Best Practice Guidelines for Male Infertility Diagnosis and Management

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Key Points

- Infertility is defined as the inability to achieve a natural pregnancy within 1 year in sexually active couple.
- The American Urological Association (AUA), the American Society for Reproductive Medicine (ASRM), and the European Association of Urology (EAU) are three predominant organizations that regularly develop and update guidelines for the diagnosis and management of the infertile male.
- Comprehensive medical history and physical examination with two semen analyses are the essential components of the initial evaluation for the infertile male.
- The AUA and ASRM recommend andrological evaluation if the patient has abnormal findings on initial assessment or one of two semen analyses. The EAU differs in its recommendation, requiring two abnormal semen analyses prior to proceeding with andrological evaluation.
- Differences between accepted WHO semen analysis reference values create potential for discrepancies between patients selected for andrological evaluation. The EAU and ASRM reference the latest criteria published in 2010, while the AUA still cites the 1999 version.

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62.1 Introduction

Classically, infertility is defined the inability to conceive a natural pregnancy within 1 year in a sexually active couple [1]. The American Society for Reproductive Medicine describes infertility as the result of any disease process (an interruption, cessation, or systemic disorder) of the male or female genital tracts that prevents natural conception over a 1-year period or, in females, the inability to maintain a pregnancy to delivery [2]. Recent estimates predict between 8 and 15% of couples are unable to conceive with regular, unprotected intercourse at 12 months [2]. While recent cross-sectional studies within limited populations suggested male infertility rates are around one in ten or 10.1% (CI 9.2–11.1), a recent collaboration by the WHO suggests that numerous confounding factors, variation in geographical fertility rates, and lack of uniformly accepted criteria for infertility make global estimates extremely difficult [3, 4].

Male factor infertility can be due to a number of congenital or acquired urogenital irregularities. Systemic diseases, environmental/lifestyle (e.g., obesity, gonatotoxins, smoking, etc.) erectile dysfunction, genetic abnormalities, variations in scrotal temperature (i.e., varicocele), urogenital tract infections, urogenital trauma, and improper coital habits can all result in some degree of male infertility [5]. Nearly half of all cases fail to determine an identifiable cause for male infertility. In large part, this is due to limited understanding of the intricacies that underlie natural conception and the limited capability of current diagnostic testing to identify abnormalities [6]. The AUA estimates that, despite best management efforts, nearly 5% of couples will remain unable to conceive due to some combination of male or female factor infertility [7]. There are emerging interests into developing new treatments for unexplained male factor infertility. These efforts are largely centered upon stem cell biology and gene therapy, but have yet to transition into guideline-based practice and are typically used empirically after conventional management has failed [8].

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Recent recognition for the need and utility of clinical guidelines to aid practitioners in the assessment of the infertile male has been spurred by increased understanding of the medical complexities that underlie infertility. Standardized diagnosis and treatments have been outlined in these guidelines in order to help improve efficiency. Well-known organizations from around the world have developed guidelines through multidisciplinary collaborations in order to achieve this goal [2, 7, 9, 10]. Of these sources, urologists and practitioners specializing in reproductive medicine commonly utilize three predominant guidelines for the evaluation and treatment of male infertility: (i) American Urological Association (AUA) best practice statements for the evaluation of the infertile male [7], (ii) the ASRM Practice Committee Report on the diagnostic evaluation of the infertile male [2], and (iii) the European Association of Urology (EAU) guidelines on male infertility [9].

While several concurrent collaborations from different organizations have developed expert opinion panels and best practice statements, the previously cited institutions present the most comprehensive and up-to-date guidelines. These organizations utilize multidisciplinary teams using clinical evidence to develop recommendations. These recommendations meet the criteria for "Clinical Practice Guidelines" created by the Institute of Medicine (IOM). The IOM defines clinical practice guidelines as "statements that include recommendations, intended to optimize patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" [11]. Guidelines are not intended to be used as a legal agent. They should be employed as a set of principles that provide a template for standardization of care and help to improve diagnostic efficiency while preserving physician autonomy. A combination of physician judgement and guideline-based management is likely most representative of the current standard of care [12].

62.2 AUA Best Practice Statement: Optimal Evaluation of the Infertile Male

The AUA Board of Directors initially created the Male Infertility Best Practice Policy Committee in 1999. This subsequently became a collaborative initiative between the AUA and the ASRM in 2001 with a goal of developing a series of best practice statements in regards to management of male factor infertility. The initial goal of the committee was "to develop recommendations, based on expert opinion, for optimal clinical practices in the diagnosis and treatment of male infertility." In the most recent update entitled "The optimal evaluation of the infertile male: Best practice statement," the AUA Practice Guidelines Committee selected a ten-person panel composed of nine urologists and one research andrologist [7]. The members of the panel were not reimbursed for their contributions and provided disclosures regarding conflicts of interest to the AUA before participating.

In 2015, the AUA released the American Urological Association Clinical Practice Guidelines Development Standard Operating Procedure [13]. This document details the methodology for the formulation of AUA best practice statements and guidelines across all non-oncologic subdisciplines within urology. This is outlined on the AUA website and an unabridged version is available for free download. Initially, topics for guidelines are nominated by either Practice Guidelines Committee members or by AUA members online. Depending on the topic in question, a panel is formed with special attention paid to the particular expertise of the candidate members. As previously stated, these potential panel members cannot have a conflict of interest with the guideline under consideration. The panel then develops the scope of study by setting parameters for exclusion/inclusion criteria and creating research questions to be investigated. An initial literature review is performed and the results of which are subjected to data extraction, analysis, and synthesis prior to the development of an evidence report. At this point, a final literature review is performed and the guidelines are written for peer review [13]. This methodology, adopted in 2015, has yet to be implemented into the development of AUA infertility guidelines as the most recent update was released in 2011.

In the 2011 update of the AUA Best Practice Statement: Optimal Evaluation of the Infertile Male, the panel suggests that initial infertility workup should be performed if natural pregnancy has not occurred by 1 year of regular unprotected vaginal intercourse. Consideration for earlier workup is recommended if the male and/or his female partner have known infertility risk factors. The best practice statement provided in the manuscript recommends the initial evaluation for male infertility includes both a thorough reproductive history with a urogenital physical exam and two properly obtained semen samples. Additional tests should be considered if (i) abnormalities are identified during the initial evaluation, (ii) the etiology of infertility cannot otherwise be identified, and (iii) problems with infertility continue despite appropriate treatment of the female partner. Table 62.1 details the breadth and methodology used in the creation of the AUA guidelines.

62.3 ASRM Guidelines

The ASRM recommendations and best practice statements have undergone multiple revisions since its inception in 2006. Initially presented in conjunction with the AUA as detailed above, the Practice Committee of the ASRM has released updated guidelines and best practice statements in 2012 and again republished in 2015 in Fertility and Sterility [2].

Table 62.1 AUA, ASRM, and EAU: Scope and methods for development of guidelines for the evaluation of the infertile male

	AUA	ASRM	EAU
Guideline title	Optimal evaluation of the infertile male: AUA best practice statement	Diagnostic evaluation of the infertile male: a committee opinion	Guidelines on male infertility
Goal	To offer recommendations for the optimal diagnostic evaluation of the male partner of an infertile couple	To provide clinicians with principles and strategies for the evaluation of couples with male infertility problems	To assist urologists and healthcare professionals from related specialties in the treatment of male infertility
Intended users	Physicians	Physicians	Physicians
Collection and evidence selection	Medline literature review from 1999 through October 2007 was supplemented by hand searches of published literature	Not stated	Literature search using EMBASE, Medline, Cochrane review databases limited to RCT, and meta-analyses spanning at least 3 years. Other high-level evidence and other organizations' high-quality guidelines
Analysis of the evidence	Review of published meta-analyses and systematic reviews	Not stated	Preferred reporting items for systematic reviews and meta-analyses (PRISMA)*
Assessment of quality and strength of evidence	Not stated	Not stated	Modified Oxford Centre for Evidence-Based Medicine – Levels of Evidence approach [aa]
Methods used to formulate the recommendations	Expert consensus	Expert consensus	Expert consensus
Description of methods used to formulate the recommendations	The Practice Guidelines Committee (PCG) chair appoints panel chair based on expertise and leadership ability. The panel chair nominates up to seven additional members. The number of panel members from each institution is limited to two The objective the panel is to develop evidence-based recommendations either by analytical means or group consensus that help guide best practices on management of male infertility	A panel of 16 members drafted the first edition offering consensus and evidence-based recommendations in the context of clinical practice. Ethical and fiscal considerations are included when applicable	A collective panel of actively practicing academic urologists, endocrinologist, and gynecologists with special interest and experience in infertility and andrology. Literature reviewed and quality of evidence assessed using PRISMA* methodology. Grading recommendations are performed via the modified Oxford Centre for Evidence-Based Medicine – Levels of Evidence [a]
Methods for determining strength of evidence	Not stated	Not stated	Modified grading of recommendations assessment, development and evaluation (GRADE)**
Guideline validation technique	External and internal peer review	Proposed documents are circulated among members of the society for review before final approval and publication	External and internal peer review
Guideline algorithm(s)	Not provided	Not provided	Not provided
Implementation strategy	Abridged and unabridged versions of the optimal evaluation of the infertile male are available for viewing or download from the AUA at: https://www.auanet.org/education/guidelines/male-infertility-d.cfm Guidelines and best practice statements from the SSMR are available for viewing or download at: http://www.ssmr.org/professionals/male-infertility-guidelines.aspx	The practice committee of the ASRM published a report in Fertility and Sterility in 2015 and have it on the ASRM website for viewing: http://www.asrm.org/Guidelines/	Annual reprint of the long version of EAU guidelines. Text available on CD with hyperlinks for references (http://www.uroweb.org/guidelines/online-guidelines) Additional condensed pocket versions of the EAU guidelines reprinted each year available for free to all EAU members. Abridged versions published in European urology as original papers. Guidelines, in all mediums of content, are published and presented in 25 different languages

(continued)

Table 62.1 (continued)

	AUA	ASRM	EAU
Cost analysis provided	No	No	Yes
Publication history	Initial release in 2001 in collaboration with the practice committee of the ASRM. Revised in 2010 with confirmation of validity in 2011	Since its first edition in collaboration with the AUA in 2001, the practice committee has provided updates in 2006 and 2012. The report was most recently published in Fertility and Sterility in 2015	First published in 2001, followed by full-text updates in 2004, 2007, 2010, 2014, and 2015
Where guidelines can be found	Available for viewing or download at AUAnet.org: https://www.auanet.org/common/pdf/education/clinical-guidance/Male-Infertility-d.pdf	Available for viewing and download by ASRM members or view-only for nonmembers (http://www.asrm.org/Guidelines/)	Available for online viewing or download at EAU society website: http://www.uroweb.org/guidelines/online-guidelines/
Date released	2001 April (revised 2010; reviewed and validity confirmed 2011)	2012 June	2010 April (revised 2013 March)

RCT randomized controlled trials

[a]Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) is an evidenced-based minimum criteria for evaluating and performing systematic reviews and meta-analyses. This particular method is aimed at the reporting of RCTs, but can be utilized for reporting systematic reviews of other evidence [14]

[b]The Modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach is a method adopted by the EAU to assess the quality of evidence included in guidelines. This helps to provide a structured approach to defining a grading system [15]

[c]Levels of Evidence

1a: Evidence obtained from meta-analysis of randomized trials

1b: Evidence obtained from at least one randomized trial

2b: Evidence obtained from one well-designed controlled study without randomization

2b: Evidence obtained from at least one other type of well-designed quasi-experimental study

3: Evidence obtained from well-designed nonexperimental studies, such as comparative studies, correlation studies, and case reports

4: Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

[d]Rating scheme for the grade of recommendations

Grade A: Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial

Grade B: Based on well-conducted clinical studies, but without randomized clinical trials

Grade C: Made despite the absence of directly applicable clinical studies of good quality

This committee was composed of 125 physicians and basic science researchers from the fields of urology, reproductive andrology, gynecology, family medicine and primary care, andrology, and reproductive medicine. The 2012 revision entitled "Diagnostic evaluation of the infertile male: a committee opinion" has garnered the approval of the Board of Directors of the AUA and the ASRM. The stated goal of the Practice Committee's report is "to provide clinicians with principles and strategies for the evaluation of couples with male infertility problems" [2]. This document suggests that it stands to serve as an adjunct to clinical care stating, "although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations" [2]. An itemized summary of the breadth and methodology used to develop the ASRM guidelines can be found in Table 62.1. A comparison of AUA and ASRM guidelines and major recommendations can be found in Table 62.2.

Table 62.2 AUA (2011) and ASRM (2012) guidelines

	AUA	ASRM
Goals for evaluation	Initial screening for male infertility should be performed if pregnancy has not occurred within 1 year of regular and unprotected intercourse. Evaluations before the 1-year threshold may be considered in certain circumstances (i.e., history of bilateral cryptorchidism or advanced female age). A full evaluation should be performed by a urologist or other reproductive specialist when initial screening an abnormal semen analysis or medical history. A full evaluation may also be considered in cases of persistent infertility despite diagnosis and treatment of female factor	Evaluation for infertility is indicated for couples who fail to achieve a successful pregnancy after 12 months or more of regular unprotected intercourse. Earlier evaluation and treatment may be considered, based on medical history and physical findings, and is warranted after 6 months or more in couples with females greater 35 years of age. Men having concerns about their future fertility also merit evaluation. At a minimum, the initial screening evaluation should include reproductive history and analysis of at least one semen sample
Components of a full evaluation	A full evaluation of the infertile male should start with a comprehensive medical and reproductive history and physical examination performed by a urologist or reproductive specialist. This should be accompanied by at least two semen analyses. These samples should be produced at least one month apart. Ideally, an "abnormal" sample should have at least two abnormal semen parameters prior to proceeding with a full evaluation. Additional components of the full evaluation (detailed below) should be employed at the discretion of the urologist or reproductive specialist to help elucidate the etiology of infertility	When an initial evaluation elicits an abnormal history or abnormal parameters on semen analysis, a more detailed evaluation should be considered. This should be performed by a urologist or other male reproductive specialist. The full evaluation should include the medical history, physical exam, and semen analysis obtained in the initial screening in addition to a variety of diagnostic tests and procedures (detailed below) to be utilized at the discretion of the healthcare professional
Endocrine evaluation	Endocrine evaluations should include at least a morning serum testosterone and FSH. This evaluation is encouraged for abnormal semen analysis (especially when sperm concentration is <ten million/ml), when sexual function is impaired, or other clinical findings suggest underlying endocrinopathy (e.g., hyperprolactinemia)	Endocrine evaluation should be considered in men having (1) abnormal semen parameters, especially with sperm concentrations below 10 million/mL, (2) impaired sexual function, or (3) clinical findings that suggest an endocrinopathy. At minimum, it should include a measurement of serum testosterone and FSH concentrations. When T level is low (<300 ng/mL), a second early morning total T level with serum free testosterone (T), LH, and prolactin should be obtained. Inhibin B has been shown to correlate better with sperm parameters. However, due to cost of measuring inhibin B, FSH should be utilized first
Post-ejaculatory urinalysis	Post-ejaculatory urinalysis should be considered when absent or low volume (<1 ml). This test should *not* be performed in those patients with diagnosed CBAVD or clinical signs of hypogonadism	Post-ejaculatory urinalysis is indicated in men having an ejaculate volume less than 1 mL, except in those diagnosed with hypogonadism or CBAVD
Transrectal ultrasonography	Transrectal ultrasonography should be considered in azoospermic patients with palpable bilateral vasa and low ejaculate volumes. Seminal vesicles measuring greater than 2.0 cm in anteroposterior diameter should raise concern for ejaculatory duct obstruction	TRUS is indicated in low-volume, acidic azoospermia or in samples without fructose. Seminal vesicles measuring greater than 1.5 cm in anteroposterior diameter should raise concern for complete or partial ejaculatory duct obstruction
Scrotal ultrasonography	Scrotal ultrasonography should be employed when clinical examination of scrotal structures is difficult or when a testicular mass is suspected	Scrotal ultrasonography can be considered when careful physical examination is unable to identify structures or pathology

(continued)

Table 62.2 (continued)

	AUA	ASRM
Strict sperm morphology	Sperm morphology using strict criteria has not been shown to reliably predict fertility. It should not be utilized as the sole diagnostic test to guide therapeutic decisions	No specific recommendation presented
DNA integrity	Insufficient evidence in literature to support the routine application of DNA integrity testing in the full evaluation of the infertile male. Furthermore, no proven therapies have been developed to treat abnormal tests	Sperm DNA damage is more common in infertile men and may contribute to infertility. However, data regarding reproductive outcomes and DNA integrity is too limited to routinely recommend testing of the male partner
Reactive oxygen species (ROS)	ROS have not been shown to be predictive of fertility. Insufficient evidence exists to support the routine use of ROS testing in infertility evaluations. Furthermore, presently no proven medical or surgical interventions exist to treat ROS in semen samples	No specific recommendation provided
Specialized tests	*Quantitation of leukocytes* Patients with true pyospermia (greater than one million leukocytes per ml) should be evaluated for genital tract infection	*Quantification of leukocytes* Men with true pyospermia (> one million WBCs/mL) should be evaluated for genital tract infection or inflammation
	Antisperm antibody assay Should be considered in cases of isolated asthenospermia with otherwise normal semen parameters	*Antisperm antibody assay* Routine testing not indicated. Should not be performed when ICSI is planned
	Sperm viability test May be utilized in cases with viable, nonmotile sperm in consideration for ICSI	*Sperm viability test* Can be utilized to assess whether nonmotile sperm would be viable for ICSI
	Sperm-cervical mucus interaction Subject to variable interpretation and often negated by the use of assisted reproductive technology	*Sperm penetration assay* May be beneficial for evaluating ICSI candidates, but often superseded due the routine use of ICSI in IVF
	Zona-free hamster oocyte test Sperm penetration assay (SPA) should be reserved for patients in whom abnormal tests will direct therapeutic decisions. Subject to variable interpretation	*Sperm chromosome aneuploidy* Sperm with severely abnormal morphology, men with karyotypic abnormalities, or nonobstructive azoospermia may benefit from sperm aneuploidy testing. However, testing is cost-limiting and identifying sperm to be used in ICSI is difficult. It is not routinely recommended
	Computer-aided sperm analysis (CASA) Useful for assessing motility and motion parameters. Not routinely used	
	⁎not required for diagnosis of male infertility. May aid in selecting therapy in specific circumstances	
Genetic screening and testing	Congenital bilateral absence of vasa deferentia should warrant cystic fibrosis transmembrane conductance regulator (CFTR) mutation testing. If positive, female partners should be offered CFTR testing prior to assisted reproductive efforts to harvest sperm. Conversely, unilateral absence of vasa deferentia should be followed up with renal imaging. CFTR evaluation should, at minimum, test common point mutations associated with cystic fibrosis and the 5 T allele Gene sequencing may be considered in couples where the wife is a carrier and the husband with CBAVD tests negative for the routine CFTR panel Karyotyping and genetic counseling should be offered to all patients with nonobstructive azoospermia and severe oligospermia (<five million/ml) Insufficient data available to recommend a minimum number of sequence tagged sites to test for patients undergoing Y chromosome microdeletion analysis. Patients with large deletions involving azoospermia factor (AZF) region a or b often have a poor prognosis. However, this result cannot reliably exclude the presence of viable sperm	Men with nonobstructive azoospermia or severe oligozoospermia (<five million/mL) should be evaluated for genetic abnormalities Testing for chromosome 7 CFTR gene mutations should be considered in cases of CBAVD. Patients with unilateral absence of vasa deferentia should be offered renal imaging and it is not recommended that they be tested for CFTR mutations Karyotype testing for chromosomal abnormalities should be employed in men with nonobstructive azoospermia or severe oligozoospermia when getting evaluated for ICSI Y chromosome microdeletions, also known as azoospermia factor (AZF) regions, can have proximal, central, or distal regional mutations. Distal mutations (AZFc) have the only potential for fecundity using IVF. AZF should therefore be tested in men with nonobstructive azoospermia or severe oligozoospermia before performing ICSI

CLIA Clinical Laboratory Improvement Amendments, *CBAVD* congenital bilateral agenesis of the vas deferens, *TRUS* transrectal ultrasound, *ICSI* intracytoplasmic sperm injection

62.4 European Association of Urology Guidelines

The European Association of Urology (EAU) guidelines office (given this title in 2004 after its conception in 1996) was challenged with the task of developing European clinical urological guidelines [16]. This panel, consisting predominantly of urologists, gynecologists, and reproductive endocrinologists, created the "EAU Male Infertility Guidelines." Since its initial release in 2001, these guidelines have undergone regular updates with the most recent edition published as a full-text update in 2015 [9]. While many non-urologic medical practitioners commonly utilize these guidelines. The EAU has made it their focus to create a resource for urologists. The respective members of the panel (all of which were members of the EAU) were required to submit nondisclosure statements and inform the EAU of any potential conflicts of interest prior to participating in the development of guidelines. Panel members were considered on the basis of their scientific and clinical merits and their willingness to commit considerable amounts of time to produce well-founded and thorough guidelines. Each member's commitment is for a 4-year term which may be renewed for one additional term. The panel is led by an EAU guidelines office appointment chairman. In an interest to keep the focus of these guidelines within the field of urology, the chairman appointed is always a board-certified and full-time urologist. Once the panel has formulated a preliminary guideline, new edition, or best practice statement, a minimum of 3–4 reviewers are asked to provide an assessment and formal review of the document submitted. These reviewers may or may not be associated with the EAU and receive no monetary compensation [9]. As of the last update in 2015, the EAU significantly reduced the volume of text in non-oncology guidelines and standardized formatting for ease of use [9].

Development of evidence-based recommendations has long been an emphasis of the committee. This is due to the fact that the EAU clinical guidelines are predominantly intended to enhance the practitioner's clinical decision-making. In accordance with this goal, the development of incremental levels of evidence and the associated grades for each recommendation helps quantify each recommendation based on the quality of underlying evidence. This helps to preserve physician autonomy and allows clinicians to gauge how strictly they adhere to each individual recommendation [9, 16]. Table 62.1 provides a summary of the scope and methods used by the committee to formulate the EAU guidelines.

In creating new guidelines or new editions of current guidelines, the panel gathers and appraises evidence from current literature. In the 2015 update, a total of 409 unique records were initially collected from an extensive literature review and screened for validity and relevance. Of these, nine publications were selected for inclusion into the formulation of new recommendations [16]. This information gets formulated into a series of statements. The statements are summarized as recommendations and presented along with their associated levels of evidence. The strength of each recommendation is graded (grade of recommendation = GR) depending upon the quality of underlying evidence (level of evidence = LE) (Appendix 1). The GR does not always follow a linear relationship with LE. This is due, in large part, to the variability of study design, limitations in methodology, and/or disparity in available data on a given recommendation. The inverse is also true. Statements without high-level evidence may receive high-grade recommendations if dictated by overwhelming clinical experience and/or general consensus. These instances are typically documented in the text as "upgraded based on panel consensus" [9]. A comprehensive evaluation of each recommendation is performed after a grade is assigned to ensure that each statement, while supported by underlying scientific evidence or group consensus, is equitable with value, preference, and costs. As of the 2018 update, the EUA reported using a modified GRADE methodology, a structured approach in assessing the evidence used in formulating recommendations [15, 17]. This essentially aims to eliminate the ambiguity of a grade A, B, or C recommendation and recategorizes the statements as either "strong" or "weak" recommendations [16]. Additionally, meta-analyses are only utilized as part of a systematic review if multiple randomized control trials address the same question and the outcomes are reported in a similar manner. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance is followed in these instances [18].

The clinical practice guidelines supplied by the EAU address 13 different topics within male infertility. These include epidemiology and etiology, disorders of ejaculation, testicular dysfunction, varicocele, obstructive azoospermia, genetic disorders, germ cell malignancy with testicular microcalcification, and semen cryopreservation. Table 62.3 provides selected recommendations from the EAU that are aimed at helping the clinician evaluate and manage male factor infertility. Many national urological associations have filed formal replies to incorporate EAU guidelines into their respective guidelines. Over 50 national societies from around the world have submitted endorsements of EAU guidelines [16].

Table 62.3 EAU (2018) guideline recommendations on the evaluation of the infertile male

Area	Recommendation	Grade of Recommendation
Epidemiology and etiology	Both partners should be evaluated simultaneously to characterize infertility	Strong
	Men who are diagnosed with infertility or with abnormal semen parameters should be examined	Strong
Diagnostic evaluation of the infertile male	Female partner fertility status should be included in the evaluation and treatment of subfertile males as this may affect fertility outcomes	Strong
	Semen analyses should be performed in accordance with guidelines from *WHO Laboratory Manual for Examination and Processing of Human Semen (fifth ed)*	Strong
	Full andrological assessment should be reserved for patients with at least *two* abnormal semen analyses	Strong
	Adherence to the 2000 WHO manual for the standard evaluation, diagnosis, and management of the subfertile male	Weak
Primary testicular deficiency	Even with a negative genetic panel, men who are undergoing sperm retrieval should be given appropriate genetic counseling	Strong
	Testicular biopsies (TESE or micro-TESE) should be performed in men with nonobstructive azoospermia. This can aid in determining degree of spermatogenesis, cryopreserve sperm, and diagnose germ cell neoplasia in situ	Strong
Genetic disorders and male infertility	Karyotype analysis should be considered in all men with impaired spermatogenesis (spermatozoa <10 million/mL). This should be performed for diagnostic purposes	Strong
	Genetic counselling should be provided for all couples when genetic abnormalities are elicited on clinical or genetic evaluation and in patients who may be a carrier for an inheritable disease process	Strong
	Patients with Klinefelter's syndrome should be provided with long-term endocrine follow-up and appropriate medical treatments, when appropriate	Strong
	Microdeletion testing in men with obstructive azoospermia (OA) should not be performed as spermatogenesis is often unaffected	Strong
	Patients with Yq microdeletions wishing to attempt intracytoplasmic sperm injection (ICSI) should be informed that microdeletions will be passed to male offspring, but not female	Strong
	Patients with structural abnormalities of the vasa deferentia should be tested along with their partner for cystic fibrosis transmembrane conductance regulator (CTFR) gene mutations	Strong
Obstructive azoospermia (OA)	Microsurgical vasovasostomy or tubovasectomy should be performed for OA secondary to epididymal or vasal obstruction	Strong
	Sperm retrieval techniques (i.e., microsurgical epididymal sperm aspiration, testicular sperm extraction, and percutaneous epididymal sperm aspiration) should be performed only when cryopreservation facilities are available	Strong
Varicocele	Adolescents with a varicocele and physical findings revealing ipsilateral testicular volume loss or other signs of testicular dysfunction should be treated	Weak
	Subclinical varicoceles and infertile men with normal semen analysis should not be treated	Strong
	Men with clinical varicoceles, findings of oligospermia on semen analysis, and otherwise unexplained infertility should be treated	Weak
Hypogonadism	Symptomatic patients with primary or secondary hypogonadism who are not considering fertility should be offered testosterone replacement therapy	Strong
	Men diagnosed with hypogonadotropic hypogonadism should be offered effective drug therapy (human chorionic gonadotropin, human menopausal gonadotropins, recombinant follicle-stimulating hormone, highly purified FSH).	Strong
	Testosterone replacement therapy should not be used to treat infertility	Strong
Cryptorchidism	Hormonal therapy should not be used to treat cryptorchidism in adults	Strong
	Simultaneous testicular biopsy should be performed for detection of intratubular germ cell neoplasia in situ in adult patients undergoing correction for undescended testes	Weak
Idiopathic male infertility	Patients with hypogonadotropic hypogonadism should be offered medical treatment	Strong
	The use of gonadotropins, antioxidants, and anti-estrogens lacks sufficient evidence to provide sound recommendations	Strong
Male contraception	Use cauterization and fascial interposition during vasectomy have been proven to be most effective techniques in preventing recanalization postprocedure	Strong
	Patients pursuing vasectomy should be informed about the surgical technique, risk of failure, possible irreversibility, the necessity for contraception after the procedure until clearance, and the risk of potential complications	Strong
	Microsurgical epididymal sperm aspiration, percutaneous epididymal sperm aspiration, or testicular sperm extraction utilized in conjunction with intracytoplasmic sperm injection can be used as a second-line option for men who decline vasectomy reversal and those who failed vasectomy reversal surgery in order to achieve pregnancy	Weak
Male accessory gland infections	Provide instruction for patients with epididymitis secondary to proven or suspected *N. gonorrhoeae* or *C. trachomatis* infections. Refer sexual partners for evaluation and treatment	Strong

Table 62.3 (continued)

Area	Recommendation	Grade of Recommendation
Germ cell malignancy and testicular microcalcification	Men with evidence of testicular microcalcification (TM) should be encouraged to perform self-examination for early detection of testicular germ cell tumor (TGCT)	Weak
	Testicular biopsy, follow-up scrotal ultrasound, biochemical tumor markers, or abdominal/pelvic CT imaging should not be used in men with isolated TM without associated risk factors (i.e., infertility, cryptorchidism, testicular cancer, and atrophic testis)	Strong
	Testicular biopsy should be considered in men with testicular microcalcification (TM) who belong to one of the following high-risk groups: Bilateral ™, atrophic testes (less than 12 cc), history of undescended testes or TGCT	Strong
	Concerning findings on physical examination or sonographic evaluation in patients with TM or associated lesions should be followed with surgical exploration consisting of testicular biopsy and possible orchiectomy	Strong
	Men with TGCT should be followed for increased risk of hypogonadism and/or sexual dysfunction	Strong
Disorders of ejaculation	Specific treatments for ejaculatory disorders should be offered before performing sperm collection and assisted reproduction technique (ART). Short-acting SSRIs such as dapoxetine with or without topical anesthetics for premature ejaculation	Strong
Semen cryopreservation	Cryopreservation should be offered to men who are scheduled to undergo chemotherapy, radiation, or surgery that may interfere with spermatogenesis or cause ejaculatory dysfunction	Strong
	Sperm cryopreservation should be offered if testicular biopsies are performed for fertility indications	Strong
	If cryopreservation is not available locally, inform patients about the possibility of visiting or transferring to a cryopreservation unit before therapy starts	Strong
	Take precautions to prevent transmission of viral, sexually transmitted or any other infection by cryostored materials from donor to recipient and to prevent contamination of stored samples. These precautions include testing of the patient and the use of rapid testing and quarantine of samples until test results are known. Do not store samples from men who are positive for hepatitis virus or HIV in the same container as samples from men who have been tested and are free from infection	Strong

62.5 An Assessment of the Guidelines for the Evaluation of the Infertile Male

Given the AUA's and ASRM's history of collaboration, it is not surprising that many of the guidelines and best practice statements overlap. In fact, the first editions from each organization produced in 2001 were developed by the AUA's Male Infertility Best Practice Policy Committee in concordance with the Practice Committee of the ASRM [19]. These documents were subsequently reviewed and updated with AUA revisions in 2010/2011 and ASRM revisions in 2006/2012. These documents do differ in varying capacities from the ones provided by the EAU [9].

While many similarities exist between the AUA/ASRM and EAU guidelines, there are some notable discordances. For instance, the AUA/ASRM guidelines recommend a minimum initial evaluation of the infertile male including a medical/surgical history and semen analysis [2, 7]. The EAU guidelines opt not to specify a minimum initial workup. It makes mention that history and physical exam are "standard assessments" in all patients and that a semen analysis should be included [9]. AUA and ASRM documents suggest that a full evaluation must be done by a urologist or other reproductive specialists when an initial evaluation reveals an abnormal semen analysis or the clinical history/findings are suggestive of endocrinopathy. On the contrary, the EAU guidelines state a complete andrological evaluation should only be performed if a minimum of two semen analyses are abnormal per WHO criteria [20]. This implies that normal semen analyses exclude dysfunctional sperm as the etiology for infertility, while many patients with unexplained infertility have normal semen characteristics. Unexplained infertility occurs when female factors of infertility have been excluded and the male has no identifiable cause on history, physical examination, and semen analysis [6]. The reported prevalence of unexplained infertility is highly variable (between 6 and 30%) and dependent on diagnostic criteria and population demographics [5, 6, 21–23].

Despite the aforementioned discrepancies between guidelines, all three committees clearly place an emphasis on the diagnostic importance of the traditional semen analysis. In all three guidelines, an abnormal semen analysis (two in the EAU guidelines) is required before a full andrological evaluation can be performed. The latest guidelines from the EAU and ASRM consider the updated 2010 WHO [20] semen analysis criteria, while the AUA guidelines still adhere to the version published in 1999 [24]. This discrepancy can have major clinical implications as the lower reference ranges for normal semen parameters in the updated 2010 version may exclude many patients from further evaluation. Up to 15% of men with at least one abnormal parameter in the 1999 WHO criteria were reclassified within normal limits in the 2010 WHO criteria in comparison study [24, 25]. Another study

with similar methodology found that upwards of 19% of men were reclassified as "normal" after having at least one abnormal semen analysis on the 1999 WHO criteria [26]. While many men who were originally eligible for a full evaluation may be excluded with the adoption of new criteria, an argument can be made that the new reference values provide a more accurate representation of natural variance. This may provide a more cost-effective parameter to eliminate unnecessary evaluations and will certainly be a topic for further research going forward.

Regardless of reference values and guideline specifics, it is clear that all three associations place a significant emphasis on the diagnostic value of the conventional semen analysis. This calls into question the validity of the test as a marker for male infertility [27]. Semen parameters aimed to delineate between fertile and infertile males are not always well defined and only ~40% of infertile men fall within the accepted reference ranges [28–30]. While inherent natural variability among semen samples does exist, confounding factors like diagnostic errors, the functionality of accessory sex organs, and ejaculatory abstinence do exist and should not be ignored [31–35]. Recent evidence has suggested that variability can exist both within individuals and particular laboratories performing the semen analysis. One study comparing intra-facility variation in semen analysis suggested that the highest variability in measurements were seen with morphology (coefficient variability above 80%) and count (coefficient variability greater than 60%) [36]. Another component of this study suggested that standardizing training for evaluating specific semen parameters only showed subsequent improvement with morphology. Another study assessing intraindividual variability using healthy participants over a 10-week interval showed the highest variation among sperm concentration (26.8%), then morphology (19.6%), and progressive motility (15.2%) [32]. The lowest variability was seen among assessments for vitality (10.3%).

The utility of parameters formed from population means and analysis of semen characteristics is largely linked to the individual variability within each characteristic. Reference values for those semen characteristics with significant variability may offer limited clinical value [37, 38]. Analysis of semen from donors for artificial insemination showed regression towards the mean when selecting those samples with abnormal characteristics in the first test. This result was amplified when repeated in a second test [37]. Assessing multiple samples from each individual helps account for variability within each characteristic and, ultimately, increases the accuracy of the parameter [38]. While this has a limited effect in preventing regression towards the mean, the averages from multiple samples help reduce its magnitude.

Therefore, it stands to question the legitimacy of a single "normal" semen analysis, as suggested by guidelines from both the AUA and the ASRM. A recent retrospective review using 2010 WHO criteria analyzed 5132 semen samples from 2566 patients who had provided at least two semen samples and found that 51.2% of second analyses confirmed the first [39]. When initial samples were found to be "normal," roughly 27% of second samples were found to be pathological. Conversely, when an initial sample was found to be abnormal, 23% of the second samples were found to be normal. Even with a "normal" semen analysis, many men remain infertile for reasons not explained by conventional semen characteristics and parameters. Intrinsic sperm dysfunction seen in DNA damage or immature chromatin has been described in roughly 30% of males with "unexplained infertility." These men's sperm dysfunction can only be explained by functional sperm evaluations (oxidative stress, DNA/chromatin integrity, and antisperm antibody assays) [40–42]. While the use of semen analysis does have certain limitations, the AUA and ASRM guidelines do suggest that further workup for male factor should be considered in cases when unexplained infertility persists and female factors have been ruled out or treated.

While addressing the application and parameters of the semen analysis, all three guidelines emphasize the importance of obtaining a properly performed analysis. Institutional quality control standards from the WHO [20] or the Clinical Laboratory Improvement Amendments (CLIA) [43] have been adopted by all three guidelines. However, existing data from surveys of laboratory practice indicate that semen analyses are still poorly standardized. The need for global standardization among laboratories has been well documented [44–48]. A clinician should have reasonable confidence in the accuracy and reproducibility of the semen analysis given its clinical value in evaluating the infertile male.

Beyond varying interpretations of the conventional semen analysis, discrepancies between AUA/ASRM and EAU guidelines persist in regard to what defines a "full evaluation." AUA/ASRM guidelines provide detailed descriptions of the components of the evaluation including when further procedures or invasive tests should be utilized. These include diagnostics like post-ejaculatory urinalysis, transrectal/scrotal ultrasound, sperm function tests, genetic testing, and endocrine evaluations (Table 62.2). Conversely, EAU guidelines refer to WHO manual for the standardized investigation, diagnosis, and management of the infertile couple (Box 62.1 and Table 62.4). This manual, first developed in 1993 and revised in 2000, aimed to provide detailed guides for medical history, physical examination techniques, and laboratory tests [1]. While it was reliable and accurate at the time, many argue that this manual is in need of revision to reflect significant advancements in technology and understanding over the last 18 years.

Table 62.4 Lower reference limits (fifth centiles and their 95% CIs) for semen characteristics

Parameter	Lower reference limit (range)
Semen volume (mL)	1.5 (1.4–1.7)
Total sperm number (106/ejaculate)	39 (33–46)
Sperm concentration (106/mL)	15 (12–16)
Total motility (PR + NP)	40 (38–42)
Progressive motility (PR, %)	32 (31–34)
Vitality (live spermatozoa, %)	58 (55–63)
Sperm morphology (normal forms, %)	4 (3.0–4.0)
Other consensus threshold values	
pH	>7.2
Peroxidase-positive leukocytes (106/mL)	<1.0
Optional investigations	
MAR test (motile spermatozoa with bound particles, %)	<50
Immunobead test (motile spermatozoa with bound beads, %)	<50
Seminal zinc (μmol/ejaculate)	≥2.4
Seminal fructose (μmol/ejaculate)	≥13
Seminal neutral glucosidase (mU/ejaculate)	≤20

Box 62.1. WHO recommendation: semen analysis

Standard evaluation in all men should include a medical history and physical exam in addition to scrotal ultrasonography and semen analysis. Andrological evaluation is should be performed when semen analysis demonstrates abnormalities when compared to reference values (Table 62.4). Standardization of laboratory reference values helps guide important treatment decisions. The WHO has provided the WHO laboratory manual for the examination and processing of human semen (fifth edn.). It is the consensus that modern spermatology must abide by these reference values (per EAU recommendations)

While many of the recommendations from both the AUA/ASRM and EAU are evidence-based, some of the guidelines are still supported by nonrandomized clinical trials, retrospective studies, and expert opinion (Table 62.3). The aforementioned GRADE methodology adopted by the EAU has attempted to address this by delineating between those guidelines with and without quality supporting data. The assigned "strong" or "weak" GR intends to simplify the grading system, yet it requires inherently subjective evaluation of the recommendation using a template of principles [15, 16]. Conversely, the AUA Practice Guidelines Committee found insufficient evidence to develop a formal evidence-based guideline, stating that the majority of recommendations are derived from nonrandomized trials, expert opinion, or some combination of the two [7]. This certainly leaves the opportunity for further research and improvement going forward.

62.6 Conclusion

The goal of guidelines is to provide urologists and other reproductive specialists with a reference to help improve quality and efficiency of care while protecting the patient from potentially harmful or unnecessary interventions. Of the many sources available, the most commonly referenced and up-to-date guidelines are the AUA best practice statement for the evaluation of the infertile male, the ASRM Practice Committee Report on the diagnostic evaluation of the infertile male, and the EAU guidelines on male infertility.

While these guidelines are intended to help guide the practitioner in clinical practice, variable methodology used to develop the recommendations can alter both the strength and quality of the statements provided. Of the three associations detailed in this chapter, only the EAU has committed to developing evidence-based grades for recommendations given. However, the evidence cited is often based on nonrandomized clinical trials, expert opinion, and retrospective studies. This certainly offers opportunity for further research into various areas within male infertility and for the development of higher-quality recommendations.

Despite the aforementioned differences, the AUA, ASRM, and EAU guidelines recommend similar initial evaluations for male infertility. This starts with a thorough medical/surgical history and a properly executed semen analysis. If initial screening yields abnormal medical history or semen analysis (two abnormal semen analyses in EAU guidelines), a full evaluation may be considered. Ultimately, these guidelines act as a reference. A physician's clinical judgment should always be incorporated into the implementation of these guidelines in order to provide optimal care on a case-by-case basis.

62.7 Review Criteria

A systematic search of the most current and updated guidelines on the diagnosis and management of male infertility was performed for the American Urological Association (AUA), the American Society for Reproductive Medicine (ASRM), the European Association of Urology (EAU), and the World Health Organization (WHO) [semen analysis parameters] as provided on their respective web addresses. Extensive searches of the most recent relevant studies using search engines such as PubMed, Google Scholar, CINAHL Complete, and Cochrane Library were performed between September 2018 and December 2018 with the following

keywords: "male infertility," "infertility rate," "semen analysis," "semen analysis parameters," "infertility diagnosis," and "infertility guidelines." Articles published in languages other than English were not considered. Data published for presentations, conferences, meetings, books, or websites were not included. Book chapters and specific websites were cited to help provide contextual content for discussion.

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