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

Non-obstructive Azoospermia (NOA)

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


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


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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Infertility History

<table>
<thead>
<tr>
<th>Table 1. Type of information to gather during a patient’s history</th>
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<tbody>
<tr>
<td><strong>General information</strong></td>
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<tr>
<td>1. Infertility history</td>
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<td>2. The general health of the man</td>
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<td>3. Any proven or suspected genito-urinary infections, testicular infections or inflammation</td>
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<td>4. Any surgery of the reproductive tract</td>
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<td>5. Exposure to medications and therapies which might have an adverse impact on spermatogenesis</td>
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<td>6. Environmental exposures</td>
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<td>7. Any recreational drugs</td>
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<td>8. History of any genetic abnormalities in the patient or his family</td>
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Physical Examination

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

Investigations

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

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

Flannigan R, Schlegel P. Azoospermia, Testicular Biopsy and Surgical Sperm Retrieval. AUA Update Series. 2017;36:85-93
Diagnosing NOA

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

Flannigan R, Schlegel P. Azoospermia, Testicular Biopsy and Surgical Sperm Retrieval. AUA Update Series. 2017;36:85-93

Diagnosing NOA

• 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

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

Histopathology

Normal spermatogenesis

(Late) Maturation arrest

Hypospermatogenesis

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

Flannigan R, Schlegel P. Azoospermia, Testicular Biopsy and Surgical Sperm Retrieval. AUA Update Series. 2017;36:85-93

microTESE

Flannigan R, Schlegel P. Azoospermia, Testicular Biopsy and Surgical Sperm Retrieval. AUA Update Series. 2017;36:85-93
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


Testicular Sperm Aspiration

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

Hormonal Control of Spermatogenesis

![Hormonal Control of Spermatogenesis Diagram]

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

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


Medical Therapy

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

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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%)**
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)


FSH Level

• “...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

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)
Varicocele

- 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

Y chromosome microdeletions

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

- 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)
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

Acknowledgements

• Dr. Ryan Flannigan
• Dr. Mark Nigro
• Dr. Victor Chow
References

41. Schlegel PN. Testicular sperm extraction: microdissection improves sperm yield with minimal tissue excision. Hum Reprod. 1999 Jan;14(1):131–135. PMID: 10374109

References