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MALE SEXUAL DYSFUNCTION AND DISORDERS (N THIRUMAVALAVAN, SECTION EDITOR)

What Every Provider Should Know About the 2020–2021 Updated AUA/ASRM Guidelines on Male Factor Infertility

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Abstract

Purpose of Review Infertility is a medical condition in which a couple is unable to conceive after 12 months of attempted conception. Male factor infertility contributes to approximately half of the cases of infertility. We highlight the most critical aspects of the updated 2020 AUA/ASRM Guidelines on Male Factor Infertility.

Recent Findings The updated 2020 AUA/ASRM Guidelines on Male Factor Infertility provides fifty-two practice statements based on varying levels of data and evidence. In addition to the focus on the assessment and management of the male patient, the guidelines also emphasize the associated co-morbidities which may influence fertility. The specific goals of the male factor assessment is to identify possibly correctable etiologies amenable to medical or surgical treatment, possible co-morbid conditions that may require additional attention, or genetic anomalies that might put offspring at risk.

Summary The overall improvement in diagnostic and therapeutic capabilities has allowed for the improved understanding of specific etiologies that may be underlying male factor infertility. The AUA/ASRM male factor infertility guidelines provide a framework to assess for these etiologies in order to improve the reproductive potential of the infertile male.

Keywords Male infertility · Semen analysis · Microsurgical testis sperm extraction

Introduction

Infertility, defined by the World Health Organization is a condition that results in "failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse" [1]. The global prevalence of infertility among all couples is estimated to be approximately 15%, with the male factor contributing to half of these cases [2]. Male factor infertility can be attributed to congenital urologic conditions, genetic abnormalities, hormonal imbalances, erectile dysfunction, and underlying medical co-morbidities [3••, 4]. Some of these etiologies may be reversible with medical or surgical treatment; therefore, a thorough assessment is warranted. The goals of the assessment of the male patient are to identify underlying conditions that (1) are potentially reversible, (2) require medical attention or are genetic, and (3) may be transmitted to the offspring.

Methodology

The American Urological Association and the American Society for Reproductive Medicine (AUA/ASRM) has released an updated series of guidelines regarding the assessment and management of the infertile male patient, with fifty-two practice statements. In order to utilize the most relevant evidence, the Emergency Care Research Institute (ECRI) Evidence-based Practice Center team searched PubMed®, Embase®, and Medline from January 2000 through May 2019 using a PICO framework. The statements were assigned a rating based on the strength of the body of the evidence supporting the guideline as well as the net benefit (or harm) of the statement to the patient. If the body of evidence was insufficient to support a practice guideline, the

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statement is categorized as a Clinical Principle and Expert Opinion.

Assessment of Male Factor Infertility

Infertility in a couple can be attributed to male factor, female factor, or a combination of both; hence, it is recommended that the initial evaluation for infertility involves both partners [5]. The strongest predictor of fertility outcomes in a couple undergoing evaluation is maternal age [6]. The initial evaluation of *both* partners generally involves a reproductive history, a physical examination, and diagnostic studies of reproductive function.

For the male partner, this includes evaluation with a semen analysis, which provides valuable information on the quality and quantity of sperm production. Parameters measured in a semen analysis should include semen volume, sperm concentration, sperm motility, morphology, and semen pH (Table 1). To note, a single abnormal semen parameter cannot definitively diagnose the etiology of male infertility as it has been well established that men with abnormal semen parameters can conceive through natural conception [7••]. Hence, for males being evaluated for infertility with one or more abnormal semen parameters, it is recommended that these patients be referred to a male reproductive expert for further assessment.

The reference ranges for abnormal parameters on semen analysis is determined by the World Health Organization's analysis of 4,500 fertile fathers across 14 countries and 4 continents (Table 1) [8••]. Based on this analysis, the mean ejaculate volume was 3.7 mL, with the 5th percentile marked at 1.5 mL. The mean sperm concentration was 73 million sperm per mL of ejaculate, and the 5th percentile of sperm concentration is 15 million sperm per mL of ejaculate. The mean sperm motility was 61%, and the 5th percentile was 40% motility. However, abnormal morphologic sperm are commonly seen in fertile men, as the mean sperm with strict normal morphology was 15%, with the 5th percentile at 4%.

Relationships Between Infertility and General Health/Associated Diseases

Studies have demonstrated that approximately 1–6% of men undergoing an infertility evaluation have an undiagnosed medical disease [9•, 10]. Infertility may be the first presenting sign of an underlying medical disease, manifesting as abnormal spermatogenesis. A meta-analysis involving several studies has revealed an elevated Charlson Comorbidity Index in infertile male patients as compared to fertile controls [11]. The updated guidelines recommend that clinicians counsel patients on the associated health conditions associated with abnormal sperm production and optimize the overall health of the patient. Testicular cancer is one such medical pathology that has been extensively studied in its association with abnormal sperm parameters. Four studies evaluated in the systematic review demonstrated higher rates of testicular cancer in men with abnormal semen parameters [12–15]. Low sperm counts appear to be the most predictive parameter with regard to developing testicular cancer. Individual studies have also examined the risk of other medical co-morbidities and their association with infertility. Glazer et al. examined the risk between diabetes and male factor infertility in a retrospective cohort study and found increased diagnosis of diabetes mellitus in patients that had pursued in vitro fertilization as compared to fertile controls [16••]. A nationwide observational study found that men who fathered children through assisted reproduction techniques had a 64% increased risk of early onset prostate cancer [17].

Additionally, in many cases, the etiology for a man's infertility can be attributed to syndromic conditions that have other health manifestations that should be addressed or be referred to a specialist. Klinefelter syndrome, marked by a XXY karyotype, is associated with testosterone deficiency with impaired spermatogenesis, abnormal muscle mass, osteoporosis, and autoimmune disorders. Testosterone deficiency itself is believed to be a risk factor for diabetes, metabolic syndrome, cardiovascular disease, Alzheimer's disease, and all-cause mortality. Cystic fibrosis is associated with the congenital absence of bilateral vas deferens along

Table 1 The World Health Organization distribution of values for semen parameters from men whose partners became pregnant within 12 months of discontinuing contraceptive use and nomenclature used to describe semen quality

Parameter (units)	Median (± 2 S.D.)	Nomenclature
Semen volume (mL)	3.7 (1.5–6.8 mL)	*Aspermia* — no semen emission
Sperm concentration (million per mL)	73 (15–213 10^6/mL)	*Azoospermia* — no spermatozoa in the ejaculate *Oligozoospermia* — total number of spermatozoa below the lower reference limit
Total motility (%)	61 (40–78 %)	*Asthenozoospermia* — percentage of progressive motile sperm below the lower reference limit
Normal forms (%)	15 (4–44 %)	*Teratozoospermia* — percentage of morphologically normal spermatozoa below the lower reference limit

with pulmonary disease, pancreatic insufficiency, and dental caries. Lastly, a history of cryptorchidism is associated with both infertility and a higher rate of testicular cancer.

Paternal Age and Male Infertility

While maternal age is often implicated in infertile couples, advanced paternal age has also been identified as both a cause for infertility and a risk for adverse outcomes to the offspring. A meta-analysis examining the relationship between age and male infertility found an age-dependent decline in semen analysis parameters except for sperm concentration [18]. These effects are likely secondary to changes in reproductive hormones and testicular morphology and decrease in sexual function [19]. Additionally, with increasing paternal age, a large meta-analysis has demonstrated that there is an increased accumulation of de novo mutations associated with a higher miscarriage rate (19%), pre-term birth (2%), genetic syndromes (13%), achondroplasia, schizophrenia (31%), and autism (78%) [20, 21]. Per the AUA guidelines, it is advised that clinicians discuss with couples with a paternal age greater than 40 these associated health risks (Table 2).

Diagnosis/Assessment and Evaluation

Barring azoospermia or complete asthenozoospermia, an individual abnormality on semen analysis is a weak predictor of infertility. Generally, semen analysis results are most significant when there are multiple abnormal semen analysis parameters. The odds ratio for infertility increases as the number of semen parameter abnormalities increases, although is not possible to predict whether a patient is infertile solely on sperm analysis parameters [7••].

The ASRM recommends endocrine evaluation for the infertile male who is endorsing symptoms of impaired libido or erectile dysfunction, oligospermia below 10 million/mL, or physical examination findings concerning for a hormonal abnormality, such as atrophic testicles. Hormonal evaluation begins with testosterone levels, measured in the morning, and the gonadotropin, follicle-stimulating hormone [22]. If the morning testosterone level is less than 300 ng/dL, it is recommended that a total and free testosterone be obtained, along with serum LH, estradiol, and prolactin levels. For men with azoospermia, follicle-stimulating hormone helps differentiate from an obstructive process (< 7.6 IU/L) from impaired spermatogenesis (> 7.6 IU/L) [23]. When there is concern for impaired spermatogenesis, a karyotype and Y-chromosome microdeletion may elucidate the etiology. Chromosomal abnormalities to consider include Klinefelter syndrome and Robertsonian translocations. The azoospermia factor (AZF) region on the long arm of the Y-chromosome encodes genes associated for spermatogenesis and microdeletions in this region may result in impaired spermatogenesis (Figure 1). Men with complete microdeletions involving the AZFa or AZFb region on the Y-chromosome will not have sperm retrieved on a microscopic testicular sperm extraction (micro-TESE), whereas 50% of men with microdeletions on the AZFc region may have sperm retrieved on a micro-TESE [24]. Along with a karyotype, micro-TESE is indicated in men with a sperm concentration of less than 5 million/cc. For male patients with physical examination findings concerning for vasal agenesis or idiopathic obstructive azoospermia, the guidelines recommend to evaluate both the

Table 2 Effect of paternal age on reproductive function, semen parameters and associated birth risks

Parameter	Effect of increase in male age[>Reference]
Semen volume	Decreased[18]
Sperm concentration	Unchanged[18]
Total sperm count	Decreased[18]
Sperm motility	Decreased[18]
Normal morphology	Decreased[18]
DNA fragmentation	Decreased[18]
Luteinizing hormone	Increased[19]
Follicle Stimulating hormone	Increased[19]
Testosterone	Decreased[19]
Sertoli cells	Decreased number, increased vacuolization[19]
Leydig cells	Decreased number[19]
Seminiferous tubules	Narrowing due to thickness of basal membrane[19]
Miscarriage rate	Increased[21]
Pre-term birth	Increased[21]
Genetic syndromes	Increased[21]
Schizophrenia	Increased[21]
Autism	Increased[21]

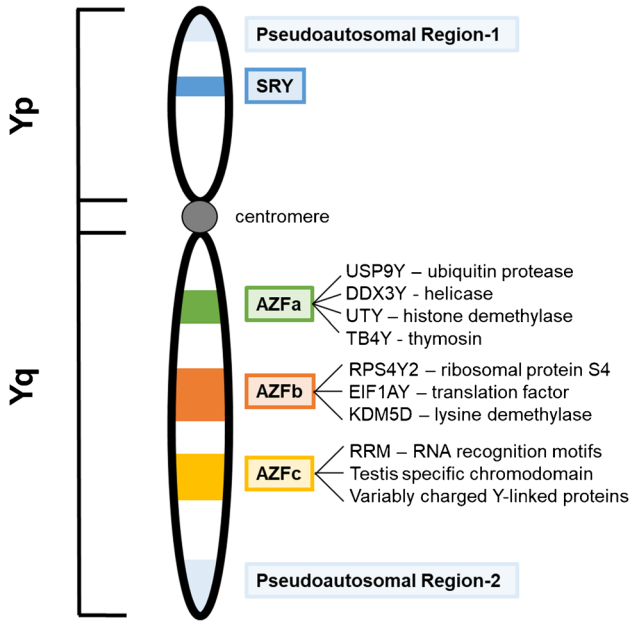

Fig. 1 Schematic representation of the human Y-chromosome (not to scale) with AZF regions on the q arm of the chromosome.

male and female patient for mutations associated with cystic fibrosis. Studies suggest that approximately 78% of patients with bilateral absence of the vas deferens has a mutation in the CFTR gene [25]. Evaluation of both partners is recommended as if both partners are carriers of the CFTR gene mutation; there is a 50% chance of transmissibility of the mutation to the offspring and a 25% likelihood that the child is homozygous for the mutation with manifestation of the disease.

When a semen analysis reveals > 1 million round cells per milliliter of ejaculate, further studies are necessary to differentiate the identity of the round cells. Round cells in the semen can either be immature sperm or pyospermia in which there is an increased number of white blood cells in the semen. Several stains can be utilized to differentiate between germ and white blood cells including o-toluidine to identify cellular peroxidase (absent in white blood cells) and immunohistologic stains specific for antigens on leukocytes [26]. The increased presence of immature sperm has not been directly shown to affect fertility. Pyospermia may be a sign of an underlying systemic or localized infection or inflammation of the male reproductive tract. Sperm of men with increased leukocytes in the semen analysis have been demonstrated to have a decreased ability to penetrate the cervical mucus in in vitro studies [27]. These patients may be treated with antibiotics or address an underlying cause such as smoking or other causes of high oxidative stress in the semen.

Diagnostic evaluations that are not recommended for the initial evaluation of the infertile couple include sperm DNA fragmentation analysis, anti-sperm antibody analysis, and testicular biopsy. These diagnostic studies lack prospective studies that directly evaluate their impact on the management of the infertile couple. Sperm DNA fragmentation studies are indicated when the couple experiences recurrent pregnancy losses, as paternal chromosomal structural defects may be contributory. Additional evaluation that should be performed in the male partner with recurrent pregnancy losses include karyotype and testing for sperm aneuploidy. DNA fragmentation testing may also be indicated in couples where there is multiple failure in vitro fertilization cycles.

In the azoospermic male, diagnostic biopsy alone should not be performed to differentiate between obstructive and non-obstructive azoospermia. This should be a combined diagnostic and therapeutic biopsy that will allow sperm to be retrieved at the same sitting and cryopreserved for future use.

Imaging

The role for imaging is limited in the initial evaluation of the infertile male. In men with unilateral vasal agenesis, as many as 75% of men will have ipsilateral renal anomalies, and hence, abdominal imaging is recommended [28, 29]. Transrectal ultrasound (TRUS) can be considered in the patient with painful ejaculation, low semen volume, and acidic semen with palpable vas deferens to evaluate for ejaculatory duct obstruction [30]. In addition, clinicians should not routinely perform abdominal imaging for the sole indication of an isolated small or moderate right varicocele. This was previously thought to be important as it might be caused by an abdominal source or mass.

Varicoceles and Repair

For men with palpable varicoceles, a meta-analysis assessed that pregnancy rates were higher in men with surgical repair as compared to no treatment [31]. For patients with non-palpable varicoceles detected on imaging, no effect was seen on the likelihood of achieving a pregnancy [32]. Thus, the routine use of scrotal ultrasonography is not recommended for the evaluation of non-palpable varicoceles as treatment of non-palpable varicoceles does not improve fertility. For men with both varicoceles and non-obstructive azoospermia, there lacks definitive data to support varicocele repair prior to ART.

Sperm Retrieval

The guidelines recommend that for men with non-obstructive azoospermia, a micro-TESE should be performed. A systemic reviewed performed on different sperm retrieval techniques demonstrates that micro-TESE was associated

with improved success rates for extraction compared to conventional non-microsurgical and aspiration techniques [33••]. During a micro-TESE, the surgeon will attempt to identify specific dilated seminiferous tubules under the microscope, with sperm retrieval rates noted to be around 50–65% [34]. Additional options for sperm retrieval include percutaneous sperm aspiration, open random sampling, testis mapping, and conventional TESE. Micro-TESE is 1.5 times more likely than conventional TESE and twice as likely as aspiration techniques to retrieve sperm. Additional factors to consider include a history of anabolic steroid use and receipt of radiation or chemotherapy due to concern for spermatogenic impairment [35, 36].

For men with obstructive azoospermia, the source of the sperm has no impact on fertility outcomes as pregnancy and live birth rates were similar for sperm that was extracted from the testicle as compared to the epididymis [37]. Epididymal sperm extraction may occur through microscopic sperm aspiration or percutaneous extraction and may be performed fresh or utilized after cryopreservation to be used with ICSI.

For men with ejaculatory dysfunction, limited literature exists to recommend surgical sperm extraction from induced ejaculatory stimulation for obtaining sperm. The eventual method for obtaining sperm will be dependent on the cause of the patient's ejaculatory dysfunction and a discussion with the patient and the provider. Methods to induce ejaculation include sympathomimetic agents, penile vibratory stimulation, vasal ampulla electro-ejaculation, or sperm retrieval.

For men with infertility thought to be associated with retrograde ejaculation, the initial evaluation consists of both a sperm analysis and a post-orgasmic urinalysis. If there is a component of antegrade ejaculation which is sufficient for reproduction, no additional work up or treatment is necessary. However, for men with minimal antegrade ejaculation and significant retrograde ejaculation, initial treatment begins with sympathomimetic agents along with alkalization of urine. Surgical sperm retrieval can also be utilized.

Obstructive Azoospermia (Including Post-Vasectomy Infertility)

Men that have obstructive azoospermia have absence of sperm in the ejaculate despite normal spermatogenesis in the testicle. Etiologies of this include congenital absence of the vas deferens, ejaculatory duct obstruction, epididymal obstruction, or a vasectomy. For couples that are interested in conceiving following a vasectomy, both surgical reconstruction with a microsurgical vasoepididymostomy versus vasovasotomy and surgical sperm retrieval are potential options [38]. Microsurgical reconstructive surgery performed in post-vasectomy males has reported fertility rates as high as 70% [39]. Ejaculatory duct obstruction is a rare form of male infertility and is diagnosed with a transrectal ultrasound and is managed with a transurethral resection of ejaculatory duct (TURED) [40].

Advanced Reproductive Technologies

In vitro fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI) are two forms of advanced reproductive technologies that have been utilized to overcome male factor infertility. As long as viable sperm are injected into oocytes, ICSI overcomes sperm abnormalities such as concentration, motility, and morphology seen on semen analysis and allows for comparable pregnancy rates that would be expected with normal sperm [41]. Another form of ART is intra-uterine insemination (IUI), which involves placing processed semen samples directly into the uterine cavity to facilitate implantation. Men with low total motile sperm count after processing (less than 5 million) are candidates for IUI and should be counseled on a lower likelihood of pregnancy.

Endocrine Modulation

For men with infertility secondary to testosterone deficiency, endogenous testosterone production can be increased via the use of aromatase inhibitors, hCG, or selective estrogen receptor modulators. However, the FDA has not approved the use of aromatase inhibitors and selective estrogen receptor modulators in men, and use of these agents are off-label. Human chorionic gonadotropin or hCG is an injectable medicine that directly stimulates the Leydig cells to produce testosterone in a similar means by which LH would and is approved by the FDA for use in men with hypogonadotropic hypogonadism [42]. Aromatase inhibitors function by preventing the peripheral conversion of testosterone into estrogen, also reducing the negative feedback on LH secretion by the pituitary gland. Evaluation of long-term efficacy of aromatase inhibitors is limited for men with potential side effects including osteoporosis and joint disorders [43].

Selective estrogen modulators, such as clomiphene citrate, competitively bind to estrogen receptors on the hypothalamus and pituitary gland, resulting in increased LH and FSH secretion. Clomiphene citrate may raise serum testosterone levels comparable to that of exogenous testosterone administration with associated improvement in symptoms of testosterone deficiency without negatively impacting sterility [44, 45]. Exogenous testosterone monotherapy provides negative feedback to the hypothalamus and pituitary gland, resulting in inhibition of gonadotropins and negatively impacting spermatogenesis, and should not be offered to men with symptomatic testosterone deficiency as monotherapy.

The off-label use of FSH analogues has also been described in men with idiopathic infertility with normal FSH levels. In these men treated with FSH, an increase in sperm concentrations and pregnancy rates were seen [46].

Gonadotoxic Therapies and Sperm Preservation

Men in their adolescence and young adulthood diagnosed with cancers may be offered radiation therapy or chemotherapy which may lead to temporary or long-term gonadal injury and a major impact on spermatogenesis. Patients being planned for receipt of gonadotoxic therapies should be informed of the possible side effects of these medications before starting therapy. Alkylating chemotherapies such as cyclophosphamide, busulfan, mechlorethamine, and cisplatin target spermatogonial stem cells may result in long-standing azoospermia at therapeutic doses [47]. Chemotherapy agents that selectively target the differentiating germ cells without impacting the spermatogonial stem cell result in a temporary decrease in sperm parameters followed by gradual recovery after 6 months of cessation of therapy [48]. For patients undergoing gonadotoxic treatments, the guidelines recommend preventing conception for at least 12 months following completion of therapy to avoid teratogenic and mutagenic effects. Additionally, sperm should not be cryopreserved for at least 6 months and preferably 12 months after receiving gonadotoxic chemotherapy. Studies suggest that by 2 years following treatment, the rate of chromosomal abnormalities of children fathered by men exposed to gonadotoxic therapies is similar to that of controls [49•]. For men with testicular cancer, a retroperitoneal lymph node dissection may be a component of treatment therapy, and patients undergoing this therapy should be counseled on the risk of aspermia. For men that are seeking paternity but are persistently azoospermic after gonadotoxic therapies, testis sperm extraction or TESE may be a treatment option. Based on a systematic meta-analysis, sperm retrieval rate with a microsurgical TESE was 42% for men with azoospermia exposed to gonadotoxic therapies [50].

Conclusion

We present a comprehensive review of the American Urological Association and the American Society for Reproductive Medicine (AUA/ASRM) updated practice guidelines for the assessment and management of the infertile male patient, highlighting what we believe every provider should know about the guidelines. This review highlights the important guideline changes from the previous version. Male factor infertility may be reversible and treatable; hence, referral to a male infertility specialist is warranted to address this. In this most recent version of the guidelines, a higher degree of emphasis is placed on the various health conditions that may be associated with male factor infertility. Additionally, the guidelines are further stratified by sub-section to address the various aspects of male factor infertility with each practice statement being categorized based on the level of evidence available to support the statement. With the current set of guidelines still backed by expert opinion, we anticipate that as additional research is performed within the field, these practice statements can be recommended at a stronger lever supported by data.

Declarations

Ethics Approval This article does not contain any studies with human or animal subjects performed by any of the authors

Conflict of Interest The authors declare no competing interests.

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•• Of major importance

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