Easy Interventions to Improve Male Infertility

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Objectives:
- Describe ASRM guidelines for varicocele ligations
- Summarize available literature for role of genitourinary infection in subfertility
- Review advances in sperm testing and function essays
- Define the role and treatment of oxidative stress in male infertility
Easy Interventions for Male Fertility

Edmund Sabanegh, Jr., M.D.

Chairman, Department of Urology
Glickman Urological and Kidney Institute
Cleveland Clinic
### Male Subfertility

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Incidence (%)</th>
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<tbody>
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<tr>
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<td>3</td>
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Ultimately, almost 40% of male infertility patients may be candidates for some form of medical therapy.
**Categories of Therapy**

Lifestyle Intervention

Specific Medical Therapy
  - Endocrinopathy
  - Genitourinary Infections
  - Ejaculatory Dysfunction

Non-specific (empiric)
  - Endocrine
  - Antioxidant/ nutraceutical
Personal Health Factors

- Diet
- Exercise
- Obesity
- Stress

Other factors:

- Endocrine disruptors
- Genetic
- Oxidative Stress
Tobacco

Effect of Smoking on Sperm Vitality, DNA Integrity, Seminal Oxidative Stress, Zinc in Fertile Men

Emad A. Taha, Azza M. Ez-Aldin, Sohair K. Sayed, Nagwa M. Ghandour, and Taymou Mostafa


Smokers were significantly associated with:
- lower hypo-osmotic swelling test
- lower seminal zinc levels
- higher sperm DNA fragmentation percent
- higher seminal reactive oxygen species levels
Marijuana

Effects of delta-9-tetrahydrocannabinol, the primary psychoactive cannabinoid in marijuana, on human sperm function in vitro

Lynne B. Whan, Ph.D., a Mhairi C. L. West, Ph.D., a Neil McClure, M.R.C.O.G., a,b and Sheena E. M. Lewis, Ph.D. a


Sperm incubated with THC at concentrations equivalent to therapeutic and recreational plasma levels
31 healthy male volunteers without infertility divided into 2 groups:

**Physically Active (n = 16):** had practiced endurance activities, except bicycling, for over a year

**Sedentary (n=15):** had NOT had regular physical activity during the previous year
Active men demonstrated higher:
- progressive motility
- normal morphology
- serum FSH, LH, and testosterone
- T / Cortisol ratio (indicative of an anabolic state)
Men (n=188) aged 18–22yrs from the Rochester Young Men’s Study assessed via questionnaire for:

- Physical Activity (hours/week of moderate-vigorous exercise)
- TV watching (hours/week of TV, video, or DVD watching)
Sedentary Lifestyle and Fertility

Findings

Sperm concentration and total sperm count - directly related to physical activity after multivariable adjustment.

Men in highest quartile of activity (≥15 hr/wk)- 73% higher sperm concentration than lowest quartile (<5 hr/wk)

TV watching inversely associated with sperm concentration and total count
While studies of the association between BMI and semen parameters have yielded conflicting results, there does appear to be a **negative** relationship between obesity and fertility outcomes as well as endocrine profiles.

**Review of the Danish National Birth Cohort reveals that among men with a BMI $\geq 18.5$ kg/m$^2$, there exists a dose-response relationship between increasing BMI and subfecundity (time to pregnancy $> 12$mo). Odds ratio 1.2.**

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**Subfecundity in overweight and obese couples**

C.H. Ramlau-Hansen$^{1,2,5}$, A.M. Thulstrup$^2$, E.A. Nohr$^3$, J.P. Bonde$^2$, T.I.A. Sørensen$^4$ and J. Olsen$^1$
Obesity and Assisted Reproduction

Retrospective analysis (n=305) of ICSI outcomes demonstrated that increased paternal BMI is associated with:

- decreased blastocyst development
- decreased clinical pregnancy rates
- decreased live birth outcomes
Anabolic Steroids

Definition: family of hormones which includes testosterone with anabolic (muscle-building) and androgenic (masculinizing) properties

Prevalence- 3 million users in US (Souza, 2011)

Pathophysiology- suppresses hypothalamic-pituitary axis

- low FSH, LH levels

- supraphysiologic serum testo level reduces intratesticular testosterone levels required for spermatogenesis

- severe oligospermia/azoospermia
Anabolic Steroids

Cessation of steroids- spontaneous recovery in 4-12 months in most although may take up to 5 years (Turek, 1995)

Variety of successful treatment regimens have been reported with small series- hCG alone, hCG/hMG, clomiphene citrate
Practice Patterns of AUA Urologists (N=387) 
Empiric Medical Therapy for Infertility

Agents used for empiric medical therapy for idiopathic male infertility

- Clomid
- hCG
- Testosterone
- Anastrazole
- Tamoxifen
- hMG/FSH
- GnRH
- Letrozole
- Testolactone
- DHEA

Sabanegh, Brannigan: J Urol, 2012
## Endocrinopathy and Male Infertility*

<table>
<thead>
<tr>
<th></th>
<th>Excess</th>
<th>Insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pituitary</strong></td>
<td>Hyperprolactinemia</td>
<td>Hypogonadotropic Hypogonadism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Kallman’s Syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Acquired insufficiency</td>
</tr>
<tr>
<td><strong>Thyroid</strong></td>
<td>Hyperthyroidism</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td><strong>Androgens</strong></td>
<td>Congenital Adrenal Hyperplasia</td>
<td>Exogenous Steroids</td>
</tr>
</tbody>
</table>

*Account for 3-10% of causes of infertility*
Hyperprolactinemia

- Mechanism: complex effects: inhibits GnRH release
- Cause: pituitary adenomas, medications
- Therapy
  - remove causes (meds)
  - treat macroadenoma (> 1cm dimension, Prolactin level > 200microgm/L)
    » Dopamine agonist therapy (cabergoline 0.125-1.0 mg twice weekly)
    » Surgical removal
- Medication therapy for idiopathic
  » Cabergoline X 6 months- significant improvements in semen parameters (De Rosa, 2006)
  » Fertility in 53% of men on cabergoline (Melmed, 2011)
Hypogonadotropic Hypogonadism

Low FSH, LH, testosterone levels

Causes

- Congenital- inadequate GnRH secretion
  - Anosmic form or Kallmann’s syndrome
  - Idiopathic hypogonadotropic hypogonadism
- Acquired- inadequate GnRH or gonadotropin secretion
**Hypogonadotropic Hypogonadism**

**Therapy**

- Gonadotropin Replacement
  - **LH activity** - hCG 1500-2500 IU 3X/week X 3-6 months
  - **FSH activity** - hMG 75-150 IU 3X/week (alternative: recombinant FSH 100-150 IU 2-3X/week)
    - 90% of patients will have return of spermatogenesis (Haidl, 2002)
- Pulsatile GnRH (men with intact pituitary function)
- Clomid therapy - effective for select patients presenting post-puberty

**Results**

- Most conceive with therapy although 71% oligospermic
- Postpubertal onset patients - often respond to hCG alone
- 10% maintain spermatogenesis post treatment cessation (Raivio, 2007)
Leukocytospermia

Associated with

• Lower motility
• Higher seminal oxidative stress
• Antioxidant capacity (TAC)

Agarwal et al, Fert Steril 2008
Genitourinary Infection

Screen men with leukocytospermia (WHO defn > 1 mil/ml)

elevated oxidative stress (ROS)

Both bacterial and viral (HSV) infections – sperm oxidative damage (Potts, J 2000; Kapranos, 2003)

Antibiotic therapy may improve semen parameters (Vicari, 2000; Sabanegh, 2012)

Reduced oxidative stress

Improved motility and natural conception rates (28 vs. 5%) with therapy of cx+ ureaplasma/chlamydial infection

Addition of NSAID, L-carnitine - incremental benefit over antibiotic alone (Vicari, 2002; Gambera, 2007)
Ejaculatory Dysfunction

Premature ejaculation

Anejaculation
  – Spinal cord injury
  – Diabetes
  – Medications
  – Retroperitoneal surgery (RPLND)
  – Idiopathic

Retrograde ejaculation
  – Bladder neck surgery
  – Diabetes
  – Medications
Retrograde/ Anejaculation

- Correct reversible causes (medications)
  - Selective serotonin reuptake inhibitors (SSRI)
  - Alpha blockers

<table>
<thead>
<tr>
<th>Agent</th>
<th>Incidence of reduced ejaculatory volume (%)</th>
</tr>
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<tbody>
<tr>
<td>Placebo</td>
<td>12</td>
</tr>
<tr>
<td>Tamsulosin (0.8mg)</td>
<td>90 (35% anejaculatory)</td>
</tr>
<tr>
<td>Alfuzosin</td>
<td>21</td>
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Hellstrom, 2006
Retrograde Ejaculation

- Medication regimens (sympathomimetic, anticholinergic)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudoephedrine</td>
<td>120mg po bid</td>
</tr>
<tr>
<td>Ephedrine sulfate</td>
<td>25mg po bid</td>
</tr>
<tr>
<td>Imipramine</td>
<td>25 mg po tid</td>
</tr>
</tbody>
</table>

- Assisted reproduction
  - Urinary alkalinization
  - Sperm recovery from bladder
  - Intrauterine insemination
Why Empiric Therapy?

Distribution of Final Diagnostic Categories Found in the Male Fertility Clinic

<table>
<thead>
<tr>
<th>Male factor problem</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic abnormal semen (OAT syndrome) or no demonstrable cause</td>
<td>75.1</td>
</tr>
<tr>
<td>Varicocele</td>
<td>12.3</td>
</tr>
<tr>
<td>Infectious factors</td>
<td>6.6</td>
</tr>
<tr>
<td>Immunological factors</td>
<td>3.1</td>
</tr>
<tr>
<td>Other acquired factors</td>
<td>2.6</td>
</tr>
<tr>
<td>Congenital factors</td>
<td>2.1</td>
</tr>
<tr>
<td>Sexual factors</td>
<td>1.7</td>
</tr>
<tr>
<td>Endocrinal disturbances</td>
<td>0.6</td>
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Disclosure

**Minimal level 1 evidence**

- small uncontrolled series
- poor quantification of interventions
- multiple unidentified confounding variables

<table>
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<tr>
<th>Level of Evidence</th>
<th>Grading Criteria</th>
<th>Grade of Recommendation</th>
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<tbody>
<tr>
<td>1a</td>
<td>Systematic review of RCTs including meta-analysis</td>
<td>A</td>
</tr>
<tr>
<td>1b</td>
<td>Individual RCT with narrow confidence interval</td>
<td>A</td>
</tr>
<tr>
<td>1c</td>
<td>All and none studies</td>
<td>B</td>
</tr>
<tr>
<td>2a</td>
<td>Systematic review of cohort studies</td>
<td>B</td>
</tr>
<tr>
<td>2b</td>
<td>Individual cohort study and low quality RCT</td>
<td>B</td>
</tr>
<tr>
<td>2c</td>
<td>Outcome research study</td>
<td>C</td>
</tr>
<tr>
<td>3a</td>
<td>Systematic review of case-control studies</td>
<td>C</td>
</tr>
<tr>
<td>3b</td>
<td>Individual case-control study</td>
<td>C</td>
</tr>
<tr>
<td>4</td>
<td>Case-series, poor quality cohort and case-control studies</td>
<td>C</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion</td>
<td>D</td>
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Source: Ann Surg © 2004 Lippincott Williams & Wilkins
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but, it is what it is.....
Empiric Therapy

Anti-estrogens
Aromatase inhibitors
Gonadotropin-releasing hormone agonists
Gonadotropins

Caveat: these are not FDA approved indications for these medications
Anti-estrogens

Mechanism of action

» block estrogen receptors at hypothalamus and pituitary, preventing negative feedback of estrogen on gonadotropin secretion

» Increased GnRH, FSH, LH and resultant increase in serum testosterone (and spermatogenesis)

Agents

» Clomiphene citrate

» Tamoxifen citrate
Clomiphene Citrate

Dose: 12.5-25mg po q day

Side effects: weight gain, hot flashes, mood swings, gynecomastia, decrease in semen count, DVT/PE

Supporting evidence

- Meta-analysis- improved pregnancy rates -odds ratio of 2.47 (O’Donovan, 1993)
- Randomized trial- 58 vs 16% pregnancy rate with clomid vs. control in patients with normal baseline semen parameters (Check, 1989)
- Improved semen parameters but no improvement in pregnancy rates (Wang, 1983; Ronnberg, 1980; Micic, 1985)

Not supporting

- Meta-analysis- no improvement in pregnancy rates (Liu, 2003)
Aromatase Inhibitors

Mechanism of action

» Aromatase localizes to adipose tissue, liver, testis (Leydig and Sertoli cells)

» Alterations in testosterone/estrogen ratio negatively impacts spermatogenesis

  – Decreased LH, FSH levels due to direct feedback inhibition of HPG axis

  – Inhibits androgen synthesis in testis

  – Direct adverse effect on germ cells
Aromatase Inhibitors

Agents

- Steroidal
  
  Testolactone (50-100mg po bid)

- Non-steroidal
  
  Anastrozole (1mg po daily)
  Letrozole

Use- empiric therapy for idiopathic oligospermia in patients with Testosterone/Estrogen ratios of <10
Aromatase Inhibitors
Treatment Results

Testolactone (Pavlovich, 2001; Raman, 2002)
- 50-100 mg po bid for 5 months
- Significant increase in T/E2 ratio; Improved semen parameters

Anastrazole (Raman, 2002)
- 1mg po daily for 4-5 months
- Increase T/E2 ratio (5.3 pre treatment to 12.4)
- Semen parameters- count increased from 5.5 mil/cc to 12.4 mil/cc; motility increased from 14 to 21%; morphology improved from 6.5 to 12.8%
- Pregnancy rates were not evaluated
Antioxidant Therapy

Types
- Preventative: metal chelators and metal binding proteins
- Scavenger: vitamins E and C, lycopene, carnitine, etc.

Fertility outcomes
- Vit E+C supplementation- decreased semen ROS (DeFoore, 2004)
- Vit C (200-1000mg/day)- increased sperm counts in infertile males (Dawson, 1987)
- Randomized crossover study of Vit E (600IU q day)-improved zona binding but other parameters unchanged
- Cocharane Collaboration meta-analysis (2011- 17 trials)
  - Marked heterogeneity in regimens
  - 82% improvement in sperm quality and/or pregnancy rates
- Improved ICSI outcomes (Greco, 2005)
L-Carnitine

Effects - mitochondrial metabolism/spermatozoal energy production and motility in epididymis

Infertility and carnitine

- Reduced free and total seminal carnitine levels in infertile men (Zopfgen, 2000)
- Reduced acetyl L-carnitine to L carnitine ratios in patients with reduced motility (Bartellini, 1987)
Antioxidant Therapy with L-Carnitine

Efficacy

- Increased sperm density (Vitali, 1995)

- Improved motility- randomized double blind placebo controlled crossover study- 2 grams/day (Lenzi, 2003)
Empiric Therapy for Male Subfertility

Surveys suggest widespread non-standardized use throughout urologic community

Not FDA approved indication at present

Efficacy conclusions limited by lack of well designed large studies although certainly some small series support anti-estrogen, aromatase inhibitor use in targeted subgroups

Antioxidant therapy has low toxicity profile and potential benefits for idiopathic subfertility patients
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Androgen Therapy

Earliest empiric therapies

» Low dose- “improve epididymal maturation and boost spermatogenesis”

» Rebound- induce azoospermia with improved spermatogenesis in recovery phase

Bottom line- there is no role for routine testosterone therapy in the management of male infertility- in fact, the therapy is counterproductive in most patients

- Results: meta-analyses -no improvement in fertility (Kamischke, Human Repro, 1999; Liu, Human Repro Update, 2003)
Other Anti-estrogens

Similar results in tamoxifen trials as clomid

Metanalysis of 10 studies/783 men receiving either clomid or tamoxifen- no difference in pregnancy rates with antiestrogen therapy (Vandekerckhove P, Cochrane Database Sys Rev 2000)

? Role of combination therapy for idiopathic oligospermia

Bottom line- there may be a subpopulation of oligospermic patients without other correctable problems that will benefit from empiric anti-estrogen therapy but further properly designed and powered studies are needed to stratify this population
Frequent use for idiopathic infertility

- 62% general urologists
- 73% subspecialty trained in male infertility

Indications

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<tr>
<th>Sperm Concentration (mil/ml)</th>
<th>Threshold for Use (%)</th>
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<tr>
<td>&lt;5</td>
<td>12</td>
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<tr>
<td>5-10</td>
<td>29</td>
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<tr>
<td>10-20</td>
<td>32</td>
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<tr>
<td>&gt;20</td>
<td>7</td>
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Sabanegh, Brannigan: J Urol 2012