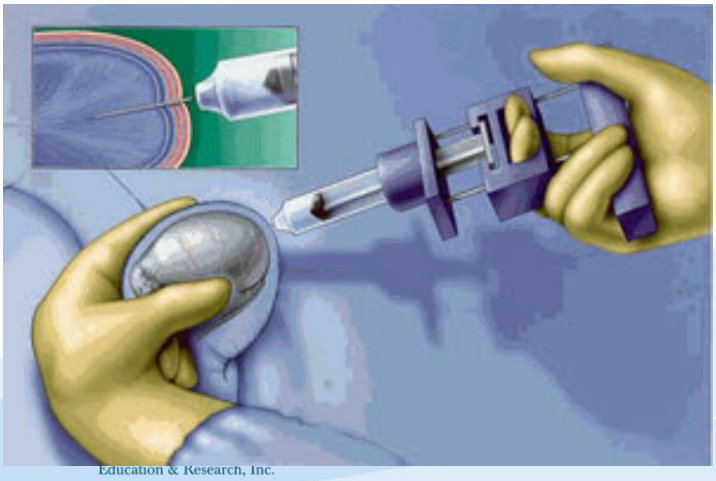
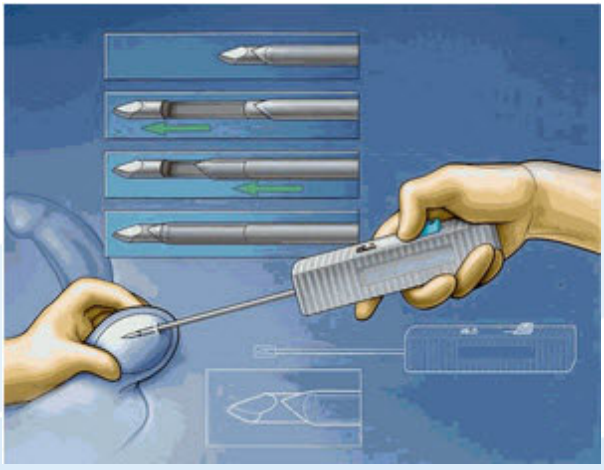
# Diagnostic Testicular Biopsy





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# Varicocele: Who Should be Treated?

- Indications for Repair (AUA & ASRM Best Practice Statement)
  - Palpable Varicocele (NOT subclinical)
  - Documented Infertility
  - Female with normal or potentially correctable infertility
  - Abnormal semen analysis
  - Adolescents with varicocele and ipsilateral atrophy

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Practice Committee of American Society for Reproductive Medicine. Report on varicocele and infertility. Fertil Steril 2008.

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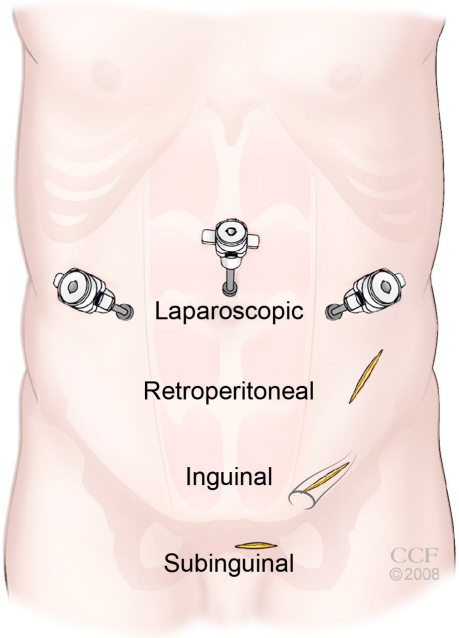
# Varicocele Ligation

- Percutaneous or Surgical Approach

- Surgical Approach:
  - Open Subinguinal
  - Open Inguinal
  - Laparoscopic
  - Retroperitoneal

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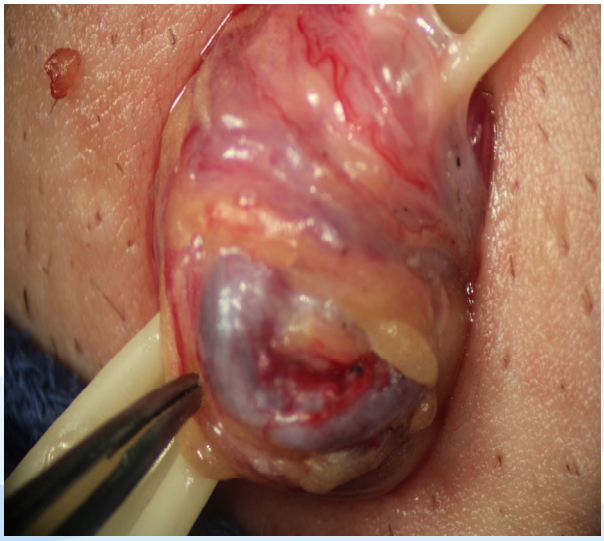
# Varicocele Ligation



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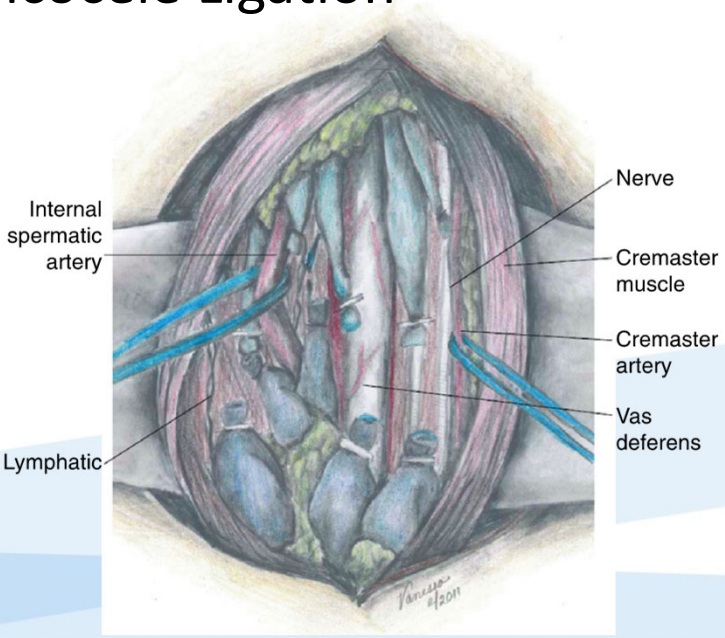
# Varicocele Ligation

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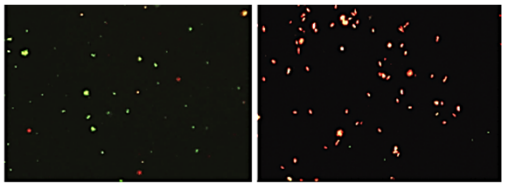
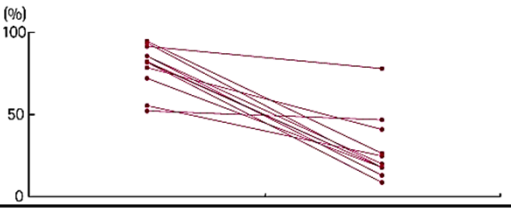
# Varicocele Outcome

- Meta-analysis of 17 studies (Agarwal et al, Urology 2007)
  - sperm density increased by 9.7 million/mL
  - motility increased by 9.9%
  - WHO sperm morphology improvement of 3%
  - Improved DNA fragmentation






| | pre-operative | post-operative | p |
|---|---|---|---|
| TUNEL positive, % | 79.6 ± 13.6 | 27.5 ± 19.4 | <0.001 |

Value are given as means ± SD.

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Sakamoto Y, BJU Int 2008

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# Varicocele Outcomes

| STUDY | PATIENTS (No.) | VARICOCELE GRADE | PREGNANCY RATE (%) TREATMENT | PREGNANCY RATE (%) CONTROL | ODDS RATIO |
|---|---|---|---|---|---|
| Nilsson (1979) | 96 | III | 8 | 18 | 0.394 |
| Baker (1985) | 651 | I-III | 47 | 21 | 3.37 |
| Madgar (1995) | 45 | II-III | 60 | 40 | 13.5 |
| Nieschlag (1998) | 125 | I-III | 29 | 25 | 1.20 |
| Grasso (2000) | 68 | I | 3 | 6 | 0.485 |
| Krause (2002) | 67 | I-III | 16 | 18 | 0.875 |

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# Surgical Management of Obstructive Azoospermia

- Surgical correction of obstruction
- Retrieval of sperm for IVF/ICSI

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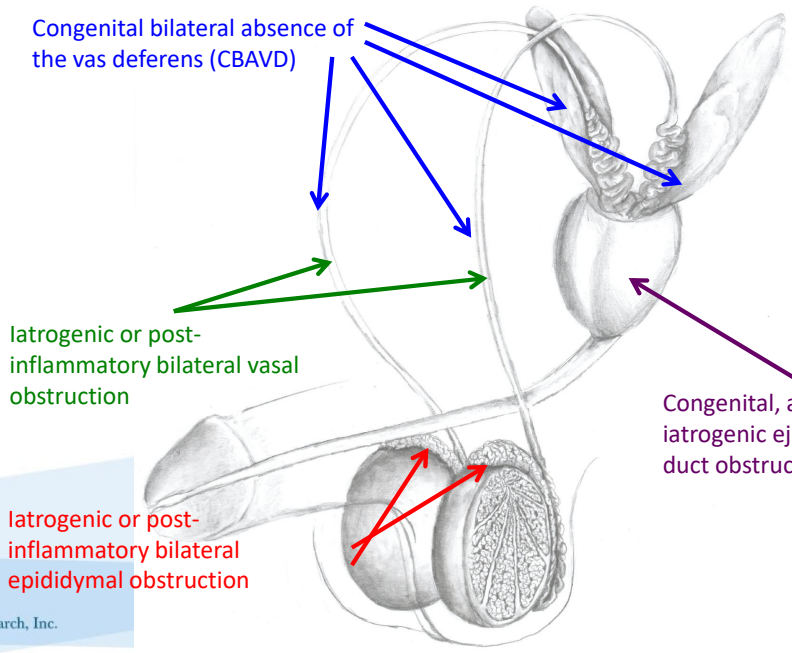
# Obstructive Azoospermia

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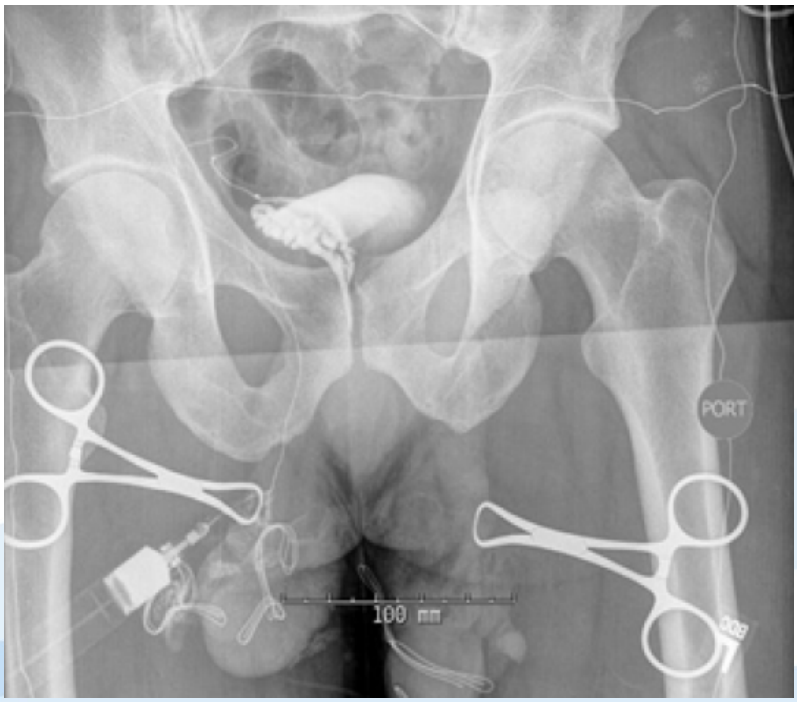
# Vasogram

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# TURED

- Used to treat ejaculatory duct obstruction
- Several techniques have been described
  - Injection of contrast dye or indigo carmine into the SV under TRUS guidance followed by resection
  - Resection done using cutting current at the verumontanum
- Outcomes: 60-85% improvement in semen parameters, 13-27% pregnancy rate (El Assmy et al 2012, Tu et al 2011)
- Complications: Reflux of urine into the Ejac Ducts

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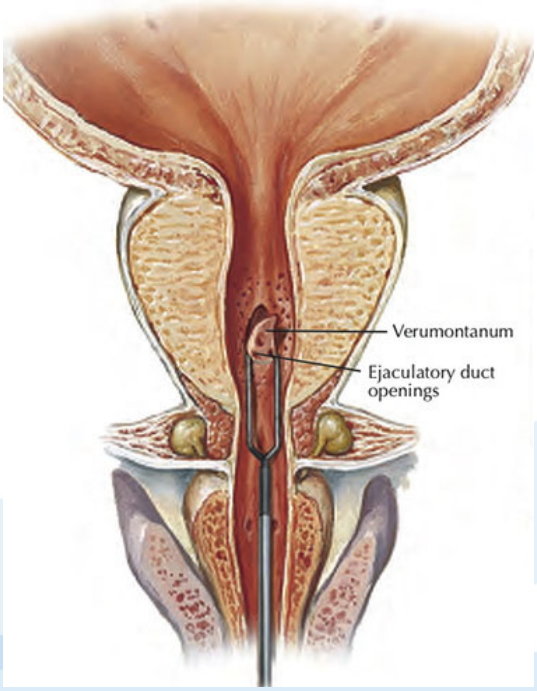
# TURED

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# Vasectomy Reversal

- "Microsurgical reconstruction of the reproductive tract is preferable to sperm retrieval with IVF/ICSI in men with prior vasectomy if the obstructive internal is less than 15 years and no female fertility risk factors are present" – AUA Best Practice Statement

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# Vasectomy Reversal: Predictors of Success

- Obstructive Interval
- Sperm granuloma presence
- Surgeon experience
- Use of clips as compared to suture
- Quality of vasal fluid
- Female fertility
- Same female partner

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Bolduc et al, Can Urol Assoc 2007
Belker AM et al J Urol 1991

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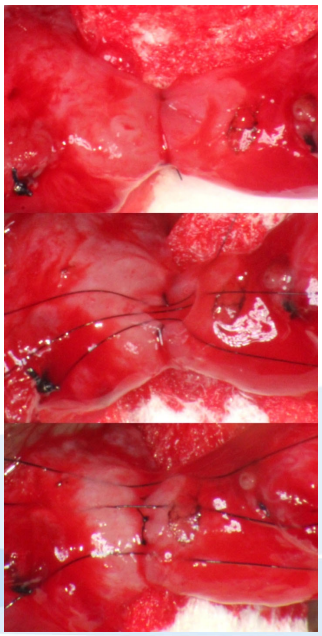
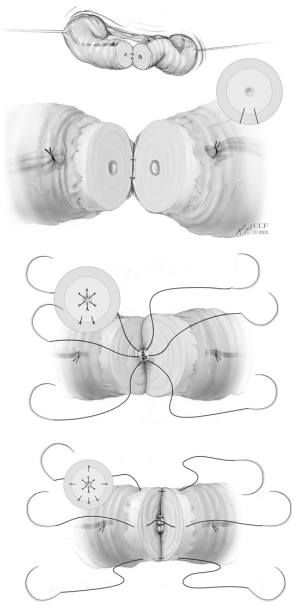
# Vasovasostomy





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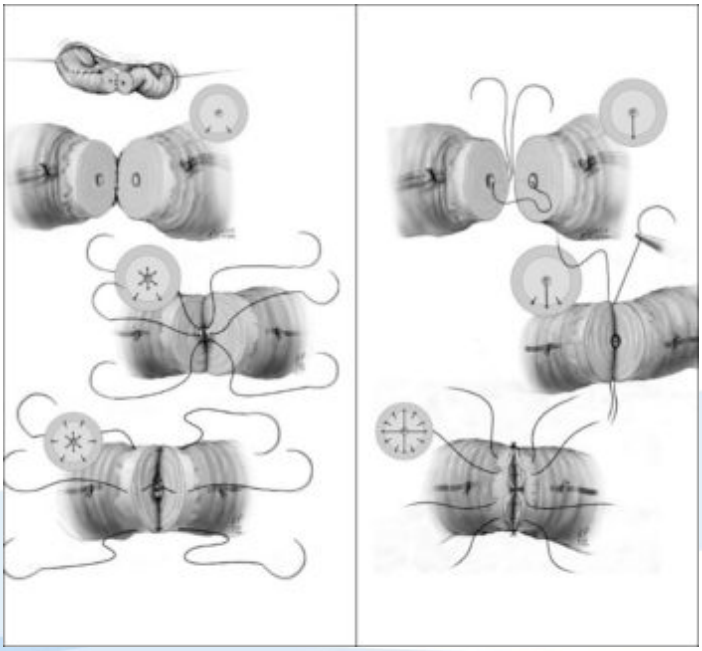
# Vasovasostomy

- Modified 1-layer technique equivalent success to 2-layer technique (Herrel et al, 2014)
- Microsurgical > Loupe-Assisted



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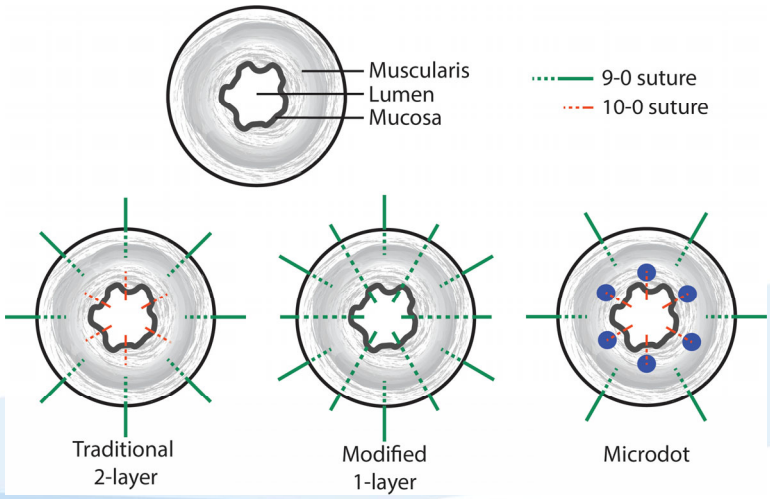
# Vasovasostomy

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# Vasovasostomy

Vasal Fluid and Surgical Approach

| Fluid characteristics | Microscopic findings | Surgery indicated |
|---|---|---|
| 1. Copious, clear | No sperm | *VV* |
| 2. Copious, cloudy | Sperm w/ tails | *VV* |
| 3. Copious, creamy, yellow | Sperm heads | *VV* |
| 4. Thick, toothpaste-like | No sperm | *EV* |
| 5. White, thin | No sperm | *EV* |
| 6. Dry or just "sweat" | No sperm | *EV* |

VV- vasovasostomy
EV- epididymovasostomy

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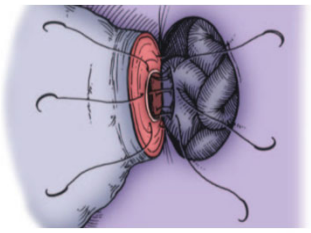
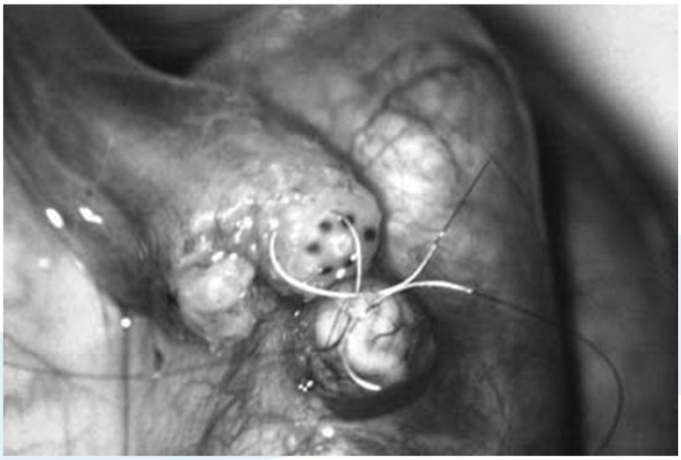
# Vasoepididymostomy





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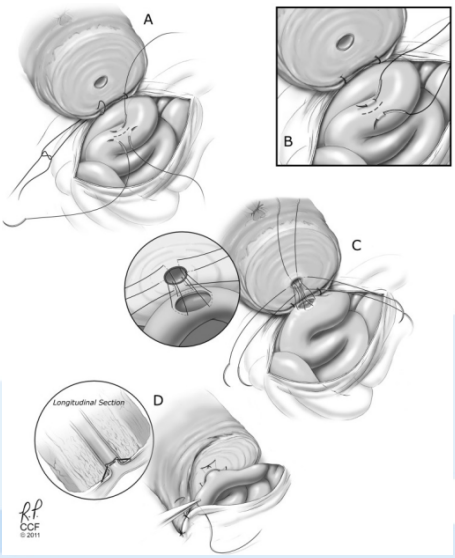
# Vasoepididymostomy

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# Vasectomy Reversal Outcomes

- Vasovasostomy Study Group (Belker at al, 1992):
  - 1469 men undergoing microsurgical VR at 5 institutions
  - 86% overall patency rate, 52% overall pregnancy rate
  - Patency rates varied by obstructive interval
    - < 3 years: 97%
    - 3 – 8 years: 88%
    - 9 – 14 years: 79%
    - > 15 years: 71%
  - Repeat procedures: 75% success
    - > 75% will require VE (Hernandez et al, 1999)

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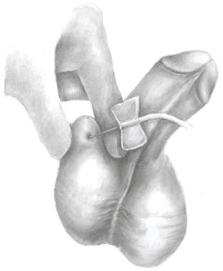
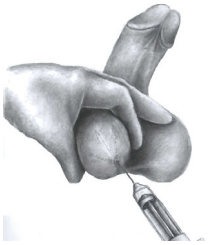
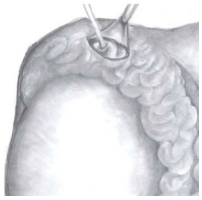
# Surgical Management of Obstructive Azoospermia



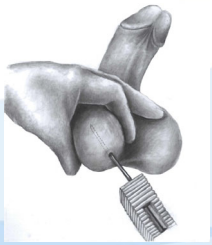
PESA



FNA



MESA



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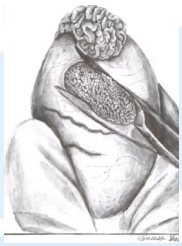

TESE

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Stahl PJ et al. Human Fertility, Human Press Inc., New York, N

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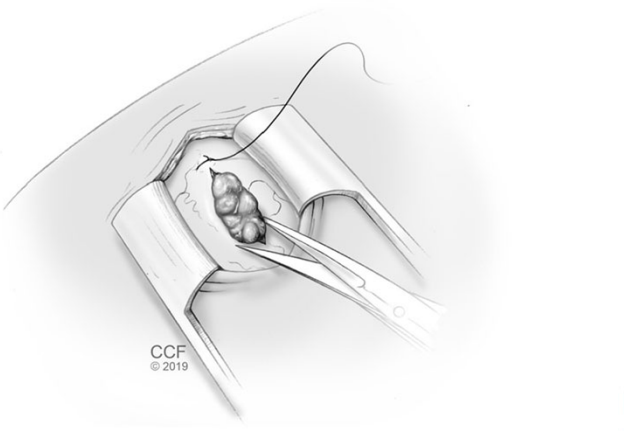
# Surgical Sperm Retrieval for NOA

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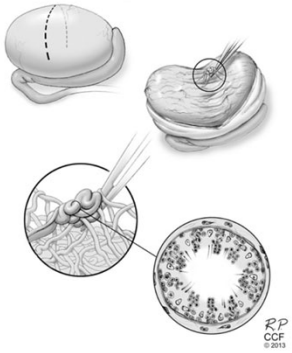


Micro TESE

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# Assisted Reproductive Techniques

- Total Motile Sperm Count generally determines candidacy for ART
  - Concentration x Volume x Motility (%)
- Intrauterine Insemination:  Introduction of motile sperm in to the uterus with a catheter
  - TMSC > 5 Million
- In Vitro Fertilization
  - TMSC > 1 Million
- Intracytoplasmic Sperm Injection
  - Very few sperm

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# Hypogonadism
# Testosterone Deficiency

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# Physiology of Testosterone

- 90% of Circulating Testosterone is synthesized from Leydig Cells in the Testis
- 10% synthesized in the adrenal gland
- Metabolized to DHT by 5-alpha reductase and to estradiol via aromatase
- Critical to function of muscle, bone, skin, spermatogenesis, sexual function, brain, peripheral nerves, hematopoiesis
- Biologically active T: Free T (2-3%) and albumin-bound T

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# Symptoms/Signs of Hypogonadism

Most Specific

- Low libido
- Decreased Erections
- Gynecomastia
- Pubic hair Loss
- Testicular shrinkage
- Reduced bone density
- Reduced muscle strength
- Hot flashes, sweats

Less Specific

- Decreased energy
- Depressed mood
- Decreased concentration
- Mild anemia
- Increased fat mass

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Wu et al, NEJM 2010

# Diagnosis of Hypogonadism

- Two total testosterone measurements drawn in the early morning
- Proposed cut off of 300 ng/ml
  - Significant assay variability, intra-individual variation, reference ranges
- Must have symptoms or signs to meet the criteria for treatment for testosterone deficiency (exceptions on later slide)
- Free T (calculated or assay) in patients with low normal T, condition that might elevate SHBG, and symptoms

American Urological Association Education & Research, Inc.

Mulhall JP, Evaluation and management of testosterone deficiency: AUA guideline. J Urol 2018.

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# Diagnosis of Hypogonadism

- Measure LH if Testosterone is low
  - Endo Society Guidelines: LH & FSH
- Measure prolactin if Testosterone is low and LH is low/low normal
- Measure Estradiol if gynecomastia/breast symptoms

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Mulhall JP, Evaluation and management of testosterone deficiency: AUA guideline. J Urol 2018.
Endocrine Society Clinical Practice Guideline (2018)

# Primary vs. Secondary Hypogonadism

- Primary
  - Failure of the testis to produce normal levels of testosterone despite sufficient LH
- Secondary
  - Failure at the hypothalamic or pituitary level leading to insufficient testosterone levels

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Mulhall JP, Evaluation and management of testosterone deficiency: AUA guideline. J Urol 2018.

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# Primary vs. Secondary Hypogonadism

**Table 1. Classification of Hypogonadism and Causes of Primary and Secondary Hypogonadism**

| Primary Hypogonadism | Secondary Hypogonadism |
|---|---|
| **ORGANIC** | |
| KS | Hypothalamic/pituitary tumor |
| Cryptorchidism, myotonic dystrophy, anorchia | Iron overload syndromes |
| Some types of cancer chemotherapy, testicular irradiation/damage, orchidectomy | Infiltrative/destructive disease of hypothalamus/pituitary |
| Orchitis | Idiopathic hypogonadotropic hypogonadism |
| Testicular trauma, torsion | |
| Advanced age | |
| **FUNCTIONAL** | |
| Medications (androgen synthesis inhibitors) | Hyperprolactinemia |
| End-stage renal disease[a] | Opioids, anabolic steroid use, glucocorticoids |
| | Alcohol and marijuana abuse[a] |
| | Systemic illness[a] |
| | Nutritional deficiency/excessive exercise |
| | Severe obesity, some sleep disorders |
| | Organ failure (liver, heart, and lung)[a] |
| | Comorbid illness associated with aging[a] |

[a]Combined primary and secondary hypogonadism, but classified to usual predominant hormonal pattern. Adapted with permission from Bhasin *et al.* (7).

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Endocrine Society Clinical Practice Guideline (2018)

# Testosterone Replacement

- Prior to Initiation of Therapy
  - Hemoglobin/Hematocrit
  - PSA if over 40
- Endocrine Society Guidelines:
  - Contraindications: men with beast/prostate cancer, palpable prostate nodule, PSA > 4 ng/ml, PSA > 3 ng/ml with high risk of prostate cancer, elevated Hct, untreated severe OSA, severe LUTS, uncontrolled heart failure, MI or stroke within the last 6 months, thrombophilia

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# Testosterone Replacement

- Primary Goal is SYMPTOM improvement
  - Exceptions: HIV-infected men with weight loss, osteoporosis with significant T deficiency
  - AUA Guidelines: Consider T measurement in men with unexplained anemia, bone density loss, diabetes, exposure to chemotherapy, exposure to testicular radiation, HIV/AIDS, chronic narcotic use, male infertility, pituitary dysfunction, and chronic corticosteroid use
- Ensure adequate dosage and re-evaluate to determine whether to continue treatment

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Mulhall JP, Evaluation and management of testosterone deficiency: AUA guideline. J Urol 2018.

Endocrine Society Clinical Practice Guideline (2018)

# Benefits of Treatment

- Improved glycemic control
- Improved bone density
- Improved sexual function
- Improved lean body mass
- Less fatigue
- Improved mood

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Yassen et al, Diabetes Care 2019
Snyder et al, NEJM 2016

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# Risks of Treatment

- Fertility Impairment
- Prostate Cancer
  - Controversial
- Venothrombolic Events
  - Data is inconclusive
- Erythrocytosis (Hct > 54%) most frequently reported adverse event – treated with dose reduction, therapeutic phlebotomy
- Acne, Oily Skin
- Gynecomastia

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Endocrine Society Clinical Practice Guideline (2018)

# Risks of Treatment – Major Adverse Cardiovascular Events

Original Investigation

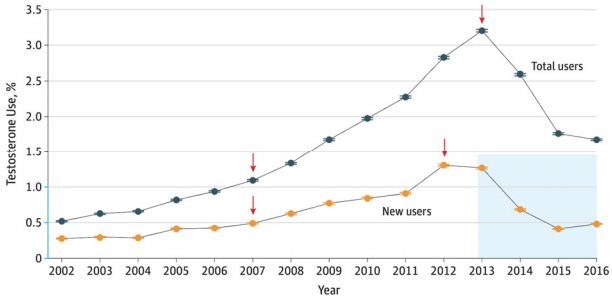
**Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels**

Rebecca Vigen, MD, MSCS; Colin I. O'Donnell, MS; Anna E. Barón, PhD; Gary K. Grunwald, PhD; Thomas M. Maddox, MD, MSc; Steven M. Bradley, MD, MPH; Al Barqawi, MD; Glenn Woning, MD; Margaret E. Wierman, MD; Mary E. Plomondon, PhD; John S. Rumsfeld, MD, PhD; P. Michael Ho, MD, PhD

**IMPORTANCE** Rates of testosterone therapy are increasing and the effects of testosterone therapy on cardiovascular outcomes and mortality are unknown. A recent randomized clinical trial of testosterone therapy in men with a high prevalence of cardiovascular diseases was stopped prematurely due to adverse cardiovascular events raising concerns about testosterone therapy safety.

**OBJECTIVES** To assess the association between testosterone therapy and all-cause mortality, myocardial infarction (MI), or stroke among male veterans and to determine whether this association is modified by underlying coronary artery disease.

Editorial page 1805
Author Video Interview at jama.com
JAMA Patient Page 1872
Supplemental content at jama.com

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Vigen et al JAMA 2013

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- Retrospective analysis of > 8000 men with T < 300 ng/dl who underwent coronary angiography
- Reported absolute rate of MACE
- Relative rate lower in T-treated group
- 100 women included
- Several corrections to article – request for retraction by JAMA

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Vigen et al JAMA 2013

## Risks of Treatment – Major Adverse Cardiovascular Events

- Several studies published to date showing 1.5-2x increased risk of MACE in hypogonadal men
  - Correlation or Causation?

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Vigen et al JAMA 2013

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## Formulations of Testosterone Replacement

- Injections (IM or subcutaneous) – short and long acting
- Topical (gels/creams) – can transfer to partner, less erythrocytosis
- Patch – site irritation
- Buccal – BID dosing, gum irritation
- Pellets – office procedure to place, extrusion, hematoma
- Nasal - BID or TID, epistaxis, fertility preservation
- Oral – BID or TID, with fatty meals

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# Monitoring on TRT

- Follow-up Testosterone level to ensure normalization
- Measure T, CBC, PSA every 6-12 months
- Do not continue treatment if no symptom or sign improvement (exceptions noted previously)

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# Monitoring on TRT

| | | | |
|---|---|---|---|
| Hemoglobin / Hematocrit | Recommendation:<br>Measure baseline levels to ensure pre-treatment level is <50% | Optional:<br>Clinical judgment is recommended to determine need for hemoglobin/ hematocrit monitoring depending on baseline levels and the duration of time required to reach therapeutic target levels | Recommendation:<br>Measure every 6-12 months, or sooner depending on prior values, to maintain hematocrit levels below 54% |
| PSA | Recommendation:<br>Measure in testosterone deficient patients over 40 years of age and in those testosterone deficient patients with a history of prostate cancer | Not Recommended | Recommendation:<br>In men without a history of prostate cancer, testing should be conducted utilizing a shared decision-making approach, in accordance with the AUA Early Detection of Prostate Cancer Guideline<br><br>Prostate cancer patients on testosterone therapy should have their PSA levels monitored on the same schedule as men without testosterone deficiency; however, clinicians may choose to increase the frequency of testing |

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Mulhall JP, Evaluation and management of testosterone deficiency: AUA guideline. J Urol 2018.

# Question #1

A 29 yo male presents for fertility evaluation. His wife is 28 with normal work-up. He has a hx of L inguinal hernia repair as an infant. SA demonstrates an ejaculate volume of 1.2 ml and azoospermia. PE reveals testis size of 26 cc (R), 10 cc (L). His R vas is not palpable, his L vas is palpable. The next step is:

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# Question 2:

A 32 year old male has the following semen parameters: 4M/ml, 30% motility, ejaculate volume 2 ml. He has a Grade 2 varicocele. His wife is 39 years old with irregular cycles. The next best steps is:

A. Hormone Profile
B. Varicocele Repair
C. Testicular Sperm Extraction
D. Referral of Wife to REI

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# Question 3:

A 28 year old male presents with azoospermia. His exam reveals testis size of 10 cc bilaterally, palpable vas deferens. His history is unremarkable. His FSH is 18, LH 11, Testosterone 410. The next step is:

A. Microsurgical Testicular Sperm Extraction
B. Testicular Sperm Aspiration
C. Genetic Testing
D. Empiric Treatment with Clomiphene Citrate

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