



The Workup and Management of Non-Obstructive Azoospermia

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Objectives



- Review the clinical features and etiology of infertility, particularly non-obstructive azoospermia (NOA)
- Summarize the workup of NOA, including history, physical, and relevant investigations
- Discuss medical and surgical management options for NOA
- Review histologic and clinical predictors of treatment success in NOA

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Infertility

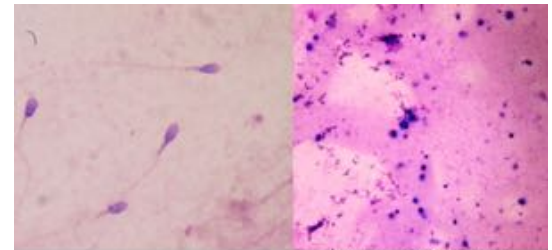
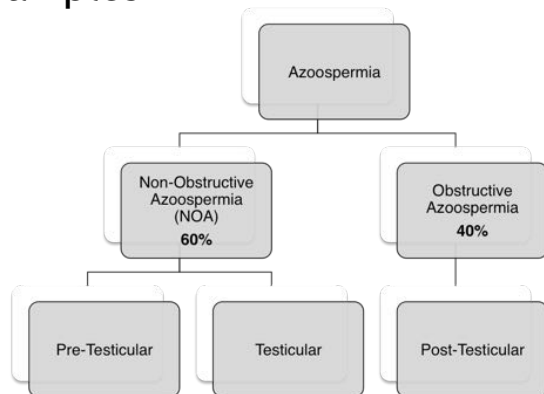


- Failure to achieve pregnancy after one year of regular unprotected intercourse
- 15% North American couples
- 50% male factor
- 10-20% infertile men are azoospermic

Azoospermia



- Complete absence of sperm in **two** samples



*Left: Semen sample with sperm.
Right: Azoospermic sample, WBCs only*

Flannigan R, Schlegel P. Azoospermia, Testicular Biopsy and Surgical Sperm Retrieval. AUA Update Series. 2017;36:85-93
Images courtesy of user Bobjgalindo. Wikimedia Commons. https://commons.wikimedia.org/wiki/File:Sperm_stained.JPG and https://commons.wikimedia.org/wiki/File:Semen_analysis.JPG

Non-obstructive Azoospermia (NOA)



- Pre-testicular causes rare (2% of cases)
 - Congenital
 - Hypo/hypo, Kallmann
 - Acquired
 - Radiation, tumour, surgery, exogenous/excessive androgen

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K Jarvi, et. al. CUA Guideline: The workup and management of azoospermic males. Can Urol Assoc J. 2015;9(7-8):229-35.
Flannigan R, Schlegel P. Genetic diagnostics of male infertility in clinical practice. Best Practice & Research Clinical Obstetrics and Gynaecology. 2017

Non-obstructive Azoospermia (NOA)



- Exogenous androgen common, especially in young men
 - Lifetime male prevalence 3% (Kanayama 2009)
 - **21% of hypogonadal men had used anabolic steroids (Coward 2013)**
 - Mean age 40.4 ± 8.4

Kanayama G, Brower KJ, Wood RI, Hudson JI, Pope HG. Anabolic-Androgenic Steroid Dependence: An Emerging Disorder. *Addiction*. 2009 Dec;104(12):1966-1978.
Coward RM, Rajanahally S, Kovac JR, Smith RP, Pastuszak AW, Lipshultz LI. Anabolic Steroid Induced Hypogonadism in Young Men. *The Journal of Urology*. 2013 Dec 1;190(6):2200-2205.

Non-obstructive Azoospermia (NOA)



- Majority of NOA is intrinsic testicular failure
 - Acquired
 - Chemotherapy/radiation, infection, varicocele
 - Congenital
 - Klinefelter, Y microdeletion, mixed gonadal dysgenesis
- 15-20% NOA genetic
- 30-60% idiopathic

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K Jarvi, et. al. CUA Guideline: The workup and management of azoospermic males. *Can Urol Assoc J*. 2015;9(7-8):229-35.
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Infertility History

Table 1. Type of information to gather during a patient's history

General information	Examples and areas of focus
1. Infertility history	<ul style="list-style-type: none"> • Duration of infertility • Whether the infertility is primary or secondary • Any treatments to date • Libido • Sexual function • Sexual activity
2. The general health of the man	<ul style="list-style-type: none"> • Diabetes; • Respiratory issues • Recent illnesses
3. Any proven or suspected genito-urinary infections, testicular infections or inflammation ⁸	<ul style="list-style-type: none"> • Sexually transmitted infections • Epididymo-orchitis • Mumps orchitis
4. Any surgery of the reproductive tract	<ul style="list-style-type: none"> • Testis cancer • Undescended testis • Hydrocelectomies • Spermatocelectomies • Varicocelectomies • Vasectomies
5. Exposure to medications and therapies which might have an adverse impact on spermatogenesis	<ul style="list-style-type: none"> • Hormone/steroid therapy • Antibiotics (sulphasalazine) • Alpha-blockers • 5-alpha-reductase inhibitors • Chemotherapeutic agents • Radiation • Finasteride⁹ • Narcotics
6. Environmental exposures	<ul style="list-style-type: none"> • Pesticides • Excessive heat on the testicles
7. Any recreational drugs	<ul style="list-style-type: none"> • Marijuana • Excessive alcohol
8. History of any genetic abnormalities in the patient or his family	

Physical Examination

- Virilization status/signs of feminization
- Testicular examination
 - **Size** and consistency
 - Varicocele
 - Vas deferens
 - Scars
- Abdominal examination
 - Surgical scars
 - DRE

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Investigations

- **Semen analysis x 2**
- FSH, LH, testosterone
- Karyotype
- Y micro deletion testing

- If obstruction suspected
 - Post-ejaculatory urinalysis
 - TRUS
 - CFTR testing

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Diagnosing NOA



- Semen analysis
- History (exclude obstruction)
- Testicular size (long axis)
- FSH, LH, T
- Genetic testing
 - Karyotype
 - Y microdeletions

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Diagnosing NOA



J Urol. 2002 Jan;167(1):197-200.

The role of testicular biopsy in the modern management of male infertility.

Schoor RA¹, Elhanbly S, Niederberger CS, Ross LS.

- Testicular long axis < 4.6 cm
 - Sensitivity 72%, specificity 78%
- FSH > 7.6 mIU/mL
 - Sensitivity 77%, specificity 93%
- Long axis < 4.6 cm and FSH >7.6 mIU/mL
 - **89% diagnostic accuracy for NOA**

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Diagnostic Testicular Biopsy



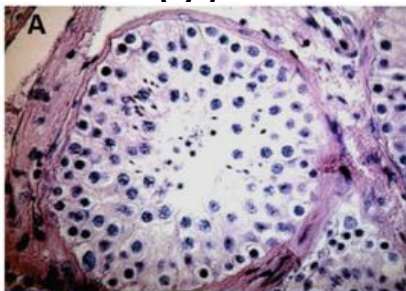
- To diagnose when workup is inconclusive, only if patient interested in further management
- Separately or at time of sperm retrieval/reconstruction
- Open excisional biopsy preferred over percutaneous
- Perform repeat semen analysis prior to intervention
 - 5-10% have viable sperm

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Schlegel PN, Liotta D, Hariprashad J, Veeck LL. Fresh testicular sperm from men with nonobstructive azoospermia works best for ICSI. Urology. 2004 Dec;64(6):1069-1071.

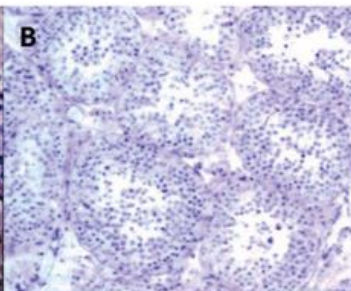
Histopathology



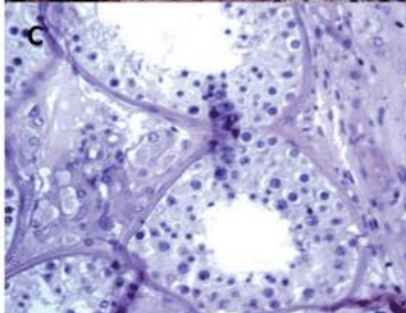
Normal spermatogenesis



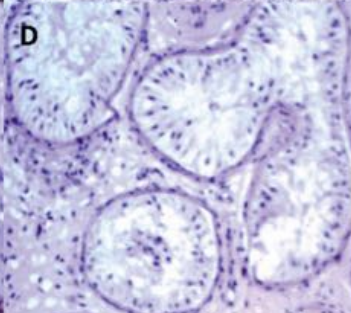
Hypospermatogenesis



(Late) Maturation arrest



Sertoli-only syndrome



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Management of NOA



- Testicular sperm extraction (TESE)
- Microscopic TESE (microTESE)
- Testicular sperm aspiration
- Medical management

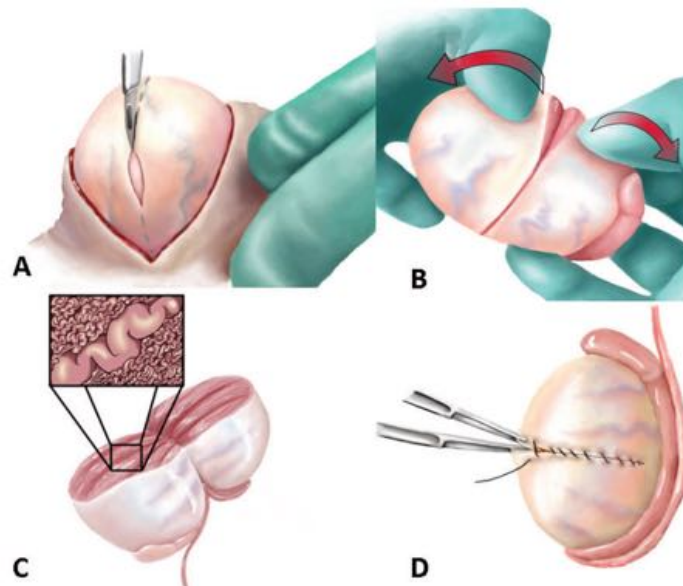
TESE

- Original operation for NOA
 - Multiple random biopsies
 - Uncertainty re: number and location of biopsies
- Largely succeeded by microTESE



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microTESE



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K Jarvi, et. al. CUA Guideline: The workup and management of azoospermic males. Can Urol Assoc J. 2015;9(7-8):229-35.
Schlegel PN. Testicular sperm extraction: microdissection improves sperm yield with minimal tissue excision. Hum Reprod. 1999 Jan;14(1):131-135.

microTESE vs. TESE

- **Sperm retrieval rate (SRR) benefit**
 - 43-63% vs. 16-45% (DeRuyver 2014)
 - 52% vs 35% (Bernie 2015)
- **Secondary measures**
 - Less tissue excised, more sperm retrieved
 - Fewer hematomas and less fibrosis on ultrasound

Bernie AM, Mata DA, Ramasamy R, Schlegel PN. Comparison of microdissection testicular sperm extraction, conventional testicular sperm extraction, and testicular sperm aspiration for nonobstructive azoospermia: a systematic review and meta-analysis. *Fertility and Sterility*. 2015 Nov 1;104(5):1099-1103.e3.

Deruyver Y, Vanderschueren D, Van der Aa F. Outcome of microdissection TESE compared with conventional TESE in non-obstructive azoospermia: a systematic review. *Andrology*. 2014 Jan;2(1):20-24. PMID: 24193894

Ramasamy R, Yagan N, Schlegel PN. Structural and functional changes to the testis after conventional versus microdissection testicular sperm extraction. *Urology*. 2005 Jun;65(6):1190-1194. PMID: 15922422

Testicular Sperm Aspiration

- **Minimal role therapeutically in NOA**
 - SRR 28% (Bernie 2015)
- **Sperm mapping**
 - Grid of 4-18 aspiration sites
 - Separate mTESE

Bernie AM, Mata DA, Ramasamy R, Schlegel PN. Comparison of microdissection testicular sperm extraction, conventional testicular sperm extraction, and testicular sperm aspiration for nonobstructive azoospermia: a systematic review and meta-analysis. *Fertility and Sterility*. 2015 Nov 1;104(5):1099-1103.e3.

Shin DH, Turek PJ. Sperm retrieval techniques. *Nat Rev Urol*. 2013 Dec;10(12):723-730. PMID: 24296703

Hormonal Control of Spermatogenesis

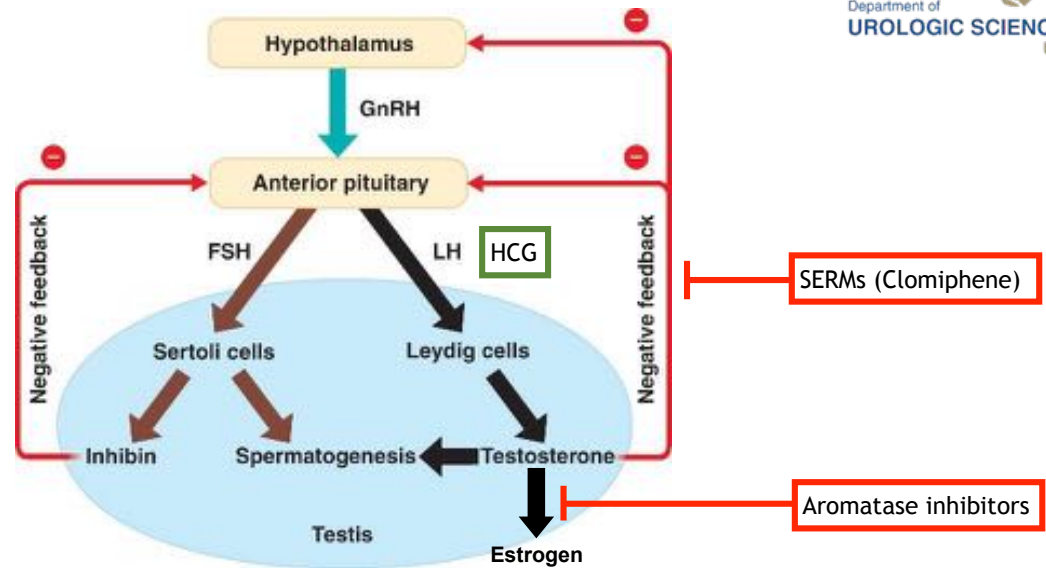


Image credit: College of DuPage, Biology 1152 Class Page. <http://bio1152.nicerweb.com/Locked/media/ch46/androgens.html>

Medical Therapy



- Gonadotropins effective at restoring spermatogenesis in pre-testicular NOA
 - 65-78% achieved sperm counts > 1M/mL
- Evidence for hormonal therapy is equivocal in testicular NOA

Burgués S, Calderón MD. Subcutaneous self-administration of highly purified follicle stimulating hormone and human chorionic gonadotrophin for the treatment of male hypogonadotropic hypogonadism. Spanish Collaborative Group on Male Hypogonadotropic Hypogonadism. Hum Reprod. 1997 May; 12(5):980-986.

Nieschlag E, Bouloux P-MG, Stegmann BJ, Shankar RR, Guan Y, Tzontcheva A, McCrary Sisk C, Behre HM. An open-label clinical trial to investigate the efficacy and safety of corifollitropin alfa combined with hCG in adult men with hypogonadotropic hypogonadism. Reprod Biol Endocrinol. 2017 Mar 7;15(1):17. PMID: PMC5341390

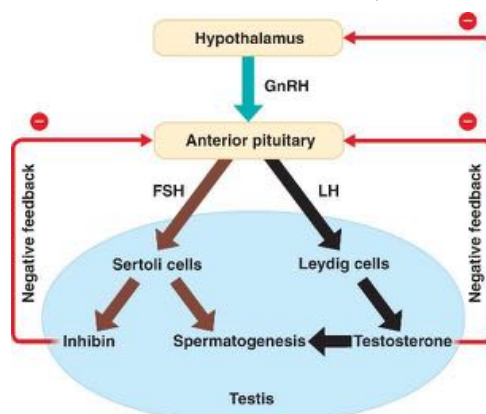
Medical Therapy

- Hussein et al., 2013
 - SRR 57% vs. 34%
- Ramasamy et al., 2009
 - No improvement in SRR
- Reifsnyder et al. 2012
 - No improvement in SRR

Hussein A, Ozgok Y, Ross L, Rao P, Niederberger C. Optimization of spermatogenesis-regulating hormones in patients with non-obstructive azoospermia and its impact on sperm retrieval: a multicentre study. *BJU International*. 2013 Mar 1;111(3b):E110–E114.
 Ramasamy R, Ricci JA, Palermo GD, Gosden LV, Rosenwaks Z, Schlegel PN. Successful fertility treatment for Klinefelter's syndrome. *J Urol*. 2009 Sep;182(3):1108–1113.
 Reifsnyder JE, Ramasamy R, Hussein J, Schlegel PN. Role of optimizing testosterone before microdissection testicular sperm extraction in men with nonobstructive azoospermia. *J Urol*. 2012 Aug;188(2):532–536.

Medical Therapy

- CUA does not recommend any hormonal therapy for NOA
- Androgen therapy is contraindicated (Level 1, Grade A)



Objectives

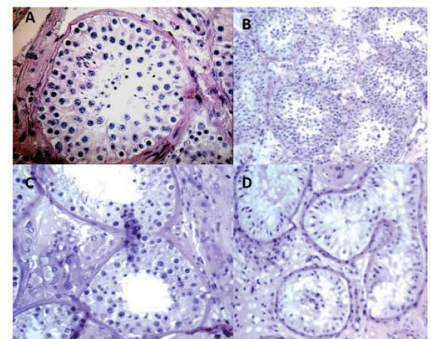


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Histologic Subtype



- **Hypospermatogenesis (SRR 47-100%)**
- Maturation arrest (SRR 10-52%)
 - Early (40%) vs. Late (72%)
- Sertoli-only syndrome (32-42%)



Bernie AM, Shah K, Halpern JA, Scovell J, Ramasamy R, Robinson B, Schlegel PN. Outcomes of microdissection testicular sperm extraction in men with nonobstructive azoospermia due to maturation arrest. *Fertil Steril.* 2015 Sep;104(3):569-573.e1. PMID: 2607238.

Caroppo E, Colpi EM, Gazzano G, Vaccalluzzo L, Scropo FI, D'Amato G, Colpi GM. Testicular histology may predict the successful sperm retrieval in patients with non-obstructive azoospermia undergoing conventional TESE: a diagnostic accuracy study. *J Assist Reprod Genet.* 2017 Jan 1;34(1):149-154.

Guler I, Erdem M, Erdem A, Demirdağ E, Tunc L, Bozkurt N, Mutlu MF, Oktem M. Impact of testicular histopathology as a predictor of sperm retrieval and pregnancy outcome in patients with nonobstructive azoospermia: correlation with clinical and hormonal factors. *Andrologia.* 2016 Sep 1;48(7):765-773.

Yildirim ME, Koc A, Kaygusuz IC, Badem H, Karatas OF, Cimentepe E, Unal D. The association between serum follicle-stimulating hormone levels and the success of microdissection testicular sperm extraction in patients with azoospermia. *Urol J.* 2014 Sep 6;11(4):1825-1828. PMID: 25194084

FSH Level



- **Conflicting evidence on significance of FSH levels**
 - FSH > 15: lower mTESE SRR (8.3% vs. 43%) (Yildirim 2014)
 - FSH > 10: lower TESE SRR (29% vs. 77%) (Bromage 2007)
 - FSH not associated with SRR (Ramasamy 2013)
 - FSH not associated with SRR (Seo 2001)

Bromage SJ, Falconer DA, Lieberman BA, Sangar V, Payne SR, Floth A, Dohle GR. Sperm Retrieval Rates in Subgroups of Primary Azoospermic Males. *European Urology*. 2007 Feb 1;51(2):534-540.

Bernie AM, Ramasamy R, Schlegel PN. Predictive factors of successful microdissection testicular sperm extraction. *Basic Clin Androl*. 2013;23:5.

Ramasamy R, Lin K, Gosden LV, Rosenwaks Z, Palermo GD, Schlegel PN. High serum FSH levels in men with nonobstructive azoospermia does not affect success of microdissection testicular sperm extraction. *Fertil Steril*. 2009 Aug;92(2):590-593. PMID: 18973887

Ramasamy R, Padilla WO, Osterberg EC, Srivastava A, Reifsnnyder JE, Niederberger C, Schlegel PN. A Comparison of Models for Predicting Sperm Retrieval Before Microdissection Testicular Sperm Extraction in Men with Nonobstructive Azoospermia. *The Journal of Urology*. 2013 Feb 1;189(2):638-642.

Seo JT, Ko W-J. Predictive factors of successful testicular sperm recovery in non-obstructive azoospermia patients. *International Journal of Andrology*. 2001 Oct 21;24(5):306-310.

Yildirim ME, Koc A, Kaygusuz IC, Badem H, Karatas OF, Cimentepe E, Unal D. The association between serum follicle-stimulating hormone levels and the success of microdissection testicular sperm extraction in patients with azoospermia. *Urol J*. 2014 Sep 6;11(4):1825-1828. PMID: 25194084

Zitzmann M, Nordhoff V, von Schönfeld V, Nordsiek-Mengede A, Kliesch S, Schüring AN, Luetjens CM, Kamischke A, Cooper T, Simoni M, Nieschlag E. Elevated follicle-stimulating hormone levels and the chances for azoospermic men to become fathers after retrieval of elongated spermatids from cryopreserved testicular tissue. *Fertil Steril*. 2006 Aug;86(2):339-347. PMID: 16753155

FSH Level



[Basic Clin Androl](#). 2013 Oct 2;23:5. doi: 10.1186/2051-4190-23-5. eCollection 2013.

Predictive factors of successful microdissection testicular sperm extraction.

[Bernie AM](#)¹, [Ramasamy R](#)¹, [Schlegel PN](#)¹.

- “...a majority of evaluations have shown that the predictive value of FSH for success of TESE and other sperm retrieval methods is either low or non-existent”
- Should not influence decision to proceed with sperm retrieval

Testis Size



- Testis volume has not been shown to reliably predict sperm retrieval success

Ramasamy R, Padilla WO, Osterberg EC, Srivastava A, Reifsnnyder JE, Niederberger C, Schlegel PN. A Comparison of Models for Predicting Sperm Retrieval Before Microdissection Testicular Sperm Extraction in Men with Nonobstructive Azoospermia. *The Journal of Urology*. 2013 Feb 1;189(2):638-642.

Devroey P, Liu J, Nagy Z, Goossens A, Tournaye H, Camus M, Van Steirteghem A, Silber S. Pregnancies after testicular sperm extraction and intracytoplasmic sperm injection in non-obstructive azoospermia. *Hum Reprod*. 1995 Jun;10(6):1457-1460.

Tsujimura A, Matsumiya K, Miyagawa Y, Takao T, Fujita K, Koga M, Takeyama M, Fujioka H, Okuyama A. Prediction of successful outcome of microdissection testicular sperm extraction in men with idiopathic nonobstructive azoospermia. *J Urol*. 2004 Nov;172(5 Pt 1):1944-1947. PMID: 15540761

Varicocele



- Conflicting evidence on value of varicocele repair in NOA
- Return of viable sperm to ejaculate
 - 9.6% (Schlegel 2003)
 - 55% (Matthews 1998)
- Improved SRR
 - 53% vs. 30% (Inci 2009)
 - 60.8% vs 38.5% (Haydardedeoglu 2010)

Schlegel PN, Kaufmann J. Role of varicolectomy in men with nonobstructive azoospermia. *Fertil Steril*. 2004;81(6):1585-1588. doi: 10.1016/j.fertnstert.2003.10.036.

Matthews GJ, Matthews ED, Goldstein M. Induction of spermatogenesis and achievement of pregnancy after microsurgical varicolectomy in men with azoospermia and severe oligoasthenospermia. *Fertil Steril*. 1998;70(1):71-75. doi: 10.1016/S0015-0282(98)00108-3

Haydardedeoglu B, Turunc T, Kilicdag EB, Gul U, Bagis T. The effect of prior varicolectomy in patients with nonobstructive azoospermia on intracytoplasmic sperm injection outcomes: a retrospective pilot study. *Urology*. 2010 Jan;75(1):83-86. PMID: 19913887

Inci K, Hascicek M, Kara O, Dikmen AV, Gurgan T, Ergen A. Sperm retrieval and intracytoplasmic sperm injection in men with nonobstructive azoospermia, and treated and untreated varicocele. *J Urol*. 2009 Oct;182(4):1500-1505. PMID: 19683732

Varicocele



Asian J Androl. 2016 Mar-Apr;18(2):246-53. doi: 10.4103/1008-682X.169562.

Outcome of varicocele repair in men with nonobstructive azoospermia: systematic review and meta-analysis.

Esteves SC¹, Miyaoka R, Roque M, Agarwal A.

- 43.9% men with NOA and varicocele had sperm in ejaculate after treatment
 - 13.6% achieved pregnancy without ICSI
- Improved sperm recovery in men with treated varicocele
 - OR 2.65
- CUA guideline: reasonable to offer treatment, but most men will need ICSI

Klinefelter Syndrome (KS)



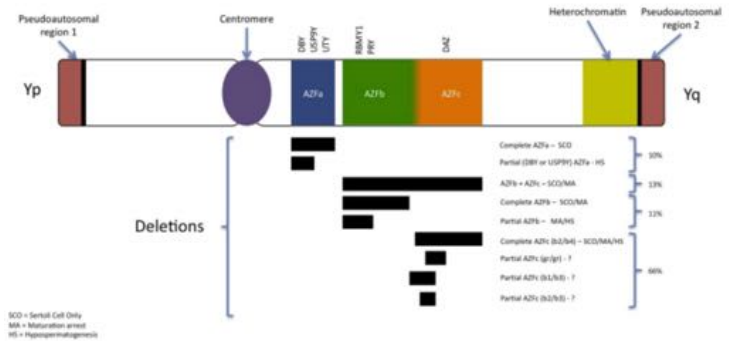
- 0.1-0.2% general population
- 3-4% infertile men, 10-12% azoospermic men
- SRR 42-68%
 - 44% (Corona 2017)
- No predisposition to KS in children of KS fathers

Corona G, Pizzocaro A, Lanfranco F, Garolla A, Pelliccione F, Vignozzi L, Ferlin A, Foresta C, Jannini EA, Maggi M, Lenzi A, Pasquali D, Francavilla S, Klinefelter ItaliaN Group (KING). Sperm recovery and ICSI outcomes in Klinefelter syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2017 May 1;23(3):265-275. Flannigan R, Schlegel PN, Genetic diagnostics of male infertility in clinical practice, Best Practice & Research Clinical Obstetrics and Gynaecology (2017), <http://dx.doi.org/10.1016/j.bpobgyn.2017.05.002>
Paduch DA, Bolyakov A, Cohen P, Travis A. Reproduction in Men with Klinefelter Syndrome: The Past, the Present, and the Future. Semin Reprod Med. 2009 Mar;27(2):137-148.
Ramasamy R, Ricci JA, Palermo GD, Gosden LV, Rosenwaks Z, Schlegel PN. Successful fertility treatment for Klinefelter's syndrome. J Urol. 2009 Sep; 182(3):1108-1113. PMID: 19616796

Y chromosome microdeletions



- Azoospermia factor (AZF) region of Yq
 - 3 loci: a, b, c
- 10% azoospermia patients



1.

Flannigan R, Schlegel P. Genetic diagnostics of male infertility in clinical practice. *Best Practice & Research Clinical Obstetrics and Gynaecology*. 2017.

Georgiou I, Syrrou M, Pardalidis N, Karakitsios K, Mantzavinos T, Giotitsas N, Loutradis D, Dimitriadis F, Saito M, Miyagawa I, Tzoumis P, Sylakos A, Kanakas N, Moustakareas T, Baltogiannis D, Touloupides S, Giannakis D, Fatouros M, Sofikitis N. Genetic and epigenetic risks of intracytoplasmic sperm injection method. *Asian Journal of Andrology*. 2006 Nov;8(6):643-673.

Stahl PJ, Masson P, Mielnik A, Marean MB, Schlegel PN, Paduch DA. A decade of experience emphasizes that testing for Y microdeletions is essential in American men with azoospermia and severe oligozoospermia. *Fertility and Sterility*. 2010 Oct 1;94(5):1753-1756.

Vogt PH, Edelmann A, Kirsch S, Henegariu O, Hirschmann P, Kiesewetter F, Köhn FM, Schill WB, Farah S, Ramos C, Hartmann M, Hartschuh W, Meschede D, Behre HM, Castel A, Nieschlag E, Weidner W, Gröne H-J, Jung A, Engel W, Haidl G. Human Y Chromosome Azoospermia Factors (AZF) Mapped to Different Subregions in Yq11. *Hum Mol Genet*. 1996 Jul 1;5(7):933-943.

Y chromosome microdeletions



- No reports of positive sperm detection on microTESE in complete AZFa and AZFb deletions
 - Sertoli cell-only or early maturational arrest pattern
- AZFc deletions (60% of Y microdeletion)
 - Up to 70% have detectable sperm in ejaculate (Georgiou 2006)
 - 50-60% SRR with mTESE (Stahl 2010)

1.

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Take-home Points

- NOA can be diagnosed on history, exam and lab values
- Ask about exogenous androgens
- Micro-TESE is gold standard
- Hormonal therapy not recommended
- FSH/testis size may not be useful to predict SRR
- Offer varicocele therapy
- Klinefelter is a common cause of azoospermia
- AZFc deletion: good chance at fertility with sperm retrieval



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