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Updates to Male Infertility: AUA/ASRM Guideline (2024)

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Purpose: In 2023 the American Urological Association (AUA) requested an Update Literature Review (ULR) to incorporate new evidence generated since the 2020 publication of this Guideline. The resulting 2024 Guideline Amendment addresses updated recommendations to provide guidance on the appropriate evaluation and management of the male partner in an infertile couple.

Materials and Methods: In 2023, the Male Infertility Guideline was updated through the AUA amendment process in which newly published literature is reviewed and integrated into previously published guidelines. An updated literature search identified 4093 new abstracts. Following initial abstract screening, 125 eligible study abstracts met inclusion criteria. On data extraction, 22 studies of interest were included in the final evidence base to inform the Guideline amendment.

Results: The Panel developed evidence- and consensus-based statements based on an updated review to provide guidance on evaluation and management of male infertility. These updates are detailed herein.

Conclusions: This update provides several new insights, including revised thresholds for Y-chromosome microdeletion testing, indications for pelvic MRI imaging in infertile males, and guidance regarding the use of testicular sperm in nonazoospermic males. This Guideline will require further review as the diagnostic and treatment options in this space continue to evolve.

Key Words: male infertility, infertility, pregnancy loss, miscarriage, IVF, ART, male, in vitro, in vitro fertilization, intrauterine insemination, assisted reproductive technology

BACKGROUND

Infertility 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 intrauterine insemination (IUI) and assisted reproductive technologies (ART) (in vitro fertilization [IVF] with or without intracytoplasmic sperm injection [ICSI]), evaluation of

Abbreviations and Acronyms

ART = assisted reproductive technology
ASRM = American Society for Reproductive Medicine
AUA = American Urological Association
AZF = azoospermia factor
CBAVD = congenital bilateral absence of the vas deferens
CFTR = cystic fibrosis transmembrane conductance regulator
DFI = DNA fragmentation index
DNA = deoxyribonucleic acid
EDO = ejaculatory duct obstruction
FSH = follicle-stimulating hormone
hCG = human chorionic gonadotropin
ICSI = intracytoplasmic sperm injection
IHH = idiopathic hypogonadotropic hypogonadism
IUI = intrauterine insemination
IVF = in vitro fertilization
micro-TESE = microdissection-testicular sperm extraction
MRI = magnetic resonance imaging
NIH = National Institutes of Health
NOA = non-obstructive azoospermia
RCTs = randomized controlled trials
RE = retrograde ejaculation
SA = semen analysis
SERMs = selective estrogen receptor modulators
SRR = sperm retrieval rates
TESA = testicular sperm aspiration
TESE = testicular sperm extraction
TRUS = transrectal ultrasonography
TURED = transurethral resection of ejaculatory ducts
ULR = update literature review
WHO = World Health Organization

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the male is important to most appropriately direct therapy. Some male factor conditions are treatable with medical or surgical therapy, and others may require donor sperm or adoption, if appropriate. Some conditions are life threatening, while others have health and genetic implications for the patient and potential offspring. A male evaluation is necessary to adequately determine the management of the patient and the couple. Without an adequate male partner workup, the female partner may pursue unnecessary costly, time-consuming, and invasive treatment options.

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; or sexual conditions incompatible with the ability to deposit semen in the vagina.

The common terms of semen analysis (SA) have been defined in Table 1.[1,2] A summary of diagnostic and treatment recommendations are found in the Algorithm (Figure).

GUIDELINE STATEMENTS

Assessment

Clinicians should include a reproductive history during initial evaluation of the male for fertility. (*Clinical Principle*) Clinicians should also include one or more semen analyses during initial evaluation of the male. (*Strong Recommendation; Evidence Level: Grade B*)

Clinicians should counsel infertility patients that the WHO[3] lower limits of semen parameters are based on the lowest fifth centile of values for fertile males whose partners became pregnant in $\leq$ 12 months (Table 2).[4,5] In the interpretation of SA, clinicians should remember that semen parameters are highly variable biological measures and may fluctuate substantially from test to test. Therefore, at least 2 SAs obtained a month apart are important to consider, especially if the first SA has abnormal parameters.

Increasing numbers of patients are using point-of-care and mail-in semen tests. While these kits may provide some information regarding a patient's semen parameters, patients and clinicians should understand that numerous factors can impact the accuracy of a given test. Each test must be considered individually to assess its accuracy and reliability, and the results from one testing modality should not be extrapolated to others. At this time there is no substitute for the information provided by SA testing conducted in a specialized andrology laboratory for a comprehensive evaluation of male fertility.[6]

Male reproductive experts should evaluate patients with a complete history and physical examination as well as other directed tests, when indicated by one or more abnormal semen parameters or presumed male infertility. (*Expert Opinion*)

Male evaluation may inform some couples of treatment options other than IUI and ART. For example, investigators suggested that varicocele treatment may be more cost effective than IUI and ART, and the improved semen parameters seen after varicocele correction can lower the intensity of treatment needed for the female partner.[7,8] Like varicocele correction, the treatment of other male-centered issues identified during evaluation of the male may result in improved semen parameters and/or decreased sperm DNA damage levels. These improvements in male reproductive health may allow couples to conceive by less invasive and more accessible technologies, such as IUI instead of IVF or pregnancy by intercourse instead of IUI.[9]

In couples with failed assisted reproductive technology cycles or recurrent pregnancy losses (two or more), clinicians should evaluate the male partner. (*Moderate Recommendation; Evidence Level: Grade C*)

In this clinical setting, male partners should be evaluated by male reproductive experts, and clinicians should consider karyotype and sperm DNA fragmentation testing. An increasing number of studies have linked poor IVF outcomes and recurrent pregnancy loss with abnormal male partner karyotype[10,11] and elevated levels of sperm DNA fragmentation.[12]

Lifestyle Factors and Relationships Between Infertility and General Health

Clinicians may discuss risk factors (ie, lifestyle, medication usage, environmental exposures, occupational exposures) associated with male infertility, and counsel the patients that the current data on the majority of risk factors are limited. (*Conditional Recommendation; Evidence Level: Grade C*)

Clinicians should discuss with patients the strategies to decrease or prevent exposure to risk factors for infertility. A summary of such factors can be found in Table 3.[13-15]

Diagnosis and Evaluation

Clinicians should initially evaluate azoospermic males with physical exam, semen volume, semen pH, and serum follicle-stimulating hormone (FSH) levels to differentiate genital tract obstruction from impaired sperm production. (*Expert Opinion*)

Table 1. *Common Terms in Semen Analysis*[a]

Term	Definition
Aspermia	Complete absence of semen in ejaculate, indicating the absence of seminal fluid production or blockage in the reproductive tract.
Azoospermia	Absence of spermatozoa in the semen, typically resulting from a blockage in the reproductive tract (obstructive azoospermia) or dysfunction in sperm production (non-obstructive azoospermia).
Oligozoospermia	Low sperm concentration in the semen.
Asthenozoospermia	Reduced sperm motility, where a significant portion of spermatozoa display sluggish or abnormal movement, impacting fertility.
Teratozoospermia	Abnormal sperm morphology, characterized by a high percentage of spermatozoa with morphological defects, potentially affecting fertility.
Normozoospermia	Normal semen parameters including sperm concentration, motility, morphology, and volume, indicating optimal fertility potential.
Retrograde Ejaculation	Condition where semen flows backward into the bladder instead of exiting through the urethra during ejaculation, leading to reduced fertility.

[a] This table provides concise definitions for common terms used in semen analysis, facilitating understanding for researchers, clinicians, and individuals seeking information about male fertility assessment.

Azoospermia is defined as absence of sperm in the ejaculate. 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. Obstructive azoospermia is suspected if the physical examination reveals testes of normal size, fully descended into the scrotum and bilaterally dilated and/or indurated epididymides with or without absence of the vas deferens. In these cases, FSH levels are usually less than approximately 7.6 IU/L.[16] In contrast, when the testes are atrophic, especially in the presence of FSH greater than 7.6 IU/L, spermatogenic failure (non-obstructive azoospermia) is more likely the cause.[17] A low volume, acidic pH, azoospermic ejaculate is typically indicative of distal obstruction in the genital tract.[17] This is commonly seen in patients with congenital bilateral absence of the vasa deferentia (CBAVD) or ejaculatory duct obstruction (EDO). Distal obstruction that limits or prevents the seminal vesicle contribution will lead to low ejaculate volume (<1.4 mL) with acidic semen (pH < 7.0). Males with a normal semen pH are unlikely to have these forms of complete distal genital tract obstruction.[18]

Clinicians should recommend karyotype testing for males with primary infertility and azoospermia or sperm concentration < 5 million sperm/mL when accompanied by elevated FSH, testicular atrophy, or a diagnosis of impaired sperm production. (*Expert Opinion*)

Karyotype abnormalities are the most common known genetic abnormalities that cause male infertility.[19] 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. 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.[19-21]

Clinicians should recommend Y-chromosome microdeletion analysis for males with primary infertility and azoospermia or sperm concentration ≤ 1 million sperm/mL when accompanied by elevated FSH, testicular atrophy, or a diagnosis of impaired sperm production. (*Moderate Recommendation; Evidence Level: Grade B*)

Y-chromosome microdeletions are estimated to be present in 8% to 12% of males with non-obstructive azoospermia and 3% to 7% of males with severe oligospermia[22] and 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 3 areas encoding genes involved in spermatogenesis (AZFa, AZFb, AZFc). Sperm have not been retrieved by microdissection testicular sperm extraction (micro-TESE) in males with complete AZFa, AZFb, AZFab, or AZFabc microdeletions. Males with isolated AZFc microdeletions may experience either severe oligospermia or azoospermia.[23] In males with AZFc deletions and azoospermia, sperm may be found through micro-TESE approximately 50% of the time.[24] When sperm is obtained, given the risk of male progeny inheriting an AZFc deletion and thus also being infertile, males should be counseled regarding these risks and the consideration for preimplantation genetic testing with ART, as some couples may favor selection of female embryos for future implantation to avoid male progeny with congenital infertility.[25]

A meta-analysis assessing the frequency of Y-chromosome microdeletions in severely oligospermic males in North America and Europe found that Y-chromosome microdeletions were found in 5% of males with sperm concentrations 0 to 1 million

Male Infertility Algorithm

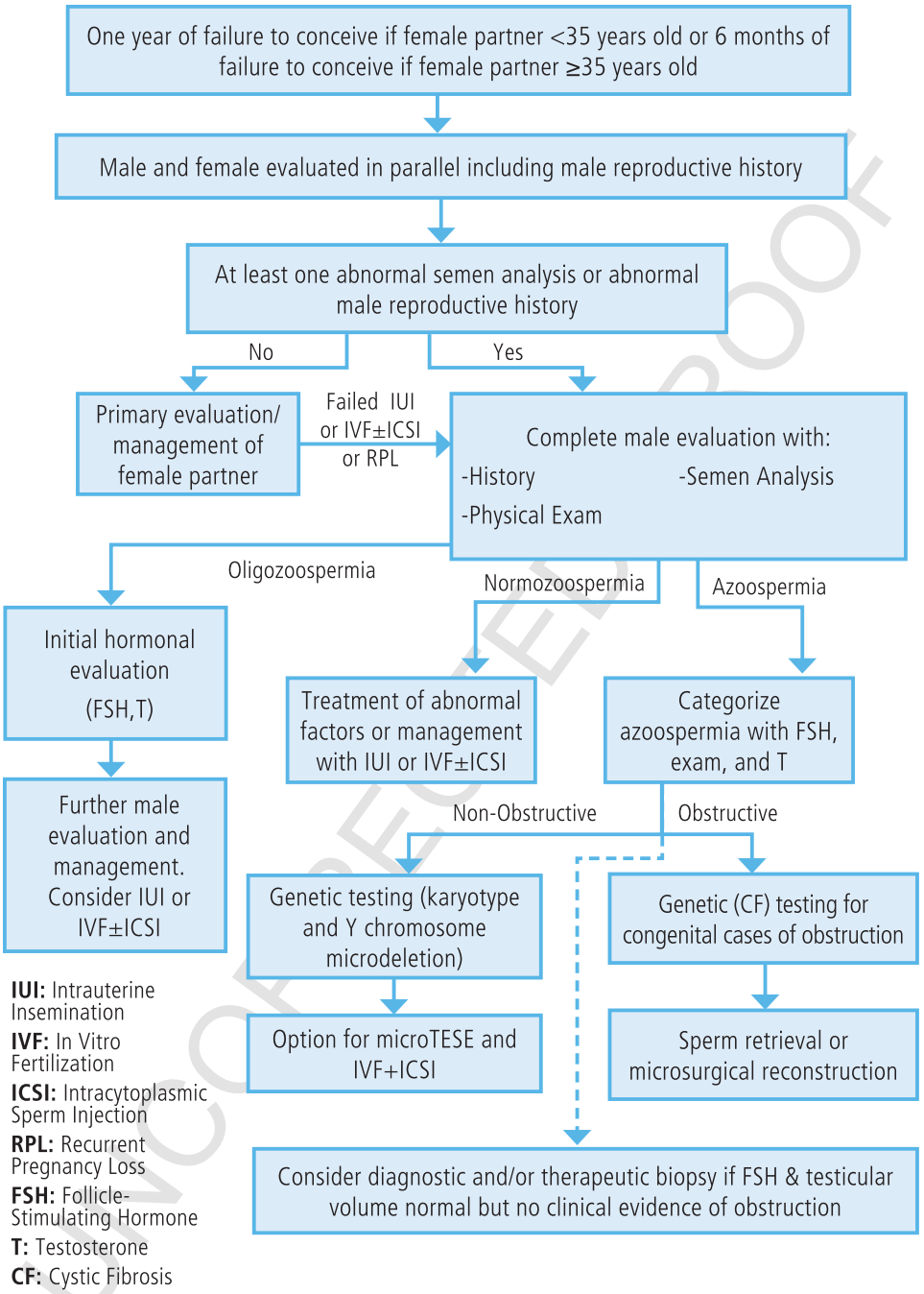

Figure. Male infertility algorithm.

sperm/mL and in only 0.8% of males with sperm concentration > 1 to 5 million sperm/mL.[26] While prior AUA Guidelines recommended screening males with sperm concentrations < 5 million sperm/mL, given the paucity of Y-chromosome microdeletions in males with sperm concentrations > 1 to 5 million sperm/mL, the Panel now recommends screening for Y-chromosome microdeletions in azoospermic males suspected to have impaired sperm production and in severely oligospermic

Table 2. *World Health Organization Reference Limits for Human Semen Characteristics*[a]

Semen Parameter	One-Sided Lower Reference Limit (Fifth Centiles With 95% Confidence Intervals [CI])
Semen Volume	1.4 mL (1.3-1.5 mL)
Total Sperm Number	39 million per ejaculate (35-40 million per ejaculate)
Sperm Concentration	16 million/mL (15-18 million/mL)
Vitality	54% Live (50-56%)
Progressive Motility	30% (29-31%)
Total Motility (Progressive + Non-Progressive)	42% (40-43%)
Morphologically Normal Forms	4.0% (3.9-4.0%)

[a] Semen samples from 3589 males (males with proven fertility, with unknown fertility status and other males who were normozoospermic) from 12 countries and 5 continents were analyzed. Males described above were all fertile (Partners' time-to-pregnancy ≤12 months) and their parameters were selected to calculate the values.

males when sperm concentrations are ≤ 1 million sperm/mL.

Imaging

Clinicians should not routinely perform scrotal ultrasound in the initial evaluation of the infertile male. (*Expert Opinion*)

Routine use of ultrasonography to investigate presumed varicocele is to be discouraged, as treatment of non-palpable varicoceles is not associated with improvement in either semen parameters or fertility rates. These outcomes are in contrast to the correction of palpable varicoceles, which results in improvement in both semen quality and fertility. Scrotal ultrasound can be used before repair to confirm the presence of varicocele and also following correction to determine procedural success, in the context of shared decision-making with the patient.

Clinicians should not perform transrectal ultrasonography (TRUS) or pelvic magnetic resonance imaging (MRI) as part of the initial evaluation of the infertile male. Clinicians may recommend TRUS or pelvic MRI in males with SA suggestive of ejaculatory duct obstruction (EDO) (ie, acidic, azoospermic semen with volume < 1.4 mL, with normal serum T, palpable vas deferens). (*Expert Opinion*)

For the purposes of an infertility evaluation, imaging of the pelvis seeks to identify the anatomy of the primary organs/structures involved in ejaculation including the prostate, seminal vesicles, vasal ampulla, and ejaculatory ducts.[27] TRUS can be useful in identifying distal genital tract obstruction leading to obstructive azoospermia or severe oligospermia with very low motility, such as seen in men with EDO. Pelvic MRI is now widely available and may provide more accurate measurements of ejaculatory duct and seminal vesicle dilation. Additionally, pelvic MRI can identify and characterize prostate cysts, including paramedian (ie, ejaculatory duct) cysts, and midline (ie, Müllerian duct and prostatic utricle) cysts that can cause ejaculatory duct obstruction.

The clinician should be suspicious of distal male genital tract obstruction when the ejaculate volume is low (<1.4 mL), with acidic semen (pH < 7.0). Most of these males will have absent fructose in semen, although fructose testing is relatively unreliable and is not necessary especially in males for whom there is a high index of suspicion (ie, SA shows low volume, acidity, azoospermia or oligospermia with very low motility). For these males, TRUS or pelvic MRI should be considered to evaluate for anatomic abnormalities.[28] 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 males with testosterone deficiency may have low semen volume and the utility of pelvic imaging 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). Males with a normal semen pH are unlikely to have a complete distal genital tract obstruction.[18]

Congenital abnormalities may also affect normal genital duct anatomy. Mutations in the *CFTR* gene can lead to vasal and seminal vesicle agenesis/atresia. In males with CBAVD, pelvic imaging does not contribute to the diagnosis or treatment, so it should not be done for evaluation of such infertile males.[18]

Beyond infertility, ejaculatory pain may also trigger evaluation with TRUS or pelvic MRI as a diagnosis of obstruction may lead to treatment recommendations to improve symptomatology. In males with normal ejaculation and semen volume, the results of TRUS or pelvic MRI evaluation will not usually change the management of an infertile male. As such, without symptoms (eg, painful ejaculation) or semen parameter indications (eg, low semen volume with azoospermia and palpable vasa, or low semen volume and significant asthenospermia), pelvic imaging should not be included in an infertility evaluation.

Sperm Retrieval

For males with non-obstructive azoospermia undergoing sperm retrieval, clinicians should

Table 3. *Summary of Findings for Risk Factors of Infertility*

Risk Factor	Methodology Conclusion
Age	Older males have mildly reduced fertility
Obesity with or without metabolic syndrome	Males with obesity with or without metabolic syndrome have mildly 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	Evidence inconclusive
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 males than fertile males; zinc levels are lower in infertile males than fertile males; evidence inconclusive on copper levels in semen
Cadmium	Cadmium levels are higher in infertile males than fertile males

perform a micro-TESE. (*Moderate Recommendation; Evidence Level: Grade C*)

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 males with non-obstructive azoospermia (NOA) have baseline testosterone deficiency. 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.[29]

In a meta-analysis of published studies for males with NOA, micro-TESE was observed to result in successful extraction 1.5 times more often than non-microsurgical testis sperm extraction, and conventional TESE was 2 times more likely to yield sperm when compared to testicular aspiration.[30]

In males undergoing surgical sperm retrieval by a clinician, intracytoplasmic sperm injection may be performed with fresh or cryopreserved sperm. (*Conditional Recommendation; Evidence Level: Grade C*)

For males 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. The choice between fresh and cryopreserved sperm is often dictated by preferences of the ART lab collaborating with the surgeon.

For males with NOA, some centers prefer sperm extraction in advance of IVF because the female partner can be spared going through IVF if no sperm are found. Other centers prefer simultaneous sperm retrieval with ART because the numbers of sperm obtained may be limited and sperm may not survive cryopreservation and thawing. For those couples where the male has NOA and sperm are frozen and survive freeze-thaw, ART is possible with those sperm.

In males with azoospermia due to obstruction undergoing surgical sperm retrieval, clinicians may extract sperm from either the

testis or the epididymis. (*Conditional 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 males with azoospermia due to obstruction.[31] However, epididymal sperm retrieval should be avoided if future microsurgical reconstruction (ie, vasovasostomy or epididymovasostomy) might be pursued due to the risk of epididymal scarring and obstruction.[32]

Clinicians may consider the utilization of testicular sperm in nonazoospermic males with an elevated sperm DNA Fragmentation Index (DFI). (*Clinical Principle*)

A recent meta-analysis highlights 11 studies where use of testicular sperm for men with elevated DFI had similar fertilization rates but improved clinical outcomes in terms of clinical pregnancy rate, live births, and reduced pregnancy loss rates.[33]

The use of testicular sperm in nonazoospermic males with elevated DFI provides an alternative option for fertility treatment.[34] Testicular sperm retrieval procedures, such as testicular sperm aspiration (TESA) or testicular sperm extraction (TESE), may offer viable sperm with lower DFI, potentially improving the chances of successful assisted reproduction.[35]

It is essential for urologists to collaborate with reproductive endocrinologists and embryologists to determine the most appropriate course of action based on individual patient characteristics and preferences. For couples with elevated sperm DNA fragmentation levels, it is also advisable to discuss alternative treatment options such as lifestyle modifications (including smoking cessation), varicocele repair, and the potential use of microfluidic processing as a sperm processing technique.[36]

Questions arise regarding the ideal threshold for sperm DFI that warrants TESE, as well as the efficacy of testicular sperm in various clinical scenarios such as failed fertilization, impaired blastulation, elevated rates of aneuploid embryos, or even following unsuccessful implantation of euploid embryos. While these questions persist without definitive answers due to the current limitations in published literature, it is imperative to recognize the ongoing ambiguity surrounding DFI and TESE. Moreover, the debate continues regarding the comparative benefits of utilizing fresh vs frozen testicular sperm in such contexts, with no clear consensus emerging at this time.

Clinicians may treat infertility associated with retrograde ejaculation with sympathomimetics (with or without alkalinization and/or urethral catheterization), induced ejaculation, or surgical sperm retrieval. (*Expert Opinion*)

Partial retrograde ejaculation (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.[37] However, if the antegrade ejaculate is poor and substantial RE is present as demonstrated by post-ejaculatory urinalysis, various therapies may be required (eg, oral sympathomimetics with alkalinization of urine and/or instillation of sperm wash media into the bladder via urethral catheter before climax, with recovery of sperm from the bladder post climax). Induced ejaculation and surgical sperm retrieval are also therapeutic options in this setting.

Obstructive Azoospermia, Including Post-Vasectomy Infertility

For infertile males with ejaculatory duct obstruction (EDO), clinicians may consider transurethral resection of ejaculatory ducts (TURED) and/or surgical sperm extraction. (*Expert Opinion*)

EDO is rare in infertile males. If the diagnosis is confirmed or suspected based on TRUS or pelvic MRI findings, then treatment should be considered. Findings on pelvic imaging that suggest obstruction include seminal vesicle anterior-posterior diameter $>$ 15 mm, ejaculatory duct caliber ($>$2.3 mm), or dilated vasal ampulla ($>$6 mm) as well as prostatic cysts (midline prostatic cyst or paramedian/ejaculatory duct cyst). If a seminal vesicle aspirate reveals the presence of sperm in an azoospermic male, then TURED may be offered.[18] The goal of the surgery is to resolve the ejaculatory duct obstruction and thus allow sperm to enter the ejaculate, which can be used for unassisted conception, IUI, or ART.

Medical and Nutraceutical Interventions for Fertility

Clinicians may manage male infertility with assisted reproductive technologies. (*Expert Opinion*)

IVF treatment requires more than a week of ovarian stimulation, procedures for oocyte retrieval and intrauterine embryo transfer; each attempt typically allows for a 37% live delivery rate per initiated IVF cycle.[38] Pregnancy and live birth results are closely related to female age, with progressively lower success with increased female age (over 35 years). Approximately 12.5% of all deliveries involve twins, and additional pregnancies may result from one IVF cycle if additional embryos are available for cryopreservation.[38]

In a patient presenting with hypogonadotropic hypogonadism, clinicians should evaluate the patient to determine the etiology of

the disorder and treat based on diagnosis. (*Clinical Principle*)

Exogenous testosterone therapy is often prescribed to patients with idiopathic hypogonadotropic hypogonadism (IHH), but this treatment inhibits intratesticular testosterone production and suppresses spermatogenesis, thus impairing fertility.[39] This is a common issue among pubertal males with IHH, who are often started on exogenous testosterone for pubertal induction, but then sometimes remain on this therapy into adulthood and their reproductive years.[40]

The usual first-line drug for the treatment of IHH for restoration of testosterone production and spermatogenesis is human chorionic gonadotropin (hCG). The degree of response correlates with the size of the testis prior to treatment.[41] Initial treatment is with hCG injections (500-2500 IU, 2-3 times weekly) followed by FSH injections, when indicated, after testosterone levels are normalized on hCG. Pulsatile gonadotropin releasing hormone is not currently approved in the U.S. or Europe. If medical therapy for the male with IHH fails to result in a pregnancy, but some sperm are found in the ejaculate, referral for IUI or ART is recommended.

For the male interested in current or future fertility, clinicians should not prescribe exogenous testosterone therapy. (*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 oligospermia or azoospermia.[42] Although recovery of sperm to the ejaculate occurs in most azoospermic males after cessation of testosterone therapy, the time course of recovery may be prolonged and can be months or rarely years.[43] Therefore, exogenous testosterone therapy should be avoided in males 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 testosterone's inhibitory effects on spermatogenesis and the time course required for resumption of spermatogenesis after cessation. In those wanting to pursue paternity in the more distant future (soonest 6-12 months), some small studies have demonstrated preservation of spermatogenesis by adding hCG alone or combination therapy (hCG, and/or selective estrogen receptor modulate [SERM], and/or recombinant FSH) to exogenous testosterone, but the literature is too limited to recommend this approach. If a patient decides to proceed with exogenous testosterone therapy alone, then he must be counseled about the potential negative effects on spermatogenesis and the time course (and treatments) required for resumption of spermatogenesis. Some males, despite cessation of testosterone therapy, never fully recover sperm production and may remain either infertile or sub-fertile and may therefore require future fertility treatments.[44,45]

In data from 2 studies, use of a short-acting, nasal testosterone formulation was associated with preserved spermatogenesis.[46,47] While additional studies are needed to assess long-term reproductive outcomes, including semen parameters and fecundity, the early and short-term outcomes for this modality merit further study. However, given the lack of long-term data, this agent, like other forms of exogenous testosterone, should not be routinely used by males attempting to conceive. For further information, please refer to the AUA Guideline on the Evaluation and Management of Testosterone Deficiency, Statement 16: https://www.auanet.org/guidelines-and-quality/guidelines/testosterone-deficiency-guideline.

Clinicians should counsel patients that the benefits of supplements (eg, 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. (*Moderate Recommendation; Evidence Level: Grade B*)

A randomized controlled trial (RCT) of 174 males published in 2020 by the National Institutes of Health (NIH) Reproductive Medicine Network did not show adequate effect on semen parameters or DNA integrity in the initial screening arm to proceed to full patient accrual.[48] A second RCT, also published in 2020, explored the potential effect of folic acid and zinc on semen parameters and live birth rates in nearly 2400 males presenting as part of an infertile couple; no significant changes were seen in either semen quality or live births.[49]

In patients with non-obstructive azoospermia, clinicians may inform the patient of the limited data supporting pharmacologic manipulation with selective estrogen receptor modulators, aromatase inhibitors, 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 in order to optimize male reproductive hormones with the goal of inducing sperm release in the ejaculate or improving surgical sperm retrieval

rates (SRR). Unfortunately, only a subset of males will be eligible for medical therapy based on an initial hormonal evaluation, and limited data are available with respect to treatment outcomes with use of these agents preoperatively.[50]

Gonadotoxic Therapies and Fertility Preservation

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

A patient should be offered the opportunity, if medically feasible, to bank sperm prior to gonadotoxic therapies. This may consist of several semen samples being provided to an andrology laboratory over several days. Sperm cryopreservation can also be performed via mail-in kits in situations where access to care is limited. In the event that the patient is unable to ejaculate, electroejaculation or TESE can be considered; for males with no viable sperm in the ejaculate, TESE is an option.[51]

Clinicians should inform males seeking paternity who are persistently azoospermic after gonadotoxic therapies that microdissection testicular sperm extraction is a treatment option. (*Strong Recommendation; Evidence Level: Grade B*)

Micro-TESE has become a mainstay in the management of the male with NOA when the azoospermia is unrelated to gonadotoxic therapy. Depending upon a number of factors, SRR using micro-TESE have been cited in the 40% to 60% range.[52,53] While the experience is extensive in the non-cancer population, there is significantly less experience using micro-TESE in males exposed to gonadotoxic therapies.

The systematic review process used to inform this Guideline found 7 studies assessing the use of surgical sperm retrieval (4 conventional TESE, 3 micro-TESE) in males exposed to gonadotoxic therapies.[52-58] These studies included males with mixed types of cancer. The elapsed time between exposure to gonadotoxic therapy and sperm retrieval was 11 years (range: 5-19 years). Sperm extraction attempts are typically deferred until at least 2 years after chemotherapy. While all 7 studies reported SRR, only one reported pregnancy/live birth rates.

FUTURE DIRECTIONS

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 males to improve not only their fertility potential, but also their overall health.

The impact of certain lifestyles and behaviors remains relatively unknown. For example, vaping and cannabis use are highly prevalent among young adults, but the short- and long-term effects of these agents on reproductive health remain unclear.[59-62] While obesity and metabolic syndrome can impair male fertility via numerous pathophysiological mechanisms, the ability to restore reproductive potential through weight loss and enhanced metabolic health remains understudied. The emergence of the agonists of glucagon-like peptide-1 receptors class of drugs are proving to be highly efficacious in treating obesity and type 2 diabetes; the effect of these therapies on reproductive health remains to be determined. 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 males. The future looks promising for improving the health and fertility of the infertile male through precision medicine and the application of advanced technologies.

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