Male Factor Infertility

Monica Moore, MSN, RNC

PART 1: DIAGNOSIS AND TREATMENT

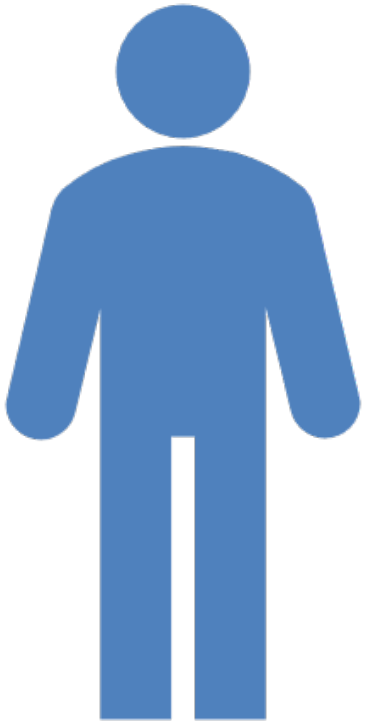
Objectives

- Review the incidence and prevalence of male factor infertility
- Discuss the structure of the sperm cell and spermatogenesis

Principle of Male Fertility

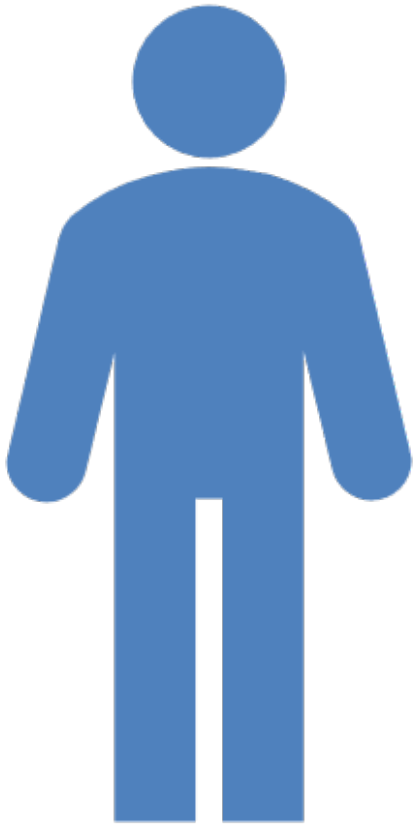
Healthy sperm must be adequately produced and must have the appropriate anatomy to be delivered in order for fertilization to take place

INCIDENCE AND PREVALENCE OF MALE FACTOR INFERTILITY

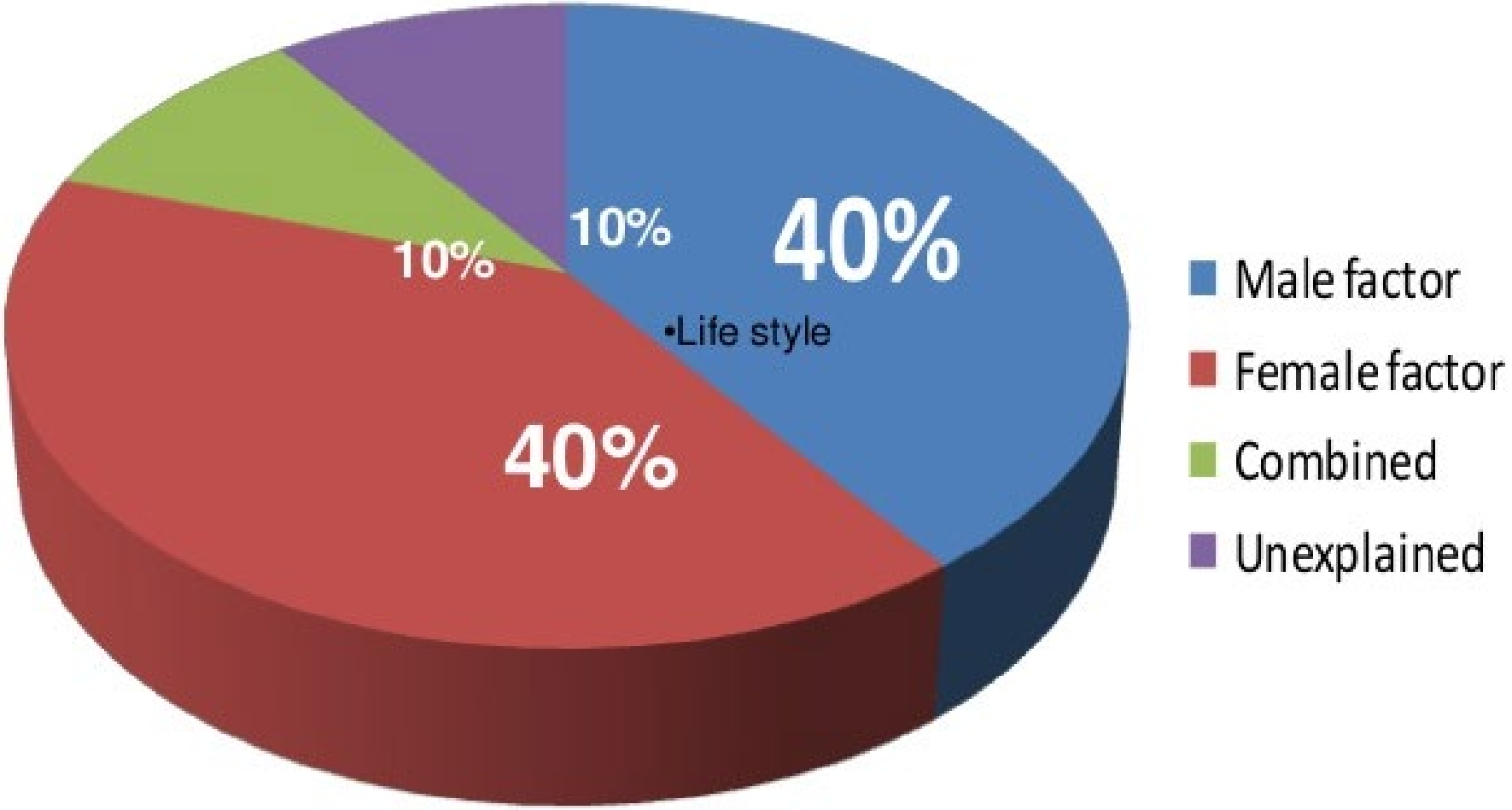


Incidence and Prevalence of Male Factor Infertility

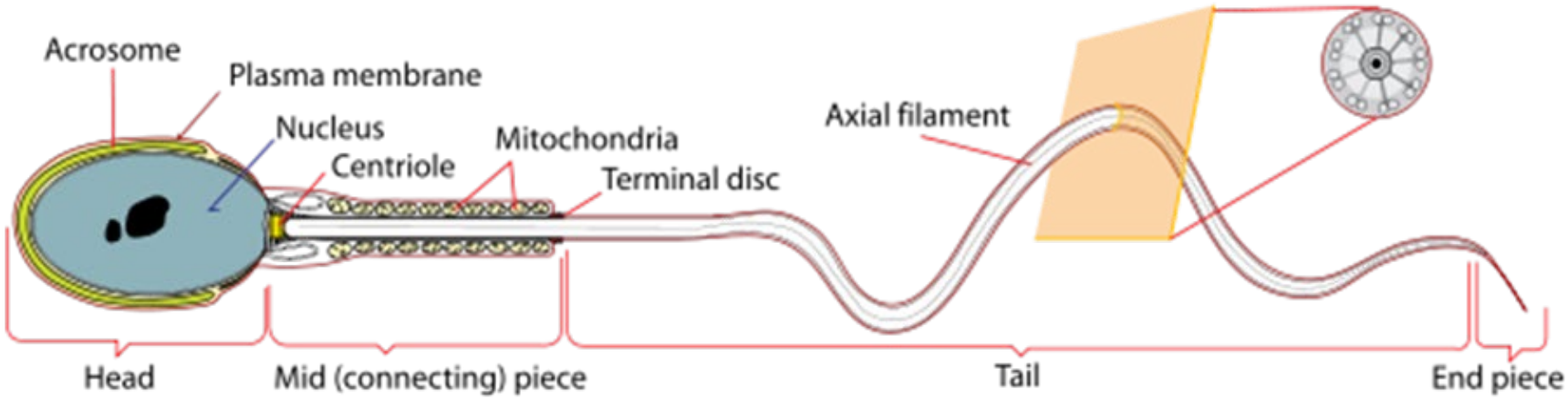
- 10% of population (or 1/10 couples) trying to conceive suffer from infertility
- In 1/3 cases the ‘culprit’ is the male and in another 1/3 cases, the male and female both contribute to infertility
- So, in fully 50% of couples who are trying to conceive, there is a male factor component.
- The earlier the diagnosis, the easier it is to formulate a plan.



Causes of infertility



Anatomy of a Sperm

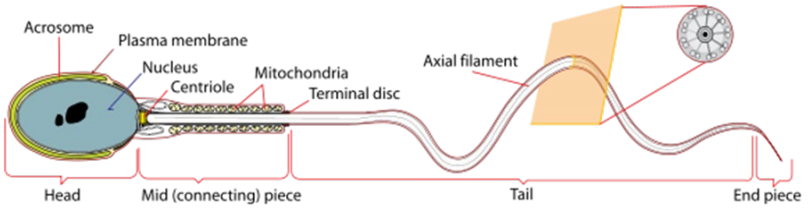


Basic Principles of Sperm Function

- Must reach and penetrate the zona
- Must “work” once it’s there to activate the ovum and resume cell division
- Is the paternal contribution to the zygote
- Determines the sex of the embryo

Anatomy of a Sperm

- Goal is simply to swim up through female reproductive tract, penetrate egg and deliver paternal DNA
- Sperm cells have very little cytoplasm
  - So might be missing some protective mechanisms that other cells have
  - Rely on the seminal fluid for protection and nutrients

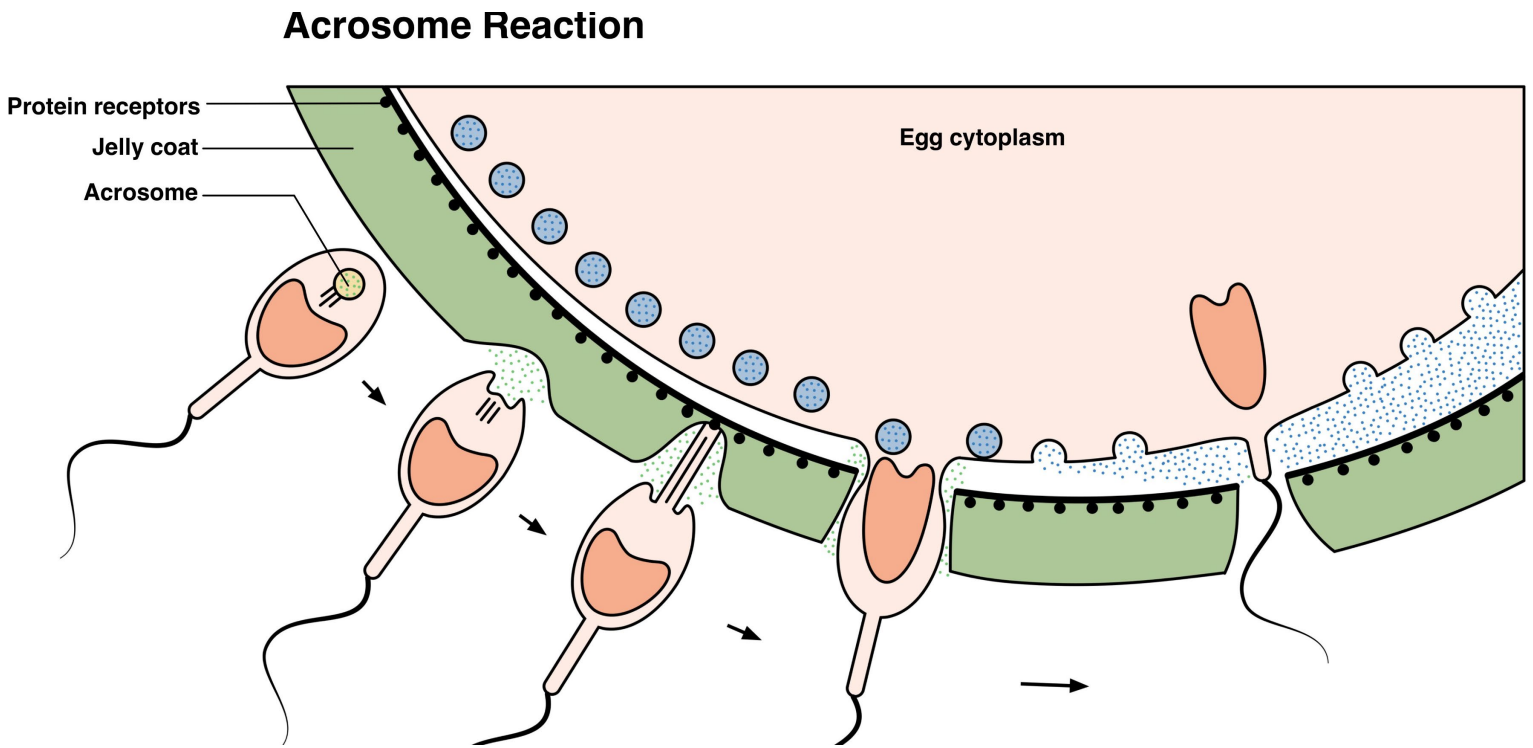


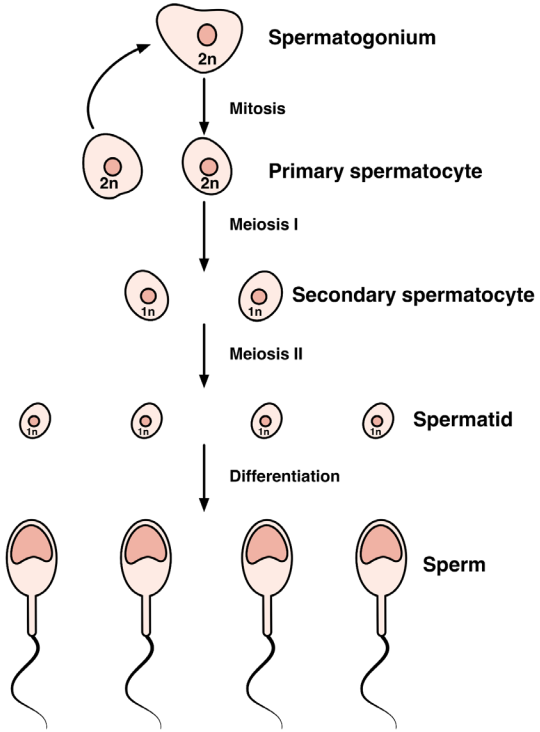
Capacitation

- Removal of cholesterol
- Increases permeability to Ca which increase cAMP levels which increase motility

Acrosome Reaction

- Acrosome-organelle that develops over the head in the spermatozoa
- Contains digestive enzymes-break down zona pellucida
- Shedding of it is called acrosome reaction
  - Stimulated by follicular fluid or progesterone?

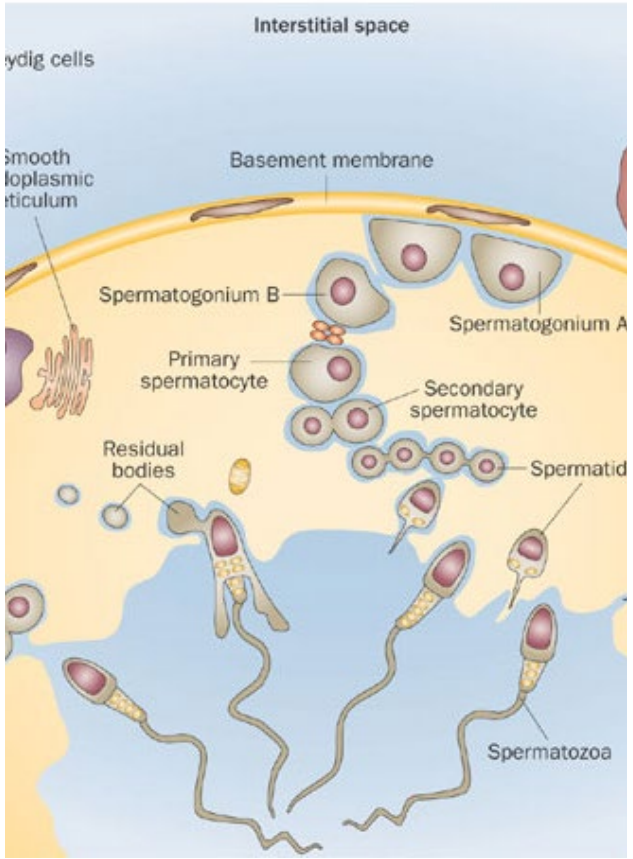




SPERMATOGENESIS

Spermatogenesis

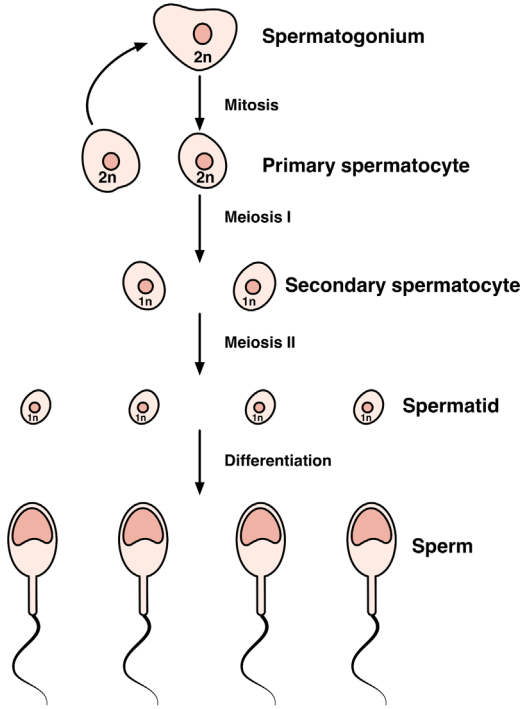
- Sperm are produced in the seminiferous tubules in the testes.
- Spermatogenesis is the cellular division and transformation that produces male haploid germ cells from diploid spermatogonial stem cells.



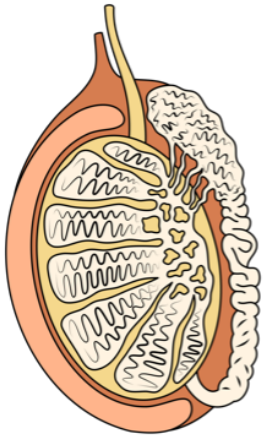
www.nature.com

Spermatogenesis

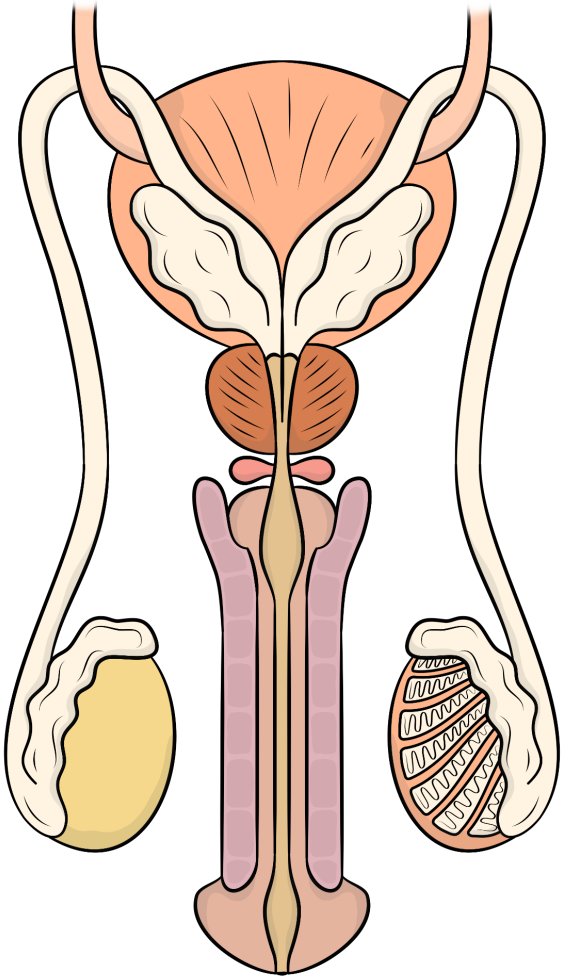
- Continuous sperm production is dependent upon several intrinsic (Sertoli cells and germ cells) and extrinsic (hormonal) factors.
  - Meiosis I yields haploid secondary spermatocytes.
  - Meiosis II yields four equalized spermatids that migrate toward the lumen where fully formed spermatozoa are finally released
- Spermiogenesis is when spermatids disengage excess cytoplasm and become elongated with tails

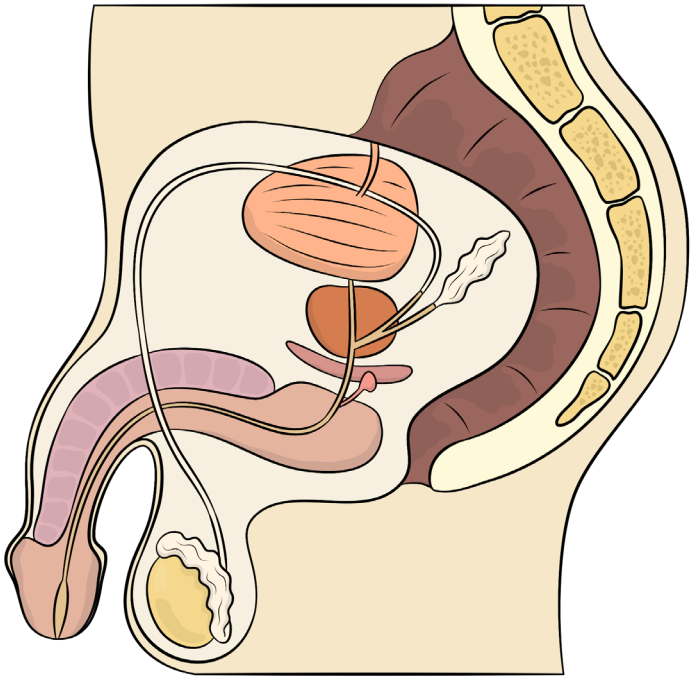


PART 2: MALE ANATOMY AND STRUCTURES AND THE SPERM JOURNEY



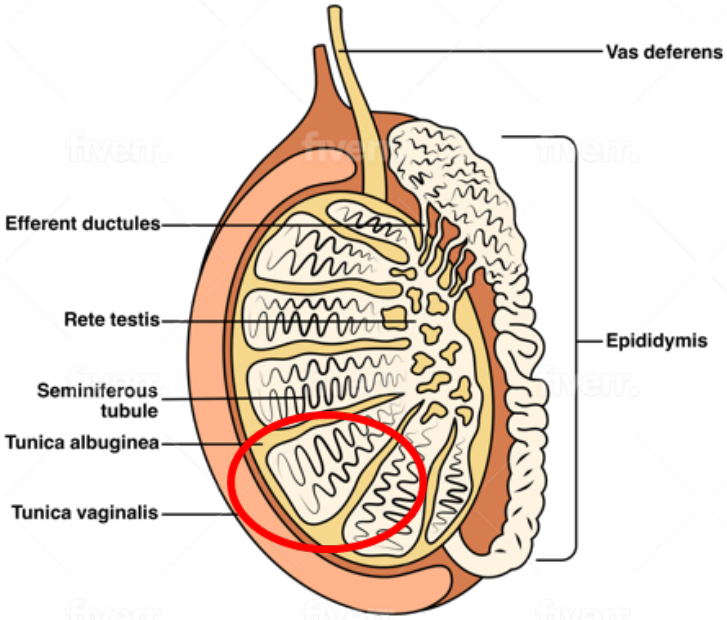
Male Anatomy

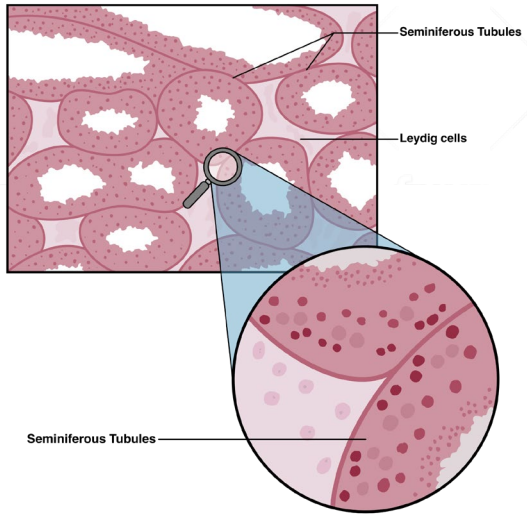




Testes: Seminiferous Tubules

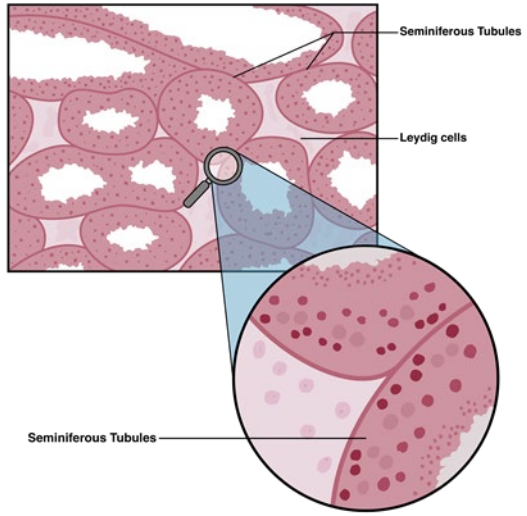
- Where spermatogenesis occurs
- Each tubule consists of a basement membrane lined with spermatogonia (germ cells) and sertoli cells.

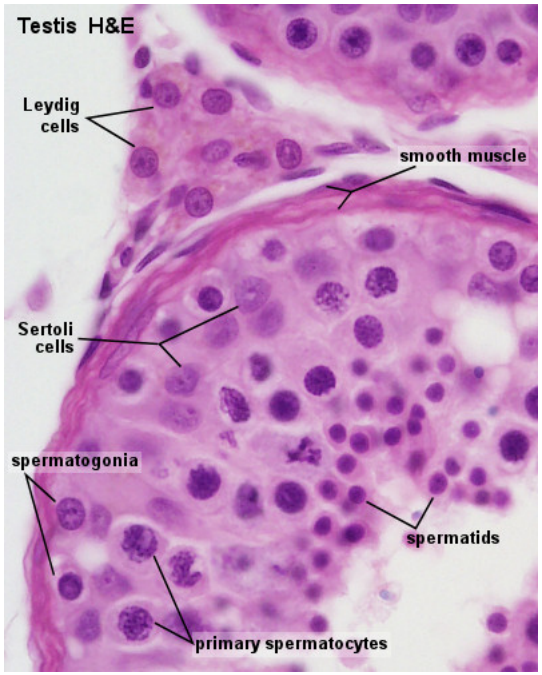




Sertoli Cells

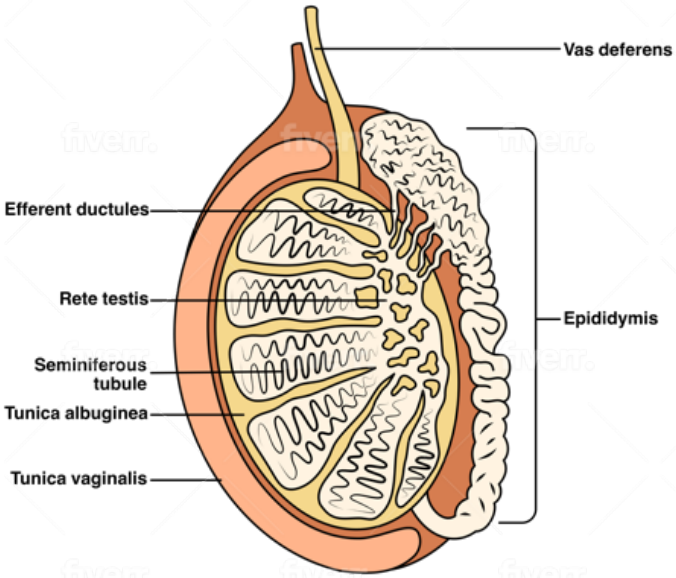
- Join to form protective blood-testis barrier
  - Prevents contact between fragile sperm and body's blood stream and toxins
- Nourish developing sperm and destroy defective germ cells
- Secrete fluid, protein and hormones





Epididymis

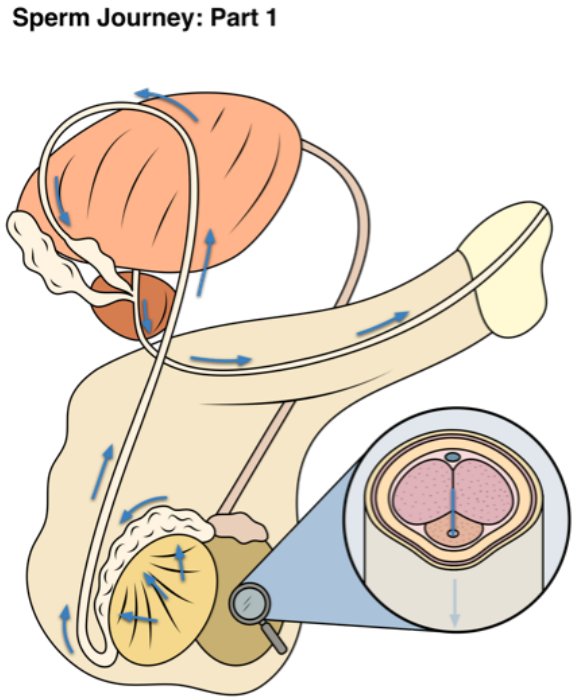
- Where sperm mature and are stored (2 to 3 months)
- When they enter initially, they are immobile and don’t have capacity to fertilize an egg
- During transit they become mobile and capable of fertilization
- Final maturation is in reproductive tract (in-vivo) or lab (in-vitro)



THE SPERM JOURNEY

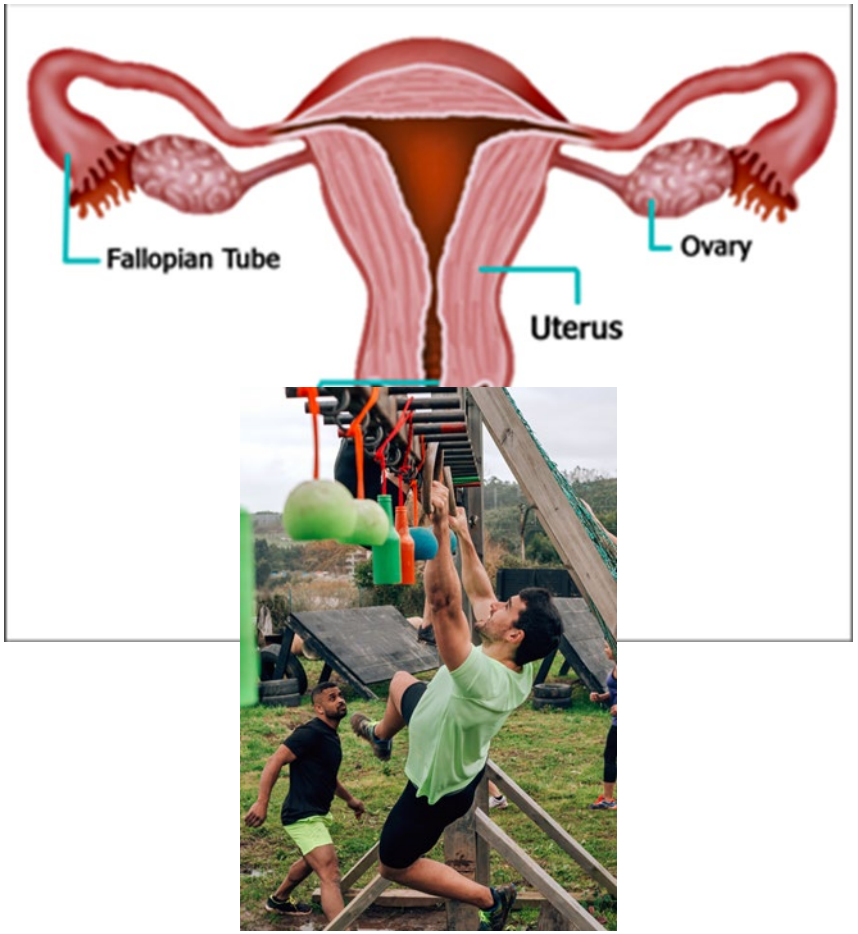
How do sperm travel?

- During ejaculation, sperm are propelled from the urethra by peristaltic contractions of the vas deferens
- Enzymes from the seminal vesicles coagulates some of the semen to prevent backflow into bladder
    - Fructose from seminal vesicles serves as an energy source



Sperm Journey

- Many millions of sperm are deposited near cervix at time of ejaculation
  - Acid level of vagina can kill sperm
  - Only about 200 reach the fertilization site
    - Most degenerate and are absorbed
- Use their flagellum to move through cervix
  - Cervical mucus becomes less thick at ovulation to allow this to happen
- Some sperm are delayed at the cervix, then gradually released into the cervical canal
- Sperm survive approximately 48 hours once ejaculated.



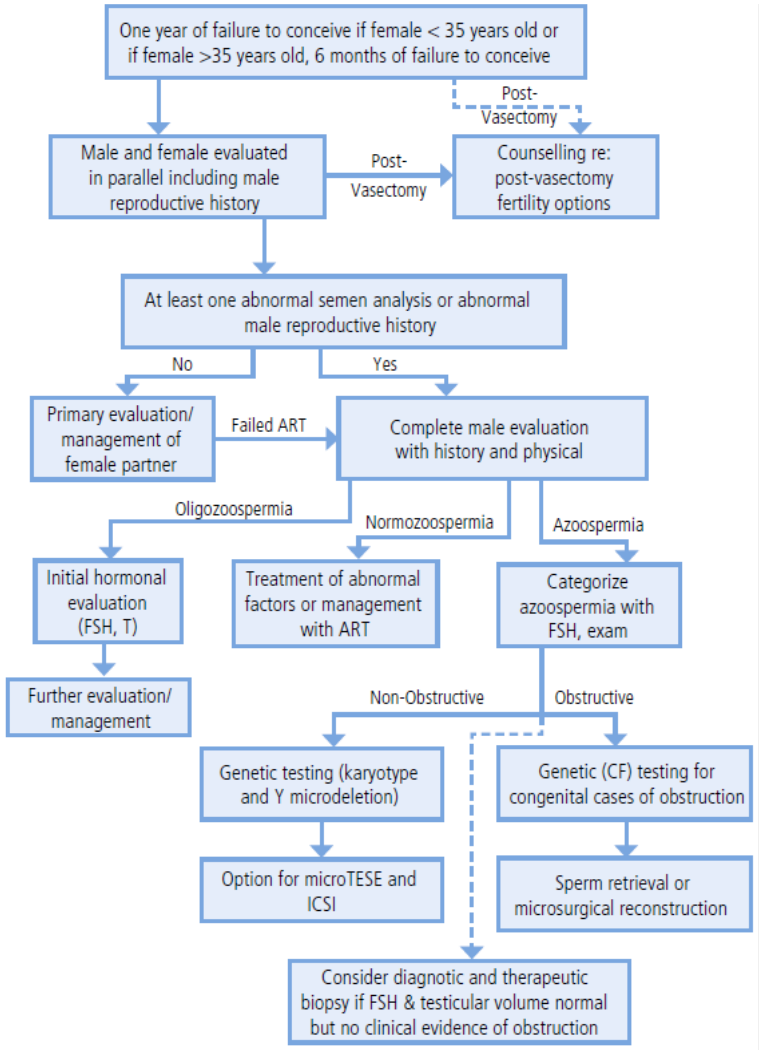
PART 3: DIAGNOSIS OF INFERTILITY IN MEN: THE SEMEN ANALYSIS AND SPERM DNA

Diagnosis and treatment of infertility in men: AUA/ASRM guideline part I

Peter N. Schlegel, M.D.,[a] Mark Sigman, M.D.,[b] Barbara Collura,[c] Christopher J. De Jonge, Ph.D., H.C.L.D.(A.B.B).,[d] Michael L. Eisenberg, M.D.,[e] Dolores J. Lamb, Ph.D., H.C.L.D.(A.B.B).,[f] John P. Mulhall, M.D.,[g] Craig Niederberger, M.D., F.A.C.S.,[h] Jay I. Sandlow, M.D.,[i] Rebecca Z. Sokol, M.D., M.P.H.,[j] Steven D. Spandorfer, M.D.,[f] Cigdem Tanrikut, M.D., F.A.C.S.,[k] Jonathan R. Treadwell, Ph.D.,[l] Jeffrey T. Oristaglio, Ph.D.,[l] and Armand Zini, M.D.[m]

[a] New York Presbyterian Hospital-Weill Cornell Medical College; [b] Brown University; [c] RESOLVE; [d] University of Minnesota School of Medicine; [e] Stanford University School of Medicine; [f] Weill Cornell Medical College; [g] Memorial-Sloan Kettering Cancer Center; [h] Weill Cornell Medicine, University of Illinois-Chicago School of Medicine; [i] Medical College of Wisconsin; [j] University of Southern California School of Medicine; [k] Georgetown University School of Medicine; [l] ECRI; and [m] McGill University School of Medicine

Retrieved from: [ASRM Practice Committee Publishes New Guidelines with AUA and Updates Opinions | ASRM]



Clinical Evaluation

- Medical history
  - Lifestyle factors
- Physical exam
- Semen analysis
- Endocrine profile if severe oligo/azoo: Free T, FSH, PRL, E, LH
- Other testing:
  - Sperm DNA testing
  - Sperm antibodies?

Semen Analysis

- Evaluates characteristics of semen and sperm
- Should be collected either via masturbation or special collection condom
  - 2-7 days of abstinence
  - If done at home, maintain at body temp and deliver to laboratory within an hour
  - Avoid lubricants
- If abnormal, repeat
  - Semen parameters within the same individuals are highly variable
  - The purpose of the second SA is not to see the impact of the intervention, but to see the variation within that individual
- Limitations
  - No individual sperm parameter is highly predictive of fertility of diagnostic of infertility.
  - Clinicians managing results from an SA should counsel patients that ‘multiple significant abnormalities in semen parameters increase their relative risk for infertility’. (ASRM/AUA 2020).

WHO Criteria

Parameter	Lower Reference Limit
Volume	1.5 ml
Concentration	15 M/ml
Motility (progressive)	32%
Total Motility	40%
Total Sperm Count	39 M
Morphology (strict)	4%

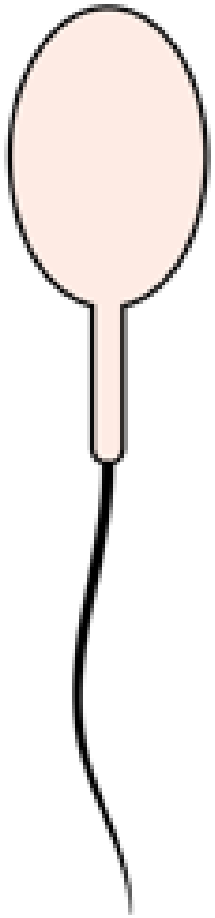
Total Motile Sperm (concentration, motility and volume). How many sperm cells in an entire ejaculate are motile?

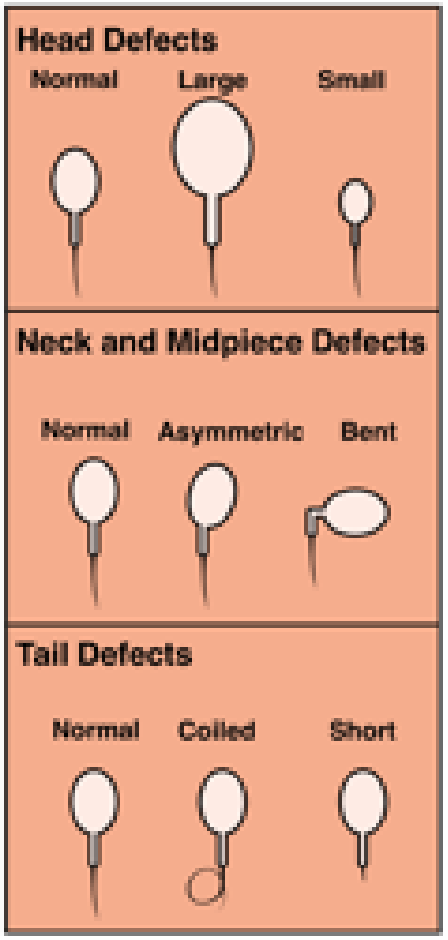
WHO Laboratory Manual for the Examination and Processing of Human Semen, Fifth Edition, WHO 2010

Terminology

Term	Results
Normospermia	Normal ejaculate
Oligospermia	Sperm Concentration <20 M/ml
Asthenospermia	Poor sperm **motility**
Teratospermia	Sperm have more **morphological** defects than accepted
Azoospermia	No sperm in ejaculate
Aspermia	No ejaculate/absence of semen

Sperm Morphology





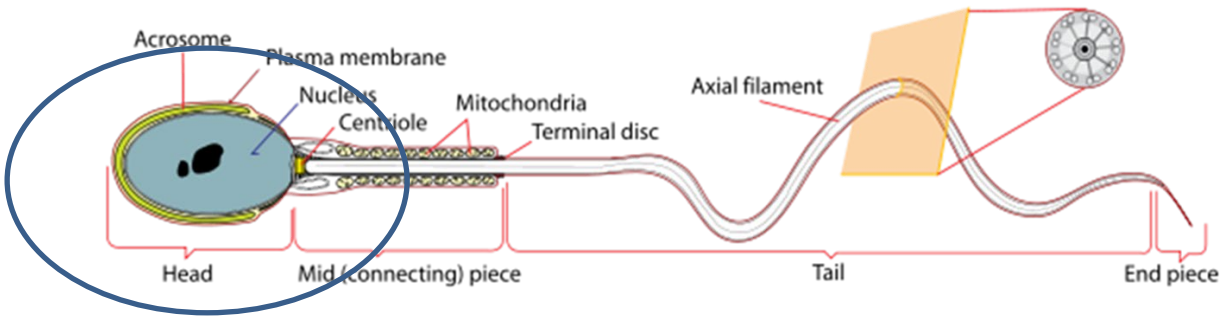
S/A parameters and Treatment(s)

- Chance of couples conceiving naturally is 15-20% per month
  - With insemination, can increase the chance by 5-15%.
- When total motile sperm count <10 million, IVF with ICSI more cost-effective than IUI*
  - <10 M/ml, per cycle preg rate with IUI=2.5%
  - <5 M/ml-per cycle rate 1%

*VanVoorhis, BJ, Fertil Steril 2001 Apr; 75(4). **Dickey RP fertil Steril 1999 Apr:71(4)

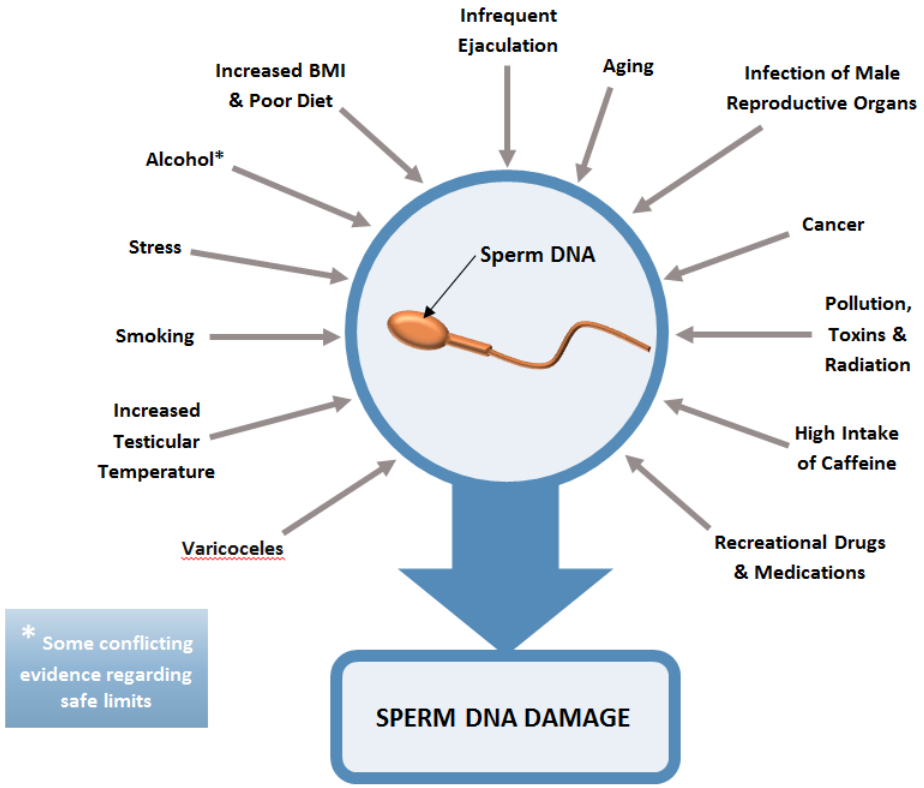
Sperm DNA Integrity

DNA Fragmentation



- Sperm chromatin consists of DNA and proteins
- DNA is tightly compacted in the head of the sperm
  - Like a coiled telephone wire
- DNA has to 'uncoil' in order to begin the process of fertilization.
  - When it 'uncoils' it can get tangled on itself.
- DNA damage can occur by:
  - Defective chromatin condensation during spermiogenesis
  - Initiation of apoptosis during spermatogenesis or transport
  - Oxidative stress

Effect of Free Radicals on Sperm



DNA Fragmentation

- DNA fragmentation tests assess whether the DNA is ‘packaged properly’ not if it is damaged in terms of mutations or genetic issues.
- If a male has DNA fragmentation at a higher percentage than normal (above 30%) the chances of achieving a pregnancy naturally or through IUI are diminished (but not zero).
  - We are not sure that DNA fragmentation affects IVF with ICSI (literature is mixed).*
  - We are not sure if the proactive nature of ICSI is enough to overcome the fragmentation issue.
- Might be indicated if during IVF cycle, eggs looked good but poor fert or embryo development or in cases of RPL.

Conversation with Dr Natan: retrieved from: https://youtu.be/DXSkqQ8H9s0

Sperm DNA Fragmentation Testing: Conclusion ASRM/AUA 2020

- ***Since there are no prospective studies that have directly evaluated the impact of DNA fragmentation testing on clinical management of infertile couples (fertility outcomes of those who had testing are not different than those who have not) this test is NOT routinely performed in the initial evaluation of the infertile male***.
  - *There may be an increased risk of miscarriage for couples in which the male has abnormal DNA fragmentation, so testing for sperm DNA fragmentation indicated in couples with RPL.*

PART 4: CAUSES AND TREATMENTS OF MALE FACTOR INFERTILITY

Causes of Male Factor Infertility

- Genetic
- Hormonal
- Varicocele
- Infection
- Anatomical malformations
- Chemical insult
- Idiopathic oligospermia- accounts for 30%

Genetic Factors

- Chromosomal abnormality can be found in about 15% of azoospermic men and 6% of men with severe oligospermia
- Klinefelter syndrome (47XXY)
  - Nondisjunction in meiosis 1 or 2
- Congenital absence of the vas deferens
- Kallman's syndrome-genetic condition that results in hypogonadotropic hypogonadism (and inability to smell)

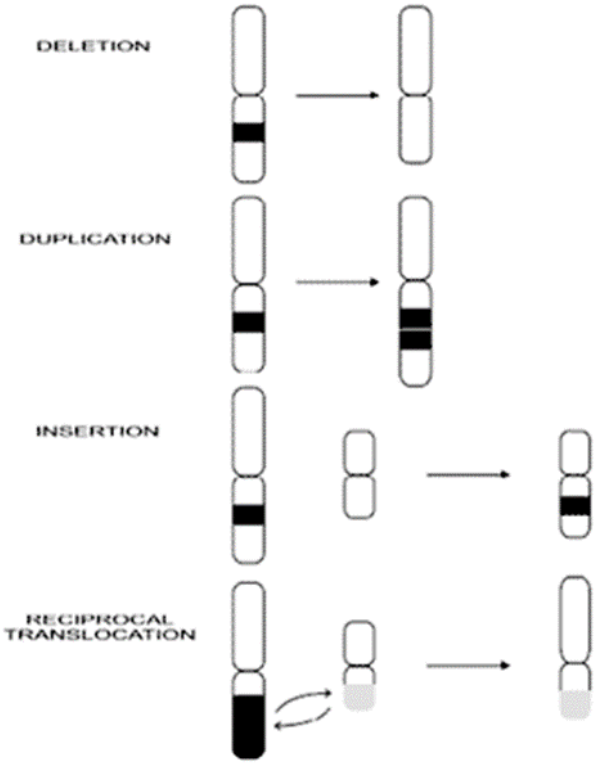
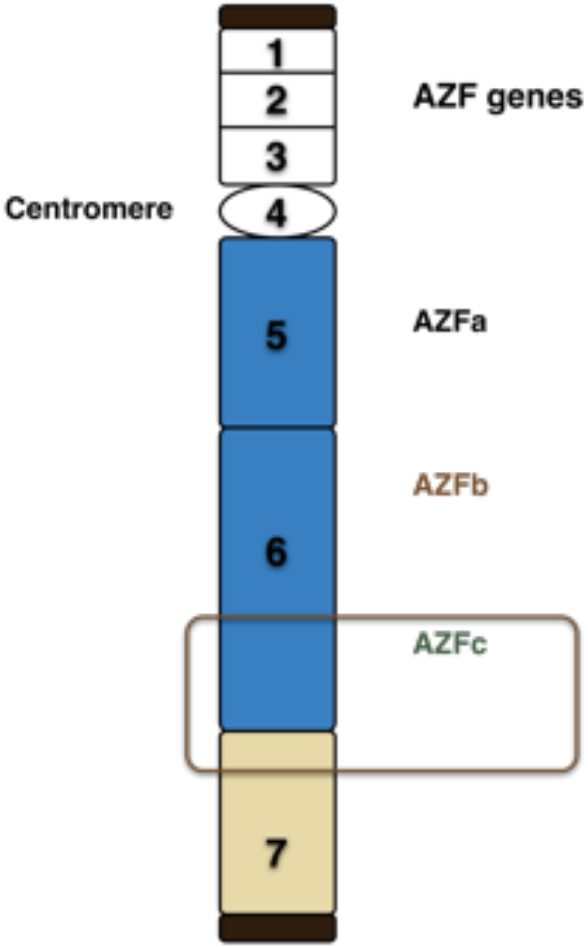


***Figure 2** - Structural chromosome abnormalities including deletions gene duplications, insertions and translocations. The lower part depicts a reciprocal, balanced translocation.*

Y Chromosome Microdeletion

- Missing gene(s) in the long arm of the Y chromosome that are associated with spermatogenesis
- May not have any symptoms but reduced fertility
- Prevalence about 7%

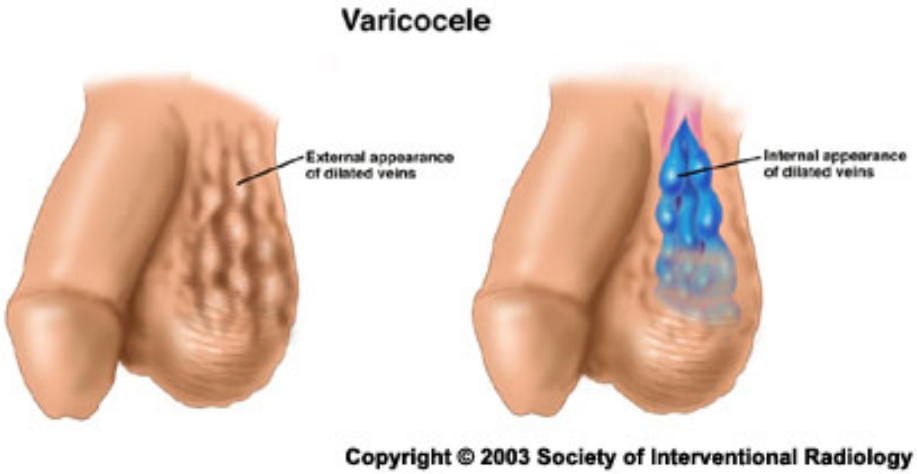


Factors affecting spermatogenesis

- Stress
- Age
- Toxins (lead, plastics, tobacco, ETOH, cannabis)
- Exposure to radiation or chemo
- Prolactinoma
- Cryptorchidism (absence of one or both testes from the scrotum) usually undescended and will descend by first year of life.
- Infections:
  - Mumps, chickenpox, STDs
  - Can cause orchitis (testicle infection)
  - Prostatitis
- Heat- hot tubs, sauna, long distance running, biking, truck drivers, tight underwear

Varicocele

- 35% of subfertile men
  - Lower sperm count and quality
  - Lower sperm function
  - Elevated oxidative stress-elevated sperm DNA damage



Miyaoka & Esteves, Adv Urol 2012; Agarwal, Esteves, Hamada; Nature Urol Rev 2013

Varicocele Repair

- Varicocelectomy
  - Done under microscopic guidance might improve outcome
  - Wait around 6 months to resume treatment
  - 60-70% show improvement
  - 40-50% pregnancy rate

ASRM Practice Guideline- Varicocele Tx

- Indications for varicocele repair
  - Infertile couples
  - Normal female or treatable female infertility
  - Abnormal S/A or sperm function test
- Some studies have shown that treating the varicocele prior to ICSI can increase # of fert eggs, live birth % and miscarriage rate (Esteves, SC et al, journal of urology vol 184: 1442-6, 2010)
- Probability of semen improvement: 50-70%

Male Obesity:

- Increases risk of hypogonadotropic/hypogonadism (leptin alters GnRH)
- Is risk factor for subfertility
- Negative correlation between elevated BMI, Total and Free T
- Oligo- and Asthenospermia increase with increasing BMI
- Decreases sperm, embryo quality and placental development
- In animal study, rate of embryo implantation and fetal development decreased in mice with obese fathers by up to 15%*.

*Binder, et al. 2012. Abstract presented at ESA-SRB

PART 5: TREATMENTS FOR MALE FACTOR INFERTILITY

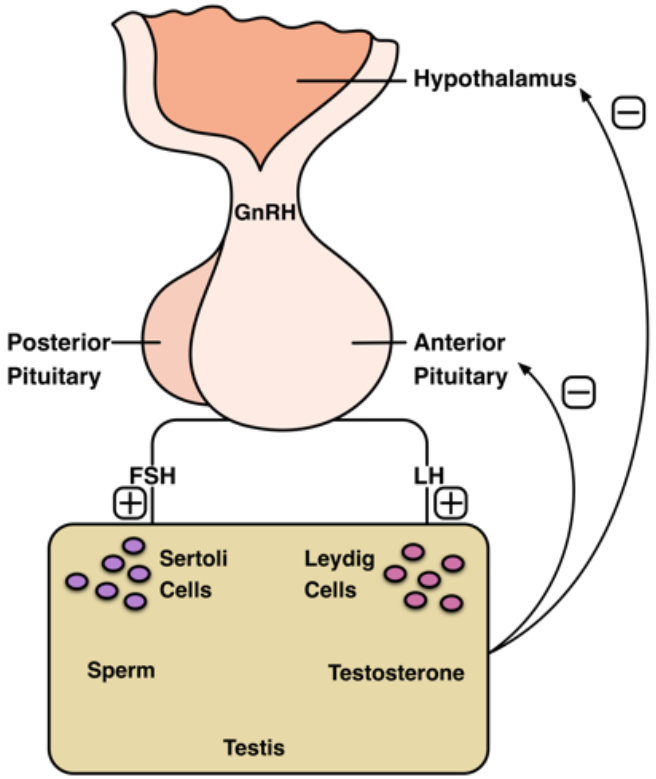
Inadequate Sperm Delivery

- Erectile dysfunction
- Hypospadias
- Premature ejaculation
- Use of spermicidal lubricants
- Retrograde ejaculation
  - Beta Blockers
  - Diabetes

Medical Treatments

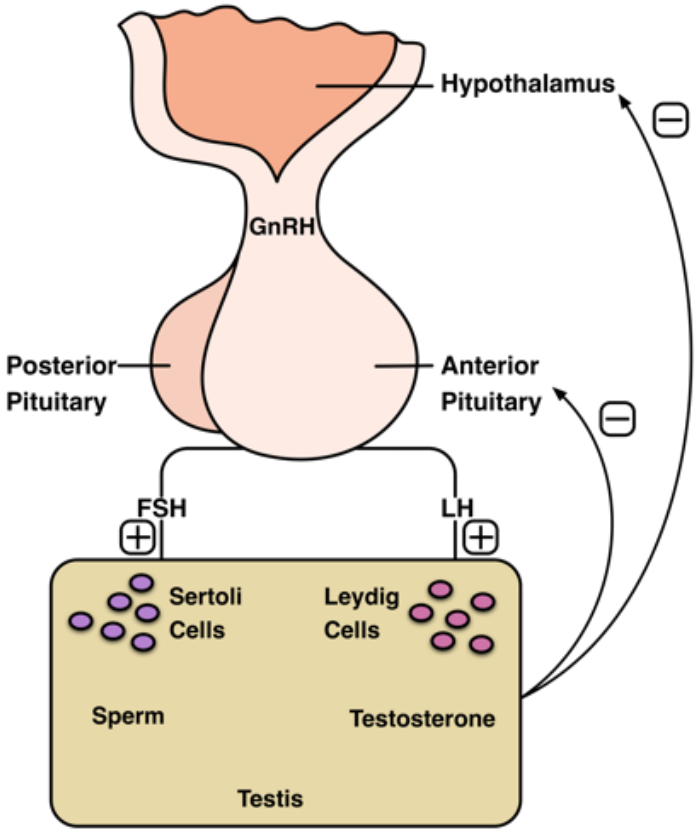
- Ejaculatory disorders
  - Sympathomimetic drugs
  - Electroejaculation (EEJ)
- Erectile dysfunction
  - PDE-5 inhibitors (Viagra, Cialis, Levitra)
- Retrograde ejaculation
  - Sperm rescue from urine (after urine is alkalized)
- Antisperm antibodies
  - Immunosuppressive drugs: variable success

HP Testicular Axis



Clomiphene Citrate Therapy

- Increasing gonadotropin levels might increase sperm production
  - (if FSH and LH already increased, this won't work)
- Anti-estrogens decrease negative feedback to pit/hypo axis, increasing GnRH release and subsequent FSH/LH release
- Clomiphene citrate 12.5 mg daily or 25 mg QOD
  - Also can use tamoxifen or aromatase inhibitors
- Might increase T and E2 levels, but not necessarily improve pregnancy rates
- Used in men with low/normal levels of T

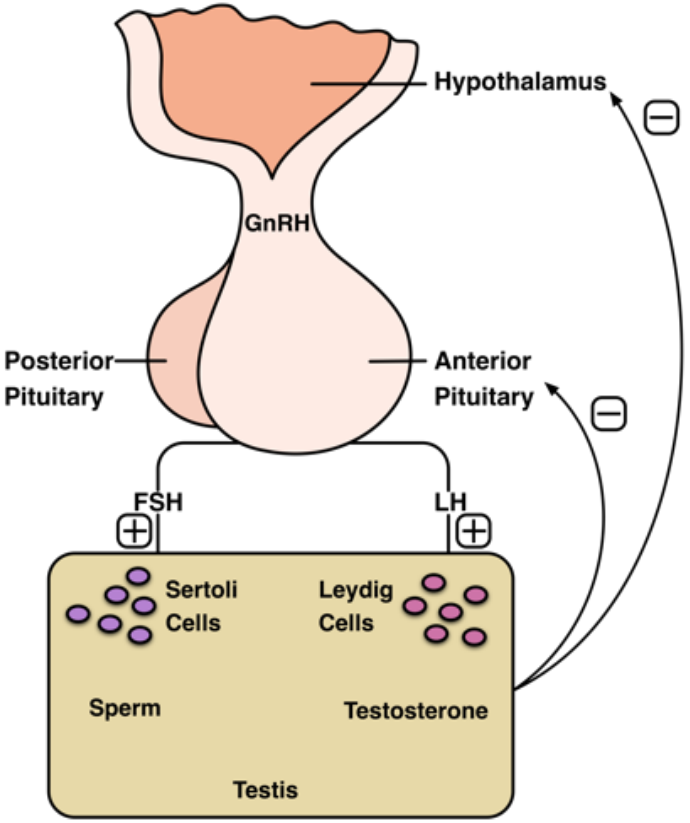


Male Hypogonadotropic Hypogonadism

- Congenital: Kallman syndrome; Prader-Willi
- Acquired: pituitary tumor, steroid abuse, T replacement therapy
- Symptoms:
  - Azoospermia
  - Deficient virilization
  - Atrophic/hypotrophic testes
  - Low levels of FSH, LH and T

Therapy for Male HH

- Injectable hCG
  - Can increase total T level, testicular volume and sperm count
  - 1000 U SQ daily X 5 days (test dose)
  - 500-1000 U SQ 3x/week
- hMG
  - 75 IU SQ 3x/week
- Monitor T levels and sperm parameters. Continue until sperm appears



Other Treatments

- Decrease % of sperm fragmentation
  - Treat infection
  - Antioxidants (Vit C, Vit E, Selenium)
    - Selenium-present in sperm in high amounts and might affect motility
  - Zinc supplementation-necessary for T production and might boost sperm quality
  - Stop smoking, healthy BMI, limit alcohol
  - Avoid hot tubs, jacuzzis
- IVF with ICSI

Supplements

- L-carnitine and Acetyl-L-carnitine
  - Provides energy for sperm motility
  - Present in high levels in epididymis
  - Might increase sperm concentration and total sperm count but no significant benefit on preg rates*
- L-Arginine
  - A.A. which is building block in head of sperm
- Cysteine
  - Anti-oxidant-protects against DNA damage

(Costa, 1994; Campaniello, 1988; Loumbakis, 1995, Moncada, 1992)

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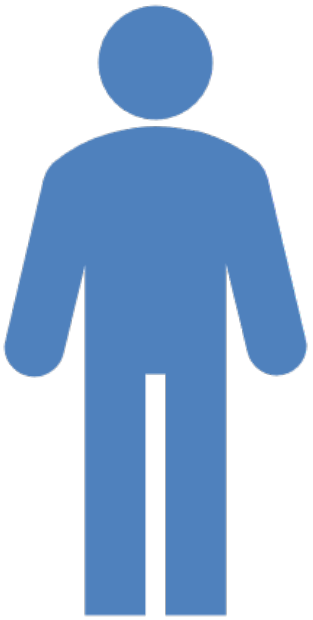
SURGICAL OPTIONS



Options depend on whether defect is obstructive or non-obstructive azoospermia

Obstructive	Non-Obstructive
Normal sperm production	Sperm production deficient or absent
Mechanical Blockage	2/3 of men with azoospermia
Vasectomy, post-infection, CBAVD, hernia repair, injuries or surgery in the scrotal/inguinal region	Cryptorchidism, radiation, chemo, trauma, genetic, orchitis, varicocele, gonadotoxins, unexplained
May be treated with corrective surgery: vasovasostomy or vasoepididymostomy (vasectomy reversal) but can take 6-10 months TTC	

Vasectomy Reversal

- Both sperm retrieval with ART and microsurgical reconstruction are options
- Decision by couple based on their preferences after needs and characteristics identified
  - If female partner has normal fertility potential, couple may choose to undergo microsurgical reconstruction
  - If female partner already needs IVF, consider aspiration with ICSI

Obstructive Azoospermia

- Surgical techniques can be needle aspirations
- No substantial differences in ICSI success rates when either cryopreserved or fresh sperm used, so sperm retrieval and cryopreservation can be done prior to VOR.
  - If number of sperm presumed to be low, then will be performed day of VOR as sperm may not survive the freeze/thaw process.

Obstructive Azoospermia

Acronym	Name of surgical procedure
PESA	Percutaneous Epidymal Sperm Aspiration
MESA	Microsurgical Epididymal Sperm Aspiration
TESA	Testicular Sperm Aspiration

Micro-TESE

- Recommended as the surgical sperm retrieval procedure for men with NOA (2020).
  - 1.5x more successful than non micro-surgical extraction
- Open biopsy of testis
- Tubules containing sperm look fuller under the microscope
- Uses principle that sperm production might only occur in small areas of the testis

Conclusions

- https://rmany.com/male-infertility/
- @RMAofNY Dr. Bar-Chama
- Instagram: https://www.instagram.com/nbarchama_rmany/

“Male Infertility with Dr. Natan Bar-Chama” retrieved from: https://youtu.be/DXSkqQ8H9s0