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Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline Part I

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Abbreviations and Acronyms

ART = Assisted reproductive technologies (eg, IVF, ICSI)

ASRM = American Society for Reproductive Medicine

AUA = American Urological Association

CBAVD = Congenital Bilateral Absence of the Vas Deferens

CF = Cystic fibrosis

CFTR = Cystic Fibrosis Transmembrane Conductance Regulator

FSH = Follicle-Stimulating Hormone

NOA = Non-Obstructive Azoospermia

PGC = Practice Guidelines Committee

RPL = Recurrent Pregnancy Losses

SA = Semen Analysis

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Purpose: The summary presented herein represents Part I of the two-part series dedicated to the Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline. Part I outlines the appropriate evaluation of the male in an infertile couple. Recommendations proceed from obtaining an appropriate history and physical exam (Appendix I), as well as diagnostic testing, where indicated.

Materials/Methods: The Emergency Care Research Institute Evidence-based Practice Center team searched PubMed®, Embase®, and Medline from January, 2000 through May, 2019. When sufficient evidence existed, the body of evidence was assigned a strength rating of A (high), B (moderate), or C (low) for support of Strong, Moderate, or Conditional Recommendations. In the absence of sufficient evidence, additional information is provided as Clinical Principles and Expert Opinions (table 1). This summary is being simultaneously published in Fertility and Sterility and The Journal of Urology.

Results: This Guideline provides updated, evidence-based recommendations regarding evaluation of male infertility as well as the association of male infertility with other important health conditions. The detection of male infertility increases the risk of subsequent development of health problems for men. In addition, specific medical conditions are associated with some causes for male infertility. Evaluation and treatment recommendations are summarized in the associated algorithm (figure).

Conclusion: The presence of male infertility is crucial to the health of patients and its effects must be considered for the welfare of society. This document will undergo updating as the knowledge regarding current treatments and future treatment options continues to expand.

Key Words: male infertility; evaluation; chemotherapy; surgery; health

BACKGROUND

The overall goal of the male evaluation is to identify conditions that may affect management or health of the patient or their offspring. The specific goals of the evaluation of the infertile male are to identify the following:

- potentially correctable conditions;
- irreversible conditions that are amenable to assisted reproductive technologies (ART)using the sperm of the male partner;
- irreversible conditions that are not amenable to the above, and for

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Table 1. *AUA nomenclature linking statement type to level of certainty, magnitude of benefit or risk/burden, and body of evidence strength*

	Evidence Strength A (High Certainty)	Evidence Strength B (Moderate Certainty)	Evidence Strength C (Low Certainty)
Strong Recommendation (Net benefit or harm substantial)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears substantial Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears moderate Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (No apparent net benefit or harm)	Benefits = Risks/Burdens Best action depends on individual patient circumstances Future research unlikely to change confidence	Benefits = Risks/Burdens Best action appears to depend on individual patient circumstances Better evidence could change confidence	Balance between Benefits & Risks/Burdens unclear Alternative strategies may be equally reasonable Better evidence likely to change confidence
Clinical Principle	A statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	A statement, achieved by consensus of the Panel, that is based on members clinical training, experience, knowledge, and judgment for which there is no evidence		

which donor insemination or adoption are possible options;
- life- or health-threatening conditions that may underlie the infertility or associated medical comorbidities that require medical attention; and
- genetic abnormalities or lifestyle and age factors that may affect the health of the male patient or of offspring particularly if ART are to be employed.

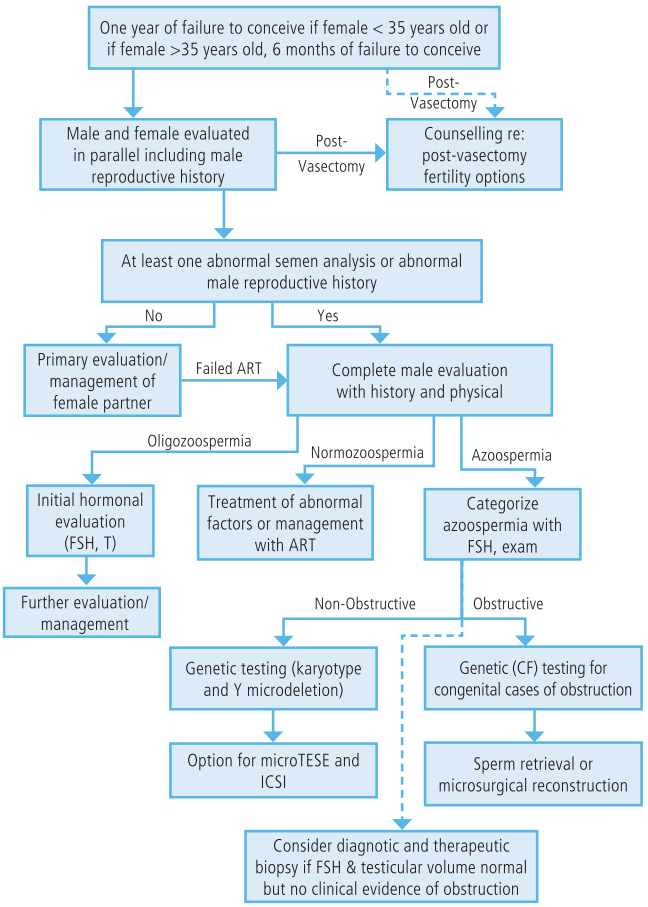
In this guideline, the term "male" or "men" is used to refer to biological or genetic men.

GUIDELINE STATEMENTS

Assessment

1. For initial infertility evaluation, both male and female partners should undergo concurrent assessment. (Expert Opinion)
2. Initial evaluation of the male for fertility should include a reproductive history. (Clinical Principle) Initial evaluation of the male should also include one or more semen analyses (SAs). (Strong Recommendation; Evidence Level: Grade B)
3. Men with one or more abnormal semen parameters or presumed male infertility should be evaluated by a male reproductive expert for complete history and physical examination as well as other directed tests when indicated. (Expert Opinion)
4. In couples with failed ART cycles or recurrent pregnancy losses (RPL) (two or more losses), evaluation of the male should be considered. (Expert Opinion)

Couple infertility may be due to male factors, female factors or a combination of male and female factors therefore parallel evaluation of both partners is always required. To interpret male infertility studies in isolation from female factors is not appropriate for these couples. Maternal age is the strongest predictor of fertility outcome for couples. A male in an infertile couple should have an initial SA and male reproductive history evaluation. The reproductive history assessment provides important information about functional sexual, lifestyle and medical history including medications that can contribute to reduced fertility or sterility. The SA is an important component in the initial clinical evaluation of the male and his reproductive health. Semen parameter values falling above or below the lower limit do not by themselves predict either fertility or infertility.[1] In the interpretation of the SA, the clinician should remember that semen parameters are highly variable biological measures and may vary substantially from ejaculate to ejaculate. Therefore, at least two SAs, ideally obtained at least one month apart, are important to obtain, especially if the first SA has abnormal parameters. Evaluation and treatment of the male can improve SA and fertility outcomes allowing some couples to conceive naturally and potentially lower treatment costs. In addition to treatment benefits, 1-6% of men evaluated for infertility have significant undiagnosed medical pathology including malignancies even when they have so-called "normal" SAs.[2,3] Just as all infertile women are treated by those with specialized gynecologic training and expertise, all infertile men be evaluated by specialists in male reproduction.[4]



Male infertility algorithm

Lifestyle Factors and Relationships Between Infertility and General Health

5. Clinicians should counsel infertile men or men with abnormal semen parameters of the health risks associated with abnormal sperm production. (Moderate Recommendation; Evidence Level: Grade B)
6. Infertile men with specific, identifiable causes of male infertility should be informed of relevant, associated health conditions (Moderate Recommendation; Evidence Level: Grade B)
7. Clinicians should advise couples with advanced paternal age (≥40) that there is an increased risk of adverse health outcomes for their offspring. (Expert Opinion)
8. Clinicians may discuss risk factors (ie, lifestyle, medication usage, environmental exposures) associated with male infertility, and patients should be counseled that the current data on the majority of risk factors are limited. (Conditional Recommendation; Evidence Level: Grade C)

It is increasingly recognized that male reproductive and overall health are related with infertile subjects having more comorbidities compared to fertile controls.[5] Men with abnormal semen parameters have higher rates of testicular cancer[6–9] and men with azoospermia have higher rates of cancer in general than fertile men.[10] In addition, mortality rates have been positively associated with abnormal SAs.[11]

Over 50% of the time, the cause of a man's infertility can be attributed to one of several conditions many of which have health implications beyond fertility. It is important for the clinician to understand the various etiologies of male infertility and provide adequate counseling regarding associated conditions or consider referral to a specialist for the diagnosed conditions (table 2). Data indicate that advanced paternal age increases de novo intra- and inter-genic germline mutations, sperm aneuploidy, structural chromosomal aberrations, sperm DNA fragmentation, birth defects, and genetically-mediated conditions (eg, chondrodysplasia, schizophrenia, autism) in the offspring. Genetic counseling may be considered for couples with advanced paternal age to discuss the low absolute risk (but high relative risk) of increased paternal age on at least certain genetic risks in their offspring, including de novo gene mutations as well as multiple medical conditions including schizophrenia and autism.

While a number of putative risk factors for male factor infertility (eg, demographic, lifestyle, medical treatments, environmental exposures) have been studied, data are limited on the specific factors that actually affect male fertility. There is low-quality evidence for some association between diet and male infertility. Most of these studies have suggested that men with a diet lower in fats and meats (with more fruits and vegetables) is preferable to a higher-fat diet. Similarly, low-quality evidence (due to high risk of bias) exists to link smoking with a small impact on sperm concentration, motility, and morphology. Ongoing use of anabolic steroids suppresses spermatogenesis and interferes with fertility. It is recommended that if there is concern about the influence of a particular medication on fertility, clinicians may consult reviews on this subject or databases with data on reproductive effects of medications for additional information.[12]

Diagnosis/Assessment/Evaluation

9. The results from SA should be used to guide management of the patient. In general, results are of greatest clinical significance when multiple SA abnormalities are present. (Expert Opinion)
10. Clinicians should obtain hormonal evaluation including follicle-stimulating hormone (FSH) and testosterone for infertile men with impaired libido, erectile dysfunction, oligozoospermia or

Table 2. *Summary of evidence on medical comorbidities from systematic review*

Condition	Multiple studies indicate increased risk	Single study indicates increased risk	Evidence is unclear or conflicting
Klinefelter syndrome	• Testosterone deficiency	• All-cause mortality • Specific-cause mortality (perinatal disorders, congenital anomalies and genetic disorders, respiratory diseases, cardiovascular diseases, endocrine diseases, and malignant neoplasms)	• Other specific-cause mortality (infections, nervous system diseases, digestive diseases, musculoskeletal diseases, trauma, other causes) • Metabolic syndrome
Cystic fibrosis	• Tooth enamel defects of permanent teeth • Pulmonary • Pancreatic		• Dental caries • Plaque • Gingival bleeding • Dental calculus
Hypospadias			• Urinary anomalies
Cryptor-chidism	• Testicular cancer		
Testosterone Deficiency	• Diabetes • Metabolic syndrome • CVD • Hypertension • All-cause mortality • CVD mortality • CVD morbidity • Alzheimer's disease	• Peripheral artery disease • Intima-media thickness • Rapid bone loss • Lung cancer • Testicular cancer	• Charlson Comorbidity Index • Periodontal disease • Ischemic heart disease • Prostate cancer • Colorectal cancer

azoospermia, atrophic testes, or evidence of hormonal abnormality on physical evaluation. (Expert Opinion)

11. Azoospermic men should be clinically evaluated to differentiate genital tract obstruction from impaired sperm production initially based on semen volume, physical exam, and FSH levels. (Expert Opinion)
12. Karyotype and Y-chromosome microdeletion analysis should be recommended for men with primary infertility and azoospermia or severe oligozoospermia (<5 million sperm/mL) with elevated FSH or testicular atrophy or a presumed diagnosis of impaired sperm production as the cause of azoospermia. (Expert Opinion)
13. Clinicians should recommend Cystic Fibrosis Transmembrane Conductance Regulator *(CFTR)* mutation carrier testing (including assessment of the 5T allele) in men with vasal agenesis or idiopathic obstructive azoospermia. (Expert Opinion)
14. For men who harbor a *CFTR* mutation, genetic evaluation of the female partner should be recommended. (Expert Opinion)
15. Sperm DNA fragmentation analysis is not recommended in the initial evaluation of the infertile couple. (Moderate Recommendation; Evidence Level: Grade C)
16. Men with increased round cells on SA (>1million/mL) should be evaluated further to differentiate white blood cells (pyospermia) from germ cells. (Expert Opinion)
17. Patients with pyospermia should be evaluated for the presence of infection. (Clinical Principle)
18. Antisperm antibody (ASA) testing should not be done in the initial evaluation of male infertility. (Expert Opinion)
19. For couples with RPL, men should be evaluated with karyotype (Expert Opinion) and sperm DNA fragmentation. (Moderate Recommendation; Evidence Level: Grade C)
20. Diagnostic testicular biopsy should not routinely be performed to differentiate between obstructive azoospermia and non-obstructive azoospermia (NOA). (Expert Opinion)

SA and a male reproductive history should be obtained for all couples interested in fertility. Abnormalities in any one or more semen parameters can compromise a man's ability to naturally impregnate his female partner except in cases of azoospermia, some types of teratozoospermia (eg, complete globozoospermia), necrozoospermia, or complete asthenozoospermia. With the exception of the aforementioned anomalies (which clearly cause infertility), none of the individual sperm parameters (eg, concentration, morphology, motility) are highly predictive of fertility or diagnostic of infertility. The odds ratio for infertility increases as the number of abnormal parameters increases.[13] Clinicians managing results from a SA should counsel patients that multiple significant abnormalities in semen parameters increase their RR for infertility. An endocrine evaluation of the infertile male with serum FSH and testosterone is not recommended as a primary first-line test in the evaluation of male infertility, but is indicated if oligospermia (<10 million sperm/mL) is present. Further evaluation of the male with luteinizing hormone is indicated for men with low serum testosterone (<300 ng/dL) as well as PRL evaluation for men with hypogonadotropic hypogonadism or decreased libido.

Azoospermia is defined as the absence of sperm in the ejaculate, including the absence of sperm after examination of a centrifuged semen pellet. The

Table 3. *Hormonal assessment expected in azoospermic men with severely impaired spermatogenesis, obstruction, and hypogonadotropic hypogondadism*

	Severely impaired spermatogenesis	Obstructive azoospermia	Hypogonadotropic hypogonadism
LH	↑ or NI	NI	↓
FSH	↑	NI	↓
Testosterone	↓ or NI	NI	↓

history, physical examination and hormonal studies can help differentiate obstructive azoospermia from NOA (table 3). Men with azoospermia and small volume testes, elevated FSH and normal semen volume will typically have NOA (azoospermia due to impaired sperm production). Men with normal testis volume (eg, testis length >4.6 cm), FSH <7.6 and/or semen volume <0.5 or 1.0 mL most likely have obstructive azoospermia, especially if the proximal epididymis is enlarged on physical examination or the vasa deferentia are absent on exam.

Men with severe oligospermia (<5 M/mL) including NOA should be evaluated with a karyotype and Y microdeletion studies.[14] The most common abnormal karyotypic pattern is Klinefelter syndrome (the presence of extra X chromosomes). There may be rare foci of spermatogenesis found upon microdissection-testicular sperm extraction in at least 50%-60% of 47, XXY men. Y chromosome microdeletions are the second most common known genetic cause of infertility in the male. Although sperm may be found in the ejaculate of some men and through testicular sperm extraction in at least 50% of men with an AZFc deletion, sperm have not been retrieved by testicular sperm extraction in men with complete AZFa and/or AZFb microdeletions, so surgical intervention is not indicated.

Men with congenital obstructive azoospermia, including congenital bilateral absence of the vas deferens (CBAVD) should have cystic fibrosis (CF) testing. Mutations in the *CFTR* gene are present in up to 80% of men with CBAVD, 20% of men with congenital unilateral absence of the vas deferens (CUAVD) and 21% of men with idiopathic epididymal obstruction.[15–17] As the goal of genetic testing is to help identify the etiology as well as provide counseling on potential offspring transmission, expanded carrier screening or gene sequencing including a test for the 5-thymidine (5T) allele of *CCFTR* should be considered. In cases where the male patient has a mutation in the *CFTR* gene and the partner is also a carrier, there is a risk of an affected offspring (25% if both partners are carriers, and up to 50% if the male has mutations in both alleles with a female partner who is a carrier). Thus, the female partner should also be screened for *CFTR* carrier status, as is routinely done in pre-conception counseling.

Sperm DNA fragmentation may adversely affect the outcome of ART treatments as well as attempts at natural fertility, including an increased miscarriage rate. Since there are no prospective studies that have directly evaluated the impact of DNA fragmentation testing on the clinical management of infertile couples (ie, that the fertility outcomes of those who had testing are different from those who did not), this assay should not be routinely performed in the initial evaluation of the infertile male. However, sperm DNA fragmentation may affect male fertility, and some causes of abnormal sperm DNA fragmentation (such as anti-depressant use or the presence of genitourinary infection) are easily reversible, whereas others may be managed by use of testicular sperm in selected cases.

Increased levels of round cells in the semen may result from a spermatogenic problem where spermatocytes and/or round spermatids are present in the ejaculate or from the presence of elevated levels of white blood cells in the semen (pyospermia). Special stains are required to differentiate germ cells and somatic cells. White blood cells in the semen may result from infection or inflammation in the proximal or distal male genital tract. Routine semen cultures have not been prospectively demonstrated to benefit infertile couples, so many male reproductive experts do not routinely screen for infection unless pyospermia is present. ASA testing should only be considered if it will affect management of the patient, for example, to suggest the presence of reproductive tract obstruction.

The clinician should discuss the importance of paternal structural autosomal defects in the evaluation of the couple with RPL and the need for the male partner to have a karyotype analysis. Given the increased risk of miscarriage for men with abnormal sperm DNA fragmentation, testing for sperm DNA fragmentation is also indicated for males in couples with RPL.

As noted above, differentiation of obstructive azoospermia from NOA may most frequently be predicted from clinical and laboratory results without the need for surgical diagnostic biopsy. In the rare cases where the man has normal semen volume, normal testicular volume and FSH<7.6 without evidence of epididymal engorgement on exam, a testis biopsy may be done primarily for diagnostic purposes, sperm cryopreservation from the sample should be attempted if ART is an option.

Imaging

21. Scrotal ultrasound should not be routinely performed in the initial evaluation of the infertile male. (Expert Opinion)
22. Transrectal ultrasonography (TRUS) should not be performed as part of the initial evaluation.

Clinicians should recommend TRUS in men with SA suggestive of ejaculatory duct obstruction (ie, acidic, azoospermic, semen volume<1.5mL, with normal serum T, palpable vas deferens). (Expert Opinion)

23. Clinicians should not routinely perform abdominal imaging for the sole indication of an isolated small or moderate right varicocele. (Expert Opinion)
24. Clinicians should recommend renal ultrasonography for patients with vasal agenesis to evaluate for renal abnormalities. (Expert Opinion)

The scrotum may sometimes be difficult to examine, for example in an obese patient or when the dartos muscle remains contracted even in a warm room during the physical exam. In these infrequent cases, color Doppler ultrasound may be used to examine spermatic cord veins. However, routine use of ultrasonography to identify subclinical (non-palpable) varicocele is discouraged, as treatment of these varicoceles is not helpful.

A commonly repeated clinical dictum without evidence has been to perform abdominal imaging for men with an isolated right varicocele. A more recent retrospective study of over 4,000 men with varicoceles (8% right), reported no difference in cancer diagnoses in these men based on varicocele laterality ($p=0.313$) despite the observation that over 30% of men with right varicoceles received abdominal computed tomography scans compared with just 8.7% of men with left varicoceles and 11.2% of men with bilateral varicoceles.[18] Thus, routine imaging based solely on the presence of a right varicocele is unnecessary. Clinical judgement suggests that abdominal imaging should be considered for men with a new onset or non-reducible varicocele, especially if the varicocele is large.

The clinician should be suspicious of distal male genital tract obstruction when the ejaculate volume is low (<1.5mL), with acidic semen (pH <7.0). For these men, TRUS evaluation should be considered to evaluate for anatomic abnormalities. Mutations in the *CFTR* gene can lead to vasal and seminal vesicle agenesis/atresia. In men with CBAVD, TRUS does not contribute to the diagnosis or treatment, so it should not be done for evaluation of such infertile men.

In men with unilateral absence of the vas deferens, approximately 26-75% of men will have ipsilateral renal anomalies including agenesis.[19,20] In men with bilateral vasal agenesis, the prevalence is lower at 10%.[21] As such, abdominal imaging should be offered to men with vasal agenesis regardless of the CFTR status to allow for optimal patient counseling.

SUMMARY

Evaluation and management of men in a couple with infertility involves a step-wise process of evaluation and consultation regarding treatment options. An increasing understanding of general health conditions associated with male infertility is valuable for counselling, as well as diagnosis of the underlying cause of the fertility. Evaluation should proceed in parallel for both male and female members of a couple to optimize treatment success.

FUTURE DIRECTIONS

The causes of male infertility, including their genetic basis, have only been superficially explained at this time. The interactions of male infertility with other health conditions requires a deeper understanding as well. Sperm clearly affect stages of embryo development, implantation and maintenance of pregnancy via mechanisms that are incompletely defined at this time. However, use of ART allows unique insight into the interaction of sperm with egg and development of the resulting embryo. The potential to recover spermatogenesis for men who have lost germ cells throughout the testis and are azoospermic will require novel interventions with stem cell technology, possibly coupled with additional techniques to support germ cell development. Since men with severely impaired spermatogenesis appear to often have underlying genetic defects responsible for their testicular dysfunction, understanding of the specific cause of spermatogenic dysfunction may be critical for successful interventions. Fortunately, progress continues to be made on each of these fronts.

DISCLAIMER

This document was written by the Male Infertility Guideline Panel of the American Urological Association Education and Research, Inc., which was created in 2017. The Practice Guidelines Committee (PGC) of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the Panel included specialists in urology and primary care with specific expertise on this disorder. The mission of the panel was to develop recommendations that are analysis based or consensus-based, depending on panel processes and available data, for optimal clinical practices in the treatment of early stage testicular cancer. Funding of the panel was provided by the AUA. Panel members received no remuneration for their work. Each member of the panel provides an ongoing conflict of interest disclosure to the AUA, and the Panel Chair, with the support of AUA Guidelines staff and the PGC, reviews all disclosures and addresses any potential conflicts per AUA's Principles, Policies and Procedures for Managing Conflicts of Interest. While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As

medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases. Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses ('off label') that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not intended to provide legal advice about use and misuse of these substances. Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices. For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.

DISCLOSURES

All panel members completed COI disclosures. Disclosures listed include both topic– and non-topic-related relationships. **Consultant/Advisor:** Barbara Collura: WHO, COMMIT, EMD Serono, ACOG; Christopher De Jonge, PhD: WHO; Michael L. Eisenberg, MD: Sandstone Diagnostics, Roman, Dadi, Gilead, Underdog, Illumesense; Dolores J. Lamb, PhD: Celmatix; John P. Mulhall, MD: Vault; Craig S. Niederberger, MD: COMMIT; Peter N. Schlegel, MD: Theralogix, Inc, Roman Health. **Scientific Study or Trial:** Delores J. Lamb, PhD: NIH, American Board of Bioanalysts; Craig S. Niederberger, MD: Ferring Pharmaceuticals; Cigdem Tanrikut, MD: Ferring Pharmaceuticals. **Leadership Position:** Delores J. Lamb, PhD: American Board of Bioanalysts; John P. Mulhall, MD: Association of Peyronie's Disease Advocates (APDA), Sexual Medicine Society of North America, Journal of Sexual Medicine; Craig S. Niederberger, MD: ASRM, NexHand; Peter N. Schlegel, MD: ASRM. **Investment Interest:** Armand S. Zini, MD: YAD-Tech. **Health Publishing:** Cigdem Tanrikut, MD: Fertility Research and Practice, F&S Reviews. **Other:** Barbara Collura: RESOLVE: The National Infertility Association; Delores J. Lamb, PhD: WHO; Peter N. Schlegel, MD: RESOLVE; Cigdem Tanrikut, MD: New England Cryogenic Center, Swimmers.

Appendix. *Male reproductive health physical examination*

General	• Body habitus as overweight obesity is associated with impaired spermatogenesis. • Virilization to assess pubertal development/androgen status • Gynecomastia may be a marker for endocrine disorders
Abdominal exam	• Examination of any scars from prior surgical procedures that may involve the pelvis or impact the urogenital system.
Phallus	• Meatal location as hypospadias/epispadias may make semen deposition in the vagina challenging • Penile plaque as Peyronie's disease may make vaginal intercourse difficult • Penile lesions/ulcers/discharge may be a sign of sexually transmitted infection
Scrotum/Testes	• Examination for prior scars suggesting prior scrotal surgery/trauma • Location as scrotal position of the testes is important for normal function • Size/consistency/contours as a majority of the testis is devoted to spermatogenesis. The exam may also reveal masses consistent with a testicular cancer
Epididymides	• Shape/consistency as normal development should be identified to determine atresia that could be identified by the presence of a *CFTR* mutation. Induration/dilation could suggest obstruction. Epididymal cysts or spermatoceles may also lead to obstruction.
Vas Deferens	• Shape/consistency as normal development and contour should be confirmed to rule out agenesis as may be seen in the presence of a *CFTR* mutation or aberrant Wolffian duct embryogenesis • The presence/location of any vasectomy defect or granuloma should also be assessed
Digital Rectal Examination	• Midline prostatic cysts or dilated seminal vesicles may assist in the diagnosis of EDO

The goal of the physical examination is to identify potential etiologies of reproductive impairments, health ailments, or factors that can be optimized to improve health or reproductive success.

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