MALE INFERTILITY

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DISCLOSURES

- ForHims-Medical Advisory Board

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OUTLINE

- Male Infertility
- Common Clinical Encounters in Male Infertility: Varicoceles and Hypogonadism
- Clinical Pearls in Male Infertility
- Disparities in Access to Male Fertility Services
- Transgender Fertility
- Conclusions

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MALE INFERTILITY

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INTRODUCTION

- The inability to produce a pregnancy within 12 months of consistent attempts
- Infertility affects ~15% of couples worldwide
- Male factor infertility exclusively accounts for about 20-30% of infertility cases, but contribute about 50% of infertility cases overall
- In North America, male infertility affects about 4.5-6% of men
- Global rates of male infertility range from 2.5-12%

Agarwal et al. A unique view on male infertility around the globe. Reproductive Biology and Endocrinology. 13: 37 (2015)

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EPIDEMIOLOGY

- Quantifying true numbers accurately is difficult for several reasons
  - Cultural and societal historical trends ("it's the woman's fault")
  - Religious beliefs
  - Infertile males lacking or not participating in surveys targeted at infertility
  - Varied definitions of time frames for infertility across studies
  - Male infertility not viewed as "disease"

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WHY IS REPRODUCTIVE HEALTH IMPORTANT?

- Men don't routinely engage with a physician between ages 18-50
- Reproductive Health visits are ideal times to engage with men
  - Male factor infertility is increasingly drawing younger men into the health system
  - Prime demographic for vasectomy evaluation is in the early 30s to late 40s
- Erectile dysfunction (ED), an important marker of cardiovascular disease, is usually not considered in men under 50, and is often dismissed by patients and physicians
- T deficiency, which impacts fertility and sexual function, is also a risk factor for cardiovascular disease
- There is a gap in care for reproductive services for transgender women and urologists are an important component of their multidisciplinary care
- Therefore, many aspects of reproductive health represent unique opportunities to also impact public health

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MAJOR CAUSES OF MALE INFERTILITY

- Anatomic
  - Varicoceles (most common), undescended testes, vasectomy status
- Hormonal
  - Hypogonadism
- Genetic
  - Y chromosome microdeletions, Chromosomal abnormalities, Mutations in the CFTR gene
- Gonadotoxins
  - Pharmacologic agents, environmental exposures, biological agents

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CLASSIFICATION OF MALE INFERTILITY BY LOCATION

Location	Examples
Pretesticular	Hypogonadotropic (Secondary) hypogonadism, Prolactinoma
Testicular	Hypergonadotropic (Primary) hypogonadism, Varicoceles, Cryptorchidism, Klinefelter's Syndrome, Sertoli Cell Only Syndrome, Maturational Arrest, Gonadotoxins, Genetic abnormalities, Structural sperm defects, testes infections
Post-testicular	Ejaculatory Duct Obstruction, Vasectomy, Congenital Absence of the Vas

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OTHER CLASSIFICATIONS OF MALE INFERTILITY

Type	Examples
Primary or Secondary	• Primary: Male was never fertile • Secondary: Male was fertile at some point, but now is not
Sperm parameters	• Normospermia: Normal parameters • Oligospermia: <15 million sperm cells/mL in ejaculate • Azoospermia-no sperm in the ejaculate • Asthenospermia: Impaired sperm motility • Teratospermia: Abnormal sperm morphology • Aspermia: No ejaculate
Obstructive status	• Obstructive: Partial or complete • Non-obstructive

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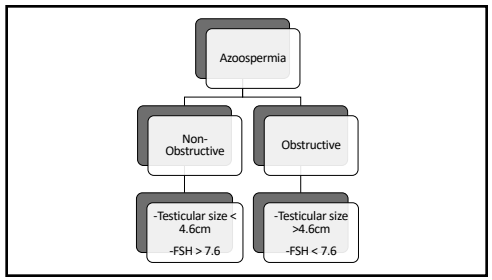

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HISTORY OF THE MALE INFERTILITY PATIENT

- Any prior Testosterone Replacement Therapy (TRT)
- Supplements (lots of male supplements have derivatives of testosterone)
- Family history of infertility
- Repeated respiratory infections as a child
- Genital trauma
- Radiation or chemical exposures
- Hernia surgeries
- Signs and symptoms of testosterone deficiency
- Any prior partners pregnant

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PHYSICAL EXAM FOR THE MALE INFERTILITY

- Physical stature (very tall or short)
- Gynecomastia
- Testicular size (normal about 16cc, can use Prader orchiometer), consistency, and symmetry
- Presence and size of epididymis and associated spermatoceles
- Palpable vasa
- Presence of varicoceles
- Presence of hernias
- Penile size and anatomy

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SEMEN ANALYSIS

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COMMON CLINICAL ENCOUNTERS IN MALE INFERTILITY

1. *Varicoceles*
2. *Hypogonadism*

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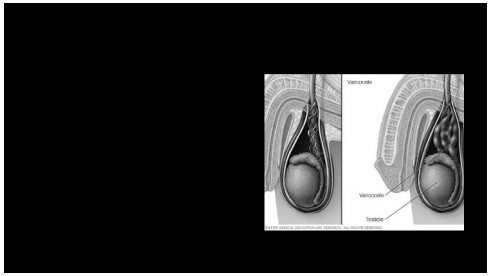

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CLINICAL VARICOCELE GRADING (DUBIN AND AMELAR)

- Examine patient standing up, during cough, or Valsalva
- Subclinical Grade: Only seen on ultrasound, not on physical exam
- Grade 1: Small, **palpable** thrill with Valsalva
- Grade 2: Moderate, **palpable** without Valsalva
- Grade 3: Large, "bag of worms", **visible** without Valsalva

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Review Article

Systematic Review of the Impact of Varicocele Grade on Response to Surgical Management

Denise Asafu-Adjei,* Clark Judge, Christopher M. Deibert, Gen Li, Doron Stember and Peter J. Stahl

From the Departments of Urology, Columbia University Medical Center York (DA-A, PJS) and Mount Sinai Hospital (CS) and Department of Biostatistics, Mailman School of Public Health (GL), New York, New York, Section of Urology, University of Chicago Medical Center (CJ), Chicago, Illinois, and Division of Urological Surgery, University of Nebraska Medical Center (CMD), Omaha, Nebraska

- Evaluate impact of varicocele grade in response to varicocelectomy or embolization
- Review of 20 studies
- Mean improvements in sperm concentrations were significant and overall motility were greater for Grade 2-3 varicocele repairs and likely to be clinically significant

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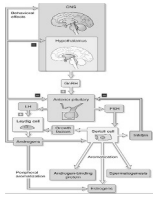
HYPOGONADISM (LOW TESTOSTERONE)

- Total testosterone level below 300 ng/dL
- Diagnosis made after 2 confirmatory total testosterone levels conducted in the early morning
- Testosterone has physiologic contributions to muscle, bone, skin, spermatogenesis, sexual function, and brain function
- Testosterone is made via the HPG axis
- 90% of T is made by Leydig cells in the testicles
- 10% of T is made by the adrenals



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EPIDEMIOLOGY OF HYPOGONADISM

- A multi-ethnic, population-based observational study of 1,475 men ages 30-79 in the U.S.
  - ➢24% of subjects had serum T <300 ng/dL
  - ➢Prevalence of *symptomatic* androgen deficiency 5.6% (Total T<300 and symptoms)
    - ➢Rose markedly to 18.4% among age >70

Prevalence of symptomatic androgen deficiency in men.
Araujo AB, Esche GR, Kupelian V, O'Donnell AB, Travison TG, Williams RE, Clark RV, McKinlay JB.
J Clin Endocrinol Metab. **2007** Nov;92(11):4241-7. Epub **2007** Aug 14.

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SIGNS AND SYMPTOMS OF T DEFICIENCY

Table 5: Symptoms and Signs Associated with Testosterone Deficiency
Physical Symptoms and Signs
Reduced energy
Reduced endurance
Diminished work performance
Diminished physical performance
Loss of body hair
Reduced beard growth
Fatigue
Reduced lean muscle mass
Obesity
Cognitive Symptoms and Signs
Depressive symptoms
Cognitive dysfunction
Reduced motivation
Poor concentration
Poor memory
Irritability
Sexual Symptoms and Signs
Reduced sex drive
Reduced erectile function

Source: American Urological Association, Guidelines for Evaluation and Management of Testosterone Deficiency

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HIGH RISK POPULATIONS FOR HYPOGONADISM

- HIV/AIDS
- Unexplained anemia
- Bone density loss
- Diabetes
- Chemotherapy
- Testicular radiation
- Chronic narcotics
- Male Infertility
- Pituitary dysfunction
- Chronic corticosteroids

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CONTRAINDICATIONS TO TRT

- **Men actively trying to conceive**
- Breast cancer
- Prostate cancer (known or suspected)
- Polycythemia
- Cardiovascular event within 6 months
- Relative Contraindications
  - Uncontrolled Obstructive Sleep Apnea
  - Uncontrolled Congestive Heart Failure
  - High baseline hematocrit

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ALTERNATIVE THERAPIES FOR TRT/OPTIONS FOR MEN DESIRING FERTILITY

- **Clomiphene citrate**
  - Anti-estrogen agent
  - Binds to the hypothalamic and pituitary estrogen receptor sites, thereby blocking estrogen's central feedback inhibition of gonadotropin secretion
  - Increased gonadotropin levels and increased testosterone production
- **Tamoxifen**
  - Inhibits hypothalamic and pituitary estrogen receptors, which blocks estrogen negative feedback on gonadotropin release.
  - Hypothalamic pituitary-gonadal gonadotropin release is increased
- **Anastrazole**
  - Inhibits conversion of testosterone to estradiol
- **hCG**
  - Shares a common alpha subunit with LH and FSH
  - It stimulates Leydig cells to make testosterone
- **Menopur**
  - FSH and LH analog

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CLINICAL PEARLS IN MALE INFERTILITY

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OTHER LAB TESTS AND IMAGING FOR FERTILITY

- Y-chromosome microdeletion: looks for one of three deletions in the AZF region.
  - AZFa and AZFb = unable to conceive
    - AUA Guidelines statement: "Although the prognosis for sperm retrieval is poor in patients having large deletions involving AZF region a or b, the results of Y chromosome deletion analysis cannot absolutely predict the absence of sperm."
  - AZFc = can conceive
- Karyotype will assess chromosomal abnormalities
- There are many genetic and chromosomal defects in infertile men, affecting hormonal regulation, spermatogenesis, meiosis, spermiogenesis, genital tracts, and sperm-oocyte interactions. Insufficient lab tests for everything and still so much more we do not know
- **Scrotal ultrasound should not be routinely performed in the initial workup of male infertility**

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SURGICAL INTERVENTIONS FOR MALE INFERTILITY

Non-Obstructive Azoospermia	Obstructive Azoospermia
• Varicocelectomy (microscopic, laparoscopic, open) • Percutaneous Epididymal Sperm Aspiration (PESA) • Microsurgical Epididymal Sperm Aspiration (MESA) • Testicular sperm extraction (TESE) • microTESE	• Same options as obstructive azoospermia • Endoscopic incision of ejaculatory ducts • Vasectomy reversal

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ALTERNATIVES TO CONVENTIONAL CONCEPTION

- Intrauterine insemination
- In vitro fertilization
- Donor sperm
- Adoption

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PEARLS FOR THE INITIAL MALE INFERTILITY OFFICE VISIT

- **Exogenous testosterone should be avoided!**
- Scrotal ultrasound should not be routinely performed in the initial workup
- Males **AND** females should have an initial fertility evaluation
- Advance paternal age is 40+ →increased risk of adverse health outcomes for offspring

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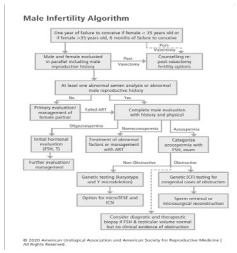

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DISPARITIES IN ACCESS TO MALE INFERTILITY SERVICES

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FACTORS CONTRIBUTING TO ACCESS DISPARITIES IN MALE INFERTILITY

1. Urological Workforce
2. Awareness and Education
3. Insurance Inequities
4. Financial Barriers
5. Donor Sperm Utilization
6. Ethical Considerations

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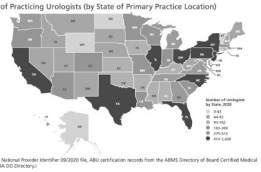
1. THE UROLOGICAL WORKFORCE

Number of Practicing Urologists (by State of Primary Practice Location)



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MALE INFERTILITY SPECIALISTS

Fellowship Areas

Fellowship Areas	Practicing Urologists Represented		
	Number	Percent (%)	+/- MOE (%)
Oncology	1,668	12.5	1.4
Pediatrics	1,111	8.3	1.1
Robotic Surgery	975	7.3	1.3
Endourology/Stone Disease	944	6.8	1.3
Female Pelvic Medicine and Reconstructive Surgery	825	4.7	0.7
Male Genitourinary Reconstruction	566	4.5	0.9
Erectile Dysfunction	486		0.8
Male Infertility	458		0.7
Laparoscopic Surgery	413		0.7
Renal Transplantation	253	1.9	0.5

(Data source: Weighted samples from the 2005 AUA AMA and Census.) Fellowship experience was reported on programs with a duration of one year or longer. The respondents could select more than one answer, so the total number of urologists may differ from the total number of practicing urologists.

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2. MALE INFERTILITY AWARENESS AND EDUCATION

- There continues to be a global lack of education and awareness that men can suffer from infertility, driving the overall low rates of men seeking medical care for this
- Stigmas about male infertility and implications on masculinity continue to permeate many communities, still deeming it a "woman's problem"
- Early education and awareness about fertility lags in men, compared to women

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3. INSURANCE INEQUITIES

- Despite infertility being a disease, it is well established that infertility care is expensive and is not a covered benefit in most insurance plans
- There are gender disparities in insurance coverage, with only half of the states with mandated coverage for infertility mentioning male infertility
- Excluding male infertility makes it less likely for men to seek evaluations and places undue burden on female partners

Dupree. *Insurance Coverage of Male Infertility: What Should The Standard Be?* Translational Andrology and Urology. 2018. 7 Supp 3: S263-S66

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4. FINANCIAL BARRIERS

- Infertility care is expensive! An average IVF cycle is about $25K, with increased pricing for donor egg/sperm and surrogacy
- Elliott et al. Urology Practice. 2016. 3(4): 256
  - Survey study of men receiving infertility care
  - About 16-20% of annual incomes were spent on infertility-related expenses
  - Out of pocket expenses: 64% spent ≥ $15,000, 16% spent ≥ $50,000
- Wu et al. J Urol. 2014. 191
  - College educated, high income couples had more access to infertility care

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5. DONOR SPERM UTILIZATION

- Donor sperm remains vastly underutilized and difficult to access
- Private sperm banks are not required to release the ethnic origins of their donors publicly and pricing is not regulated
- Donor insemination grew significantly between 2015-2017, with estimated 440,986 using donor sperm (Arocho et al)
- Most users were White, urban, college-educated, older age, and had higher incomes (Arocho et al)

Arocho et al. Estimates of Donated Sperm Use in the United States: National Survey of Family Growth 1995-2017. Fertility and Sterility. Oct 2019; 112(5): 718-723.

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6A. MEDICAL MISTRUST AMONGST AFRICAN-AMERICAN MEN

- Widespread distrust stems from centuries of unethical, yet sanctioned medical experimentation on African-Americans
- In the reproductive health space, the Tuskegee Syphilis Study (1932-1972) and federal funded sterilization programs throughout the 1900s have contributed to significant mistrust when discussing male infertility and possible treatments
- Although bioethical research has advanced, donation and utilization of sperm (e.g. microTESEs) can still be seen as "experimental," with skepticism who will have access to this sperm

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6B. RELIGIOUS CONSIDERATIONS

- Religion is a major driver of attitudes regarding infertility treatments and can influence attitudes toward infertility care and result in access disparities
- There are varying degrees of support and allowances for male infertility treatment in Catholicism, Islam, and Judaism
- Religion can also dictate support for married/unmarried couples and those who identify as LGBTQ

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TRANSGENDER FERTILITY

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INTRODUCTION

- 0.6% of U.S. adults (1.4 million people) and 0.7% of U.S. adolescents identify as transgender
- **Transgender woman →Birth sex male whose gender identity is female (MtF)**
- **Transgender man→Birth sex female whose gender identify is male (FtM)**

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FERTILITY PRESERVATION

- Couples seeking care for infertility has grown significantly due to availability of technology
- It is well established that gender affirming treatments and surgeries have negative, sometimes permanent effects, on fertility
- The extent to which transgender patients are being educated about the effects of various hormonal treatments on fertility and available preservation options is unknown
- There are currently no guidelines for clinicians providing fertility preservation and reproductive care to transgender patients

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OPTIONS FOR FERTILITY PRESERVATION

- Insurance coverage for Assisted Reproductive Technology in transgender patients remains unclear

Table 1. Fertility preservation methods for transgender people [11, 12]

Transmen (assigned female at birth)	Transwomen (assigned male at birth)
Postpubertal options Oocyte cryopreservation Embryo cryopreservation (with partner's or donor's gamete)	Postpubertal options Sperm cryopreservation Embryo cryopreservation (with partner's or donor's gamete)
Prepubertal options Ovary/ovarian tissue cryopreservation (experimental)	Prepubertal options Testicular tissue cryopreservation (experimental)

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EFFECTS OF HORMONAL THERAPY ON TESTICULAR FUNCTION

- Spermatogenic suppression
- Data has shown that discontinuation of anti-androgen treatments prior to GAS results in increased intra-testicular and serum testosterone levels, with adequate recovery of spermatogenesis
- 11 studies between 1977 and 2015 showed a range of effects on spermatogenesis, from significant arrest to unchanged spermatogenesis (Schneider et al)

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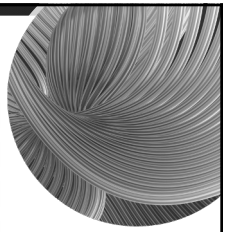
ETHICAL ISSUES IN TRANSGENDER FERTILITY

- The phase of life that people transition to transgender and the birth-assigned gender can affect reproductive choices
- Access to information on fertility-preserving technologies in MtF patients is challenging and leads to uninformed decision making
- Many patients unaware that hormone treatments for MtF transitions are less easily reversible than FtM transitions
- Social stigma and discrimination from providers against transgender patients and their right to reproduce



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CONCLUSIONS

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CONCLUSIONS

- Male infertility is a common **disease** and needs to be addressed and treated as such
- A strong understanding of endocrinology is an integral part of Male Reproductive Health and Male Infertility
- There are several key barriers in accessing to care for male infertility services that contribute to significant health disparities
- There are multiple effective medical and surgical treatment options for male infertility
- Addressing Male Reproductive Health is an important aspect of major public health issues and Men's Health clinicians are in a unique position to address that
- Transgender fertility care requires a multidisciplinary approach and a good understanding of patient goals
- A reproductive health visit could be a man's only engagement with a health professional for decades, so make these encounters count!

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THANK YOU!
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