Physiology, Epidemiology, Pathophysiology, Evaluation

Editors:

Alexander W. Pastuszak, MD, PhD

Authors:

James M. Dupree, MD, MPH

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Key Points:

1. Infertility is a disease of the reproductive system and is defined as inability to conceive within 6-12 months of regular, unprotected intercourse
2. One in eight couples in the U.S. have infertility
3. Male infertility is a contributing factor in approximately 50% of infertile couples
4. Men and women should have concurrent infertility evaluations
5. Male evaluations should include a careful history, physical exam, semen analysis, and select specialized testing

1. Introduction

Male reproduction is a highly integrated process that involves the hypothalamic-pituitary-gonadal (HPG) axis, the testicles, and the excurrent ductal system. Male fertility can be hampered by a wide array of anomalies involving any of these structures, as will be detailed in this section. While the evaluation and treatment of infertile couples has historically focused on the female partner, it is now clear that evaluating and optimizing male reproductive health is a critical part of infertility care. This important section highlights both the complexity of normal male fertility as well as the numerous pathophysiological mechanisms by which this delicate balance in normal function can be disrupted.

1.1 Key Words

ejaculation, epididymis, fertility, follicle stimulating hormone (FSH), infertility, luteininzing hormone (LH), semen analysis, sperm, testicle, testosterone, varicocele, vas deferens

2. Definition

Infertility is defined as a couple's inability to achieve a pregnancy following **one year of unprotected intercourse**. Despite this definition, couples may elect to undergo an infertility evaluation prior to one year, particularly in cases where male risk factors (such as history of bilateral cryptorchidism) are present, when the female partner is of advancing age (>35 years), or if underlying fertility is

questioned.[1]

3. Epidemiology

Although infertility prevalence rates vary by geographic region and study methodology, an estimated **8-14%** of couples are affected, among whom a **male factor** is contributory in **36-75%** of cases.[2,3,4,5,6,7] Select populations are at higher risk for infertility including those with prior histories of **congenital genitourinary (GU) malformations, undescended/ascending testes, testicular cancer, malignancy requiring chemotherapy or radiation, hormonal disorders, genetic abnormalities, select genetic syndromes (cystic fibrosis, Kallman, primary ciliary dyskinesia), prior GU or inguinal surgery, or a history of GU infections** , among others. Infertile males may also be at increased risk for subsequent development of **testicular malignancy**, with reported incidences ranging from **0.3-0.9%.**[8,9,10] Compared with normal controls, **men with one or more abnormalities on semen analysis (SA) experience an estimated 2-20 fold increased risk of testicular malignancy, and those with two or more abnormalities have an estimated 2.3-fold increased risk of death** and should be informed of these health risks during their infertility evaluations.[10,11,12] Infertile males may additionally be at increased risk for colorectal carcinoma, melanoma, prostate cancer and have a higher rate of comorbidities, including diabetes, ischemic heart disease, alcohol and drug abuse and should be advised about these possible risks as well.[13,14,15]

4. Objectives of Evaluation

Based on AUA Best Practice statements, there are several objectives for the evaluation of the infertile male:[1,16] (i) Recognize and treat reversible conditions (ii) Identify disorders potentially amenable to assisted reproductive techniques (ART) using the male partner's sperm (iii) Identify irreversible disorders not amenable to assisted reproductive techniques (ART) using the male partner's sperm (iv) Identify syndromes and/or medical conditions which may be detrimental to the patient's health (v) Distinguish genetic abnormalities which can be transmitted to or affect the health of offspring. Information obtained during the evaluation process may not only improve chances for subsequent paternity, but also enhance quality/quantity of life, reduce sequelae of comorbid conditions, and permit appropriate counseling as to the health of the patient and future children.

5. Physiology

5.1 Spermatogenesis

The seminiferous tubules are responsible for spermatogenesis and comprise approximately **70-80%** of the testicular volume, with an estimated 83,000,000 diploid germ cells present prior to pubertal development.[17,18] Spermatogonial cells are represented by three sub-populations, each of which have distinct roles: A (dark), A (pale), and B spermatogonia.[19,20,21] **A (dark) spermatogonia** function as a quiescent, diploid reserve and are active only during initial pubertal development and following stem cell depletion from gonadotoxic exposures.[22,23,24] **A (pale) spermatogonia** are more mitotically active and serve as eternal progenitor cells, with self-renewal occurring with each mitotic division.[25,26] **Type**

B spermatogonia are immediate precursors to primary spermatocytes and subsequently undergo two meiotic divisions to ultimately produce spermatids. Due to the high mitotic activity of the **A (pale) and B spermatogonia, they are more susceptible to gonadotoxic exposures than the A (dark) and Leydig cells**. This likely accounts for the transient arrest in spermatogenesis and preservation of testosterone (T) production observed following limited doses of chemoradiation therapy.[27,28,29]

The process of spermatogenesis occurs over a period of **~74 days** in a tightly regulated microenvironment.[30,31] The male reproductive system represents an immunoprivileged site, with blood-testis (via Sertoli tight junctions) and blood-epididymal barriers restricting passage of large molecules, specific transporters regulating the intraluminal milieu, and immunologic sequestration of germ cells modulating immune responses.[32] Additionally, elevated intra-testicular levels of T and dihydrotestosterone (DHT) are essential for spermatogenesis.[33]

Following completion of spermatogenesis, spermatozoa exit the seminiferous tubules via the efferent ducts through the caput and corpus of the epididymis. Following an estimated transit time of two days, the sperm are stored predominantly in the cauda of the epididymis, where they may remain for two to three months or until the time of ejaculation.[34]

5.2 Ejaculation

Normal ejaculation consists of two phases: **emission** and **expulsion**. The emission phase is thought to be coordinated through the spinal ejaculatory generator (SEG), which is likely located in the **T12-L2 region** of the spinal cord and regulates the parasympathetic, sympathetic, and motor nerve pathways. The SEG is a putative region, based on animal studies, and additional work is needed to verify its location and role in humans. Although parasympathetic input is present, seminal emission is primarily a sympathetic-mediated event. Following sufficient stimulation, the SEG stimulates bladder neck contraction and the coordinated release of seminal fluid into the proximal bulbar and posterior urethra.[35,36] Filling of the posterior urethra subsequently stimulates the urethral-muscular reflex, which activates the sacral spinal cord (**S2-4**) and initiates the expulsion phase of ejaculation. The pudendal nerve generates rhythmic contractions of the **bulbospongiosus, ischiocavernosus,** and **levator ani** muscles and forcefully expels the ejaculate.[37]

5.3 Hypothalamic-Pituitary-Gonadal Axis

Several hormones are responsible for the development, regulation, and physiologic function of male sexual function and fertility. The hypothalamus initiates hormonal release through generation of gonadotropin releasing hormone (GnRH), which acts on the anterior pituitary to stimulate secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH). FSH binds to Sertoli cells to initiate the first round of meiosis and increase production of androgen-binding protein (which, in turn, concentrates testosterone [T], dihydrotestosterone [DHT], and 17-beta-estradiol in testes). Among other factors, Sertoli cells subsequently release inhibin, which negatively feeds back on the anterior pituitary to regulate FSH release. LH acts on Leydig cells to increase T production, which may be converted to estradiol (via aromatase) or DHT (via 5-alpha reductase). Estradiol and T negatively

feedback on the hypothalamus and pituitary to regulate FSH and LH production. [38,39]

Both FSH and LH are essential to the normal growth and development of the testicles and maintenance of spermatogenesis. T and DHT have roles in the embryologic and pubertal stages for the normal development of male primary and secondary sexual characteristics. Optimal spermatogenesis depends on adequate T and DHT concentrations, although the role and significance of DHT, including the impact of 5-alpha reductase inhibitors [5ARI], is controversial and requires additional investigation. [40,41]

Conditions affecting infertility may result in disruption of the hypothalamic-pituitary-gonadal (HPG) axis, with various hormonal profiles assisting in identifying the underlying pathology. The interpretation of hormonal testing will be discussed in greater detail in the evaluation section of the current review.

6. Pathophysiology of Male Infertility

Multiple conditions are associated with male-factor infertility, including **anatomic, behavioral and environmental, iatrogenic, idiopathic, infectious, and syndromal etiologies**. Each section will briefly review definitions, prevalence, proposed pathophysiologic mechanisms, and published associations with infertility.

6.1 Anatomic and Comorbid Diseases

6.1.1 Congenital Absence of the Vas Deferens

Congenital unilateral or bilateral absence of the vas deferens (CUAVD or CBAVD, respectively) describes a condition of unilateral/bilateral, partial/complete agenesis of the vas, epididymal hypoplasia, and seminal vesicle (SV) agenesis/hypoplasia. CBAVD most often results in **low volume, acidic, obstructive azoospermia** and is identified in **1-2% of infertile males** and **4-17% of azoospermic** patients.[41,42,43] **In the absence of detected cystic fibrosis (CF) genetic abnormalities, CUAVD (79%) and CBAVD (21%) are associated with renal anomalies** including agenesis, ectopia, and horseshoe, so all men with vasal agenesis should receive a renal ultrasound to evaluate for renal abnormalities.[16,44,45] Although vasal anomalies may occur following *in utero* dysgenesis, it is more commonly associated with inherited mutations of the cystic fibrosis transmembrane conductance regulator (**CFTR**) genes.[44,46] **CFTR gene mutations are identifiable in 99% of men with CBAVD and approximately 40% of those with CUAVD.**[47,48] Although all men with cystic fibrosis (CF) have CBAVD, not all men with CBAVD will have clinical CF.[49,50] Men with CBAVD are treated as carriers of CFTR gene mutations, regardless of testing results, because of the high prevalence of CFTR mutations, or other CF gene mutations, in men with CBAVD.

6.1.2 Cryptorchidism

Cryptorchidism denotes failure of one or both testicles to descend into the scrotum. Most commonly, this is due to incomplete descent through the inguinal canal, although secondary “ascending” entrapment of the testicles may also occur. The true prevalence of the condition is of ongoing debate,

with varying estimates reported, including **1-9% of infants at birth and 7.5-30% of premature infants.**[51,52,53,54,55] **By 12 months of age, the prevalence decreases to an estimated 0.8-6.7%.**[54,56] Cryptorchidism is associated with future infertility via several potential mechanisms, including congenital testicular and Wolffian duct anomalies, hormonal alterations, and heat-induced damage, with greater risks of infertility associated with higher testicular location and bilateral disease.[57,58,59,60,61] In contrast, men with prior orchiectomy or orchiopexy for testicular torsion demonstrate no impairments in overall fertility, further highlighting the likely developmental etiology for abnormalities observed in men with cryptorchidism.[62] Earlier repair of cryptorchidism is associated with improved fertility, with an **increasing consensus recommending repair by 6-12 months of age.**[63,64] Men with bilateral cryptorchidism experience higher rates of abnormal SA and decreased paternity, while those with unilateral cryptorchidism (treated or untreated) experience similar paternity rates to controls, despite higher rates of abnormal SA.[65,66,67] Men with azoospermia and history of treated orchiopexy demonstrate equivalent success rates during testicular sperm extraction (TESE) compared to non-cryptorchid, azoospermic controls.[68,69] In adult men presenting with cryptorchidism and azoospermia, a return of spermatogenesis and successful paternity has been reported following orchiopexy.[70] Interested readers are encouraged to refer to the 2014 AUA Guideline on cryptorchidism.[64]

6.1.3 Ejaculatory Duct Obstruction

Ejaculatory duct obstruction (EDO) describes partial or complete blockage of the ejaculatory ducts either through narrowing/obliteration of the ductal lumen or through external compression. This may result in partial/complete absence of secretions from the SVs and vasa deferentia, and may present with variable SA findings, including **low volume (<1.5 ml), acidic pH, fructose negative, reduced motility, and/or oligospermia or azoospermia.**[71] EDO affects an estimated **1-5% of infertile males**, with potential etiologies including infection/inflammation, instrumentation, trauma, prostatic/SV calculi, stenosis, and congenital/acquired cysts (Mullerian, Wolffian, utricular).[72]

6.1.4 Varicocele

Varicoceles are an abnormal dilation of spermatic cord veins (pampiniform plexus) and are hypothesized to elevate testicular temperature, with resultant increased oxidative stress and impaired fertility. Varicoceles occur in 15-25% of males and are present in 35-60% of men with sub/infertility.[73,74,75] Although the majority of men with varicoceles do not develop infertility, varicoceles are the most common reversible factor in male infertility.[76] Men with varicoceles may experience progressive impairments in sperm concentration, motility, morphology, acrosomal function, and DNA fragmentation and may develop impaired testicular endocrine function (decreased inhibin and T), independent of sperm concentration.[77,78,79,80,81,82,83] Clinically palpable varicoceles are graded on a scale of 1-3 (1-palpable with Valsalva maneuver; 2-palpable in standing position without Valsalva; 3-grossly visible). Treatment of palpable varicoceles results in significant improvements in fertility and assisted reproductive technique outcomes.[84,85] In contrast, treatment of sub-clinical varicoceles, identified only on ultrasound, has not been shown to improve overall fertility and is not

recommended in current AUA guidelines.[16]

6.1.5 Diabetes Mellitus

Diabetes mellitus may result in several impairments contributing to male sub/infertility including retrograde or anejaculation (with associated reduced semen volume). Diabetes is also associated with decreased sperm concentration and motility, abnormal morphology, and reduced normal DNA integrity.[86]

6.1.6 Other

Several other anatomic findings are of unclear significance and have been associated with male-factor infertility, including testicular/epididymal cysts, hydroceles, and autosomal dominant polycystic kidney disease (ADPKD). Intratesticular and epididymal cysts may be incidentally identified on physical examination or scrotal ultrasound, with epididymal cysts representing the most common epididymal mass.[87] The clinical significance of testicular/epididymal cysts and their role in infertility (if any) is currently unknown.[88,89]

Hydroceles have an increased prevalence in infertile males compared to fertile controls (**9-17% vs 1%),** with several authors identifying impaired vascular and semen parameters in hydrocele patients.[74,90,91,92,93] However, it is unclear if hydrocelectomy improves semen parameters or testicular function; additionally, the procedure of **hydrocelectomy** is associated with risk for **iatrogenic epididymal and/or vasal injury**, with resultant impaired fertility.[94,95]

ADPKD has been associated with impaired sperm concentration, volume, and morphology, with proposed mechanisms including uremic disruption of the HPG axis, SV and ejaculatory duct cystic obstruction, microtubular dysgenesis, and acrosomal dysfunction, among others.[96,97,98,99,100] However, the impact of ADPKD on fertility remains unclear and requires further study at the present time.

In addition to the above noted conditions, any disease state that impacts FSH, LH, testosterone, prolactin, or those produced by the thyroid, may impair male fertility.[101]

6.2 Behavioral and Environmental

6.2.1 Obesity

Obesity is variably associated with male-factor infertility, with studies demonstrating an approximately 1.1-2.0-fold, dose-dependent increased risk of sub/infertility in overweight or obese males.[102,103] BMI and waist circumference may also impact semen analyses selectively, with a longitudinal study of 468 men demonstrating linear declines in semen volume and total sperm count with increasing BMI and waist circumference and no impact noted on sperm concentration, motility, vitality, morphology, or DNA fragmentation index.[104] Other reports including meta-analyses demonstrate either selective or no association between BMI and sperm parameters.[105,106,107] Obesity may also affect fertility via hormonal imbalances. There is a bidirectional relationship between obesity and hypogonadism- both can influence the development of each other. Approximately 45-60% of men with obesity will also have secondary hypogonadism, with the reasons for this being

multifactorial.[108] Weight loss has been shown to directly correlate with T (total and free) and SHBG levels.[109] Similarly, in males undergoing bariatric surgery, postoperative weight and BMI have been found to be significant predictors of both T and IIEF. In addition to caloric restriction and weight loss, exercise has also been shown to improve endogenous T production.[110]

Among men seeking ARTs, obesity may reduce outcomes including lower sperm concentrations, higher need for intracytoplasmic sperm injection (ICSI), and decreased pregnancy and live birth rates.[111] Other studies have reported contrasting findings with assisted techniques, with no association noted with BMI.[112,113,114,115] Although the exact mechanism by which obesity impairs fertility is unknown, it may relate to epigenetic alterations of sperm DNA or indirect effects from T deficiency.[116,16]

6.2.2 Environmental Exposures

Various environmental chemicals have been associated with impaired semen quality including pesticides (dibromochloropropane [DBCP], dichlorodiphenyltrichloroethane [DDT], dichlorodiphenyldichloroethylene [DDE], ethylenebromide, organophosphates), polychlorinated biphenyls (PCBs), ambient air pollution, phthalate levels, and cellular telephone radiation.[117] Numerous additional gonadotoxic factors, which likely result in dose-dependent effects on fertility, include heavy metals, radiation, heat, toxic solvents/fumes, and poorly degradable, bio-persistent chemicals.[118,119,120] Proposed mechanisms for semen impairment include either direct gonadotoxic/spermatogenic effects or indirect effects via alteration of reproductive hormones (particularly estrogen).[117] Due to significant limitations of the many studies involved, further research is required to confirm these findings.[16]

6.2.3 Substance Abuse

Several drugs of abuse have been associated with infertility including **alcohol, cocaine, marijuana, methamphetamines, opioids, smoking tobacco, and exogenous T**.[121] The impact of these therapies is likely additive and dose-dependent. Men with baseline sub/infertility are likely at increased risk of gonadotoxicity from these agents.[122]

The two most commonly abused substances, tobacco and alcohol, result in dose-dependent and synergistic impairments in sperm quality, with a **meta-analysis demonstrating a 13-17% impairment in sperm concentration** among smokers.[123,124,122] In addition to direct effects on sperm, chronic and heavy alcohol use may further impair spermatogenesis through endocrine disruption, with alterations in sex hormone binding globulin, T, and estradiol.[125,126] Relatively limited data are available on the isolated effects of alcohol or tobacco and suggest that tobacco is likely the greater contributor to impaired fertility.[124,127,128] High quality studies evaluating the fertility impact of vaping have not yet been published.

Marijuana (tetrahydrocannabinol) has also been shown to significantly impair sperm motility and function as well as impact the HPG axis. Although the mechanism is not fully elucidated, cannabinoid receptors have been identified on sperm and serve to modulate sperm motility, capacitation, and

acrosomal reactions.[129] In two studies evaluating the impact of marijuana on semen parameters, results demonstrated dose-dependent reductions in concentration, morphology, and motility in men using marijuana more than once weekly, with impairments noted among all men, regardless of baseline semen parameters.[130,131]

Exogenous **opioids** may also result reduce fertility via modification of the acrosomal reaction. As with marijuana, the exact mechanism for impairments has not been fully described, although opioids have been shown to reduce motility and suppress the HGP axis, similar to marijuana.[132]

Cocaine may impair male fertility, with some data suggesting **an ~2-fold increase in the rate of oligospermia** among men using cocaine within the past two years, and reduced motility among those using for >5 years.[133] However, other studies, which controlled for concomitant substance use, suggested that the impact of cocaine on fertility is likely negligible.[134]

Exogenous T is well-documented to have a detrimental effect on male reproduction via disruption of the HPG axis and subsequent reduction in intratesticular T and spermatogenesis. Several RCTs have evaluated the role of steroid hormones in male contraception, with a recent Cochrane review of 33 RCTs summarizing outcomes. [134] Combined results of the 33 trials evaluated T and various progestins over treatment periods of eight weeks to one year. Although azoospermia efficacy rates ranged from 0-100%, several trials examining T and desogestrel or etonogestrel achieved azoospermia rates of at least 80% in one treatment arm.

The **AUA guidelines on testosterone deficiency**[135] and on infertility[16] recommend that men who are planning for paternity should not be prescribed testosterone supplements. **Following T discontinuation, normal spermatogenesis most commonly returns in 4-6 months, with a small percentage of men requiring three or more years**.[136,137] Clomiphene citrate, anastrozole, and human chorionic gonadotropin (HCG) have also been found to be useful in helping recover spermatogenesis in men with azoospermia from testosterone use. [138]

6.2.4 Nutritional Status and Physical Activity

Numerous studies have evaluated the role of nutrients in maintaining male-factor fertility, with several required for normal spermatogenesis and fertility, including alpha-lipoic acid, beta-carotene, cobalamin, selenium, zinc, and vitamins A, C, D, E, among others.[139,140,141,142] Potential mechanisms for impaired fertility with nutrient deficiency are numerous given the wide spectrum of processes in which the nutrients are involved. In addition to deficiencies, nutrient excess has been associated with impaired fertility with vitamin D and selenium, and is likely present with other nutrients.[116,143] A Cochrane meta-analysis of the impact of antioxidants in subfertile males concluded that based on low quality evidence, supplementation may improve live births (OR 4.2), pregnancy rates (OR 3.4), DNA fragmentation, and motility. [144]General dietary status is similarly associated with male infertility. Existing data support a nutrient rich diet with limited intake of lipophilic foods, soy isoflavones, and nutrient-poor/calorie-dense foods as supportive of optimal fertility potential.[145]

The role of physical activity in male fertility remains poorly defined. Two studies by Gaskins and colleagues reported higher sperm concentrations among those participating in more regular

moderate to vigorous activities, independent of fertility status.[146,147] In contrast, other population-based studies have failed to identify any associations between physical activity level and semen parameters. [104,148]

6.2.5. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and male infertility

In late 2019, SARS-CoV-2 emerged in the Hubei province in China. SARS-CoV-2 is the virus that causes coronavirus disease 2019, better known as COVID-19. From early in the COVID-19 pandemic, researchers have attempted to study the impact that SARS-CoV-2 (the virus) and COVID-19 (the disease) may have on male reproductive health. In May 2020, Li et al. published the results of semen samples from 38 men admitted to a hospital in Shangqiu, China with COVID-19.[149] Fifteen patients were in the acute stage of COVID-19 and twenty-three were recovering from COVID-19. Six of the 38 patients had SARS-CoV-2 detected in semen by real-time reverse transcriptase–polymerase chain reaction assay. SARS-CoV-2 was more likely to be found in men with active COVID-19 (4 of 15, or 26.7%) compared to men recovering from COVID-19 (2 of 23, or 8.7%). In June 2020, Pan et al. published the results of semen samples obtained from 34 men recovering from COVID-19. [150] SARS-CoV-2 was not detected in the semen of any of these men. It is important to note that these men were all recovering from COVID-19 and semen samples were obtained a median of 31 days after being diagnosed with COVID-19. Much remains unknown about the short- and long-term impact of SARS-CoV-2 and COVID-19 on male reproduction, but it appears likely that men with acute COVID-19 shed the SARS-CoV-2 in their semen while men recovered from COVID-19 likely do not. An excellent review of what is known and unknown about this topic was published by Patel et al in 2021. [151]

6.3 Iatrogenic

6.3.1 Chemoradiation

Chemotherapy and/or radiation for treatment of malignancy are common causes of iatrogenic infertility. The effect of either chemotherapy and/or radiation depends on **total dose delivered, site of application, specific agent(s) utilized, and schedule of administration**, with damage sustained independent of a patient's pubertal status.[24,152,153,154] Mitotically/meiotically active cells are most sensitive to damage, including A (pale) spermatogonia, which may account for transient impairments in spermatogenesis at lower therapeutic dosages. [27,28] Higher dosages may result in permanent infertility (via destruction of A [dark] spermatogonia) and T deficiency (via Leydig cell destruction).[155,156,157] Radiation therapy may induce direct or indirect (radiation scatter) DNA damage to all cell types involved in male reproduction, while the cytotoxic mechanism of chemotherapy varies by drug class. Chemotherapeutic agents most commonly associated with infertility include **alkylating agents and platinums, with antimetabolites, vinca alkaloids, and topoisomerase inhibitors** also shown to have gonadotoxic effects.[158] Radiotherapy and sarcomas were independently associated with a higher adjusted risk of developing long-term impaired spermatogenesis. [159]

The duration of impaired fertility following chemo/radiation therapy is not fully described. In men undergoing chemotherapy for Hodgkin's lymphoma or testicular cancer, abnormalities in sperm aneuploidy have been identified prior to and following chemotherapy, with the duration of aneuploidy most often returning to baseline within 24 months of completing therapy.[160,161] Given the observed aneuploidies noted among men post-chemo/radiation therapy, some have suggested an increased risk of aneuploidy conceptus if a pregnancy is achieved or sperm obtained prior to or up to 24 months are utilized for assisted techniques.[162] However, multiple, large cohort studies of men previously treated with systemic chemoradiation who are able to achieve paternity have not been shown to have an increased risk of genetic abnormalities in their offspring.[163,164,165,166] Among long-term survivors of pediatric malignancies, overall fertility rates are significantly lower than the general population (54% versus 82.5% in siblings), with key risk factors including alkylating agent dose score ≥3, surgical excision of an organ in the genital tract, testicular radiation ≥4 Gy, and exposure to bleomycin.[167]

6.3.2 Medications

Several classes of medications are associated with impairments in semen parameters and/or male fertility. Common medications include **antihypertensives** (spironolactone, calcium channel blockers), **psychotherapeutic agents** (antipsychotics, tricyclic antidepressants, phenothiazines, selective serotonin reuptake inhibitors), **hormonal agents** (including antiandrogens), **antibiotics** (nitrofurantoin, minocycline/tetracycline, macrolides, aminoglycosides), **proton pump inhibitors**, **cimetidine, cyclosporine, colchicine, allopurinol, and sulfasalazine**, among others.[168,169,170] Potential mechanisms of impaired fertility include direct gonadotoxic/spermatotoxic effects, disruption of the HPG axis, DNA synthesis impairment, and microtubular disruption, among others. Substitution or discontinuation of these medications results in significant improvements in fertility. Among men taking medications associated with impaired fertility, those who were able to substitute an alternative medication experienced significantly improved semen quality (**93% vs. 12%**) and conception rate (**85% vs. 10%**) at a mean of 7.3 months compared to those who remained on their therapies.[170]

6.3.4 Surgery

Surgical procedures may result in iatrogenic injury to the testicles, paratesticular structures, pelvic plexus, or otherwise disrupt the HPG axis. **Inguinal hernia repair** is a common pediatric and adult procedure, which may produce infertility either through direct injury to the testicular blood supply, epididymis, or vas deferens, or through entrapment and subsequent ischemic damage to the structures. **Rates of testicular atrophy or injury to the vas deferens following pediatric hernia repair are estimated at 1-2% (0.3% in adults),** while pediatric patients undergoing **bilateral repair may experience bilateral vasal obstruction in up to 40% of patients.**[171,172,173] Similarly, **hydrocelectomy is associated with inadvertent epididymal or vasal injury in up to 6% of patients.**[94,95] **Retroperitoneal, pelvic, or deep perineal surgery** may result in damage to the sympathetic chain or pelvic plexus, with subsequent loss of seminal emission and/or ejaculation, while surgery on the adrenal glands, thyroid, or central nervous system may cause disruption spermatogenesis via alteration of the HPG axis.

6.3.5 Challenges of fertility preservation

It is critical that men who may experience iatrogenic infertility be offered the opportunity to preserve their fertility, if possible. However, fertility preservation can be challenging for patients. For some men, their new medical diagnosis is surprising and emotional overwhelming, without even considering future reproductive needs. Other men may be diagnosed when they are acutely ill and require urgent gonadotoxic treatment. Most adult men can preserve fertility using an ejaculated semen sample, however men who are very ill often find it difficult to ejaculate. As a last resort, men can receive a testicular sperm extraction (TESE) or aspiration (TESA) procedure if ejaculation is not possible or if the ejaculated samples do not contain sperm.

There are also financial barriers for patients since fertility preservation procedures may not be covered by insurance. Nevertheless, the AUA infertility guidelines recommend that clinicians discuss the effects of gonadotoxic therapies (and other treatments that could impair fertility like retroperitoneal lymph node dissections) before starting those therapies. [16] After the completion of chemotherapy or radiation treatments, men should be advised to wait 12-24 months before trying to conceive using fresh sperm.[16]

Unfortunately, no fertility preservation options exist for prepubertal boys. There are clinics offering boys testicular tissue cryopreservation, but this is only done under an IRB-approved research protocol, and there is no promise that science will find ways to use that tissue later in life.

6.4 Genitourinary Infections / Inflammation

Genitourinary infections encompass several syndromes including urethritis, epididymitis, epididymo-orchitis, and male accessory gland infections (MAGI). Although urethritis and MAGI have not been causally linked with male-factor infertility, epididymitis and epididymo-orchitis may result in obstructive oligo-/azoospermia or primary testicular failure.[174,175] **Epididymitis has an annual incidence of 600,000 cases in the U.S., with concomitant orchitis occurring in 60% of cases.**[176] Acute infection results in impaired spermatogenesis, with chronic effects leading to impaired motility, concentration, and occasional obstruction.[177,178] **Mumps orchitis** is an increasingly common occurrence and leads to **subfertility in an estimated 13% of patients**, with rare cases of infertility reported.[178,179] Neisseria gonorrhea and human immunodeficiency virus are most commonly associated with infertility, while limited data suggest increased rates of infertility in men with Hepatitis B.[180] Less robust data are available on other potential infectious causes, including chlamydia, ureaplasmas, herpes simplex, and human papilloma virus. Proposed mechanisms for impaired fertility include reactive oxygen species generation from the infectious organism as well as from the host leukocyte response, testicular edema, hyalinization of seminiferous tubules, transient ischemic damage to the testicle, and anti-sperm antibody (ASA) generation.[181]

6.5 Syndromes

6.5.1 Cystic Fibrosis (CF)

See **AUA Update Series Vol.39, Lesson 31, 2020**.

CF is an autosomal recessive genetic condition, which is characterized by an abnormal chloride transporter, resulting in hyperviscous mucous secretions. **Approximately 1 in 25 people of European descent are carriers for CF.**[182] From a fertility standpoint, **CF results in CBAVD** and obstructive azoospermia. Partners of patients with CF are recommended to consider genetic testing for CFTR mutations to determine the likelihood of CF transmission to their children and to undergo appropriate genetic counseling.

6.5.2 Primary Ciliary Dyskinesia (PCD)

PCD is an autosomal recessive genetic condition, which results in functional impairments in motile cilia. Prevalence rates vary from 1:15,000 to 1:30,000, with arguably the most well-known PCD being **Kartagener Syndrome.**[183] **PCD is associated with situs inversus, bronchiectasis, sinusitis, and infertility**. Due to near-complete sperm immotility, the majority of patients will require ART to achieve pregnancy.[184,185]

6.5.3 Kallmann Syndrome (KS)

Kallman syndrome is a genetic condition resulting in the absence of GnRH production and is characterized by **anosmia/hyposmia, poorly developed secondary sexual characteristics, atrophic testicles, sub-/infertility, and hypogonadotropic hypogonadism**. It occurs in **1:10,000** to **1:84,000** men and is otherwise associated with craniofacial defects, renal anomalies, skeletal anomalies, hearing loss, and cryptorchidism.[186,187,188] **Supplementation with gonadotropins achieves a return of spermatogenesis in 95% and successful pregnancy in 72% of patients.**[189]

6.5.4 Klinefelter Syndrome

Klinefelter Syndrome (KS) is defined by the abnormal presence of one or more extra X-chromosomes (**47,XXY; 48,XXXY**) and is traditionally characterized **by atrophic testes, hypergonadotropic hypogonadism, gynecomastia, learning difficulties, and infertility.**[190] It occurs in **1:500 to 1:1000** men and is the most common sex chromosome aneuploidy anomaly in men.[187,191] Men with KS experience **increased rates of diabetes, lung diseases/cancer, epilepsy, cerebrovascular disease, breast cancer, non-Hodgkin lymphoma, and increased mortality by 1.5-2 years.**[192,193] From a fertility standpoint, men with KS have primary testicular failure, typically with non-obstructive azoospermia or severe oligospermia, low T, and elevated FSH and LH. **Testicular microdissection results in sperm retrieval rates of approximately 66%, with 45% of patients able to achieve a live birth via ART.**[194]

Men with KS also demonstrate distinct findings on scrotal ultrasound compared to non-KS, non-obstructed azoospermic men, including reduced size and increased coarse / nodular patterns, vascularization, and microlithiasis.[195]

6.6 Paternal Age

See **AUA Update Series Vol. 37, Lesson 14, 2018**

Although advancing paternal age is inconsistently associated with minimal impacts on fertility potential, it is increasingly linked to select conditions in progeny.[196,197] The AUA's 2020 infertility guidelines now advise that couples where the male partner is ≥ 40 years old be advised about increased risks of certain adverse health outcomes for their children.[16] Several neurological and psychiatric conditions, including autism, attention deficit hyperactivity disorder, psychosis, bipolar disorder, substance abuse, and schizophrenia occur in higher rates among children born to males of advancing age compared to younger cohorts.[198,199,200] Other conditions including trinucleotide repeat diseases (e.g., myotonic dystrophy, Huntington's disorder) and select malignancies (e.g. leukemia / lymphoma) also occur at increased rates.[201,202] However, it is important to note that the absolute risk of these conditions remains low, but the relative risk is increased compared to children conceived from younger fathers.

7. Evaluation

Given the subjective nature of clinical evaluations and absence of data on cost-effective practice, the majority of recommendations for evaluation and testing are obtained and summarized from the currently available AUA Guidelines.[1,16]

7.1 History and Physical Examination

A thorough reproductive history should be obtained to include coital frequency and timing, duration of infertility, prior fertility, childhood illnesses, developmental history, complete medical and surgical history, review of medications, allergies, review of lifestyle exposures (gonadotoxins), review of systems, family reproductive history, and past infections including respiratory and sexually transmitted infections. **Table 1** presents examples of appropriate questions for a thorough reproductive history.

Physical examination should include a general assessment, with special focus on the penis, urethral meatus, testes (testicular palpation and size measurement), presence and consistency of vasa and epididymides, presence of varicocele, secondary sexual characteristics including body habitus, hair distribution, and breast development, and digital rectal examination.

Table 1 - Sample Pertinent Questions for a Reproductive History

Category	Considerations*
HPI	
Patient	
Duration of infertility	
Coital timing/frequency/ lubrication	
Prior fertility	
Childhood/recent illnesses	Epididymitis, orchitis
Developmental history	Syndromes[a]
Respiratory infections	Syndromes[a]
Sexually transmitted infections	Epididymitis, orchitis
Trauma	
Erectile function	Endocrine[b]
Libido	Endocrine[b]
Obstructive urinary symptoms	Urethral stricture
Genitourinary infections (mumps, epididymitis, tuberculosis)	
Patient	
Age	ART if advanced age

Prior fertility	
Fertility evaluations performed	
Allergies	
Medications	
Antihypertensives[c]	
Psychotherapeutics, SSRIs[d]	
Hormonal agents[e]	
Antibiotics[f]	
Others[g]	
PMH	
Diabetes	Anejaculation
Hypertension	Medications
Psychiatric Conditions	Medications
Prior chemo/radiation	
Pulmonary Infections	Syndromes[a]
Sinusitis	Syndromes[a]
Undescended testes	
PSH	
Inguinal hernia repair	Vasal / vascular injury

Vasectomy	Obstructive azoospermia
Retroperitoneal, pelvic, perineal	Ejaculatory dysfunction
Hydrocelectomy	Epididymal / vasal injury
Varicocelectomy	Vasal injury
Orchiopexy	
SH	
Tobacco, alcohol, illicit substances	
Environmental exposures (pesticides)	
Gonadotoxic exposures	
Heat	
Occupation	
FH	
Siblings with infertility or syndromes	
ROS	
Anosmia	Syndromes[a]
Galactorrhea	Syndromes[a]
Headaches	Endocrine[b]

* Potential testing or differential diagnoses which may be considered if positive responses are obtained. A-Syndromes include cystic fibrosis, primary ciliary dyskinesias, Kallmann, Klinefelter; B-Minimum testing includes T and FSH, with consideration for LH, free T, and prolactin; C-Calcium channel blockers, spironolactone;

D-Antipsychotics, phenothiazines, tricyclic antidepressants; E-Androgens including testosterone, antiandrogens, estrogens; F-Nitrofurantoin, minocycline/tetracycline, macrolides, aminoglycosides; G-Cimetidine, cyclosporine, colchicine, allopurinol, sulfasalazine; ART-Assisted reproductive technique; Chemo-Chemotherapy; FH-Family history; HPI-History of present illness; PMH-Past medical history; PSH-Past surgical history; ROS-Review of systems; SH-Social history

View Image.

7.2 Laboratory Testing

7.2.1 Semen Analysis

In addition to a thorough history and physical, the standard evaluation of the infertile male includes one semen analysis (SA), but two SAs are preferred, ideally separated by at least one month. SA is preceded by a two to three day period of abstinence and should be evaluated within one hour of collection. Interpretation of values is based on World Health Organization (WHO) guidelines, with the diagnosis of **azoospermia made only after examining two, separately-obtained, centrifuged specimens.**[203] Several factors are commonly analyzed during routine SA, including semen volume, pH, sperm concentration and total count, total motility (progressive and non-progressive), progressive motility, morphology, and vitality.

Semen volume and pH are utilized in combination with other parameters to identify patients at risk for obstructive etiologies. In men without hypogonadism or CBAVD, semen volumes < 1 ml following an appropriate abstinence interval and complete collection may indicate retrograde ejaculation, absence of the vas deferens, or vasal / EDO. As the SV produce alkaline secretions and fructose, obstruction or aplasia/hypoplasia is suggested by low volume, acidic (pH < 7.0-7.2), oligo-/azoospermia. [1,204] However, semen pH and fructose testing may be misleading when not properly performed, leading many experts to rely on other clinical findings.

Interpretation of sperm concentration, motility, and morphology are complicated by a significant degree of convergence between fertile and sub-/infertile males using the current WHO criteria.[203] An analysis of semen parameters from 763 fertile U.S. men demonstrated median, 5^{th}-95^{th} percentile ranges for volume (3.7; 1.5-6.8 ml), concentration (67; 12-192 million/ml), total count (240; 32-763 million), motility (52; 28-67%), and strict morphology (1999 WHO criteria; 10; 3-20%).[205] These findings highlight the significant overlap of fertile patients with at least one semen characteristic considered abnormal based on WHO criteria. A study by Nallella and colleagues comparing semen parameters (1999 WHO criteria) between fertile and infertile males reported a 48% sensitivity in identifying infertile males based on sperm concentration (20 million/ml), 83% sensitivity / 51% specificity with strict morphology, and 74% sensitivity / 90% specificity with motility.[206] Overall results demonstrated that motility was the most significant factor, while morphology was the least predictive. Other studies have reported increasing rates of conception up to certain threshold levels for sperm concentration (40-55 million/ml), beyond which no additional benefits are noted.[207,208]

Sperm motility is currently divided between progressive and non-progressive, due to difficulty and technician bias in assigning specific rates of motility.[203] Although the significance of progressive motility remains unknown, some studies have identified a minimum threshold for sperm motility required for cervical mucus penetration.[209,210] The role and utility of morphology is similarly poor.[111] Given the poor predictive ability of even strict morphology, the recent AUA guidelines recommend against its use as a sole factor in clinical decision-making.[1] The predictive utility of strict morphology using assisted techniques is also variable, with data demonstrating inconsistent and contradictory

findings.[211,212,213]

More recently, data have suggested the use of total motile sperm counts (TMSC; volume x concentration x motility) as an improved indicator for infertility over individual WHO criteria alone.[214] Compared to infertile men with normal semen parameters, those with TMSC <1 million experienced 83% fewer spontaneous pregnancies, while those with 10-20 million had 55% fewer. Surprisingly, among men with TMSC 0-1 million, 23% were able to achieve a spontaneous pregnancy within 3 years, further highlighting the predictive and diagnostic limitations of semen analyses. TMSC was also recently shown to be a better predictor for ICSI outcomes compared to WHO values. [215]

Routine **DNA integrity** and **reactive oxygen species** testing are not currently recommended due to a lack of sufficient supporting data and inability to treat abnormal results.[16] DNA testing may have a role in select cases, however, including those with oligospermia undergoing assisted reproductive techniques. Among those found to have a DNA fragmentation index of >30%, the use of sperm retrieved from the testes achieved live-birth rates of 47% versus 26% from those utilizing ejaculated sperm. [216] These findings suggest a potential future role in determining which patients may benefit from sperm extraction procedures over ejaculated sperm for assisted techniques. Additional testing including quantitation of semen leukocytes, evaluation for bacteriospermia, ASA, sperm viability testing (hypoosmotic swelling), sperm-cervical mucus interaction, zona free hamster oocyte test, and computer-aided sperm analysis has a limited role in the diagnosis and treatment of male factor infertility. See **Table 2** for a description and summary of specialized testing. **Table 3** and **Table 4** review the 2010 WHO reference values for semen characteristics, definitions of abnormal sperm characteristics, and common SA findings with selected pathologies.

Table 2. Specialty Testing Available for Select Cases of Male Infertility

Test	Description	Notes*
Strict sperm morphology	Evaluates percentage of sperm based on established size/shape criteria	Is not consistently predictive of fecundity and should not be used alone to make clinical / prognostic decisions
DNA Integrity	Evaluated sperm DNA fragmentation	Insufficient evidence to support routine use of DNA integrity testing; no proven therapies to improve DNA integrity; may have role in predicting need for TESE for use with ART
Reactive oxygen species	Chemically-reactive molecules generated by sperm and WBC	Not predictive of pregnancy; no proven therapies to correct abnormal results
Semen WBC	>1 million/ml considered abnormal; requires specific staining techniques to differentiate from immature germ cells	>1 million/ml should prompt evaluation for genital tract infection
Antisperm antibodies	Autoantibodies against sperm cells; clinically significant if attached to sperm	Pregnancy rates may be reduced by antisperm antibodies; consider in isolated asthenospermia, sperm agglutination, abnormal postcoital test, or idiopathic infertility

Sperm viability testing	Sperm mixed with dye or treated with hypoosmotic swelling test	Determines if non-motile sperm are viable for use in intracytoplasmic sperm injection
Sperm-cervical mucus interaction	Microscopic examination of post-coital cervical mucus.	Current utility and specifics of test performance are controversial. May assist in identifying ineffective coital technique or unknown cervical factor
Sperm penetration assay / zona free hamster oocyte test	Zona pellucida is removed from hamster oocytes, which permits fusion of human sperm	Tests capacitation, acrosome reaction, and incorporation of sperm.
Computer-aided sperm analysis	Objectively measures sperm numbers, motility (including speed, velocity), and morphology	Provides additional information regarding semen parameters
* Notes and recommendations based on AUA Best Practice Statements for the evaluation of the azoospermic and infertile male (2010); TESE-Testicular sperm extraction; WBC-White blood cell		
View Image.		

Table 3. World Health Organization Reference Values for Semen Characteristics

Characteristic	Percentiles				
	5*	25	50	75	95
Semen Volume (ml)	**1.5**	2.7	3.7	4.8	6.8
Sperm Concentration (million/ml)	**15**	41	73	116	213
Total Sperm (million/ejaculate)	**39**	142	255	422	802
Total Motility (%; progressive + non-progressive)	**40**	53	61	69	78
Progressive Motility (%)	**32**	47	55	62	72
Normal Forms (%)	**4**	9	15	24.5	44
Vitality (%)	**5**	72	72	84	91

Table is generated from WHO semen parameters of fertile men whose partners achieved a pregnancy within 12 months;
*Values below 5th percentile are considered abnormal

Table 4. Definitions of Abnormal Sperm Characteristics and Common Findings with Various Pathologies

Term	Criteria
Aspermia	No ejaculate (0 ml)
Asthenospermia	<40% total motility
Azoospermia	0 sperm on 2 centrifuged specimens
Normospermia	>39 million sperm/ejaculate
Oligospermia	<39 million sperm/ejaculate
Teratospermia	Low volume, acidic pH, asthenospermia, oligo/azoospermia
Pathology	**Classic SA Findings***
CBAVD, CUAVD	Low volume, acidic pH, asthenospermia, oligo/azoospermia
Ejaculatory Duct Obstruction	Volume <1 ml, low/absent fructose, pH<7, asthenospermia, oligo/azoospermia
Varicocele	Oligoasthenoteratospermia

* Findings are suggestive only and not pathognomonic;
CBAVD-Congenital bilateral absence of the vas deferens;
CUAVD-Congenital unilateral absence of the vas deferens

7.2.2 Endocrine Evaluation

The AUA 2020 infertility guidelines recommend that men with "impaired libido, erectile dysfunction, oligozoospermia or azoospermia, atrophic testes, or evidence of hormonal abnormality on physical exam" undergo testosterone and FSH hormone testing.[16] Men with low T may additionally be assessed with total and free T, LH, and prolactin levels. Patients with a suspicion of possible acquired hypogonadotropic hypogonadism should be evaluated for pituitary tumors with measurement of serum prolactin and imaging of the pituitary gland. See **Table 5** for interpretations of various hormone profiles.

Table 5. Interpretation of Hormone Profiles

Condition	Laboratory Findings		
	FSH	LH	T
Normal Spermatogenesis	Nl	Nl	Nl
Abnormal Spermatogenesis	Nl/↑	Nl	Nl/↓
Hypergonadotropic Hypogonadism	↑	↑	↓
Hypogonadotropic Hypogonadism	↓	↓	↓
Pituitary Tumor	Nl/↓	Nl/↓	↓

FSH - Follicle stimulating hormone;
LH - Luteinizing hormone;
Nl - Normal;
T - Testosterone

7.2.3 Post-ejaculatory Urinalysis

A post-ejaculate urinalysis is recommended in men with ejaculate volume < 1ml (complete collection, appropriate abstinence interval) and without hypogonadism or CBAVD. Testing is considered positive for retrograde ejaculation if any sperm are present in the urine of an azoospermic male, or if similar numbers of sperm are present in the urine as are present in the semen or if more sperm are present in the urine than in the semen.

7.2.4 Genetic Testing

CFTR testing and genetic counseling is recommended for all men with CBAVD, those with CUAVD, those with idiopathic obstructive azoospermia, and partners of men with CBAVD. There is currently no consensus on the optimal extent of CFTR testing obtained, however, at a minimum, **common point mutations and the 5T allele** should be evaluated. Gene sequencing for CFTR may be considered in men with CUAVD or CBAVD and negative routine CFTR testing, when the female partner is a CF carrier. **Men with non-obstructive azoospermia or severe oligospermia (<5 million sperm/ml) are recommended to undergo karyotyping, Y-chromosomal micro-deletion analysis, and genetic counseling**. Testing for Y-chromosome micro-deletions in this cohort may provide prognostic information for couples, as **those with complete AZFa or AZFb deletions are unlikely to have sperm identified on surgical sperm extraction**, while **isolated AZFc deletions are more likely to have sperm present.**[217,218] Currently, there are insufficient data to recommend a minimum number of sequence tagged sites to be evaluated.

7.3 Imaging

7.3.1 Transrectal Ultrasonography

Transrectal ultrasound (**TRUS**) is utilized in the assessment of suspected ejaculatory duct obstruction (EDO) as well as to evaluate the prostate and SV. Findings on TRUS consistent with **EDO** include **SV anterior-posterior diameter of >1.5 cm**; however, this finding has poor specificity.[219,220,221] TRUS with or without SV aspiration/vesiculography is recommended in azoospermic men with low volume ejaculate (<1.0 ml) and bilateral palpable vasa. TRUS may additionally be considered in oligospermic men with low volume ejaculates, palpable vasa, and normal testicular size.

7.3.2 Scrotal Ultrasonography

Scrotal ultrasound provides additional information in infertile males including potential etiologies, prognosis, and associated pathology. However, as the majority of scrotal pathology is palpable on physical examination, and non-palpable findings are of unclear clinical significance, routine scrotal ultrasound is currently only recommended in patients where scrotal examination is difficult/inadequate, or in whom a testicular mass is suspected.[222]

7.3.3 Renal Ultrasonography

Bilateral renal ultrasound is **indicated for all men with CUAVD or CBAVD.**

7.4 Testicular Biopsy

Testicular biopsy may assist in differentiating obstructive and non-obstructive azoospermia in men with normal testicular size, at least one palpable vas deferens, and borderline elevated FSH levels. One study of diagnostic testicular biopsy results found that in males with a FSH < 7.6 and testis length > 4.3 cm, 96% of cases were obstructed. [223] Testicular biopsy may additionally be performed in cases of suspected EDO on TRUS to assess for the presence of spermatogenesis. Vasography is considered a second-line option to help identify the site of obstruction, although concerns regarding secondary scarring exist.

8. Additional Reading

- AUA Update Series __Volume 34, Lesson 7, "**Evaluation and Treatment of the Adolescent Varicocele**" (2015).
- AUA Update Series __Volume 35, Lesson 18, "**Male Infertility and Overall Health**" (2016).
- AUA Update Series __Volume 35, Lesson 33, "**A Primer on Modern Semen Analysis**" (2016).
- AUA Update Series __Volume 36, Lesson 9, "**Azoospermia, Testicular Biopsy, and Surgical Sperm Retrieval**" (2017).
- AUA Update Series: **Congenital Absence of the Vas Deferens: Bilateral and Unilateral. Shepherd S and Oates RD**, Vol. 39, Lesson 31, 2020
- AUA Update Series: **Reproductive Effects of Male Aging. Carrasquillo R, Masterson J and Ramasamy R**, Vol. 37, Lesson 14, 2018
- ABU LLL Category: Impotence, Infertility, Andrology: Topic 1: Infertility Medical Treatment
- ABU LLL Category: Impotence, Infertility, Andrology: Topic 3: Infertility Surgical Management
- AUA podcast 109: **What General Urologists Can Do To Evaluate & Successfully Treat Male Infertility**

9. Patient Resource Materials

- *"Male Infertility"* **http://www.urologyhealth.org/urologic-conditions/male-infertility**
- *"Varicoceles"* **https://urologyhealth.org/urologic-conditions/varicoceles**

Presentations

PHYSIOLOGY, EPIDEMIOLOGY, PATHOPHYSIOLOGY, EVALUATION Presentation 1

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This manuscript is invaluable because it comprehensively overviews the full evaluation of the infertile male. In addition to discussing the medical and surgical histories, laboratory tests are also described in detail. The AUA recommendations regarding specific aspects of the infertile male workup are highlighted throughout this manuscript, making it easily searchable.

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