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

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Purpose

Failure to conceive within 12 months of attempted conception is due in whole or in part to the male in approximately one-half of all infertile couples. Although many couples can achieve a pregnancy with assisted reproductive technologies (ART), evaluation of the male is important to most appropriately direct therapy. Some male factor conditions are treatable with medical or surgical therapy, and others may only be managed with donor sperm or adoption. Some conditions are life threatening, while others have health and genetic implications for the patient and potential offspring. Without a male evaluation it is not possible to adequately design management of the patient and the couple.

The purpose of this guideline is to outline the appropriate evaluation and management 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. Medical therapies, surgical techniques, and use of intrauterine insemination (IUI)/in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) are covered to allow for optimal patient management. Recommendations are based on a strict process of evaluation of published literature as discussed in the Methodology section. This process is based on the PICO question approach (Problem/Patient/Population, Intervention/Indicator, Comparison, and Outcome) as described in the Methodology section. In this guideline, the term "male" or "men" is used to refer to biological or genetic men.

Methodology

The Emergency Care Research Institute (ECRI) Evidence-based Practice Center team searched PubMed®, Embase®, and Medline from January, 2000 through May, 2019. An experienced medical librarian developed an individual search strategy for each individual key question using medical subject headings terms and key words appropriate for each question's PICO framework. 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.

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)

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 (i.e., 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)

Diagnosis/Assessment/Evaluation

9. The results from the SA should be used to guide management of the patient. In general, results are of greatest clinical significance when multiple 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 azoospermia, atrophic testes, or evidence of hormonal abnormality on physical evaluation. (Expert Opinion)
11. Azoospermic men should be initially evaluated with semen volume, physical exam, and FSH levels to differentiate genital tract obstruction from impaired sperm production. (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)

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 (EDO) (i.e., 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)

Treatment

Varicocele Repair/Varicocelectomy

25. Surgical varicocelectomy should be considered in men attempting to conceive who have palpable varicocele(s), infertility, and abnormal semen parameters, except for azoospermic men. (Moderate Recommendation; Evidence Level: Grade B)
26. Clinicians should not recommend varicocelectomy for men with non-palpable varicoceles detected solely by imaging. (Strong Recommendation; Evidence Level: Grade C)
27. For men with clinical varicocele and NOA, couples should be informed of the absence of definitive evidence supporting varicocele repair prior to ART. (Expert Opinion)

Sperm Retrieval

28. For men with NOA undergoing sperm retrieval, microdissection testicular sperm extraction (TESE) should be performed. (Moderate Recommendation; Evidence Level: Grade C)
29. In men undergoing surgical sperm retrieval, either fresh or cryopreserved sperm may be used for ICSI. (Moderate Recommendation; Evidence Level: Grade C)
30. In men with azoospermia due to obstruction undergoing surgical sperm retrieval, sperm may be extracted from either the testis or the epididymis. (Moderate Recommendation; Evidence Level: Grade C)
31. For men with aspermia, surgical sperm extraction or induced ejaculation (sympathomimetics, vibratory stimulation or electroejaculation) may be performed depending on the patient's condition and clinician's experience. (Expert Opinion)
32. Infertility associated with retrograde ejaculation (RE) may be treated with sympathomimetics and alkalinization of urine with or without urethral catheterization, induced ejaculation, or surgical sperm retrieval. (Expert Opinion)

Obstructive Azoospermia, Including Post-Vasectomy Infertility

33. Couples desiring conception after vasectomy should be counseled that surgical reconstruction, surgical sperm retrieval, or both reconstruction and simultaneous sperm retrieval for cryopreservation are viable options. (Moderate Recommendation; Evidence Level: Grade C)
34. Clinicians should counsel men with vasal or epididymal obstructive azoospermia that microsurgical reconstruction may be successful in returning sperm to the ejaculate. (Expert Opinion)
35. For infertile men with azoospermia and EDO, the clinician may consider transurethral resection of ejaculatory ducts (TURED) or surgical sperm extraction. (Expert Opinion)

Medical & Nutraceutical Interventions for fertility

36. Male infertility may be managed with ART. (Expert Opinion)
37. A clinician may advise an infertile couple with a low total motile sperm count on repeated SA that IUI success rates may be reduced, and treatment with ART (IVF/ICSI) may be considered. (Expert Opinion)
38. The patient presenting with hypogonadotropic hypogonadism (HH) should be evaluated to determine the etiology of the disorder and treated based on diagnosis. (Clinical Principle)
39. Clinicians may use aromatase inhibitors (AIs), hCG, selective estrogen receptor modulators (SERMs), or a combination thereof for infertile men with low serum testosterone. (Conditional Recommendation; Evidence Level: Grade C)
40. For the male interested in current or future fertility, testosterone monotherapy should not be prescribed. (Clinical Principle)
41. The infertile male with hyperprolactinemia should be evaluated for the etiology and treated accordingly. (Expert Opinion)
42. Clinicians should inform the man with idiopathic infertility that the use of SERMs has limited benefits relative to results of ART. (Expert Opinion)
43. Clinicians should counsel patients that the benefits of supplements (e.g., antioxidants, vitamins) are of questionable clinical utility in treating male infertility. Existing data are inadequate to provide recommendation for specific agents to use for this purpose. (Conditional Recommendation; Evidence Level: Grade B)
44. For men with idiopathic infertility, a clinician may consider treatment using an FSH analogue with the aim of improving sperm concentration, pregnancy rate, and live birth rate. (Conditional Recommendation; Evidence Level: Grade B)
45. Patients with NOA should be informed of the limited data supporting pharmacologic manipulation with SERMs, AIs, and gonadotropins prior to surgical intervention. (Conditional Recommendation; Evidence Level: Grade C)

Gonadotoxic Therapies and Fertility Preservation

46. Clinicians should discuss the effects of gonadotoxic therapies and other cancer treatments on sperm production with patients prior to commencement of therapy. (Moderate Recommendation: Evidence Level: Grade C)
47. Clinicians should inform patients undergoing chemotherapy and/or radiation therapy to avoid pregnancy for a period of at least 12 months after completion of treatment. (Expert Opinion)
48. Clinicians should encourage men to bank sperm, preferably multiple specimens when possible, prior to commencement of gonadotoxic therapy or other cancer treatment that may affect fertility in men. (Expert Opinion)
49. Clinicians should consider informing patients that a SA performed after gonadotoxic therapies should be done at least 12 months (and preferably 24 months) after treatment completion. (Conditional Recommendation; Evidence Level: Grade C)
50. Clinicians should inform patients undergoing a retroperitoneal lymph node dissection (RPLND) of the risk of aspermia. (Clinical Principle)
51. Clinicians should obtain a post-orgasmic urinalysis for men with aspermia after RPLND who are interested in fertility. (Clinical Principle)
52. Clinicians should inform men seeking paternity who are persistently azoospermic after gonadotoxic therapies that TESE is a treatment option. (Strong Recommendation; Evidence Level: Grade B)

Introduction

The Diagnosis and Treatment of the Male Factor Couple

Approximately 15% of couples are unable to conceive after one year of unprotected intercourse. A male factor is solely responsible in about 20% of infertile couples and informative in another 30-40%.[1] Despite these estimates, the true prevalence of male infertility is not clearly defined due to multiple factors including variations in definitions of infertility, differences in sources of data, and the populations studied.[2] Male factor infertility may be explained by an abnormal SA or by other sperm function defects, in the setting of a normal SA as well as functional male defects. This document offers guidance for the optimal diagnostic evaluation and management of the male partner of an infertile couple.

Male infertility can be due to a variety of conditions. Some of these conditions are identifiable and reversible, such as ductal obstruction and HH. Other conditions are identifiable and treatable but not reversible, such as bilateral testicular atrophy secondary to viral orchitis. Identification of the etiology of an abnormal SA is not possible in approximately 30% of men in which case this condition is termed idiopathic male infertility.[3] When the reason for infertility is not clear with a normal SA and partner evaluation the infertility is termed unexplained, which is found in up to approximately 25% of couples.[3] In some instances, patients with normal SAs have sperm that do not function in a manner necessary for fertility.

The overall goal of the male evaluation is to identify conditions that may affect management or health of the patient or their offspring. Identification and treatment of reversible conditions may improve the male's fertility and allow for conception through intercourse or through techniques, such as IUI or IVF, when those approaches would otherwise not be possible. Even azoospermic patients may have some degree of active sperm production within the testes or could have sperm production induced with treatment. Identification of conditions for which there is no treatment will spare couples the distress of attempting ineffective therapies and allow them to consider options, such as donor sperm or adoption, if appropriate. Male infertility is associated with other comorbidities including increased mortality, while advanced paternal age is associated with some adverse outcomes in offspring. In addition, male infertility may occasionally be the presenting manifestation of an underlying life-threatening condition.[4] Failure to identify diseases such as testicular cancer or pituitary tumors may have serious consequences, including, in rare cases, death. Detection of certain genetic causes of male infertility allows couples to be informed about the potential to transmit genetic abnormalities that may affect the health of offspring and seek genetic counseling when appropriate. Thus, an appropriate male evaluation may allow the couple to better understand the basis and implications of their infertility.

In summary, the specific goals of the evaluation of the infertile male are to identify the following:

- potentially correctable conditions;
- irreversible conditions that are amenable to ART using the sperm of the male partner;
- irreversible conditions that are not amenable to the above, and for 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.

Definitions of Infertility and Treatment Success

A wide variety of professional and international health organizations have defined infertility in general and male infertility, specifically. Since the condition of infertility reflects the outcome of a couple's attempt to achieve a pregnancy, the most common definition of infertility is "a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse."[5] The condition of infertility is categorized as a disease by the World Health Organization (WHO), the American Medical Association (AMA), and the American Society for Reproductive Medicine.[6] Evaluation for infertility is also guided by female age and other factors, such as an abnormal male reproductive history (e.g., history of cryptorchidism, chemotherapy, pelvic/retroperitoneal surgery, other conditions that have been associated with male infertility). When such factors are present, male evaluation is indicated. Infertility should be evaluated after 6 months of attempted conception when the female partner is over 35 years of age.

Male infertility is typically diagnosed by one or more factors that may include abnormal semen quality or sperm functional parameters; anatomical, endocrine, genetic, functional, or immunological abnormalities of the male reproductive system (including chronic illness); or sexual conditions incompatible with the ability to deposit

semen in the vagina. Primary male infertility refers to a male who has never initiated a clinical pregnancy and meets the criteria of being classified as infertile, whereas secondary infertility refers to a couple where the man is unable to initiate a clinical pregnancy, but who had previously initiated a clinical pregnancy (with the same or different sexual partner). Some conditions may be more common in primary or secondary infertility. Evaluation of men with secondary infertility should include a focus on conditions or exposures that have developed or occurred after initiation of the earlier pregnancy(ies).

Assessment of tests and treatments for the male is challenging due to inconsistent endpoints and the observation that many of these endpoints are dependent upon and measured from the female partner. Ideally, the endpoint for fertility trials should be "live birth (defined as any delivery of a live infant after 20 weeks of gestation) or cumulative live birth, defined as the live birth per women over a defined time period (or number of treatment cycles.)" This definition was provided by the modified Consolidated Standards of Reporting Trials for Fertility, Improving the Reporting of Clinical Trials of Infertility Treatments.[7] However, due to the variety of confounding variables present in the female, it is difficult to control for many of the most important variables and still include sufficient male subjects in a clinical trial for pregnancy or birth to be a viable outcome measure.

To address this challenge, the majority of clinical trials addressing male fertility and infertility utilize surrogate outcome metrics, the most common being the SA. However, the high variability of SA parameters make them difficult to use in the determination of interventions for male reproduction.[5] Other outcome metrics with similar challenges include other types of sperm tests and ART outcomes such as fertilization, implantation, and miscarriage rates. All attempts to measure some aspect of sperm function lessens the confounder effect of a maternal outcome, yet all are also subject to their own limitations.

Epidemiology

Most couples achieve a pregnancy in the first 3 to 6 months of attempted conception, with 75% of couples achieving a pregnancy after 6 months of trying.[8-11] In general, after one year of attempting to conceive, approximately 85% of couples will have achieved a pregnancy. After two full years of attempting to conceive, this statistic is increased to over 90% of couples.

Age of the female partner is the single most important factor when predicting the chances of conception for a couple. Fertility decreases by almost 50% in women in their late 30's compared to women in their 20's. In women under 35 years of age, infertility is considered present after 12 months of attempting to conceive. This duration is shortened in women over the age of 35 years to 6 months. [12,13]

The etiologic causes of fertility include both female and male factors. For women, these factors include ovulatory dysfunction, tubal factor, endometriosis, and uterine factors. For the woman, ovarian reserve is helpful in predicting her response to medications, but this is not an absolute predictor of fertility. In up to 50% of couples, a male factor is found as part of the etiology of the infertility.[14] In addition, between approximately 25% of couples will have unexplained infertility.

RPL is a disease that is distinct from infertility and is defined as two or more failed pregnancies.[6] The workup of RPL yields an etiology in only approximately 50% of couples as most miscarriages are related to abnormalities within the fetus itself. The risk of miscarriage after two losses is at least 25% depending on the age of the woman. After three consecutive losses, this risk increases to almost 50%. Etiologic causes of recurrent miscarriages includes genetic causes (e.g., chromosomal translocations), anatomic abnormalities of the female uterus (e.g., septum, submucosal fibroids, adhesions), infections, hematologic and immunologic disorders of the female partner, female partner endocrine issues (e.g., thyroid and diabetes), and male factor issues.[15-17] In general, for men, the common identified etiologic issues include karyotypic abnormalities and sperm DNA fragmentation.

Methodology

Panel Formation and Process

The Male Infertility Panel was created in 2017 by the American Urological Association Education and Research, Inc. (AUAER) and the American Society for Reproductive Medicine (ASRM). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chairs, who in turn appointed the additional panel members based on specific expertise in this area. The Panel included specialties from urology, andrology, endocrinology, and obstetrics & gynecology. There was also a patient advocate representative from RESOLVE: The National Infertility Association.

Search Strategy

The Emergency Care Research Institute (ECRI) Evidence-based Practice Center team searched PubMed®, Embase®, and Medline from January, 2000 through May, 2019. An experienced medical librarian developed an individual search strategy for each individual key question using medical subject headings terms and key words

appropriate for each question's PICO framework. Search strategies were reviewed by one of the project methodologists. The evidence review team also reviewed relevant systematic reviews and references provided by the Panel to identify articles that may have been missed by the database searches.

Study Selection and Data Abstraction

Study selection was based on predefined eligibility criteria for the patient populations, interventions, outcomes, and study designs of interest. Two reviewers independently screened abstracts and full text for inclusion. Conflicts between reviewers regarding eligibility of a given study were resolved through consensus.

Reviewers extracted information on study characteristics, participants, interventions, and outcomes. One reviewer completed data abstraction for each included study.

Assessment of Risk of Bias of Individual Studies

One reviewer independently assessed risk of bias (ROB) for individual studies. The Cochrane Collaboration's tool was used for assessing the risk of bias of randomized controlled trials (RCTs).[18] For non-randomized studies of treatment interventions, the reviewers used appropriate items from the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI). For diagnostic studies, reviewers used the quality assessment tool for diagnostic accuracy studies (QUADAS -2).[19] Single-arm studies were assessed by the following domains: prospective or retrospective design, consecutive/non-consecutive enrollment, incomplete outcome data, selective outcome reporting, and any other potential sources of bias. For systematic reviews, ROB was assigned based on the study authors' quality assessment of the individual studies included in the review. If such an assessment was not provided, ECRI analysts assigned a ROB rating based on the author description of the selected literature base and the designs of the included studies. The evidence review team graded strength of evidence on outcomes by adapting the AUA's three predefined levels of strength of evidence.

Determination of Evidence Strength

The categorization of evidence strength is conceptually distinct from the quality of individual studies. Evidence strength refers to the body of evidence available for a particular question and includes not only the quality of individual studies but consideration of study design; consistency of findings across studies; adequacy of sample sizes; and generalizability of study populations, settings, and interventions for the purposes of the guideline. The AUA categorizes body of evidence strength as Grade A (well-conducted and highly-generalizable RCTs or exceptionally strong observational studies with consistent findings), Grade B (RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings), or Grade C (RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data). By definition, Grade A evidence has a high level of certainty, Grade B evidence has a moderate level of certainty, and Grade C evidence has a low level of certainty.[20]

AUA Nomenclature: Linking Statement Type to Evidence Strength

The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel's judgment regarding the balance between benefits and risks/burdens (Table 1). ***Strong Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is substantial. ***Moderate Recommendations*** are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is moderate. ***Conditional Recommendations*** are non-directive statements used when the evidence indicates there is no apparent net benefit or harm or when the balance between benefits and risks/burden is unclear. All three statement types may be supported by any body of evidence strength grade. Body of evidence strength Grade A in support of a Strong or Moderate Recommendation indicates the statement can be applied to most patients in most circumstances and that future research is *unlikely to change confidence*. Body of evidence strength Grade B in support of a Strong or Moderate Recommendation indicates the statement can be applied to most patients in most circumstances, but better evidence *could change confidence*. Body of evidence strength Grade C in support of a Strong or Moderate Recommendation indicates the statement can be applied to most patients in most circumstances, but better evidence is *likely to change confidence*. Conditional Recommendations can also be supported by any evidence strength. When body of evidence strength is Grade A, the statement indicates benefits and risks/burdens appear balanced, the best action depends on patient circumstances, and future research is *unlikely to change confidence*. When body of evidence strength Grade B is used, benefits and risks/burdens appear balanced, the best action also depends on individual patient

circumstances, and better evidence *could change confidence*. When body of evidence strength Grade C is used, there is uncertainty regarding the balance between benefits and risks/burdens, alternative strategies may be equally reasonable, and better evidence is *likely to change confidence*.

Where gaps in the evidence existed, Clinical Principles or Expert Opinions are provided via consensus of the Panel. A **Clinical Principle** is a statement about a component of clinical care widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. **Expert Opinion** refers to a statement based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence in the medical literature.

Peer Review and Document Approval

An integral part of the guideline development process at the AUA is external peer review. The AUA conducted a thorough peer review process to ensure that the document was reviewed by experts in the diagnosis and treatment of male infertility. In addition to reviewers from the AUA PGC, Science and Quality Council (SQC), and Board of Directors (BOD), the document was reviewed by representatives from ASRM, as well as external content experts. Additionally, a call for reviewers was placed on the AUA website from January 8-15, 2020 to allow any further interested parties to request a copy of the document for review. The guideline was also sent to the Urology Care Foundation to open the document further to the patient perspective. The draft guideline document was distributed to 114 peer reviewers. All peer review comments were blinded and sent to the Panel for review. In total, 49 reviewers provided comments, including 24 external reviewers. At the end of the peer review process, a total of 997 comments were received. Following comment discussion, the Panel revised the draft as needed. Once finalized, the guideline was submitted for approval to the AUA PGC, SQC, and BOD for final approval. The document was also approved by the ASRM CEO Ricardo Azziz, MD, MPH, MBA, on behalf of the Board and advised by the Practice Committee.

Guideline Statements

Assessment

1. **For initial infertility evaluation, both male and female partners should undergo concurrent assessment. (Expert Opinion)**

Couple infertility may be due to male factors, female factors or a combination of male and female factors. Both the female and male are equal stakeholders in both diagnosis and treatment. Therefore, it is good clinical practice to obtain a reproductive history, perform a physical examination and basic diagnostic tests of reproductive function (Appendix I).[21]

Further, a workup of both partners is always required. Many couples have more than one fertility issue present. For the female partner, tests are indicated to evaluate ovarian reserve, ovulatory function, tubal structures as well as assessment of the uterine cavity.[22] 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 in couples undergoing therapy.[23–25] Natural conception rates decrease by almost 50% as women approach their 40's as compared to when they are in their 20's. In a large IVF study, over 80% of success was predicted by the maternal age. These findings highlight the importance of maternal age when assessing any studies using fertility as an outcome. As such, consideration of maternal age is required when interpreting male infertility studies.

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)**

A reproductive history assessment provides important information about lifestyle and sexual history 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. A SA provides critical data on testicular sperm production as reflected by total sperm number, the patency and function of the male genital tract and secretions from its associated organs, emission and ejaculation. Defects in spermatogenesis, genital tract anatomy, patency and function, as well as emission and ejaculation will impact the patient's semen parameters.

The SA should include measures of semen volume, pH if indicated, sperm concentration/sperm count, sperm motility, and sperm morphology. Abnormalities in any one or more of these parameters can compromise a man's ability to naturally impregnate his female partner. SA results cannot precisely distinguish fertile from infertile men except in cases of azoospermia; however, some types of teratozoospermia (e.g., complete globozoospermia), necrozoospermia, or

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		

complete asthenozoospermia correctly informs a diagnosis of infertility. [26]

Clinicians should counsel infertility patients that the WHO[5] lower limits of semen parameters are based on fertile men whose partners became pregnant in 12 months or less. Semen parameter values falling above or below the lower limit do not by themselves predict either fertility or infertility.[27] In the interpretation of the SA, the clinician should remember that semen parameters are highly variable biological measures and may vary substantially from test to test. Therefore, at least two SAs obtained a month apart are important to consider, especially if the first SA has abnormal parameters.

Standardized methods and essential quality control procedures for performing the SA have been codified in one or more editions of the WHO laboratory manual for the examination of human semen.[5] The WHO 5th Edition defined lower reference limits (LRL) based on SA data of recent fertile fathers (time to pregnancy <12 months) collected at multiple locations from around the world.[5,28] The calculation of evidence-based LRL for each semen parameter as determined by the application of principles of clinical chemistry was provided in the 5th WHO edition.[5,28]

Evidence demonstrates that a diagnosis of male fertility or infertility cannot reliably be made based solely on a single semen parameter. [5, 26] For example, it is clear that there are men who have abnormal semen parameters, yet they have contributed to a prior successful pregnancy through natural conception. Of note, as the number of individual semen parameters that fall below the LRL increases, the odds of correctly diagnosing a risk for subfertility increases, although the finding is not predictive for the individual.[26] Thus, it is recommended that semen parameters be considered collectively and not just individually. Accordingly, the data also show that while the relative risk (RR) of infertility on an individual patient level can be estimated, it is impossible to predict whether they are fertile or infertile based solely on SA parameters.[26] Nevertheless, the consistent presence of abnormal semen parameters suggests the presence of a male factor in an infertile couple, encouraging physicians to consider further evaluation of the male and management to enhance male reproductive function.

Table 2: World Health Organization Reference Limits for Human Semen Characteristics*

Semen Parameter	One-Sided Lower Reference Limit (Fifth Centiles With 95% Confidence Intervals)
Semen Volume	1.5 mL (1.4-1.7)
Total Sperm Number	39 million per ejaculate (33-46)
Sperm Concentration	15 million/mL (12-16 million/mL)
Vitality	58% Live (55-63%)
Progressive Motility	32% (31-34%)
Total Motility (Progressive + Non-Progressive)	40% (38-42%)
Morphologically Normal Forms	4.0% (3.0-4.0)
***Semen samples from 4500 men (men with proven fertile, with unknown fertility status and other men who were normozoospermic) from 14 countries and 4 continents were analyzed. Men described above were all fertile (Partners' time-to-pregnancy < or = 12 months) and their parameters were selected to calculate the values shown below.[17,28]**	

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)

Ideally, a reproductive evaluation will lead to maximizing the reproductive health of an individual and future offspring.[2] Indeed, the evaluation and treatment of male infertility can improve fertility outcomes allowing some couples to conceive naturally and lower treatment costs. Furthermore, a male evaluation may inform some couples to avoid ART. For example, investigators suggested that varicocele treatment may be more cost effective than ART or can lower the intensity of treatment.[29-31] This may allow couples to conceive by less invasive technologies, such as pregnancy by IUI instead of IVF or pregnancy by intercourse instead of IUI. In addition, other groups have suggested that vasectomy reversal may represent a more cost-effective option compared to IVF in couples with adequate ovarian function.[30,32,33] While over eight million children have been conceived by IVF, concern remains about risks to the reproductive and overall health of offspring due to gamete manipulation, embryo culture, cryopreservation, and other manipulation that does not occur with natural conception.[34-36] Whether the adverse outcomes observed in offspring relate to the use of the technology itself or the underlying conditions causing infertility in one or both parents remains uncertain. Nevertheless, it is clear that a reasoned approach to the evaluation and treatment of male infertility is warranted.

To help maximize reproductive health of the patient, the clinician must attend to a man's overall health. It is recognized that aberrations in reproductive fitness may be a harbinger of medical diseases in men. Investigators have demonstrated that 1-6% of men evaluated for infertility have significant undiagnosed medical pathology including malignancies even when they have a so-called "normal" SAs.[4,37] Infertile men also have a higher rate of medical comorbidities (e.g., hypertension, hyperlipidemia, obesity, diabetes) that can contribute to impaired fecundability.[38,39]

The evaluation of men with abnormal SAs and/or abnormal reproductive history, including physical examination and selected laboratory and radiologic assessment, requires expertise in male anatomy and physiology. As such, just as all infertile women are treated by those with specialized gynecologic training and expertise, so should all infertile men be evaluated by specialists in male reproduction.[40]

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)

The role of the male partner after failed ART cycles is not always considered. Even with a "normal" SA, a sperm that appears morphologically and functionally normal may not be chromosomally normal or may have a high level of DNA fragmentation. In this clinical setting, the male partner should be evaluated by a male reproductive expert and consideration given to evaluation of sperm DNA fragmentation and karyotype testing of the male. Some experts would also consider sperm aneuploidy testing, although this test is not universally available for all centers.

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)

Male infertility or abnormal SA may be a harbinger of medical diseases in men. While abnormal SA is not synonymous with male infertility, most specific male infertility diagnoses are associated with abnormal SA.

Comorbidities

As noted in the indications for male evaluation, studies suggest that 1-6% of men have undiagnosed medical diseases at the time of an infertility evaluation.[4,37] It is increasingly recognized that reproductive and overall health are related with infertile subjects having more comorbidities compared to fertile controls.[41] Indeed, the referenced report found a relatively large amount of evidence investigating whether men with abnormal SAs have higher rates of medical comorbidities including one systematic review and eleven studies reporting increased medical comorbidities associated with abnormal SAs.[42-52]

A recent metanalysis[53] identified three studies of the Charlson Comorbidity Index (CCI), each of which reported a positive association with abnormal SA. In contrast, the single-center study by Cazzaniga et al.[43] of an infertility clinic (2,185 men) found no substantial association between semen abnormalities and having a CCI of 1 or more (multivariate odds ratios [OR] 1.03 for oligozoospermia, 1.03 for teratozoospermia, and 0.97 for asthenozoospermia). The conflicting results

for associations between CCI and semen abnormalities (three studies were positive, and one showed no association) may be due to different choices and the amount of confounding variables.[43] Cazzaniga et al. controlled for age, testicular volume, FSH level, varicocele, and other semen abnormalities, which is a relatively large number of variables. The two studies assessed by Glazer et al.[53] may have controlled for fewer variables (specific variables not reported), so their positive findings may not persist if more control variables were used.

In addition, data suggest that infertile men have a higher risk of incident disease (new cases diagnosed).[38]

Cancer

For the systematic review, four studies specifically analyzed testicular cancer (two moderate-quality and two low-quality), [45-47] and all four found that men with abnormal semen parameters had higher rates of testicular cancer. The fifth study analyzed cancer in general (i.e., all types together) and found that men with azoospermia had higher cancer rates than others.[48] One study by Hanson et al. also specifically analyzed other cancers (e.g., prostate, melanoma), and all associations with abnormal semen parameters were inconclusive.[45] A large nation-wide observational study reported that men who became fathers using ART were 64% more likely to develop prostate cancer with an 86% risk of early disease.[54] The fathers with a history of ART use appeared to have a similar risk of significant prostate cancer, reflected by similar need for androgen-deprivation therapy.

Mortality

Glazer et al. published a systematic review of three studies that also considered aspects of study quality[53] in which mortality rates were positively associated with abnormal SAs.[53]This review was rated as moderate-quality as some of the men may have had multiple infertility conditions.

Other comorbidities

Other individual studies have looked at specific comorbidities (e.g., diabetes, hypertension, multiple sclerosis, sexually transmitted infections, thyroid disorders) with uncertain associations with male infertility.[51-53,55]

6. Infertile men with specific, identifiable causes of male infertility should be informed of relevant, associated health conditions (Moderate Recommendation; Evidence Level Grade: B)

An assessment of a man's reproductive health includes an evaluation for etiologies. Over 50% of the time, the cause of a man's infertility can be attributed to several known conditions bearing other health implications. 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 4).

Klinefelter syndrome is associated with testosterone deficiency, abnormal muscle mass and pubertal development, decreased facial/body hair,

Table 3: Summary of Evidence Based on Systematic Review[56]

Possible Medical Comorbidities Associated with Male Infertility			
Condition	MULTIPLE studies indicate increased risk	SINGLE study indicates increased risk	Evidence is UNCLEAR or CONFLICTING
Abnormal semen parameters	Testicular cancer Mortality CCI	Diabetes Multiple sclerosis Chronic epididymitis	Prostate cancer Melanoma Other cancers Sexually transmitted infections Thyroid disorders

Table 4. Summary of Evidence on Medical Comorbidities from Systematic Review.[56]

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
Cryptorchidism	• 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

gynecomastia, autoimmune disorders, osteoporosis, and impaired spermatogenesis.[57,58] Cystic Fibrosis (CF) is also associated with male infertility (i.e., obstructive azoospermia) as well as pulmonary problems, pancreatic deficiency, and dental carries.[59] Cryptorchidism is associated with infertility as well as a higher risk of testis cancer and can occur with other genitourinary abnormalities such as hypospadias.[44,60,61] Testosterone deficiency is associated with impaired spermatogenesis and is a risk factor for diabetes, metabolic syndrome, cardiovascular disease (CVD), hypertension, all-cause mortality, CVD mortality, and Alzheimer's disease.[62-64]

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)

The systematic review by Johnson et al. included 90 studies on the association between age and male infertility.[65] The review examined correlations between age and seven semen parameters: semen volume, sperm concentration, total sperm count, sperm motility, progressive motility, % with normal morphology, and sperm DNA fragmentation. All except sperm concentration were consistently associated with small age-dependent declines (i.e., semen parameters decrease as age increases) in multivariate analyses (Table 5).

There are also potential impacts on the offspring. Data indicate that advanced paternal age increases de novo intra- and inter-genic germline mutations, sperm aneuploidy, structural chromosomal aberrations, birth defects, and genetically-mediated conditions (e.g., chondrodysplasia, schizophrenia, autism) in the offspring.[66-68] There is no clear definition for advanced paternal age. In an extensive evaluation of studies on

Table 5: Effects of male age on reproductive function: overview[57,65,70]

Parameters of reproductive function	Effect of male age	Specific effects with increasing age
Reproductive hormones	Yes	FSH level: increasing; testosterone level: decreasing
Sexual function	Yes	Sexual activity: decreasing; male sexual dysfunction: increasing
Testicular morphology	Yes	Sertoli cells: number (n) decreasing; Leydig cells: n decreasing; germ cells: n decreasing; thickness of basal membrane of seminiferous tubules: increasing; testicular size: unchanged (until the eighth decade)
Semen parameters: sperm	Yes	Concentration: unchanged; motility: decreasing; morphology: normal; forms: decreasing
Semen parameters: semen	Yes	Volume: decreasing; fructose level: decreasing; α-glucosidase level: decreasing; zinc level: decreasing; PSA level: decreasing
Infections of the accessory glands	Yes	Prevalence: increasing
Vascular disease	Yes	Vascularization of testicular parenchyma: decreasing
Genetics: sperm aneuploidies	Yes	Chromosomes 3,6,7,8,10,11,12,13,14,17: unchanged; 1,19,18,21, X,Y: conflicting results
Genetics: aneuploidies in offspring	Yes	Trisomy 21: increasing; trisomy 13: decreasing; trisomy 18: unchanged; other trisomies: unchanged; sex chromosomes: unchanged
Genetics: Sperm DNA integrity	Yes	DNA damage: increasing
Genetics: telomeres (TL)	Yes	TL length in spermatozoa: increasing; TL in peripheral leucocytes: decreasing
Genetics: epigenetics	Yes	Methylations in somatic cells: increasing; methylations in germ cells: suggested
Fertility	Yes	Fertility: decreasing (male age effect in couples with female >35 years)
Miscarriage	Yes	Miscarriage rate: increasing (male age effect in couples with female >35 years)
C-section	Yes	C-section rate: increasing
Pre-eclampsia	Yes	Increasing for fathers younger than 25 and older than 35 years
Trophoblast disease	Yes	Increasing
Placenta previa/placental abruption	Inconclusive	Not conclusive
Preterm birth	Yes	Increasing in teenage fathers, conflicting results for higher paternal age
Adverse outcome in offspring	Yes	Increasing (clear evidence for certain diseases)

the effects of paternal factors and perinatal and pediatric outcomes, the authors report that most studies used 40 years and above as the age limit.[69] While this association is not equated with causality, genetic counseling may be appropriate for couples with advanced paternal age to discuss the magnitude of these risks.

8. **Clinicians may discuss risk factors (i.e., 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)**

While several putative risk factors for male factor infertility (e.g., demographic, lifestyle, medical treatments, environmental exposures) have been studied, data are limited due to the difficulty in isolating specific factors. Systematic reviews of the data are mostly inconclusive because the majority of the studies evaluated failed to adequately control for confounding variables. The absence of validated outcomes predictive of male fertility is another weakness in determining cause and effect between a particular risk factor and infertility. Most studies evaluated semen parameters as a surrogate outcome for male fertility. Given that few risk factors were determined to be "independent" risk factors for male infertility, a set of possible risk factors, most of which are correlated with each other, are discussed. The controllability of exposures is of clinical relevance.

The clinician should discuss with the patient what he can do to modify or prevent exposure to risk factors for infertility. A summary of the risk factors evaluated in the systematic review used to inform this guideline can be found in Table 6.

Lifestyle

Lifestyle issues, while important, are very difficult to study, particularly due to the lack of controls and risk of recall bias. Numerous studies have attempted to correlate these lifestyle factors with semen parameters and/or fertility, but very few have been found to be a significant risk. The statements below summarize these findings.

There is low-quality evidence for low association between diet and male infertility. Similarly, low-quality evidence (due to high risk of bias) exists to link smoking with a small impact on sperm concentration, motility, and morphology. The effects of smoking on DNA fragmentation were not specifically studied. Low-quality evidence for a small decrease in progressive motility is associated with stress, while cell phones have been shown to have no impact based on low-quality evidence. Further, there is low-quality evidence for no impact of anabolic steroids/exogenous testosterone on permanent infertility (not reversible); however, current use has a major impact on current fertility and spermatogenesis. Ongoing use of anabolic steroids suppresses spermatogenesis and interferes with fertility, whereas there is low quality evidence for no impact on permanent infertility.

There is moderate quality evidence of no association (except possibly sperm aneuploidy) between caffeine and male infertility, while high-quality evidence exists on the mild impact of alcohol on semen volume, sperm morphology (although not clinically significant).

In terms of exercise, a clinician may advocate for regular resistance and/or high-intensity exercise in sedentary, infertile men with abnormal semen parameters in order to improve pregnancy and live birth rates.[57] No systematic reviews met inclusion criteria for the following risk factors: recreational drug use, sleep, sports/exercise, heat exposure, type of underwear, or anatomic abnormalities of genitalia.

Medical Considerations

There is low-quality evidence for the medications listed in Table 6, none of which had any significant impact except for finasteride, which has been associated with decreased semen volume and appears to be dose-dependent. It is recommended that if there is concern about the influence of a particular medication on fertility, clinicians may consult databases with data on reproductive effects of medications such as REPROTOX® for additional information.[71]

Previous Surgery

There is moderate-quality evidence that found the impact of hernia repair on reproductive function to be inconclusive. However, it did not distinguish between unilateral and bilateral, nor the age at which the surgery took place. Further, there is moderate-quality evidence that having testis cancer impacts sperm count and concentration, but evidence is inconclusive regarding impact on motility and morphology. Additionally, it was difficult to ascertain the impact of losing a testicle (as opposed to just having testicular cancer), as well as some of the hormonal abnormalities seen, such as elevated human chorionic gonadotropin (hCG).

Environmental Factors

Studies evaluating the impact of environmental factors

Table 6. Summary of findings for risk factors of infertility[56]

Risk factor	Methodology conclusion
Demographic	
Age	Older men have slightly reduced fertility
Obesity	Obese men have moderately reduced fertility
Lifestyle	
Diet	Poor diet results in reduced fertility
Caffeine	Not a risk factor, except for sperm aneuploidy
Alcohol	Drinkers have slightly lower semen volume and slightly poorer sperm morphology, but drinking does not adversely affect sperm concentration or sperm motility
Smoking	Smokers have slightly reduced fertility
Anabolic steroid use	Anabolic steroid use is associated with reduced fertility
Stress	Stress is associated with reduced sperm progressive motility, but has no association with semen volume; data were inconclusive for sperm concentration and sperm morphology
Cellphones	Not a risk factor
Medical treatment	
Anti-rheumatic medications	Evidence inconclusive
Thiopurines	Evidence inconclusive
Systemic dermatologic medications: finasteride	5 mg/day is associated with reduced semen volume, but 1 mg/day data are inconclusive
Systemic dermatologic medications: methotrexate	Not a risk factor
Systemic dermatologic medications: corticosteroids	Evidence inconclusive
Inguinal hernia repair: Open repair without mesh	Evidence inconclusive
Inguinal hernia repair: Open repair with mesh	Evidence inconclusive
Inguinal hernia repair: Laparoscopic repair with mesh	Evidence inconclusive
Having testicular cancer	Those with testicular cancer have reduced fertility
Environmental	
Benzophenone	Evidence inconclusive
Di-2-ethylhexyl phthalate (DEHP)	DEHP exposure is associated with lower sperm quality (sperm concentration, sperm motility, sperm DNA damage)
Other chemicals in consumer products	Evidence inconclusive
Endocrine disruptors	Evidence inconclusive
Pesticides	Associations between exposure to certain pesticides (pyrethroids, organophosphates, and abamectin) and poorer semen parameters; evidence inconclusive on organochlorines, mancozeb, and other pesticides
Oil and natural gas extraction	Occupational exposure reduces semen volume and sperm motility
Outdoor air pollution	Evidence inconclusive
Lead, zinc, copper	Lead levels are higher in infertile men than fertile men; zinc levels are lower in infertile men than fertile men; evidence inconclusive on copper levels in semen
Cadmium	Cadmium levels are higher in infertile men than fertile men

on male fertility are difficult to conduct and analyze because many chemicals are ubiquitous, methods of measurement of exposure are inadequate, few biomarkers of toxicity are validated, and confounding factors complicate the interpretation of the data. Of the putative toxicants studied, evidence of an association between exposure and male infertility was determined to be conclusive for some heavy metals and pesticides, while further data indicate a potential association between the phthalate DEHP and male infertility.[56]

The data reported for the relationship between in utero exposure or early postnatal exposure to estrogenic and/or androgenic endocrine disruptors and infertility (sperm count), cryptorchidism, hypospadias, and testicular cancer were all considered to be inconclusive.[72,73] Inconclusive evidence was found for benzophenones, bisphenol A (BPA), chlorinated antimicrobial agents, parabens, and air pollution.[74]

Lead has been documented to be a reproductive toxicant for many years.[75] Routes of exposure include ingestion, inhalation, or skin contact. Sites of lead toxicity are the central nervous system and the gonad, causing direct interference with the ability of spermatozoa to undergo the acrosome reaction, thus leading to infertility. Although lead is regulated in many countries, lead continues to be found in all parts of the environment, including air, soil, water, cosmetics, ammunition, batteries, and lead-based paints, pipes, and plumbing materials in older homes in many countries. Lead in water sources is of particular concern.[76] The environmental and occupational exposure to toxic levels of lead also continues to occur in a number of industries that use lead in manufacturing.[77] For those patients thought to be at risk for heavy metal toxicity, serum testing may be performed; however, lead levels in the blood may not reflect the total lead burden throughout the body.[78] Cadmium has also been implicated as a reproductive toxicant.[79]

Similarly, agricultural chemicals were amongst the first chemicals to be implicated as male reproductive toxicants. Humans are exposed in the workplace and in the environment through ingestion, inhalation, and skin contact. Indeed, the documented toxicity of 1,2-dibromo 3-chloropropane (DBCP) and p,p'dichlorodiphenyltrichloroethane (DDT), resulted in heavy regulation or elimination of use in many countries.[80] Organophophates and pyrethoids may be associated with altered sperm parameters.[81]

Phthalates are alkyl or di-alkyl esters of 1,2-benzenedicarboxylic acids. They are primarily used as plasticizers and as solvents. High molecular weight phthalates (DEHP, Diisononyl phthalate (DINP), Dioctyl Phthalate (DOP)) are found in hundreds of products including medical tubing, vinyl flooring, automotive plastics, plastic packaging film and sheets, plastic clothing, and garden hoses. Low molecular weight phthalates (Dimethyl phthalate (DMP), Diethyl phthalate (DEP), Dibutyl phthalate (DBP)) are widely used in personal care products and are also found in enteric-coated medications. The route of entry is primarily oral and transdermal, and these chemicals are rapidly metabolized and excreted in the urine. In the 2003-2004 National Health and Nutrition Examination Survey, the majority of subjects tested had measurable levels of phthalate metabolites in their urine.[82] The mechanism of toxicity is thought to be due to modulation of androgen/estrogen action. Data obtained through animal studies are more robust than clinical data with clinical studies reporting an association between exposure and possible adverse effects on sperm concentration and motility.[83]

Diagnosis and Evaluation

9. The results from the SA should be used to guide management of the patient. In general, results are of greatest clinical significance when multiple abnormalities are present. (Expert Opinion)

The individual semen parameters measured in the SA provide a weak indicator of fertility potential. Abnormalities in any one or more of these parameters can compromise a man's ability to naturally impregnate his female partner except in cases of azoospermia, some types of teratozoospermia (e.g., complete globozoospermia), necrozoospermia, or complete asthenozoospermia. With the exception of the aforementioned anomalies, none of the individual sperm parameters (e.g., concentration, morphology, motility) are diagnostic of infertility. The OR for infertility increases as the number of abnormal parameters increases.[26] Clinicians managing results from a SA should counsel patients that multiple significant abnormalities in semen parameters increase their RR for infertility. For example, Figure 1 shows SA results for two patients being evaluated for male infertility. The table shows that Patient 1 has oligozoospermia (sperm count <15 million sperm/mL), athenozoospermia (low motility), and teratozoospermia (abnormal morphology). Based upon the Guzick et al. 2001 findings, this man has a higher OR (of 15) of infertility because he has three abnormal semen parameters.[26] Patient 2 has just one abnormality

(decreased morphology) with a slightly increased OR of about 2.5 (Figure 1). While RR of infertility for an individual patient can be estimated, it is usually not possible to predict whether a patient is fertile or infertile based solely on SA parameters.[26]

10. Clinicians should obtain hormonal evaluation including follicle-stimulating hormone (FSH) and testosterone for infertile men with impaired libido, erectile dysfunction, oligozoospermia or azoospermia, atrophic testes, or evidence of hormonal abnormality on physical evaluation. (Expert Opinion)

Although there is some controversy in the literature, an endocrine evaluation of the infertile male is not recommended as a primary first-line test in the evaluation of male infertility. ASRM states that an endocrine evaluation is warranted when the clinical findings or impaired sexual functioning suggests a defined endocrinopathy.[84] Testosterone levels should be defined based upon a blood sample drawn in the morning, since levels drop during the day. Endocrine testing is also suggested for oligozoospermic patients, particularly, men with sperm concentrations below 10 million/mL.[85] It is noteworthy that some experts still consider an endocrine evaluation important for all male infertility patients.[86,87] Given the frequent administration of exogenous testosterone to men in the absence of laboratory data consistent with a diagnosis of testosterone deficiency, evaluation of the gonadotropins (luteinizing hormone [LH] and FSH), as well as testosterone, may be warranted for men with oligozoospermia or azoospermia.

If the fasting morning total testosterone level is low (<300 ng/dL),[88] a repeat measurement of total and free testosterone (or bioavailable testosterone) as well as determination of serum LH, estradiol, and prolactin levels should be obtained. Testosterone is present in the blood as free testosterone (once considered to be the only biologically active form of testosterone) and testosterone bound to proteins in the serum (albumin, sex hormone binding globulin). Albumin, an abundant serum protein, binds testosterone albeit at much lower affinity than sex hormone binding globulin. The albumin -bound testosterone readily dissociates; presently, both free testosterone and testosterone bound to albumin are considered to be bioavailable testosterone that can subsequently diffuse into cells and bind to androgen

Semen Parameter	Lower Reference Limit 95% Confidence Intervals	Patient 1	Patient 2
Semen Volume	1.5 mL (1.4-1.7)	1.6 mL	1.4 mL
Total Sperm Number	39 million per ejaculate (33-46)	8 million / ejaculate	43 million / ejaculate
Sperm Concentration	15 million / mL (12-16 million / mL)	5 million / mL	31 million / mL
Vitality	58% Live (55-63%)	60%	70%
Progressive Motility	32% (31-34%)	5%	45%
Total Motility Progressive + Non-Progressive	40% (38-42%)	6%	58%
Morphologically Normal Forms	4.0% (3.0-4.0)	1.4%	2.3%

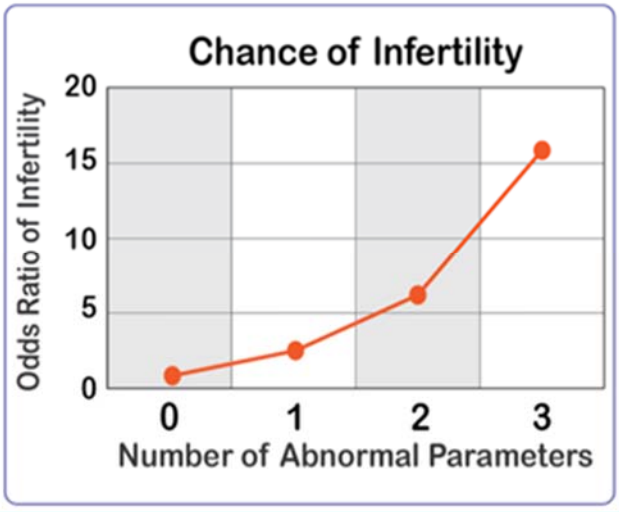

Figure 1: The Chance of Infertility Increases With Increasing Number of Abnormal Semen Parameters. The Table on the left shows the lower limit of the reference range of values for normal fertile men (WHO5), as well as the semen analysis results for two men undergoing an evaluation for male infertility. Patient #1 has oligoasthenoteratozoospermia (OAT) and Patient #2 has abnormal morphology. According to Guzick, et al., 2001 Patient #1 has an increased chance of being infertile because of his higher OR (~15) of infertility with 3 abnormal semen parameters (motility, sperm concentration and morphology) than Patient #2 with abnormal morphology (1 abnormal semen parameter) with an OR of ~2.5.

receptors in steroid responsive target cells to elicit a cellular response. Although serum gonadotropin levels are variable because they are secreted in a pulsatile manner, a single measurement is usually sufficient to determine a patient's clinical endocrine status. The relationship of testosterone, LH, FSH, and prolactin helps to identify the clinical condition. A "normal" serum FSH level (normal ranges for adult males vary somewhat by testing platform used for measurement, generally in the range of 1.0 - 20 mIU/mL) does not guarantee the presence of intact spermatogenesis; however, an FSH level even in the upper range of this reported "normal" range (above approximately 7.6 mIU/mL)[89] is indicative of an abnormality in spermatogenesis. Prolactin is measured as well for men seeking evaluation of male sexual dysfunction. Once thought to be detrimental to male sexual function/libido when elevated (i.e., due to a pituitary adenoma/ prolactinoma or other hypothalamo-pituitary disease), more recent studies show that low prolactin levels in males may be associated with male sexual dysfunction, as well.[90]

11. Azoospermic men should be initially evaluated with semen volume, physical exam, and FSH levels to differentiate genital tract obstruction from impaired sperm production.. (Expert Opinion)

Azoospermia is defined as absence of sperm in the ejaculate. The history and physical examination can provide important insights when differentiating obstructive azoospermia from NOA. When a semen analysis shows azoospermia, the laboratory should then centrifuge the ejaculate and re-suspend the pellet in a small volume of seminal plasma and examine under wet mount microscopy for the presence of rare sperm. If no sperm are present, a second SA should be performed at least one to two weeks later. If the sample is azoospermic, then another pellet analysis should be performed.

Azoospermia is distinguished from aspermia (absence of antegrade ejaculate; dry ejaculate) and RE (where semen with sperm are released into the prostatic urethra but travel backward (retrograde) into the bladder). RE can be present in men with various neuropathies (e.g., diabetes, spinal cord injury, after RPLND) and can be diagnosed with a post-ejaculate urine analysis designed for sperm assessment in the presence of a dry ejaculate. Viable sperm from urine or any location within the male reproductive tract can be used with ART to achieve a pregnancy.[91]

A low volume, acidic pH, azoospermic ejaculate can be indicative of obstruction in the genital tract.[92] Obstructive azoospermia is suspected if the physical examination reveals testes of normal size, fully descended into the scrotum and bilaterally indurated epididymides with or without absence of the vas deferens. In these cases, FSH levels are usually less than approximately 7.6 IU/L (see table 7).[89] In contrast, when the testes are atrophied and soft, especially in the presence of FSH greater than 7.6 IU/L, the results are suggestive of spermatogenic failure rather than obstructive azoospermia.[92]

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)

Karyotype abnormalities are the most common known genetic abnormalities that cause male infertility.[93] These can be chromosomal numerical anomalies, such as Klinefelter syndrome (the presence of extra X chromosomes). The most common pattern is 47, XXY but more severe cases demonstrate 48, XXXY or 49, XXXXY. Other structural anomalies (deletions, duplications, inversions of a region of an autosomal or sex chromosome) such as a Robertsonian translocation may also result in impaired or absent spermatogenesis.[93-95] Men with Klinefelter syndrome should be counseled that few non-mosaic XXY men will have sperm in the ejaculate and medically-unassisted paternity is rare.[96-100] However, there may be rare foci of spermatogenesis found upon microdissection-testicular sperm extraction (micro-TESE) in approximately 50%-60% of 47, XXY men. While no cases of sex chromosome aneuploidy in the offspring conceived after use of these sperm for ICSI have been reported, preimplantation genetic screening of embryos should be offered given the potential risk of transmission of sex chromosome aneuploidy to offspring. XX males with large duplications of the X chromosome and translocation of the sex determining region (SRY) gene from the Y chromosome can have a normal male phenotype, but testicular histology will demonstrate a complete Sertoli cell only pattern with atrophy and hyalinization of the seminiferous tubules. In addition, decreased serum testosterone and elevated estrogen and gonadotropin levels are usually present.[93] For these men, sperm will not be found if TESE is attempted, and these couples should be counseled that other pathways to parenthood should be considered.

Table 7: Hormonal assessment expected in azoospermic men with severely impaired spermatogenesis, obstruction, and hypogonadotropic hypogondadism

	Severely Impaired Spermatogenesis	Obstructive Azoospermia	Hypogonadotropic Hypogonadism
LH	- or Nl	Nl	
FSH	-	Nl	
Testosterone	or Nl	Nl	

Robertsonian translocation (the most common type of balanced translocation) carriers (who usually have a normal phenotype) and/or their partners are at a higher risk for infertility, miscarriage, or chromosomally unbalanced offspring. They should be counseled regarding these risks and the need for ART with preimplantation genetic testing for aneuploidies.

Y chromosome microdeletions are the second most common known genetic cause of infertility in the male. The majority of (but not all) genes on the Y chromosome encode proteins involved in testis determination or spermatogenesis. Y chromosome microdeletions can result from errors that occur during homologous recombination during meiosis due to the palindromic structure of the chromosome. The Azoospermia Factor (AZF) region on the long arm of the human male chromosome consists of three areas encoding genes involved in spermatogenesis (AZFa, AZFb, AZFc). Although sperm may be found in the ejaculate of some men and through TESE in approximately 50% of men with an AZFc deletion, sperm have not been retrieved by TESE in men with complete AZFa and/or AZFb microdeletions. Partial deletions of AZFa, AZFb, or AZFc are a bit more problematic to interpret because there is no standardization of the clinical Y diagnostic test for partial deletions of AZF subregions.[101,102] Many commercial laboratories use a limited number of primer sets over the AZF a, b, c regions in their Y chromosome microdeletion assay that may miss smaller microdeletions; these results can impact clinical choices for these patients. For example, men with a partial deletion of AZFa encompassing a DDX3Y deletion had spermatogenic failure, but a smaller AZFa deletion of just USPY9 showed no effect on spermatogenesis.[102] There was a similar finding for small AZFb microdeletions.[103] A higher resolution view of AZFa, b, and c based upon more detailed analysis of these regions by the clinical laboratory will further aid in the counseling of patients regarding the feasibility of finding rare sperm on testis biopsy or TESE. As such, the clinician is advised to consider these testing challenges when interpreting Y chromosome microdeletion test results. Thus, knowledge of which region(s) of AZF is microdeleted aids in clinical decision-making, as men with complete deletions of AZFa and/or AZFb should not undergo TESE for ART. Men with deletions of AZFc and smaller partial deletions of AZFa and/or AZFb should be counseled that sperm may or may not be found with TESE.[104,105]

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)

CFTR is located at the q31.2 locus of chromosome 7 and encodes a cyclic adenosine monophosphate (cAMP) dependent chloride channel. This channel is found in the apical membrane of secretory epithelial cells and is the gene responsible for CF, a congenital disease characterized by pulmonary obstruction and infection, exocrine pancreatic insufficiency. As *CFTR* regulates anion transport and fluid secretion in the excurrent ducts, it is thought that dysregulation of proper fluid dynamics leads to obstruction and/or atrophy in the epididymis and vas deferens during embryogenesis.[106,107] Indeed, some men with otherwise idiopathic genital tract obstruction are found to harbor mutations in the *CFTR* gene. In a study of 198 men, 34% of men with idiopathic obstruction had a CFTR mutation; 5 men had 2 mutations (including poly T), and 14 men had one mutation.[108]

Specifically, studies suggest that mutations in the *CFTR* gene are present in up to 80% of men with congenital bilateral absence of the vas deferens (CBAVD), 20% of men with CUAVD and 21% of men with idiopathic

epididymal obstruction. [108-110] While vasal abnormalities are apparent on physical examination, epididymal obstruction may only be diagnosed at the time of surgical exploration. As such, *CFTR* testing may necessarily occur after surgical treatment in some men.

To date, there have been over 1,500 mutations reported in the *CFTR* gene.[111] However, the frequency of many of these deletions are low with others having uncertain clinical significance. Several CF mutation testing approaches are offered by clinical laboratories that target the most common and pathologically verified mutations. However, the mutations more likely to cause obstructive azoospermia may be different than those that cause CF.[108] In addition, there are different CF mutation frequencies based on race/ethnicity.[112-115] 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 should be considered. In addition to classic mutations, the 5-thymidine (5T) variant of the polythymidine tract in the splice site of intron 8 (which regulates exon 9 splicing efficiency) is also commonly found in men with obstructive azoospermia due to *CFTR* abnormalities. Thus, "5T" analysis along with the *CFTR* mutation analysis is indicated to identify the etiology for vasal agenesis and to consider for preimplantation diagnosis if the female partner is a carrier. Men with vasal abnormalities may have one or two mutations identified on screening.[108] While *CFTR* mutations are the most common, mutations in other genes such as the Adhesion G Protein-Coupled Receptor G2 (ADGRG2) gene may cause CBAVD.[116]

It should be noted that ACOG pre-conception counseling guidelines include offering genetic screening, including CF mutations, for all couples considering pregnancy.[117]

14. For men who harbor a *CFTR* mutation, genetic evaluation of the female partner should be recommended. (Expert Opinion)

The goal of genetic testing for a *CFTR* mutation is to help identify the etiology of infertility as well as provide counseling on potential offspring transmission. CF is inherited in an autosomal recessive manner meaning that one defective allele must be inherited from each parent for a child to be affected.[113] Individuals with only one mutation are carriers but do not harbor the disease.

In cases where the male patient has a mutation in the *CFTR* gene and the partner is also a carrier, then 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). While the carrier prevalence does vary by race/ethnicity (4% of Caucasian Americans, ~2% of Hispanic Americans, 1.5% of African Americans, 1% of Asian Americans), mutations are not uncommon in the United States.[112-115] Thus, the female partner should also be screened for *CFTR* carrier status, as is routinely done in pre-conception counseling. In addition, formal genetic counseling should also be considered for a discussion of carrier status, genetic hereditability, and preimplantation genetic diagnosis for any couples who test positive for a mutation.

15. Sperm DNA fragmentation analysis is not recommended in the initial evaluation of the infertile couple. (Moderate Recommendation; Evidence Level Grade: C)

There are no prospective studies that have directly evaluated the impact of DNA fragmentation testing on the clinical management of infertile couples (i.e., that the fertility outcomes of those who had testing are different from those who did not). Further, available data are inadequate to conclude that this assay should be routinely performed in the initial evaluation of the infertile male. In available studies, DNA fragmentation was negatively associated with pregnancy rates and positively associated with miscarriages. That said, the association of high levels of DNA fragmentation with pregnancy outcomes is unclear given the variability in the definition of the upper limit of normalcy in different studies and the use of different tests of DNA fragmentation.[118-122] For male partners with high sperm DNA fragmentation, a clinician may counsel them that there is a possible association with infertility and compromised outcome after ART.

In a patient with high sperm DNA fragmentation, a clinician may consider using surgically obtained sperm in addition to ICSI. Therefore, DNA fragmentation testing may be advantageous for men in couples undergoing IVF with repeated IVF failure. Physicians should be aware that there are some data to suggest that men with very high levels of DNA fragmentation in ejaculated sperm typically have sperm with lower levels of DFI; this in combination with IVF may improve fertility outcomes. Therefore, a clinician may consider using testicular sperm as opposed to ejaculated sperm for IVF/ICSI. In a prospective cohort study of over 100 couples with high DNA fragmentation, testicular sperm yielded substantially higher live birth rates than ejaculated sperm.[123] The routine clinical application of this practice remains controversial as the quality of the

study data is low. However, some clinicians would only retrieve testicular sperm if prior attempts to achieve a pregnancy fail after the use of ejaculated sperm for IVR.

DNA fragmentation study results are not always consistent due to a variety of factors including inconsistent cutoff values defining the normal and abnormal ranges, non-standardized protocols, the use of different testing assays measuring unrelated parameters for assessment of DNA fragmentation, and the lack of RCTs. That said, it is possible that very high levels of sperm DNA fragmentation will have a more substantial adverse impact on pregnancy outcomes with IVF as well as an increased risk of miscarriages. Studies have also suggested that decreased abstinence may be an intervention to limit sperm DNA damage.[124]

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)

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). The WHO has defined the upper limit of normal as <1 million white blood cells/mL of semen.[5] Special stains are required to differentiate germ cells and somatic cells. A Papanicolaou staining procedure on a specimen smear may be used, but differentiating subtle differences in staining coloration, nuclear size, and shape can be challenging. A relatively simple assay is the o-toluidine test for cellular peroxidase (peroxidase stain) that will not stain leukocytes that have released their granules or lymphocytes, macrophages, or monocytes, which do not contain peroxidase. Immunocytochemical staining using antibodies specific for common leukocyte antigens is used to more precisely identify the seminal fluid white blood cells.[5] In contrast to peroxidase staining, the immunocytochemical method provides more information to aid in distinguishing between inflammation and those subtypes involved in fighting off infection. There is no evidence that elevated levels of immature sperm in the semen is deleterious to fertility, although they may be present in semen of infertile men and fertile men with high sperm counts.

17. Patients with pyospermia should be evaluated for the presence of infection. (Clinical Principle)

White blood cells in the semen may result from infection or inflammation in the proximal or distal male genital tract. Chronic prostatitis due to bacterial infection may require long courses of antibiotic treatment, and some cases of elevated levels of white blood cells may result from chronic nonbacterial prostatitis. Inflammation may be medically treated with anti-inflammatory drugs. Accordingly, it is important to know whether men with elevated levels of round cells in the semen have immature germ cells (a condition that cannot be treated) or an infectious or inflammatory etiology. While elevated semen white blood cells may secrete cytokines and generate free radicals in the semen (reactive oxygen species) that may be detrimental to sperm function, this is not a test of fertility.

18. Antisperm antibody (ASA) testing should not be done in the initial evaluation of male infertility. (Expert Opinion)

ASA can result from events such as trauma, mumps orchitis, testis malignancy, vasal obstruction, vasectomy that disrupts the blood-testis barrier, or the patency of the male genital tract allowing sperm antigens or genital tract infections to generate ASA.[125] ASA can result in sperm agglutination in the semen. ASA may be present without sperm agglutination and, conversely, agglutination may be present due to other factors, such as the presence of E.coli in the semen.[5]

IgA and IgG antibodies are the predominant antibodies found in semen, while IgM is rarely found. However, some laboratories measure all three immunoglobulin classes due to presence on sperm and in biological fluids. Tests used for ASA include the mixed antiglobulin reaction test, which provides less information, and the immunobead (IB) test, which gives information about the type and presence of the immunoglobulins and their localization specifically on the sperm head, midpiece or tail or covering the entire sperm.[5] In some cases, the test results may not be in agreement between these two distinct assays. For analysis of antibodies in semen, there are two versions of these tests- direct and indirect; for example, the direct IB test uses washed patient and control spermatozoa that are incubated with small beads with antibodies specific for IgG or IgA attached and are prepared in the laboratory. The IB will adhere to motile and immotile sperm that have surface bound antibodies. The percentage of motile sperm with the beads attached are counted.[5] Indirect assays are used to measure sperm-specific immunoglobulins in sperm free fluids (seminal plasma, heat-inactivated blood serum and solubilized cervical mucus). In this case,

aliquots of the fluid of interest or control immunoglobulins negative for sperm binding are incubated with normal control donor sperm prior to performing the mixed antiglobulin reaction or IB tests. Indirect testing is advantageous when the patient sample is oligozoospermic or asthenozoospermic (alone or in combination), when there is obstructive azoospermia, or when a sample cannot be immediately assayed. Depending upon collection time, the seminal fluid may be stored frozen until the time of testing.

ASA can impair sperm-ova penetration; accordingly, ICSI will negate this issue. Although there are few studies of natural conception for men with ASA, the presence of ASA following vasectomy reversal or vasoepidymostomy is well recognized, and older literature suggests that these antibodies impair sperm penetration. However, there were no significant associations between levels of ASA and pregnancy outcomes in these patients. Interpretations of these studies are challenging due to the lack of methodological standardization in these studies or consistent normal ranges.

ASA testing should only be considered if it will affect management of the patient. Conditions and findings reportedly associated with the presence ASA include obstruction of the ductal system (vasal, epididymal), prior testicular torsion, testicular surgery, and the presence of significant sperm agglutination in the SA, suggesting a potential diagnostic role of ASA testing for the detection of obstruction. However, published data on these associations are inconsistent.[126] The presence of serum ASA in an azoospermic patient with a history and physical exam findings consistent with ductal obstruction may help confirm obstruction.[127] Some have reported improved IUI pregnancy rates with specific semen processing protocols for couples with ASA compared to standard sperm washing, although the data are limited.[128] In those with ASA, ICSI yields higher pregnancy rates per cycle than IUI with semen processing designed to disrupt the bound antibodies.[129] For couples planning on ICSI, ASA testing should not be performed since it will not change management.

19. For couples with RPL, men should be evaluated with karyotype (Expert Opinion) and sperm DNA fragmentation. (Moderate Recommendation; Evidence Level Grade: C)

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. The contribution of paternal structural chromosomal defects (translocations, inversions, deletions, duplications) is not routinely clinically assessed for infertility, but these anomalies are associated with miscarriage and RPL.[10,11] Indeed, the presence of balanced translocations in either of the affected parents can become unbalanced during homologous recombination that occurs during meiosis in gametogenesis.[10] Unbalanced translocations are associated with birth defects in the offspring conceived as well as pregnancy loss. Robertsonian translocations are an example of a structural chromosomal anomaly associated with pregnancy loss.[10] These anomalies can be present in seemingly unaffected individuals but result in pregnancy loss due to unbalanced translocations. Hence, a karyotype that can reveal numerical and structural chromosome anomalies is indicated. An abnormal karyotype is present in about 6% of all infertile men.[11,130]

Infertile couples should be counseled that high levels of sperm DNA fragmentation are positively associated with miscarriage.[131-135] In a meta-analysis, pooled data from 13 studies suggest that male partners of women with a history of RPL have a significantly higher rate of sperm DNA fragmentation compared to the partners of fertile control women: mean difference 11.91, 95% CI 4.97 to 18.86.[132] Accordingly, DNA fragmentation testing should be considered in couples with unexplained RPL. When present, various treatments have been employed including using TESE with ICSI, antioxidant administration, donor sperm, varicocele repair, and/or frequent ejaculation. Currently there are no well-controlled published studies that evaluated whether any of the aforementioned therapies will decrease the risk of RPL.

When discussing DNA fragmentation test results, clinicians should mention that in infertile couples clinical pregnancy rates were higher with ICSI as compared to insemination with ART.[11,122,136,137] The basis for this finding is unclear as when sperm are selected for ICSI, it is impossible to know whether the sperm DNA is fragmented.

For couples with RPL, men may be considered for sperm aneuploidy testing. Sperm aneuploidy testing involves the use of fluorescent molecular probes for chromosomes 13, 18, 21, X, Y because the presence of an extra chromosome for these specific chromosomes is consistent with a potentially viable but affected offspring.[11,136-138] Aneuploidy of all other human chromosomes is not consistent with a viable offspring. While aneuploid ova are a well-recognized cause of aneuploid fetuses and offspring (i.e., Trisomy 21 increased incidence with advanced maternal age), the

contribution of the male to aneuploid fetuses, offspring, and RPL is rarely considered by the clinician treating the couple with RPL.[138,139] Physicians should consider ordering sperm aneuploidy testing in men with a normal somatic karyotype to identify those men with a defect resulting in improper chromosome segregation during meiosis and aneuploid sperm resulting in a paternal role in RPL. However, this test currently may not be available nationwide. Genetic counseling may be useful, because this knowledge will allow couples to alter their fertility management plan and seek alternative pathways to parenthood, such as preimplantation genetic testing with ICSI-IVF, donor sperm, adoption, or to continue attempting a natural pregnancy.[140] In uncontrolled studies looking at couples where the man had an abnormal sperm aneuploidy test, there appeared to be an improvement in outcomes when PGT-A was utilized.[141]

20. Diagnostic testicular biopsy should not routinely be performed to differentiate between obstructive azoospermia and non-obstructive azoospermia (NOA). (Expert Opinion)

Differentiation of obstructive azoospermia from NOA may most frequently be predicted from clinical and laboratory results without the need for surgical diagnostic biopsy. FSH levels greater than 7.6 IU/L and testis longitudinal axis less than 4.6 cm indicate an 89% likelihood of spermatogenic dysfunction as the etiology.[89] Conversely, FSH levels less than 7.6 IU/L and testis longitudinal axes greater than 4.6 cm indicate 96% likelihood of obstruction as the etiology.[89] In the infrequent cases with intermediate values, testis biopsy may be performed to determine the etiology, but this is not usually necessary. In the rare cases where testis biopsy is 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)

The scrotum may sometimes be difficult to examine, for example in an obese patient or when the dartos muscle remains highly contracted during the physical exam. In these infrequent cases, color doppler ultrasound may be used to examine spermatic cord veins. The standard definition of a varicocele with this technique is the presence of multiple large veins greater than 3 mm in diameter and reversal of blood flow with the Valsalva maneuver.[142,143] However, routine use of ultrasonography to investigate presumed varicocele is to be discouraged, as treatment of non-palpable varicoceles is not associated with improved semen parameters and fertility rates as has been shown for treatment of clinical varicoceles.

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 (EDO) (i.e., acidic, azoospermic, semen volume <1.5mL, with normal serum T, palpable vas deferens). (Expert Opinion)

For the purposes of an infertility evaluation, TRUS seeks to identify the anatomy of the primary organs/ structures involved in ejaculation including the prostate, seminal vesicles, vasal ampulla, and ejaculatory ducts.[144] TRUS can be useful in identifying distal obstruction leading to obstructive azoospermia such as that caused by EDO.

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). Most of these men will have absent fructose in semen, although fructose testing is relatively unreliable and is not necessary especially in men for whom there is a high index of suspicion (i.e., SA shows low volume, acidity, azoospermia). For these men, TRUS evaluation should be considered to evaluate for anatomic abnormalities.[145] Other aspects of the ejaculate should be considered. Normal semen is derived from testicular (~10%), prostatic (~20%), and seminal vesicle (~70%) fluid. All components are androgen sensitive so that men with testosterone deficiency may have low semen volume and the utility of TRUS in such circumstances may be low. In addition, seminal vesicle fluid is alkaline. Obstruction that limits or prevents the seminal vesicle contribution will lead to acidic semen (pH <7.0). Men with a normal semen pH are unlikely to have a complete distal genital tract obstruction.[146] Congenital abnormalities may also affect normal genital duct anatomy. 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.[146]

Beyond infertility, ejaculatory pain may also trigger evaluation with TRUS as a diagnosis of obstruction may lead to treatment recommendations to improve symptomatology.

In men with normal ejaculation and semen volume, the results of TRUS evaluation will not usually change the management of an infertile male. As such, without symptoms (e.g., painful ejaculation) or semen parameter indications (e.g., low semen volume with azoospermia and palpable vasa, or low semen volume and significant asthenospermia), TRUS should not be included in an infertility evaluation.

23. Clinicians should not routinely perform abdominal imaging for the sole indication of an isolated small or moderate right varicocele. (Expert Opinion)

Varicoceles occur in approximately 15% of all adult men and 40% of infertile men.[147] While 85% are left unilateral due to asymmetric gonadal vein anatomy, 15% may be either bilateral (more common) or right unilateral (less common). Due to the rarity of the isolated right varicocele, concern has existed regarding causative conditions in clinical cases. Case reports in the literature report retroperitoneal pathology such as tumors as common enough causes to warrant routine abdominal imaging when an isolated right varicocele is identified.[148-150] However, only low-quality evidence has ever supported this recommendation.

A 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 fact 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.[51] Thus, routine imaging based solely on the presence of a right varicocele is unnecessary. However, abdominal imaging should be considered for men with a new onset or non-reducible varicocele, especially if varicocele is large.

24. Clinicians should recommend renal ultrasonography for patients with vasal agenesis to evaluate for renal abnormalities. (Expert Opinion)

The male genital tract is derived from the Wolffian or mesonephric tract. It is a paired organ, which forms the epididymis, vas deferens, and seminal vesicles during embryogenesis. As it connects to the primitive kidney, abnormalities in the Wolffian duct can lead to renal anomalies. In men with unilateral absence of the vas deferens, approximately 26-75% of men will have ipsilateral renal anomalies including agenesis.[152,153] In men with bilateral vasal agenesis, the prevalence is lower at 10%.[154] Even in men with CBAVD and CFTR mutations, unilateral renal agenesis may occur.[116,155] As such, abdominal imaging should be offered to men with vasal agenesis regardless of the CFTR status to allow for optimal patient counseling.

Treatment

Varicocele Repair/ Varicocelectomy

25. Surgical varicocelectomy should be considered in men attempting to conceive who have palpable varicocele(s), infertility, and abnormal semen parameters, except for azoospermic men. (Moderate Recommendation; Evidence Level Grade: B)

The largest most recent meta-analysis by Wang et al. observed higher estimated pregnancy rates for men treated with any approach for repair of clinical varicocele compared to no treatment.[156] Pregnancy rates without treatment were assumed to be 17%, while rates were calculated to be 42% (95% CI 26% to 61%) with subinguinal microsurgical varicocelectomy, 35% (95% CI 21% to 54%) with inguinal microvaricocelectomy, 37% (95% CI 22% to 58%) with inguinal open (non-microsurgical) surgery, and 37% (95% CI 19% to 61%) with laparoscopic surgery.[156] Such findings must be interpreted with caution given that this meta-analysis included studies with non-randomized designs and selective outcome reporting. OR were lower for sclerotherapy, subinguinal open surgery, retroperitoneal open surgery, percutaneous venous embolization, and retrograde sclerotherapy. Bulk seminal parameters including sperm concentration and sperm motility were also observed to be improved with surgery.

For palpable varicoceles, the meta-analysis by Wang et al. observed the calculated estimated pregnancy rates to be 52% (95% CI 24% to 83%) for subinguinal microvaricocelectomy, 53% (95% CI 18% to 90%) for inguinal microvaricocelectomy, 55% (95% CI 27% to 88%) for inguinal open surgery, and 52% (95% CI 18% to 90%) for laparoscopic surgery.[156]

A meta-analysis of ART outcomes evaluated the chance of pregnancy using ART for couples where men had varicocele repair relative to couples where the man had an untreated varicocele. In these 7 non-randomized retrospective studies, only men with clinical varicoceles were considered. In this report by Kirby et al., the OR for pregnancy and live birth were 1.76-fold higher for men treated with varicocelectomy prior to ART.[157]

26. Clinicians should not recommend varicocelectomy for men with non-palpable varicoceles detected solely by imaging. (Strong Recommendation; Evidence Level Grade: C)

Past AUA and ASRM recommendations for non-palpable varicoceles in men with concern for fertility has been to not recommend varicocelectomy, and recent studies continue to support this recommendation.[158] Kim et al. performed a systematic review and meta-analysis of varicocelectomy for subclinical varicocele. Reviewers included 7 trials with 548 participants (276 received varicocelectomy, and 272 received either no treatment or clomiphene citrate). These trials were considered of low-quality due to issues such as unreported random sequence generation and allocation concealment, lack of blinding, and incomplete outcome data. No demonstrable benefit of varicocele repair was observed in pregnancy or bulk seminal parameters with the exception of a possible small numerical effect on progressive sperm motility that is unlikely to be clinically important.[158]

27. For men with clinical varicocele and NOA, couples should be informed of the absence of definitive evidence supporting varicocele repair prior to ART. (Expert Opinion)

Case series of men with NOA and clinical varicoceles have been reported. Since up to 35% of men with NOA will have sperm detected on subsequent SA without medical intervention, such case series must be interpreted with caution.[159] Case studies cannot be considered to reflect a therapeutic benefit of varicocele repair unless controlled. Of note, the studies published to date have not included control patients with varicoceles that were not repaired, and simply had repeat SAs done.[160] Summarized case studies reporting detection of at least one non-motile sperm in the ejaculate after varicocele repair for men with NOA indicated sperm in 36% (119/327) of treated men. Using a different outcome evaluation that may be more clinically relevant in NOA, a study that reported return of adequate motile sperm in the ejaculate to avoid surgical sperm retrieval after varicocele repair had a success rate of only 9.6%.[161] These data have to be compared to results of re-analysis of sperm in the ejaculate without any intervention beyond repeat SA using extended sperm search (35%). There are sparse studies with relatively limited numbers of men with azoospermia due to spermatogenic dysfunction that have evaluated the role of varicocelectomy in potentially increasing spermatogenesis. There are no high-quality data to support repair of varicoceles in men with NOA. In addition, varicocele repair defers treatment with ART for at least six months. For the surgeon considering varicocelectomy prior to definitive treatment with surgical sperm retrieval and ART, couples should be informed of the limited evidence supporting the benefit of varicocele repair in azoospermia.

Sperm Retrieval

28. For men with NOA undergoing sperm retrieval, microdissection testicular sperm extraction (TESE) should be performed. (Moderate Recommendation; Evidence Level Grade: C)

Systematic reviews assessing different sperm retrieval techniques for men with NOA are of low quality mainly due to limitations associated with performing surgical studies. In a meta-analysis of published studies for men with NOA, micro-TESE was observed to result in successful extraction 1.5 times more often than non-microsurgical testis sperm extraction, and testis sperm extraction was 2 times more likely to succeed when compared to testicular aspiration.[162]

Micro-TESE is a surgical procedure that involves wide opening of the tunica albuginea to allow examination of multiple regions of testicular tissue, each of which are oriented in a centrifugal pattern in parallel to the intratesticular blood supply, allowing extensive search of nearly all areas of the testis with limited risk of devascularization of tissue. Conventional TESE has been associated with decreased postoperative testosterone levels, and many men with NOA have baseline testosterone deficiency levels. Less effect on testosterone levels is seen after micro-TESE than with conventional TESE, but testosterone deficiency requiring testosterone replacement remains a risk, even after micro-TESE.[163]

29. In men undergoing surgical sperm retrieval, either fresh or cryopreserved sperm may be used for ICSI. (Moderate Recommendation; Evidence Level Grade: C)

For men with obstructive azoospermia, adequate sperm are typically present to allow sperm cryopreservation with a high chance for survival of those sperm for use with ART. There are no substantial differences in IVF success rates, so sperm retrieval and cryopreservation may be done prior to ART.

For men with NOA, some centers perform simultaneous sperm retrieval with ART because the numbers of sperm obtained may be limited and sperm may not

survive cryopreservation. For those couples where the man has NOA and sperm are frozen and survive freeze-thaw, ART is possible with those sperm.

A recent meta-analysis evaluating the use of sperm from men with NOA observed no differences in fertilization, pregnancy, or live birth rates from ICSI in men for whom sperm was extracted and used with or without cryopreservation, as long as there were sperm of adequate number and survived cryopreservation and thawing.[164]

30. In men with azoospermia due to obstruction undergoing surgical sperm retrieval, sperm may be extracted from either the testis or the epididymis. (Moderate Recommendation; Evidence Level Grade: C)

While the available studies are of low quality, fertilization, pregnancy, and live birth rates were similar for epididymal and testicular derived sperm in men with azoospermia due to obstruction.[165]

31. For men with aspermia, surgical sperm extraction or induced ejaculation (sympathomimetics, vibratory stimulation or electroejaculation) may be performed depending on the patient's condition and clinician's experience. (Expert Opinion)

Limited data exist comparing outcomes for the various procedures available to obtain sperm from men with ejaculatory dysfunction. Penile vibratory stimulation, electroejaculation, surgical sperm retrieval, or sympathomimetic agents may be utilized depending on the cause of the ejaculatory dysfunction, the patient's condition, and surgeon's experience.

It is important to differentiate dry ejaculate (aspermia) from azoospermia, where an antegrade ejaculate is present but lacks spermatozoa. Ejaculatory dysfunction may also include RE with or without an antegrade component, and low volume ejaculate.[166]

32. Infertility associated with retrograde ejaculation (RE) may be treated with sympathomimetics and alkalinization of urine with or without urethral catheterization, induced ejaculation, or surgical sperm retrieval. (Expert Opinion)

Partial RE may exist concurrently with partial antegrade ejaculation. If the antegrade specimen is sufficient for reproduction either naturally or with medical assistance, no treatment may be necessary.[143] However, if the antegrade ejaculate is poor and a substantial RE is present as demonstrated by post-ejaculatory urinalysis, various therapies may be required. These treatments include oral sympathomimetics with alkalinization of urine. These specimens may be collected from voided urine or with urethral catheterization. Many men with lack of emission associated with spinal cord injury or psychogenic anejaculation may also respond to penile vibratory therapy. For men with persistent lack of emission despite medical therapy, then electroejaculation, or surgical sperm retrieval may be employed based on severity, clinical presentation and response to other less invasive therapy.

Obstructive Azoospermia, Including Post-Vasectomy Infertility

33. Couples desiring conception after vasectomy should be counseled that surgical reconstruction, surgical sperm retrieval, or both reconstruction and simultaneous sperm retrieval for cryopreservation are viable options. (Moderate Recommendation; Evidence Level Grade: C)

Limited data exist comparing outcomes for strategies for men interested in fertility after vasectomy.[167] Surgical sperm retrieval will require the use of ART/ ICSI to achieve a pregnancy. Critical variates that would influence a couple's decision-making, such as maternal age and variable economic cost across geographic regions, have not yet been systematically explored with high-quality evidence. For couples with female factors that require ART, sperm retrieval and IVF is often the preferred option for management. For couples interested in fertility who are farther out from vasectomy (e.g., over 25 years after vasectomy), microsurgical reconstruction with vasoepididymostomy may have lower success rates and sperm cryopreservation at the time of reconstruction should be considered. At this time, the specific needs and characteristics of the couple as well as patient preference should be considered and discussed with the provider in order to render the best option for fertility after vasectomy.

34. Clinicians should counsel men with vasal or epididymal obstructive azoospermia that microsurgical reconstruction may be successful in returning sperm to the ejaculate. (Expert Opinion)

Obstructive azoospermia is a condition characterized by an absence of sperm in the ejaculate with normal sperm production in the testis. Both congenital and acquired causes of obstruction have been identified. In

men with congenital absence of the vas deferens, sperm retrieval together with ART such as IVF and ICSI are the only options for men to father their own biologic children. In most other cases of acquired or congenital obstruction, microsurgical reconstruction of the male reproductive tract may be the preferable alternative to sperm retrieval and ICSI when the female partner has normal fertility potential. Microsurgical reconstruction as vasovasostomy or vasoepididymostomy has also been suggested as a more cost-effective treatment for obstructive azoospermia, when compared to sperm retrieval and ART.[32] The most robust data for microsurgical reconstruction exist for men with vasectomy-associated infertility, since up to 6% of all married men have had a vasectomy for contraception. In this population, microsurgical reconstruction involves surgical exploration with identification of the site of obstruction, which may still be at the vasectomy site or more proximally in the epididymis. Microsurgical reconstruction is done by anastomosing the vas to the most distal site in continuity with the testis, documented by identifying sperm at this region of the reproductive tract. Higher patency and pregnancy rates after reconstruction are associated with bilateral vasovasostomy, more distal epididymal anastomoses (compared to epididymal anastomoses) for vasoepididymostomy, and the presence of intact sperm at the site of reconstruction. Although patients with shorter obstructive intervals have slightly better outcomes compared to men with longer intervals after vasectomy, the patency rate for microsurgical reconstruction more than 25 years after vasectomy have been reported to be more than 70%.[168,169] Preoperative counseling should include discussion of the surgeon's experience and results after attempted reconstruction, as well as alternative approaches to achieving pregnancy (sperm retrieval and ICSI.)

35. For infertile men with azoospermia and EDO, the clinician may consider transurethral resection of ejaculatory ducts (TURED) or surgical sperm extraction. (Expert Opinion)

EDO is rare in infertile men. If the diagnosis is confirmed or suspected based on TRUS findings, then treatment should be considered. Findings on TRUS suggesting obstruction include seminal vesicle anterior-posterior diameter >15mm, ejaculatory duct caliber (>2.3mm), or dilated vasal ampulla (>6mm) as well as prostatic cysts (midline or paramedian (ejaculatory duct). If a seminal vesicle aspirate reveals the presence of sperm in an azoospermic man, then TURED may be offered.[146,170,171] The goal of the surgery is to resolve the obstruction to allow sperm to enter the ejaculate, which can be used for unassisted conception or ART. The clinician should discuss with the patient that 63-83% of patients will have an improvement in semen parameters after the procedure, including 59% of patients with complete EDO and up to 94% of patients with partial EDO.[172-176] Over 90% of men will have improvement in semen volume,[177] 50% will improve sperm counts,[178] and 60% will convert from azoospermia to some sperm in the ejaculate. In addition, 38% of men with azoospermia or oligozoospermia may develop normal semen parameters.[177] While all patients may benefit, data suggest that men with congenital causes (e.g., Mullerian duct cysts) may have better improvement compared to men with acquired obstruction (e.g., infectious etiology).[146] In men with EDO associated with Mullerian cysts, treatment involves unroofing of the cyst, resulting in decompression of the cyst and relief from extrinsic obstruction of the ejaculatory ducts.

In addition to fertility, investigators have reported successful treatment with TURED for other symptoms including hematospermia, recurrent infection, or pain (i.e., scrotal, post-ejaculatory). [4,34] The clinician should also discuss known complications of TURED. Restenosis, pain, epididymoorchitis, urinary retention, reflux of urine into the ejaculatory ducts and seminal vesicles or substantial defects in the prostatic fossa (leading to watery ejaculate), gross hematuria, and incontinence may occur in 4-26% of cases.[146,173,174,179,180] Restenosis leading to azoospermia is a potentially serious complication in men with partial EDO and may occur in up to 27% of men.[173,176]

Surgical sperm extraction (e.g., TESE, TESA, Percutaneous Epididymal Sperm Aspiration [PESA]) for use with ART is an alternative option in men with EDO who desire fertility. The decision for the optimal method should be a shared decision with the patient/couple.[146]

Medical and Nutraceutical Interventions for Fertility

36. Male infertility may be managed with ART. (Expert Opinion)

One of the greatest advances in the management of male infertility has been the use of IVF and, subsequently, ICSI as ART. Although sperm number and quality affected the results of treatment with IVF, ICSI appeared to abrogate any adverse effects of sperm "quality" as measured by sperm concentration, motility, and morphology as long as viable sperm are present to inject into all oocytes. With IVF, abnormal sperm motility and morphology adversely affect

fertilization rates.[181] The application of ICSI during IVF treatment provided fertilization rates comparable to that observed with otherwise normal sperm. Although ART does not correct the underlying condition(s) causing male infertility and allows pregnancy for men where natural pregnancy has not previously occurred, these techniques involve limited medical risk to the female partner. Studies to date show limited known differences in birth defect rates between naturally occurring pregnancies, IVF, or ICSI-derived pregnancies. IVF treatment requires more than a week of ovarian stimulation, procedures for oocyte retrieval and intrauterine embryo transfer; each attempt typically allows for a 33% live delivery rate per initiated IVF cycle.[182] Pregnancy and live birth results are closely related to female age, with progressively lower success with increased female age (over 35 years). Approximately 19% of all deliveries involve twins, and additional pregnancies may result from one IVF cycle if additional embryos are available for cryopreservation.

37. A clinician may advise an infertile couple with a low total motile sperm count on repeated SA that IUI success rates may be reduced, and treatment with ART (IVF/ICSI) may be considered. (Expert Opinion)

IUI is a fertility treatment that involves processing a semen specimen and placing the low volume washed semen into the uterine cavity at the time of ovulation. The intervention may be done with or without ovarian stimulation of the female partner to enhance oocyte production. In general, SA parameters are not predictive of natural pregnancy or pregnancy by use of ARTs, including IUI, unless severe abnormalities exist. However, converging evidence suggests significant associations between pregnancy by IUI and total motile sperm count. As such, men with low total motile sperm count (<5 million motile sperm after processing) are expected to have lower pregnancy rates after IUI than using sperm from men with normal total motile sperm counts.

38. The patient presenting with hypogonadotropic hypogonadism (HH) should be evaluated to determine the etiology of the disorder and treated based on diagnosis. (Clinical Principle)

Patients with HH present with deficient LH and FSH secretion. In the absence of LH and FSH stimulation, the Leydig cells in the testes do not secrete testosterone, and spermatogenesis is disrupted.[183] Referral to an endocrinologist or male reproductive specialist is encouraged.

The congenital form idiopathic hypogonadotropic hypogonadism (IHH), also referred to as isolated gonadotropin-releasing hormone (GnRH) deficiency, is a rare genetic disorder that is associated with defects in the production and/or action of GnRH. The original form Kallmann syndrome is an X-linked recessive disorder and is associated with anosmia and the lack of endogenous GNRH secretion and ANOS1 mutations. Other forms of IHH are associated with a number of genetic mutations with variable forms of inheritance and often without anosmia.[184-186] Males with the more severe forms of the syndrome can present with microphallus and/or cryptorchidism as well as skeletal abnormalities such as cleft palate, and syndactyly.

A variant of IHH, referred to as adult onset or acquired IHH, presents with symptoms of sexual dysfunction and/or new-onset infertility and lower levels of testosterone in concert with inappropriately low gonadotropins.[187]

Spermatogenesis can be initiated and pregnancies achieved in many of these IHH men when they are treated with exogenous gonadotropins or GnRH. Selection of the type of hormonal therapy as well as the ultimate success of therapy depends on the severity of the defect. The usual first-line drug for the treatment of IHH for restoration of testosterone and spermatogenesis is hCG. The degree of response correlates with the size of the testis prior to treatment.[188-190] Initial treatment with hCG injections (1,500-2,500 IU, twice weekly) followed by FSH, when indicated, after testosterone levels are normalized on hCG. Pulsatile GnRH is not currently approved in the US or Europe. If medical therapy fails to result in a pregnancy, but some sperm are found in the ejaculate, referral for ART is recommended.

SERMs have been used off label as an alternative treatment to increase testosterone and sperm density in men with adult onset IHH following SERM therapy alone with the goal of pregnancy in the partner. Only a small number of studies with very few patients have reported successful pregnancies in men with adult-onset IHH.[191,192]

Secondary causes of HH include pituitary or suprasellar tumors, pituitary infiltrative disorders (e.g., hemochromatosis, tuberculosis, sarcoidosis, histiocytosis), exogenous androgens, other medications (e.g., chronic narcotic exposure), hyperprolactinemia, prior head trauma, pituitary apoplexy, and severe chronic illness.[193] The first line of treatment is directed towards the underlying disorder. Once that has been accomplished, and the patient continues to have HH, a

trial of the gonadotropin treatment regimen described above can be initiated. SERM therapy will not be beneficial if the pathology is due to primary pituitary dysfunction, such as after surgical resection.

39. Clinicians may use aromatase inhibitors (AIs), hCG, selective estrogen receptor modulators (SERMs), or a combination thereof for infertile men with low serum testosterone (Conditional Recommendation; Evidence Level: Grade C)

AIs, hCG, and SERMs act by different mechanisms to increase endogenous testosterone production. Each agent may be used separately or in combination in an effort to increase serum testosterone concentrations without impairing spermatogenesis. Although hCG is FDA-approved for use in men with HH, the other medications are not approved by the FDA for use in men. Furthermore, although the goal of testosterone optimization in the infertile male may be symptom amelioration, symptomatic outcomes and benefits may not be comparable to those achieved using standard (exogenous) testosterone replacement therapy.

Testosterone is converted to estrogen peripherally by the enzyme aromatase. AIs are oral medications that block this conversion, resulting in a relative decrease in serum estradiol levels, increase in LH secretion by the pituitary, and a relative increase in serum testosterone concentration. Clinicians may consider use of AIs for men with testosterone deficiency and elevated estradiol levels.[194,195]

hCG is an injectable medication that acts as an LH analogue, stimulating testosterone production by direct action on the Leydig cells. SERMs are oral medications that have antiestrogenic effects centrally, impeding negative feedback of the hypothalamic-pituitary-testis axis. Clomiphene citrate is the most commonly studied SERM for infertile men. Treatment with SERMs results in increased LH and FSH production by the pituitary gland; the increased LH production, in turn, stimulates Leydig cell production of testosterone. Clinically, either hCG or SERMs may be considered for testosterone optimization in men with low or normal serum LH. Men who exhibit an elevated LH, consistent with primary hypogonadism, may have a limited serum testosterone response to these medications due to inherent testicular dysfunction.

For further information on the management of testosterone deficiency, please refer to the AUA Guideline on the Evaluation and Management of Testosterone Deficiency, specifically Statement 27 and Table 6: https://www.auanet.org/guidelines/testosterone-deficiency-guideline.

40. For the male interested in current or future fertility, testosterone monotherapy should not be prescribed. (Clinical Principle)

Exogenous testosterone administration provides negative feedback to the hypothalamus and pituitary gland, which can result in inhibition of gonadotropin secretion. Depending on the degree of testosterone-induced suppression, spermatogenesis may decrease or cease altogether, resulting in azoospermia.[196] Although recovery of sperm to the ejaculate occurs in most men with cessation of testosterone therapy, the time course of recovery may be prolonged and can be months or rarely years.[197] Therefore, testosterone monotherapy for symptomatic testosterone deficiency should not be used in men pursuing or planning to pursue family building in the near future. In those that may want to pursue paternity in the more distant future, testosterone therapy may be offered, but the patient should be counseled about the effects on spermatogenesis and the time course required for resumption of spermatogenesis. For further information, please refer to the AUA Guideline on the Evaluation and Management of Testosterone Deficiency, specifically Statement 16: https://www.auanet.org/guidelines/testosterone-deficiency-guideline.

41. The infertile male with hyperprolactinemia should be evaluated for the etiology and treated accordingly. (Expert Opinion)

Men with decreased libido and/or impotence and/or testosterone deficiency accompanied by a low/low-normal LH level warrant measurement of serum prolactin to investigate for hyperprolactinemia. If prolactin is mildly elevated (≤1.5 times the upper limit of normal), a repeat fasting prolactin should be drawn to rule out a spurious elevation. While prolactin levels generally parallel tumor size, milder elevations can be found with prolactinomas as well as with other pituitary or parasellar tumors or infiltrative processes.[198,199] When evaluating prolactin levels, the clinician should be aware of assay discrepancies, which result in false values. For example, macroprolactinemia is a condition where more than 60% of circulating prolactin is made of the low biologically active macroprolactin, which results in a falsely elevated level of biologically active prolactin. The "Hook Effect" is an assay artifact caused by an extremely high level of prolactin that saturates the detecting antibody used in the PRL assay, and results in a falsely low reported value.[199-201]

For persistently elevated prolactin levels above the

normal value without an exogenous etiology, MRI is indicated. [199,200,202]

Prolactin, a polypeptide hormone, is synthesized and secreted from the pituitary gland. Hyperprolactinemia is a well-established cause of secondary hypogonadism and can lead to infertility, decreased libido, sexual dysfunction, and gynecomastia. Causes of hyperprolactinemia include pituitary tumors, and primarily prolactin producing tumors; however, it may also be due to non-lactotroph adenomas (GH, ACTH, chromophobe) and cystic adenomas. Tumors near the hypothalamus or pituitary that interfere with the secretion of dopamine or its delivery to the hypothalamus (e.g.,craniopharyngiomas) infiltrative diseases (e.g., sarcoidosis, hemochromatosis, TB), and malignant tumors that arise within or near the sella or metastasize to these areas can also elevate prolactin levels.[203]

Drugs that decrease dopaminergic inhibition of prolactin secretion also cause hyperprolactinemia. These include opioid analgesics, many antipsychotics and antidepressants, antiemetics, prokinetics, and antihypertensives. Hypothyroidism, stress, elevated estrogen levels, chronic renal failure, and chest wall injuries can increase prolactin levels.

Treatment depends on the etiology of the hyperprolactinemia.[201] Dopamine agonists are the first-line treatment for patients with pituitary prolactinomas. Transsphenoidal surgery may be considered when dopamine agonist treatment is unsuccessful or if the patient prefers surgery to life-long therapy.[204]

For men with hyperprolactinemia who do not have a pituitary adenoma, management should focus on treatment of the underlying condition or factor causing the elevated prolactin (e.g., treatment of hypothyroidism, medication changes for drugs associated with elevated prolactin levels).

42. Clinicians should inform the man with idiopathic infertility that the use of SERMs has limited benefits relative to results of ART. (Expert Opinion)

SERMs induce increased LH and FSH production by the pituitary gland. Although not FDA-approved for use in men, SERMs such as clomiphene or tamoxifen are often prescribed in infertile men who have normal serum testosterone levels with the therapeutic aim of improving semen parameters and fertility outcomes. One meta-analysis reviewed 11 studies that compared either clomiphene or tamoxifen with either placebo or no treatment in men with oligozoospermia or asthenoteratospermia.[205] Collectively, the findings suggested that SERMs may improve sperm concentration, sperm motility, and spontaneous pregnancy rate.[205] A more recent systematic review published in 2019 included 16 studies that compared clomiphene or tamoxifen to placebo, no treatment, or other treatments (e.g., supplements, other medications) in men with oligozoospermia. As anticipated based on mechanism of action of SERMs, gonadotropin and serum testosterone levels increased. Data suggested an improvement in sperm morphology and pregnancy rate with SERM administration, but no consistent impact on other semen parameters.[206] The studies included in both of these review articles were of variable quality in terms of selective reporting, bias, and blinding. As such, any possible limited benefits of SERM administration, particularly in the patient population with idiopathic infertility, are small and, therefore, outweighed by the distinct advantages offered by other forms of medically-assisted reproduction (e.g., IVF), which include higher pregnancy rates and efficiencies with respect to the earlier timeframe of conception.

43. Clinicians should counsel patients that the benefits of supplements (e.g., antioxidants, vitamins) are of questionable clinical utility in treating male infertility. Existing data are inadequate to provide recommendation for specific agents to use for this purpose. (Conditional Recommendation; Evidence Level Grade: B)

There are no clear, reliable data related to the variety of supplements (vitamins, antioxidants, nutritional supplement formulations) that have been offered to men attempting conception. Current data suggest that they are likely not harmful, but it is questionable whether they will provide tangible improvements in fertility outcomes. A recent RCT by the NIH Reproductive Medicine Network of 174 men did not show adequate effect on semen parameters or DNA integrity in the initial screening arm to proceed to full patient accrual.[207]

"Beneficial effect" means that the between-group difference was statistically significant. "No effect" means that it was not statistically significant and the 95% confidence interval ruled out the possibility of an important effect (as defined by 20% of typical values). "Inconclusive" means that it was not statistically significant and the 95% confidence interval was too wide to rule out the possibility of an important effect.

44. For men with idiopathic infertility, a clinician

may consider treatment using an FSH analogue with the aim of improving sperm concentration, pregnancy rate, and live birth rate. (Conditional Recommendation; Evidence Level Grade: B)

Exogenous FSH may be used as an adjunct for treatment of HH in order to initiate and maintain spermatogenesis with good results. To this end, some clinicians have employed exogenous FSH in infertile men without HH (i.e., baseline FSH in or slightly above the normal range) with the therapeutic goal of improving fertility outcomes despite limited published data to date. Typical treatment doses were 150 IU given daily over a 12-week period of therapy. One comprehensive meta-analysis reviewed 15 trials and described impacts of FSH administration versus placebo or no treatment on semen parameters and pregnancy rates. Overall, sperm concentrations and pregnancy rates, both unassisted and via ART, appeared to improve in the FSH-treated men.[208] A subgroup meta-analysis from this study looked at the 9 trials of FSH administration in 389 men compared to 308 controls and related unassisted pregnancy rates, with a resultant overall OR of 4.50 (CI 2.17 to 9.33, P<0.001). A second subgroup meta-analysis assessed pregnancy rates after ART; 322 men were treated with FSH compared to 275 controls, with a resultant overall OR of 1.60 (CI 1.08 to 2.37, P=0.002).

Another systematic review included 6 RCTs (225 men on FSH, 231 controls) assessing FSH versus placebo or no treatment and impact on pregnancy rate and live birth rate. FSH therapy prior to medically-assisted treatments (one study on IUI, one study on IVF-ICSI) did not conclusively affect pregnancy rates with ART.[209]

One RCT published in 2015 compared 4 different doses of FSH with placebo in 354 men with idiopathic oligozoospermia. Couples who did not achieve pregnancy within three months of initiation of therapy underwent ART. Findings were inconclusive with respect to spontaneous and ART pregnancy rates.[210]

Clinicians should be aware that FSH is not FDA-approved for use in men. Additionally, the cost-to-benefit ratio of this treatment is questionable. Of note, few studies have provided data that compare the effect of FSH to SERM therapy for infertile men.

45. Patients with NOA should be informed of the limited data supporting pharmacologic manipulation with SERMs, AIs, and gonadotropins prior to surgical intervention. (Conditional Recommendation; Evidence Level Grade: C)

For any patient with NOA, it would be ideal to optimize spermatogenesis and hence the chances of sperm recovery at the time of attempted surgical sperm retrieval. SERMs, AIs, and hCG have been used off-label to try to manipulate male reproductive hormones with the goal of inducing recovery of sperm to the ejaculate or improving surgical sperm retrieval rates (SRR). Unfortunately, limited data are available with respect to treatment outcomes. In addition, many of the published studies included medical therapy without control groups, ignoring the common detection of cryptozoospermia in men presumed to have azoospermia.

As described in Guideline 39 clomiphene citrate is the most studied of the SERMs. One single-center, prospective, non-randomized comparative study assessed men with NOA who received CC prior to micro-TESE. Of the 372 men receiving CC, 11% had sperm recovery in the ejaculate, obviating the need for micro-TESE. SRR at the time of micro-TESE in the remaining 331 men was 57.7%, as compared with 33.6% in the control group.[211]

A double-blind, multi-center RCT published in 2013 compared treatment with letrozole, an aromatase inhibitor, to placebo in men with NOA. Although all NOA men in the treatment arm did have recovery of sperm in the ejaculate (and none in the placebo group), there were no unassisted pregnancies in either the treatment or placebo groups.[212]

Two studies used gonadotropin treatment in men with NOA.[213,214] One retrospective comparison study explored the effects of hCG to no treatment in men with NOA undergoing surgical sperm retrieval; 34 men were in the treatment arm, and 49 did not receive hCG. For all patients, conventional TESE was the initial surgical approach. If no sperm were identified, the procedure was converted to micro-TESE. There was no statistically significant difference in SRR, pregnancy rate, or live birth rate between groups.[213] A second prospective, non-randomized comparative study of 108 men with NOA compared FSH treatment to no medication prior to TESE. Neither group had recovery of sperm to the ejaculate. Surgical SRR in this small study was 64% in the men who received FSH versus 33% in the no-treatment group.[214]

As these few low- to moderate-quality studies with small sample sizes demonstrate, little evidence is yet available with respect to optimization of spermatogenesis and SRR in men with NOA.

Gonadotoxic Therapies and Fertility Preservation

46. Clinicians should discuss the effects of gonadotoxic therapies and other cancer treatments on sperm production with patients prior to commencement of therapy. (Moderate Recommendation: Evidence Level Grade: C)

Radiotherapy and chemotherapy used for cancer and other medical conditions can often lead to temporary or even long-term gonadal injury in men. These therapies can have dramatic effects on a man's ability to father children, and this is particularly important with adolescents and young men hoping to preserve their fertility. Patients should be informed of the short and long-term implications of these therapies. They should be made aware that estimates are available on the risk of azoospermia associated with gonadotoxic therapy and that the treatment regimen may change during the course of therapy.[215]

The recovery of sperm production following radiotherapy and/or chemotherapy depends on the survival of spermatogonial stem cells in the testis. Radiotherapy and/or chemotherapy treatments that affect differentiating spermatogenic cells (e.g., spermatocytes, spermatids) but that do not kill stem cells in the testis will cause a temporary decline in sperm production followed by a gradual recovery of spermatogenesis after cessation of therapy.[216] However, some radiation and/or chemotherapy regimens can damage spermatogonial stem cells, resulting in delayed or incomplete recovery of spermatogenesis or even permanent azoospermia.[216,217]

The recovery of sperm in the ejaculate may take months to years when the radiation dose exceeds 1 Gy;[218-221] a dose exceeding 10 Gy will often result in permanent azoospermia.[222,223] A radiation dose exceeding 7.5 Gy has been associated with a significantly reduced probability of fertility in a large cohort study.[224] In animal models, the combination of high-dose radiation and chemotherapy may have a synergistic toxic effect on spermatogenesis.[222,223] Fractionated radiation (given over the course of weeks) may have a more detrimental effect on spermatogenesis than a single radiation dose.[221] It has been reported that for men with testicular cancer who undergo orchiectomy and radiotherapy, the rates of long-term azoospermia (beyond 2 years after radiotherapy) range from 5% to 18%.[225-228]

Certain chemotherapeutic drugs are toxic to stem cells and can cause prolonged azoospermia. Alkylating agents (e.g., procarbazine, cyclophosphamide, ifosfamide) and cisplatin target spermatogonial stem cells, and these drugs are the most likely to lead to permanent azoospermia at high doses.[2129,230] Most other chemotherapeutic agents (e.g., anthracyclines, microtubule inhibitors, antimetabolites, topoisomerase inhibitors) target differentiating germ cells in the testis (e.g., spermatids, spermatocytes, differentiating spermatogonia) and cause a transient reduction in sperm parameters with gradual recovery of sperm count observed three to six months after cessation of therapy.[231] For example, topoisomerase II inhibitors (e.g., etoposide) are most toxic to spermatocytes with little to no toxicity to stem cells.[232] Doxorobucin targets differentiating spermatogonia and spermatocytes. Most targeted monoclonal antibody therapies appear to have only minimal effects on sperm counts and male fertility potential, but the data on these agents are limited.[233]

Men with testicular cancer who undergo orchiectomy and chemotherapy have rates of long-term azoospermia ranging from 1% to 42%. [225-228,235-238] For azoospermic men with an intratesticular lesion, cryopreservation of testicular tissue should be considered during orchiectomy or excisional biopsy of the testicular lesion (an Onco-TESE approach).[239] Two of the studies on testicular cancer patients compared two different chemotherapy regimens, and both found that more intensive regimens were associated with higher azoospermia rates.[226] Brydoy et al. found that a cisplatin dose >850 mg resulted in a much higher azoospermia rate than cisplatin ≤850 mg (42% versus 20%). Similarly, Isaksson et al.[227] found that 3 to 4 cycles of cisplatin-based chemotherapy was associated with higher azoospermia rates than 1 to 2 cycles (10% versus 1%).

For men with Hodgkin's lymphoma who undergo chemotherapy, the rates of long-term azoospermia range from 0 to 82%**.**[225,240-244]Some chemotherapy regimens used for Hodgkin's lymphoma (MOPP and cyclophosphamide-based regimens such as BEACOPP) have been associated with high rates of azoospermia.[244] In contrast, none of the men who received the newer ABVD regimen have had long-term azoospermia.[244,245] Men with leukemia who undergo chemotherapy experience rates of long-term azoospermia ranging from 19% to 55%.[225,236,243,246]For prepubertal boys receiving chemotherapy and/or radiotherapy for cancer, the rates of long-term azoospermia range from 12% to 41%.[243,247-252]

47. Clinicians should inform patients undergoing chemotherapy and/or radiation therapy to avoid pregnancy for a period of at least 12

Table 8: Gonadotoxic risk of common chemotherapeutic agents.

High Risk	Intermediate Risk	Low Risk	Unknown Risk
Alkylating Agents Cyclophosphamide Ifosfamide Busulfan Chlorambucil Procarbazine Mechlorethamine	***Platinum Analogues*** Cisplatin Carboplatin Oxaliplatin	***Plant Derivatives*** Etoposide Vinca alkaloids	***Biologic Agents*** Monoclonal antibodies Tyrosine kinase inhibitors Immunomodulating agents mTOR inhibitors Histone deacetylase inhibitors Monoclonal antibodies
	Anthracyclines Doxorubicin **Taxanes** Paclitaxel Docetaxel Cabazitaxel	***Antibiotic Agents*** Actinomycin D Mitoxantrone Bleomycin	
Combination Therapy MOPP CHOP	***Combination Therapy*** ABVD BEP	***Antimetabolites*** Methotrexate Mercaptopurine 5FU FUDR	

MOPP (mechlorethamine, vincristine, procarbazine, prednisone)
COPP (cyclophosphamide,vincristine, procarbazine, prednisone)
ABVD (adriamycin, bleomycin, vinblastine, dacarbazine)
BEP (cisplatin, etoposide, bleomycin)
Adapted from: Brydøy M et al.[215]

months after completion of treatment. (Expert Opinion)

One of the major concerns regarding the effects of gonadotoxic therapies in men wishing to father children is the induction of mutations in developing testicular germ cells.[253] Studies have clearly demonstrated that radiation and chemotherapy can alter the genomic integrity of testicular germ cells. The genomic damage induced by these treatments is germ cell stage specific. This implies that during and for a defined period of time after exposure to radiation and/or chemotherapy (depending on the susceptible germ cell) a man can produce an increased proportion of genetically abnormal spermatozoa. Conceiving a child during this period can substantially increase the risk of genetic mutations in the offspring.

Most alkylating agents (melphalan, procarbazine, chlorambucil, busulfan, nitrogen mustard, cyclophosphamide, ifosfamide, and trophosphamide) induce mutations in exposed post-meiotic cells (spermatids and spermatozoa) with lesser mutagenic effects on stem cells, although these drugs can cause permanent azoospermia.[254] Topoisomerase II inhibitors (e.g., etoposide) can induce mutations in spermatocytes with little to no genomic injury to stem cells.[232] Radiation produces high levels of mutations in all stages of differentiating germ cells with lower levels in stem spermatogonia.[232] In contrast, bleomycin (antitumor antibiotic) and mitomycin C induce mutations in stem cells and differentiating spermatogonia but not in meiotic or post-meiotic cells.[255]

Based on the known mutagenic effects of gonadotoxic therapies it is important to use contraceptive measures for a period of at least 12 months after completion of therapy. Studies on the health and genetic integrity of children fathered by men exposed to chemotherapy and/or radiotherapy have generally been reassuring. This is based on numerous studies of children conceived one or more years after gonadotoxic therapy.

Yoshimoto et al.[256] observed no increase in malignancy in the children of parents exposed to atomic bomb radiation. Winther et al.[257] observed that the occurrence of abnormal karyotypes in children of treated cancer survivors was the same as that among the comparison sibling families. Signorello et al. and Al-Jebari et al. have reported that the children of cancer survivors are not at significantly increased risk for congenital anomalies due to their parent's exposure to mutagenic cancer treatments. [258,259]

Most human sperm fluorescent in situ hybridization studies report an increased rate of sperm chromosomal aneuploidy and diploidy in the first two years following chemotherapy.[260-264] Beyond the first two years post-therapy, the rate of sperm aneuploidy becomes comparable to that of controls.[264,265] These studies suggest that the effect of gonadotoxic therapy on the genomic integrity of stem cells disappears over time. Furthermore, these data are in keeping with studies demonstrating a sharp decline in conventional sperm parameters at 6 months and recovery of spermatogenesis at 12 to 24 months after cancer treatment.[228,245,266-269]

48. Clinicians should encourage men to bank sperm, preferably multiple specimens when possible, prior to commencement of gonadotoxic therapy or other cancer treatment that may affect fertility in men. (Expert Opinion)

Gonadal dysfunction is a significant long-term consequence of cancer therapy.[215,270] This is particularly important for adolescents and young adult cancer patients who are at risk of developing infertility following cancer therapy. As previously discussed, gonadotoxic therapies can cause a marked decline in sperm production as a result of acute injury to testicular germ cells. Moreover, the genomic integrity of germ cells and spermatozoa will be compromised during and shortly after gonadotoxic therapies. The recovery of spermatogenesis following radiotherapy and/or chemotherapy depends on the survival of spermatogonial stem cells in the testis. In some cases, extensive damage to spermatogonial stem cells can result in delayed and incomplete recovery of spermatogenesis or even permanent azoospermia.[216,217] As such, it is important to encourage young men to bank sperm prior to initiating gonadotoxic therapies. In keeping with this guideline, several societies (ASCO, ASRM) recommend that fertility preservation be an essential component in the management of cancer patients.[271,272]

A patient should be given a few days, if possible, to bank sperm prior to gonadotoxic therapies. This will allow the patient sufficient time to submit one or more semen samples, or potentially undergo a sperm extraction (electroejaculation or TESE) in the event of an unsuccessful attempt at sperm banking (inability to ejaculate or a semen sample with no viable sperm).[273,274]

Depending on sperm count and motility, a banked sperm sample can be used for either IUI or ART. For IUI, insemination with a minimum of 3 to 5 million motile sperm in the ejaculate is needed.[275,276] Below this motile sperm count, the success rate of the technique decreases. Since approximately 50% of sperm do not survive semen processing, a total motile count of at least 5 to 10 million sperm is usually required to allow for an adequate number of motile sperm for insemination. For ART, only a small number of motile sperm are required for the procedure.[277] Since ARTs are only moderately effective, a couple may need to undergo several cycles of IVF treatment in order to achieve a pregnancy. As such, men should be encouraged to bank multiple semen specimens and the sperm bank should divide the specimen into adequate aliquots in order to prepare for multiple attempts at assisted reproduction. Another reason for encouraging banking of multiple specimens is that men presenting with cancer will generally have poorer semen parameters than normal donors, and their sperm respond less favorably to freeze-thawing (with poorer post-thaw motility) than donor sperm.[278-280]

Studies have shown that 20 to 50% of men will bank sperm prior to chemotherapy.[281-283] The low sperm banking rates have been attributed to inadequate fertility counseling before gonadotoxic therapy and lack of desire to father children.[282] Interestingly, a very small percentage of men will use their banked sperm in assisted reproduction. In most studies, less than 10% of men who have banked sperm will later use their sperm in assisted reproduction.[225, 283-286]

49. Clinicians should consider informing patients that a SA performed after gonadotoxic therapies, should be done at least 12 months (and preferably 24 months) after treatment completion. (Conditional Recommendation; Evidence Level Grade: C)

Generally, a sharp decrease in semen quality (especially sperm concentration) occurs immediately after treatment followed by a gradual return to better quality. The nature of this return depends on numerous factors including the cancer type, type of treatment

administered, treatment dosing, and the duration after completion of treatment at which the SA is performed.

The systematic review used to inform this guideline found 15 studies assessing spermatogenesis after gonadotoxic therapies.[199,227, 228, 235, 245, 264, 266-269, 287-292] The most common cancer types studied are testis cancer and Hodgkin's lymphoma, and the most common treatments reported on were BEP and ABVD. The most commonly reported semen parameters were sperm concentration (nine studies), sperm count (seven studies), and sperm motility (six studies). The durations of follow-up were two years (eight studies), two to five years (four studies) and six or more years (three studies). Eleven of the studies were rated as moderate quality, while four were rated as low quality.

When analyzing data for the rates of azoospermia, rates were highest within the first 12 months after completion of therapy and lowest at a time point between 2 to 6 years, with the majority of studies demonstrating the nadir in azoospermia rates at a timepoint between 2 to 3 years following treatment completion. When analyzing sperm concentration after completion of treatment, significant heterogeneity existed in the data; the majority of the studies demonstrated lowest sperm concentration by 12 months and maximization of recovery in the majority of studies between 2 to 3 years after the completion of treatment. Data on sperm motility and morphology were similar to the above findings. The azoospermia and sperm concentration data were also consistent across various types of cancers and when comparing chemotherapy versus radiation for testis cancer.

The higher the dose and the greater the number of cycles (especially above 2 cycles), the greater the likelihood of failure to recover normal sperm concentrations (defined <20 million/mL). In lymphoma patients treated with ABVD, the nadir in sperm concentration occurred within the first 6 to 12 months with return to pre-treatment sperm concentration levels common within 1 to 3 years after completion of treatment.

These data strongly suggest not performing a SA within the first 12 months after treatment completion and, where possible, to assess sperm recovery at a time point 2 to 3 years after treatment ends.

50. Clinicians should inform patients undergoing a retroperitoneal lymph node dissection (RPLND) of the risk of aspermia. (Clinical Principle)

Counseling on the availability of sperm banking prior to any testis cancer treatment including RPLND should be provided by the clinician.

51. Clinicians should obtain a post-orgasmic urinalysis for men with aspermia after RPLND who are interested in fertility. (Clinical Principle)

Ejaculation is a reflex, involving a complex interplay between somatic, sympathetic, and parasympathetic pathways involving predominantly central dopaminergic and serotonergic neurons. In humans, the ejaculate is composed of fluid derived primarily from the seminal vesicle and prostate.

In antegrade ejaculation, two main processes are present: emission and expulsion.[293] Expulsion, the antegrade flow of semen through the urethral meatus, is due to the combined action of sympathetic and somatic pathways. Antegrade ejaculation requires a synchronized interplay between peri-urethral muscle contractions and bladder neck closure, contemporaneous with the relaxation of the external urinary sphincter. Sympathetic nerve fiber damage, such as that which can occur during a RPLND, can result in failure of the bladder neck to contract effectively allowing semen deposited into the prostatic urethra to pass in a retrograde fashion into the bladder (i.e., RE).

Emission is a sympathetic spinal cord reflex and involves the deposition of seminal fluid into the posterior urethra. Failure of emission (FOE) is the phenomenon whereby semen fails to be deposited into the prostatic urethra. This usually results from a greater degree of retroperitoneal sympathetic nerve fiber injury than that which results in RE. Failure of antegrade ejaculation assumes that a patient is reaching orgasm with a functional abnormality, rather than psychogenic anejaculation, where orgasm is not achieved.

RPLND is a cornerstone in the management of some patients with testis cancer. It can be performed either before the delivery of chemotherapy (pre-chemo RPLND) or after chemotherapy (post-chemo RPLND). Given the distribution of the nodes involved in drainage of the testes, the lumbar sympathetic nerve fibers responsible for ejaculation (T10-L2) are in close proximity to the node dissection templates. In the hands of an experienced testis cancer surgeon, nerve sparing RPLND should only rarely result in permanent nerve damage and long-term failure to ejaculate (RE or FOE). However, in the post-chemo RPLND patient the likelihood of this is higher. It is estimated that about

40% of patients undergoing post-chemo RPLND are candidates for nerve sparing surgery, and modern series of nerve sparing post-chemo RPLND patients report preservation of some antegrade ejaculation in 74 -96%.[273,294]

As with any neural trauma, maximum recovery can take 12 to 24 months and thus, patients who have had nerve sparing RPLND should be told that return of antegrade ejaculation may take a protracted period of time. If aspermia remains 24 months after RPLND, then the patient should be informed that this is likely to be permanent.

Differentiating between RE and FOE requires analysis of a urinalysis after the achievement of orgasm. Patients should be instructed to urinate before masturbating to orgasm. Whatever antegrade fluid is procured should be placed in a sterile cup. The urine specimen should be analyzed for the presence of semen and sperm with centrifugation and analysis of the pellet at the bottom of the centrifuge tube.

α-sympathomimetic agonists have been shown to improve bladder neck closure. Thus, they can be used in patients with aspermia. While the data are limited, it appears that men with RE are more likely to respond to α-agonists with an antegrade ejaculation than men with FOE after retroperitoneal surgery.[273] Therefore, differentiating between RE and FOE may be of benefit in planning the management of some patients with failure to ejaculate. A common oral treatment with α agonists involves 60 mg of pseudoephedrine given orally 4 times a day for two days prior to production of a sample.

52. Clinicians should inform men seeking paternity who are persistently azoospermic after gonadotoxic therapies that TESE is a treatment option. (Strong Recommendation; Evidence Level Grade: B)

Given the aforementioned incidence of long-term azoospermia after gonadotoxic therapies, some men with interest in starting a family or expanding their family size will be faced with a decision regarding how to accomplish this. While artificial insemination using donor sperm or adoption are viable options, some men will prefer to explore the possibility of using their own sperm. In these cases, a discussion should be held about the option of TESE.

TESE has become a mainstay in the management of the man with NOA, when the azoospermia is unrelated to gonadotoxic therapy. Depending upon a number of factors, SRR using TESE have been cited in the 40-60% range.[295,296] While the experience is extensive in the non-cancer population, there is significantly less experience using TESE in men exposed to gonadotoxic therapies.

The systematic review used to inform this guideline found seven studies assessing the use of TESE (four reporting conventional TESE, three micro-TESE) in men exposed to gonadotoxic therapies.[297-303] These studies included men with mixed types of cancer. The elapsed time between exposure to gonadotoxic therapy and TESE was 11 years (range 5-19). Sperm retrieval is typically deferred until at least two years after chemotherapy. While all seven studies reported SRR, only one reported pregnancy/live birth rates.

The data underwent metanalysis (i^2 = 0% indicating high homogeneity across the seven studies) with a combined rate of sperm retrieval of 42% (95% CI 34% to 49%), with no significant differences between conventional (overall sperm retrieval rate 45%, 95% CI 34% to 58%) and micro-TESE (overall sperm retrieval rate 40%, 95% CI 32% to 49%). However, the advantage of micro-TESE over conventional TESE in other forms of NOA suggests that this is the preferred approach for men azoospermic after chemotherapy. The patient numbers were too small to define if one cancer type (testis, germ cell tumors, Hodgkin's lymphoma, leukemia, sarcomas and other solid tumors) had better/poorer SRR compared to others.

Only Hsiao et al.[300] reported on pregnancy rates using ICSI with a cited overall pregnancy rate of 25% (18/73), with 21% (15/73) having a live birth using their sperm. Looked at differently, once sperm were obtained with TESE or micro-TESE, the pregnancy rate was 67% (18/27) with a live birth rate of 15/27 (56%).

FUTURE DIRECTIONS

Newer research techniques, such as next generation sequencing (whole exome and whole genome sequencing) and "-omic" technologies have been applied to better identify underlying defects that may explain infertility in men. As the mechanisms of action of these genetic, genomic, epigenetic, transcriptomic, proteomic, metabolomic defects are defined, we will have further defined the etiologies of the majority of causes of male infertility. For example, damaging mutations and copy number variants (microdeletions and microduplications) may affect reproductive system development[304-308] and function[309-311], as well as fetal, childhood, adolescent and/or adult development and/or function of other organ systems in the body. Indeed, GeneCards[312] lists >3,600 gene defects associated with human male infertility and another 3,200+ genes

associated with genitourinary birth defects causing abnormal male reproductive development and function. This knowledge will improve clinical diagnosis and treatment.

The potential impact of these genetic findings is in the area of genetic and genomic-based spermiogenesis defects causing teratozoospermia and/or asthenozoospermia (multiple abnormalities of the sperm flagella and primary ciliary dyskinesia). Today, this knowledge is used clinically to counsel patients about their chances for successful ART.[313,314] As many of these "infertility" genes are expressed in select other tissues or even broadly throughout the body, infertility may be the "canary in the coal mine" that portends an increased likelihood of other comorbidities. Given the wide range of types of genes required for fertility,[315-317] it is not surprising that male infertility is associated with other health conditions, such as mortality, malignancies, immune dysfunction, and other non-reproductive disorders.

Therapeutic advances for male infertility (except for surgical approaches for obstructive azoospermia and NOA) remain relatively stagnant. However, in the laboratory, novel methods are under development to effectively use spermatogonial stem cells to rejuvenate spermatogenesis after gonadotoxin exposures (such as chemotherapy),[318] although potential contamination of spermatogonial stem cells with malignant cells, which must be eliminated before autotransplantation, remain a concern.

Approaches using organ cultures and in vitro systems for spermatogenesis offer additional promise for the treatment of some forms of spermatogenic failure. Qualitative but not quantitative spermatogenesis has been achieved in vitro culminating in live offspring in rodents. With knowledge of the delicate microenvironment needed for completion of spermatogenesis in vitro, researchers are moving closer to achieving this goal, while still maintaining the genetic, genomic, and epigenomic integrity of the sperm.[319]

Finally, gene therapy approaches targeting the process of spermatogenesis are advantageous because of the continuous production of sperm throughout the adult lifespan. However, whether germline gene therapy in humans should occur is an ethical question. Questions about whether germline genome editing should be done even for genetic disorders and technical considerations remain problematic.[320] Genome editing can result in off-target effects and mosaicism.

In closing, the genomic revolution has placed us at the forefront of vastly improving our diagnostic abilities to define precise etiologies, co-morbidities, and eventually (perhaps) develop medically-based treatments for infertile men to improve not only their fertility potential, but also their overall health. Translation of the newer advances discussed above will be slower, but will eventually move from the laboratory to the clinical arena to provide more therapeutic options for men. The future looks promising for improving the health and fertility of the infertile male through precision medicine and the application of advanced technologies.

Appendices

Appendix I: Male reproductive health physical examination

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.

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

Abbreviations

Adriamycin, Bleomycin, Vinblastine, and Dacarbazine	ABVD
American College of Obstetricians and Gynecologists	ACOG
American Medical Association	AMA
American Society of Clinical Oncology	ASCO
American Society of Reproductive Medicine	ASRM
American Urological Association	AUA
American Urological Association Education and Research, Inc.	AUAER
Antisperm Antibody	ASA
Aromatase Inhibitors	AIs
Assisted Reproductive Technologies	ART
Azoospermia Factor	AZF
Board of Directors	BOD
Bisphenol A	BPA
Cardiovascular Disease	CVD
Charlson Comorbidity Index	CCI
Congenital Bilateral Absence of the Vas Deferens	CBAVD
Cystic Fibrosis	CF
Cystic Fibrosis Transmembrane Conductance Regulator	CFTR
Di-2-ethylhexyl phthalate	DEHP
Ejaculatory Duct Obstruction	EDO
Emergency Care Research Institute	ECRI
Failure of Emission	FOE
Follicle-Stimulating Hormone	FSH
Human Chorionic Gonadotropin	hCG
Hypogonadotropic Hypogonadism	HH
Immunobead	IB
In Vitro Fertilization	IVF
Intracytoplasmic Sperm Injection	ICSI
Intrauterine Insemination	IUI
Lower Reference Limits	LRL
Luteinizing Hormone	LH
Microdissection-Testicular Sperm Extraction	micro-TESE
Non-Obstructive Azoospermia	NOA
Odds Ratio	OR
Practice Guidelines Committee	PGC
Randomized Controlled Trials	RCTs
Recurrent Pregnancy Loss	RPL
Relative Risk	RR
Retrograde Ejaculation	RE
Retroperitoneal Lymph Node Dissection	RPLND
Risk of Bias	ROB
Science and Quality Council	SQC
Selective Estrogen Receptor Modulators	SERMs
Semen Analysis	SA
Sperm Retrieval Rates	SRR
Telomere	TL
Testicular Sperm Extraction	TESE
Transrectal Ultrasonography	TRUS
Transurethral Resection of Ejaculatory Ducts	TURED
World Health Organization	WHO

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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 govern-

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