Male Factor Infertility

What Every OB/GYN Should Know

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KEYWORDS

- Male infertility • Azoospermia • Assisted reproductive technology
- Surgical sperm retrieval • Diagnostic evaluation

KEY POINTS

- Fertility is a couple's problem; therefore, initial infertility evaluation should include a parallel assessment of both female and male factor infertility.
- A thorough history, physical examination, and semen analysis are the cornerstone of evaluating male factor infertility and differentiating between the various possible etiologies.
- Common etiologies of male factor infertility, including causes of obstructive/nonobstructive azoospermia, asthenospermia, and more, are commonly associated with other health conditions with profound implications on both reproductive and overall men's health.
- The risk factors and causes of male infertility are not fully understood. Therefore, patients should be counseled about incorporating newer diagnostics and therapeutics options and their future implications on the management of male factor infertility.
- Various safe and effective surgical sperm retrieval techniques are available to enable assisted reproductive treatment including in vitro fertilization and/or intracytoplasmic sperm injection.

INTRODUCTION

Infertility is a complex condition that has challenging medical, psychological, economic, and social implications for both patients and clinicians. Based on the International Classification of Diseases (ICD-11), the World Health Organization (WHO) defines infertility as the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse.[1] For women $\geq$ 35 years, failure to achieve pregnancy after 6 months or more of regular unprotected sexual intercourse warrants infertility evaluation.[2] Approximately 15% of couples with unknown fertility status

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are infertile after 1 year of unprotected intercourse, with male factor infertility solely responsible in ~30% of such couples and combined male and female factors present in an additional 20%.[3,4] A Global Burden of Disease survey reported in 2019 that infertility is on the rise, with the age-standardized prevalence of infertility in men increasing by 0.3% per year between 1990 and 2017.[5] Therefore, it is necessary for obstetrics and gynecology (OB/GYN) practitioners to be familiar with the standard evaluation and treatment available for male factor infertility given its implication in couple infertility.

Male factor infertility has a variety of identifiable and reversible causes, including but not limited to varicoceles, vas deferens obstruction, ejaculatory duct obstruction, and hypogonadotropic hypogonadism. Other causes of male infertility can be identified by abnormal semen analysis (SA). When abnormal SA is present without a clear etiology, male factor infertility is termed idiopathic. When female partner evaluation and SA do not explain infertility, the condition is termed unexplained.

Based on the WHOs ICD-11 definition of infertility, failure to achieve pregnancy after 12 months or more of unprotected intercourse (or 6 months if the female partner is more than age 35 years) should trigger comprehensive infertility evaluation and testing. However, several factors might suggest an earlier evaluation of a couple's fertility status is prudent. These factors include (1) risk factors for male infertility such as if a history of bilateral cryptorchidism and advanced paternal age (>40 years) are present[6]; (2) risk factors for female infertility such as advanced female age (>35 years) are present; and/or (3) the couple questions the male partner's fertility potential. Providers should recognize that men with a history of previous fertility (ie, a male patient who has successfully conceived before) can acquire a new, secondary, male infertility factor. Therefore, a history of previous fertility should not preclude a male with concerns or risk factors for infertility from evaluation, and men with possible secondary infertility should be evaluated in the same way as men who have never initiated a pregnancy and are being evaluated for primary male factor infertility.[7]

In this comprehensive review, the authors discuss strategies OB/GYN providers can use to evaluate male factor infertility with the goals of identifying and differentiating between reversible etiologic conditions, irreversible conditions amenable to ART using the male partner's sperm, irreversible conditions for which donor insemination or adoption is more advisable, and other pathologies or etiologies with implications for the patient and their family.

BACKGROUND

Epidemiology of Male Infertility

Overall, infertility affects up to 15% of couples, with up to half of those having a male factor component to the infertility.[8] Unfortunately, much of the care for men undergoing infertility workups is outside the usual reimbursement systems, thus making it difficult to accurately track outcomes and epidemiologic data.[9] The National Survey of Family Growth found that up to 27% of men within infertile couples had never been evaluated for male factor infertility.[10] Early detection and management of male infertility can improve reproductive outcomes and prevent long-term psychological distress for affected couples.

Relationship Between Male Infertility and Overall Men's Health

Recent studies have identified male infertility as a biomarker for overall men's health, particularly urologic and cardiovascular health. For example, up to 6% of men evaluated for infertility have significant undiagnosed serious medical conditions, including

testicular and/or prostate malignancies, even with normal SA.[11,12] Furthermore, numerous studies have suggested that infertile men have more comorbidities compared with their fertile controls; for example, men with abnormal semen parameters and azoospermia are more likely to have cancer compared with fertile men.[13–18] In half of cases, the underlying etiology of male infertility is known to be due to hypospadias, cryptorchidism, testosterone deficiency, or underlying genetic causes such as Klinefelter syndrome and cystic fibrosis. These male infertility-related medical conditions often warrant multidisciplinary counseling and management.[7]

Recent evidence suggests that advanced paternal age (> 40 years) could play a role in male factor infertility.[19] For example, the American Urologic Association (AUA) and the American Society for Reproductive Medicine (ASRM) Guidelines recommend that men of advanced paternal age whose offspring are at-risk for de novo intra- and intergenic germline mutations, sperm aneuploidy, chromosomal abnormalities, birth defects, and genetic conditions should be counseled on the absolute and relative risks for their offspring.

Access to Infertility Care

Although access to infertility care varies significantly by region or country, some common barriers include lack of insurance coverage, cost, cultural stigma, and geographic distance. In many low- and middle-income countries, access to infertility care is particularly limited due to a lack of resources and trained health care providers. Even in high-income countries with more robust health care systems, disparities in access persist, with marginalized communities and those with lower incomes facing significant barriers to care.

Interestingly, access to care and the characteristics of the fertility clinic in which a possibly infertile male is being evaluated are important considerations in evaluating and managing infertility. Variability in practice setting and size affect access to urologic care. Only about 11% of assisted reproductive technology (ART) fertility clinics have an on-site urologist, and variations in patient-facing educational materials can affect referral patterns to experts in male fertility evaluation. Therefore, OB/GYN providers should be aware of the importance of collaborating and partnering with reproductive urologists and andrologists to assist in evaluating and treating male factor infertility.[20] Many men seen in urology clinics have been referred by a reproductive endocrinologist and have already been treated with ART before an investigation into male factor infertility has started.[21]

Infertility can have significant financial costs for couples who are trying to conceive. Although WHO and the ASRM designate infertility as a disease, private insurance companies infrequently offer coverage for male infertility treatments. The Urologic Diseases in America project, which set out to collect male reproductive data epidemiologic data, found total expenditures of $17 million USD in 2000 for primary male infertility (excluding the cost of ART cycles, which is substantially more).[9] To date, there remain a paucity of epidemiologic data on male factor infertility, and thus, these numbers are expected to be an underestimate.

EVALUATION OF MALE INFERTILITY

Medical History

According to the AUA/ASRM guidelines, an evaluation of male infertility usually begins with a detailed medical, surgical, reproductive, and family history. This should include (1) coital frequency and timing; (2) duration of infertility and a history of prior fertility; (3) childhood illnesses (such as bilateral cryptorchidism, mumps orchitis, and other

reproductive developmental histories); (3) past medical history (such as erectile dysfunction, premature ejaculation, Peyronie's disease, diabetes mellitus,[22] genetic disorders, upper respiratory diseases and testosterone, radiotherapy or chemotherapy exposure) and surgical history (including a history of prior vasectomy, inguinal hernia surgery, penetrating or blunt testicular trauma); (5) sexual history including any history of sexually transmitted infections; and (6) potential gonadal toxin exposure, including heat or cannabis.[23,24] In select cases or when referral to a reproductive urologist is not feasible in a timely fashion, OB/GYN providers may begin guideline-based fertility evaluation as appropriate and indicated including SA and laboratory hormonal evaluation.

Physical Examination

A comprehensive and directed physical examination includes (1) examination of body habitus, hair distribution, breast development, and other secondary sex characteristics; (2) external genitalia, urethral meatus, penile plaques, lesions, or deformities; (3) testes size (by examination or orchidometer) orientation and consistency; (4) presence or absence of vas deference and epididymis bilaterally (congenital bilateral absence of the vas deferens [CBAVD]); (5) presence or absence of varicoceles; (6) a digital rectal examination to evaluate for midline prostatic cysts or dilated seminal vesicles, which may assist in the diagnosis of ejaculatory duct obstruction.

Endocrine Hormonal Laboratory Testing

Endocrine and hormonal profile testing primarily focuses on evaluating the hypothalamic-pituitary-testicular axis (**Fig. 1**)[25] for several clinical scenarios, including (1) men with oligospermia (<10 million sperm/mL); (2) men with suspected impairment of their sexual function (including reduced libido); and (3) other clinical findings in the

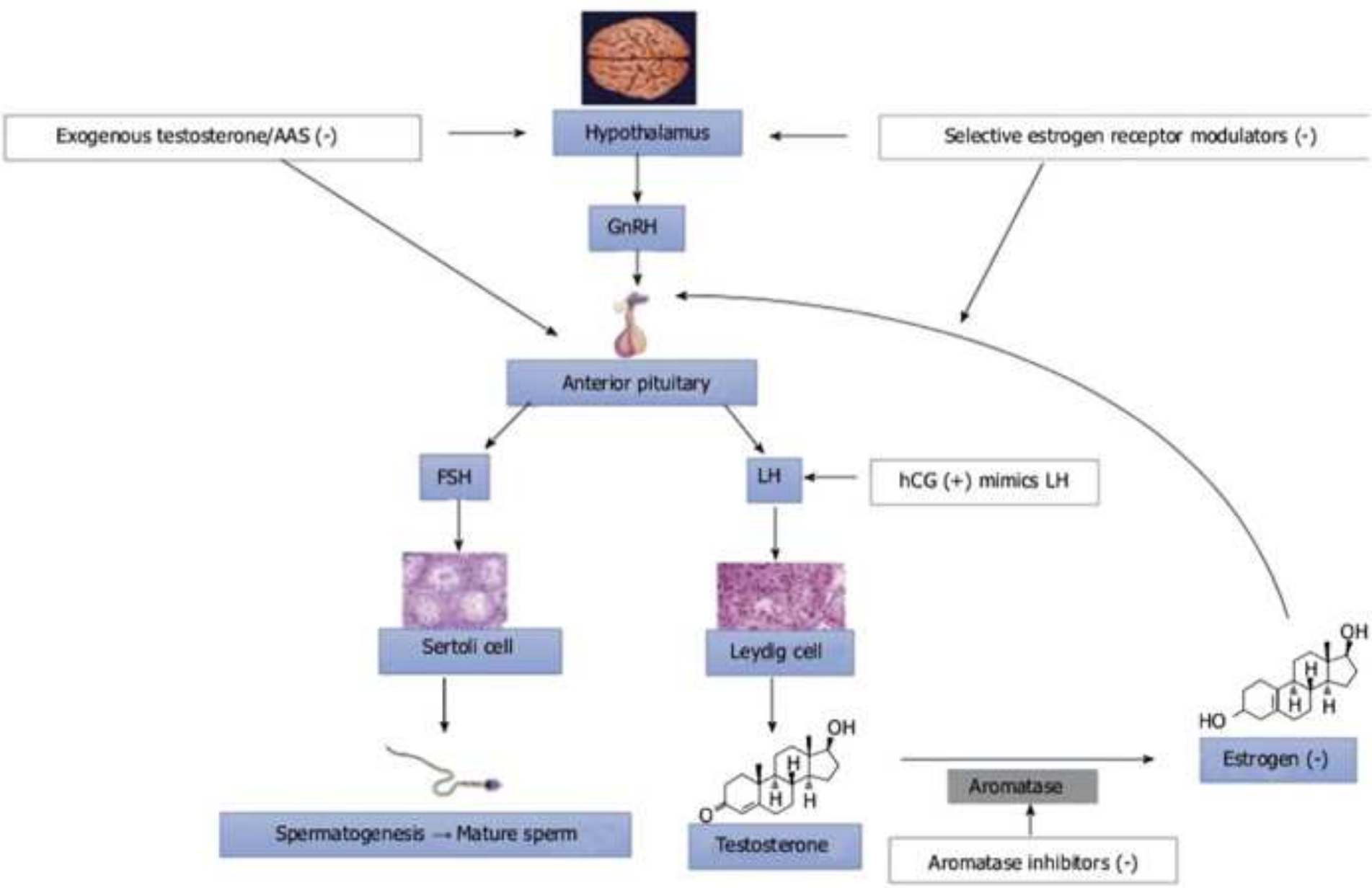

Fig. 1. Hypothalamic-pituitary-gonadal axis. (*Adapted from*: Raheem OA, Chen T, Akula KP, et al. Efficacy of Non-Testosterone–Based Treatment in Hypogonadal Men: A Review. Sex Med Rev. 2021;9(3):381 to 392. https://doi.org/10.1016/j.sxmr.2020.08.003; with permission.)

history and examination that are suggestive of endocrine abnormalities. In addition, men with a history of erectile dysfunction, oligozoospermia, or azoospermia, hormonal testing should consist of an early morning measurement of serum follicle-stimulating hormone (FSH) which is normally less than approximately 7.6 IU/L and total testosterone (T) levels. A total T level of less than 300 ng/mL warrants further endocrine evaluation, including a second early morning measurement of total T and additional testing for free T, luteinizing hormone (LH), and prolactin. **Table 1**[26] summarizes the endocrine analysis for various conditions of hormonal imbalance in the hypothalamic-pituitary-testicular axis. For example, patients with hypogonadotropic hypogonadism will have a hormonal profile of low FSH, low LH, and low T. If endocrine analysis demonstrates low T with elevated FSH and LH, the patient might have primary testicular failure (hypergonadotropic hypogonadism) such as Klinefelter's syndrome. An endocrine analysis demonstrating low T with low FSH and LH levels is suggestive of secondary testicular failure (hypogonadotropic hypogonadism), as is the case in patients with Kallman's syndrome.

Table 2 outlines the endocrine hormonal profiles in men with azoospermia (no sperm counts that will be discussed in detail later in this review). For example, men with obstructive azoospermia will have normal FSH, LH, and T levels, whereas men with pre-testicular nonobstructive azoospermia have low FSH, LH, and T levels. It is important to consider endocrine physiology in evaluating men with suspected primary or secondary testicular failure. Therefore, to accurately diagnose the underlying etiology of male infertility, the history, clinical examination, and if indicated, the hormonal analysis should all be taken together into consideration.

Semen Analysis

SA is considered a critical test in the evaluation of male infertility according to the AUA/ASRM guidelines on male infertility. SA characteristics define the severity of the male factor infertility. Physicians should be aware that proper SA requires evaluation of *at least* two semen samples, ideally obtained at least 2 weeks apart, particularly if the first SA has abnormal parameters (WHO 2021 reference ranges in **Table 3**).[27] Before semen collection, patients should be provided with instructions to complete an

Table 1
Endocrine analysis for various conditions of hormonal imbalance in the hypothalamic-pituitary-testicular axis

Conditions	Follicle-Stimulating Hormone	Luteinizing Hormone	Testosterone	Prolactin
Normal spermatogenesis	Normal	Normal	Normal	Normal
Hypergonadotropic hypogonadism (primary testicular failure)	High	High	Low	Normal
Hypogonadotropic hypogonadism (secondary testicular failure)	Low	Low	Low	Normal
Abnormal spermatogenesis	High/normal	Normal	Normal/Low	Normal
Prolactin-secreting pituitary tumor	Normal/low	Normal/low	Low	High

Adapted from Raheem OA, Hsieh TC. Clinical Approaches to Male Factor Infertility. In: Palermo GD, Sills ES, eds. Intracytoplasmic Sperm Injection. Springer International Publishing; 2018:123 to 141. https://doi.org/10.1007/978-3-319-70497-5_9 (with permission).

Table 2
Endocrine analysis for men with azoospermia

Etiology	Follicle-Stimulating Hormone	Luteinizing Hormone	Testosterone
Obstructive azoospermia	Normal	Normal	Normal
Nonobstructive azoospermia; pre-testicular	Low	Low	Low
Nonobstructive azoospermia; exogenous testosterone	Low	Low	High
Nonobstructive azoospermia; testicular	High	High	Low

abstinence period of 2 to 5 days. One option for semen sample collection is seminal collection condoms designed without spermicidal agents that can be used to collect semen at home, keep the semen sample at room (or body) temperature during transport, and allow for examination within about 1 h of collection. Alternatively, patients can be instructed on masturbation (most common collection method) or coitus interruptus, though this latter method is not ideal as part of the ejaculate may be lost during collection.

In 2021, the WHO published the 6th edition of laboratory analysis of semen with updated reference values, as summarized in Table 3. It is imperative that clinicians recognize that if a male patient has an SA profile that falls within the normal reference ranges it is possible that they may still be infertile. Similarly, it is possible for fertile male patients to have semen variables outside of the reference range. Importantly, for providers providing assisted reproductive treatment (ART) including intrauterine insemination (IUI), an SA falling within the reference range may be adequate. However, the semen parameters necessary for unassisted conception are different from those required for ART. Clinicians should also be aware that the greater the number of abnormal SA parameters, the greater the likelihood of infertility.[28]

Computer-aided sperm analysis (CASA) is an effort to improve and standardize SA. CASA involves the use of microscopic or video imaging to determine specific semen parameters, including sperm motility and motion parameters such as velocity, speed, and head movement. These variables may be important factors in determining sperm fertility potential, but are not yet standard of care and have not replaced traditional SA for evaluating male infertility.[29] Artificial intelligence has also been used to streamline SA, with some evidence suggesting artificial intelligence can be a reliable diagnostic tool for evaluating male infertility.[30] Another advancement in SA is the development

Table 3
Semen analysis normal reference ranges by World Health Organization, 2021

Parameter	Normal Range
Volume (mL)	≥1.4
Sperm concentration (million/mL)	≥16
% Motility	≥42
% Progressive motility	≥30
% Strict morphology	≥4
Total sperm number (million)	≥39

From WHO laboratory manual for the examination of human semen, Sixth Edition. Published online 2021.

of home-based sperm testing systems based on microfluidics, smartphone technology, or antibody reactions with accuracy as high as 98%. Therefore, home-based sperm testing could be a practical and affordable way to screen for male infertility in at-risk populations.[31]

Providers should be aware that SA is an imperfect tool for evaluating male infertility. WHO manuals establishing reference values have been met with criticism surrounding the generalizability of the data given the limited representation of various racial/ethnic groups and the high degree of biological variation among individuals.[32] Therefore, providers should be scrutinous in their interpretation of SA and use multiple parameters to proceed through the diagnostic workup of possible male infertility.

Specific Semen Abnormalities

Azoospermia

Azoospermia is the absence of sperm from the semen. A diagnosis of azoospermia on SA is reached when a semen specimen is centrifuged at maximum speed for ~15 minutes with pellet examination.[33] It is also important for clinicians to be able to differentiate between azoospermia and anejaculation (failing to produce antegrade semen). Once a semen abnormality of azoospermia has been established, it is critically important for clinicians to determine the etiology to treat the cause of the azoospermia or, whenever possible, retrieve sperm to enable in vitro fertilization (IVF) and/or intracytoplasmic sperm injection (ICSI). Azoospermia accounts for about 10% to 15% of male factor infertility, and nearly 1% of all men are believed to be azoospermic.[34]

The etiologies of azoospermia are characterized as obstructive/post-testicular or nonobstructive/testicular. In obstructive azoospermia, there is adequate testicular sperm production in the setting of ductal obstruction. In nonobstructive azoospermia, sperm production is absent. The history, physical examination, hormonal studies, and imaging can help to differentiate between obstructive and nonobstructive azoospermia. It is worthwhile mentioning that semen volume, semen pH (alkaline vs acidic), and presence of fructose also aid in diagnosing azoospermia.

Oligospermia

Oligospermia is characterized by low sperm count. The WHO defines oligospermia as less than 15 million/mL.[23] Treatment options for oligospermia depend on the underlying cause and can include hormone therapy, surgery, lifestyle modifications, and assisted reproductive technologies such as IVF and ICSI.

Obstructive azoospermia

Obstructive azoospermia accounts for 40% of azoospermia. Causes of obstructive azoospermia include (1) structural causes, such as trauma from prior surgeries such as vasectomy, prior inguinal hernia repairs, prior hydrocele repairs, or orchiopexy; (2) nonstructural causes, such as CBAVD, sexually transmitted infections (namely chlamydia and gonorrhea); and (3) functional problems, including spinal injury, neurologic disease, and prior retroperitoneal disease. The endocrine profiles of men with obstructive azoospermia include normal FSH, LH, and testosterone (see **Table 2**), as well as normal testes on clinical examination and/or testicular ultrasound. If the cause of an obstructive azoospermia etiology for infertility is CBAVD, clinicians should be aware of the importance of cystic fibrosis testing. Up to 80% of men with CBAVD have mutations in the cystic fibrosis transmembrane regulator (*CFTR*) gene, and mutations in *CFTR* are prevalent in 20% of men with idiopathic epididymal obstruction and congenital unilateral absence of the vas deferens (CUAVD).[35–37] Therefore, the importance of genetic testing in the setting of evaluating and managing patients with these etiologies of obstructive azoospermia cannot be overstated. Furthermore,

approximately 20% of men with CUAVD have ipsilateral renal agenesis due to abnormal mesonephric duct development with a slightly lower proportion in patients with CBAVD.[38–40] Therefore, renal ultrasound should be considered in patients with unilateral or bilateral absent vas deferens. Furthermore, for men diagnosed with CFTR mutation in the context of congenital absence of vas deference and obstructive azoospermia, it is recommended to evaluate their female partner for CFTR gene mutations before proceeding with future reproductive treatment.

Nonobstructive azoospermia

Nonobstructive azoospermia can be divided into classifications of pre-testicular and post-testicular nonobstructive azoospermia. Pre-testicular azoospermia, which presents with endocrine abnormalities suggestive of hypogonadotropic hypogonadism, has causes including Kallman's syndrome (patients presenting with anosmia and delayed puberty) and/or pituitary abnormalities (see **Table 2**). Testicular nonobstructive azoospermia, which will present with endocrine abnormalities suggestive of hypergonadotropic hypogonadism, involves impaired spermatogenesis (as is the case in the genetic disorder Klinefelter syndrome [47, XXY]), undescended testes and/or testicular torsion, varicoceles, testicular cancer, and gonadotoxins. Although pre- and post-testicular azoospermia is often treatable, testicular causes currently lack effective reversible management options.

Asthenospermia. Asthenospermia is a defect of sperm movement detected in SA by low sperm motility. The causes of asthenospermia are numerable and include genital tract infections associated with pyospermia, antisperm antibodies (ASAs), spermatozoal structural defects, ejaculatory duct obstruction, and varicoceles; asthenospermia can also be idiopathic. Additional laboratory testing for ASA can aid in the management of patients with asthenospermia. If ASAs are present, patients may be offered IUI or IVF/ICSI; alternatively, patients can be treated with immunosuppressive steroids, though the effectiveness of steroids is low and there is a risk of serious side effects.[41] If SA demonstrates low sperm motility in the setting of high viability, then disorders affecting sperm motility such as primary ciliary dyskinesia should be considered.[42]

Teratozoospermia

Teratozoospermia is a defect of sperm morphology. Sperm morphology assessment has evolved over the last several years with the recognition that even in semen from fertile men, sperm display a spectrum of what is considered normal morphology. However, sperm morphology is considered one of many indicators of sperm function and therefore has been used by some reproductive specialists to identify couples that might be better candidates for ICSI over IVF.[43] Globozoospermia is a structural defect, in which sperm have round heads, and this is often characterized by the absence of an acrosome and therefore impaired sperm function.[44] The fertility outcomes for male patients with globozoospermia are often poor.

Pyospermia

Pyospermia or leukocytospermia is the presence of white blood cells (WBCs) on SA and is defined by the presence of greater than 1×10^6 WBCs/mL under light microscope.[45] Pyospermia can result from infectious and noninfectious causes including toxins, varicocele, chronic prostatitis, and autoimmune disorders. The oxidative stress from an abnormal amount of inflammatory cells can affect the functionality of sperm, thus affecting fertilization capability.[45]

Genetic Testing

Given the association of azoospermia and severe oligospermia (<5 million) with genetic abnormalities, including mutations in the *CFTR* gene, Klinefelter syndrome (47, XXY), and the prevalence of microdeletions in the azoospermic factor (AZF) region of the long arm of the Y-chromosome (YCMD), genetic testing is strongly indicated for patients with azoospermia/severe oligospermia. Karyotyping and Y-chromosome microdeletion analysis can play a key role in the diagnostic workup and management of these patients. Specific to Y chromosome microdeletion (YCMD), there are three microdeletions (AZFa, AZFb, AZFc) on the long arm of the Y-chromosome that account for about 7% of cases of severe oligospermia/azoospermia in infertile male patients.[46] If an AZFc microdeletion is detected, microscopic testicular sperm extraction (TESE) (micro-TESE) might be indicated as micro-TESE yields a sperm retrieval rate of up to 70% in patients with AZFc microdeletions for future ART such as IVF and/or IVF/ICSI.[47] However, for patients with AZFa or AZFb microdeletions or combination, the chances of surgical sperm retrieval through micro-TESE are virtually nonexistent and donor sperm is highly recommended as per AUA/ASRM guidelines.

Given the close association of mutations in the *CFTR* gene and possible etiologies of obstructive azoospermia (CBAVD, CUAVD, and idiopathic epididymal obstruction), clinicians should consider referring patients with these conditions for genetic counseling. The AUA and ASRM recommend genetic testing to provide information on possible offspring transmission, which warrants the use of gene sequencing and carrier screening, including testing for the 5-thymidine (5T) allele of *CFTR*. If *CFTR* mutations are identified, preconception counseling should be offered to the patient and their partner to outline the risks of having a child with cystic fibrosis given the carrier status of the couple.

Karyotyping should be considered during genetic evaluation given the association of chromosomal abnormalities in patients with male infertility. In particular, Klinefelter syndrome (47, XXY) is the most common chromosomal abnormality seen in infertile men, accounting for approximately 15% of nonobstructive azoospermia. Klinefelter syndrome has an incidence of 1 in 600 phenotypic males and presents clinically with small, firm testicles, and diluted male secondary sex characteristics, including scant hair distribution.[48,49]

Specialized Testing

In select cases, conventional SA can be supplemented with additional sperm functional testing. For example, sperm function tests were developed after defective sperm-zona interaction was identified as the main reason for fertilization failure during IVF. The most commonly used assessment of sperm chromatin quality is through sperm DNA fragmentation testing, which can assess sperm chromatin structure and sperm chromatin dispersion.[50–52] Although the routine use of sperm DNA fragmentation testing is not recommended by the AUA/ASRM guideline and there is a lack of strict standardization and clear threshold values, in 2017, the Society for Translational Medicine published a clinical practice guideline for sperm DNA fragmentation testing outlining several clinical scenarios in which this testing may be warranted.[53] Sperm DNA fragmentation testing may be warranted in (1) patients with normal SA and a clinical grade 2 or 3 varicocele; (2) patients with borderline/abnormal SA and a clinical, grade 1 varicocele; (3) couples with unexplained infertility and/or recurrent pregnancy lost; (4) couples with IVF and/or ICSI failure; and (5) male patients with risk factors for male infertility, including environmental or occupational exposure to gonadotoxins[54] and lifestyle factors such as smoking,[55] alcohol consumption,[56] and recreational drug use.[57]

In certain cases of azoospermia, present vas deferens, and low semen volume SA, providers should consider ejaculatory dysfunction including retrograde ejaculation and usually recommend post-ejaculate urine analysis (PEU) to differentiate between retrograde ejaculation (with positive PEU) and other ejaculatory obstruction or dysfunction.[6]

Antisperm Antibodies

ASAs are antibodies that the body produces against sperm cells. They can be produced in response to a variety of factors including testicular trauma, vasectomy, vasectomy reversal, orchitis, cryptorchidism, neoplasm, and varicocele. ASAs affect fertility by decreasing sperm motility, agglutination, and penetration of the cervical mucus.[58]

Hyperviscosity Testing

Semen hyperviscosity refers to semen that has retained extra viscosity following the liquefication that physiologically occurs following ejaculation. Although the exact mechanisms contributing to semen hyperviscosity are incompletely understood, hyperviscous semen contributes to male infertility by negatively affecting sperm motility and semen quality.[59]

Testis Mapping and Biopsy

Traditionally, a testicular biopsy is considered to differentiate between obstructive and NOA, albeit the recent AUA/ASRM guidelines do not recommend a diagnostic testicular biopsy[60] owing to heterogeneity of spermatogenesis in men with azoospermia. On the contrary, fine-needle aspiration (FNA) testicular mapping has been popularized as an alternative diagnostic tool to stratify spermatogenesis in men with azoospermia based on the amount of sperm present or absent, early maturation arrest and Sertoli cell-only syndrome finding. FNA testis mapping consists of 12 to 18 (depending on testis size) fine-needle aspiration sites to extract the seminiferous tubules. These are then analyzed by a cytopathologist to assess the presence or absence of sperm and other findings as above. Mapping can aid in localizing sperm for future sperm retrieval techniques by identifying spermatogenesis loci for successful sperm retrieval and thus minimizing invasiveness and long-term sequelae, such as hypogonadism.

Imaging Tests

Scrotal ultrasound is typically not recommended in the initial evaluation of male infertility as per AUA/ASRM guidelines. This is because a thorough history and physical examination can typically identify the most common scrotal pathologies accounting for an infertility factor, including the presence of varicoceles, absent vasa deferens, and testicular masses. Scrotal ultrasound might be indicated in patients who are difficult to examine because of body habitus, undescended testis, testicular pain, or for patients with risk factors for malignancy and lately with the emergence of telehealth. Scrotal ultrasound can be helpful in examining spermatic cord vasculature. However scrotal ultrasound should not be routinely used to identify subclinical varicoceles as treatment of such varicoceles has little clinical utility. Traditionally, varicoceles are graded by size. Grade 0 varicoceles are subclinical and visible only via imaging; grade 1 varicoceles are palpable when patients perform the Valsalva maneuver; grade 2 varicoceles are palpable without the Valsalva maneuver; and grade 3 varicoceles are visible at rest.

Transrectal ultrasound (TRUS) is also not typically recommended as part of the initial workup for male infertility. However, in patients with possible ejaculatory duct

obstruction per SA (with low semen volume, azoospermia, acidic SA, and fructose negative), dilated seminal vesicles (>2.5 cm), and/or midline prostatic cysts can be identified by TRUS.[61] In addition, cystoscopy evaluation of the lower urinary tract including midline utricle cysts, ejaculatory duct obstruction, strictures or stones, and urethral or prostate scarring or strictures can also be documented.

Pelvic and renal ultrasound and/or cross-sectional abdominal imaging with CT/MRI can be particularly helpful in patients with suspected pelvic cystic abnormalities or vasal agenesis given the high association of renal agenesis in disorders of vasal agenesis.[38]

Treatment

Although most of diagnosable causes of male infertility do not currently have effective treatments, about 20% of cases of male infertility are reversible and treatable conditions, including obstructive azoospermia, ejaculatory duct obstruction, prostatic midline cysts, gonadotropin deficiency, sexual function disorders, vasectomy reversal, varicoceles, and reversible effects from prior testosterone exposure, gonadotoxins, and sperm autoimmunity.[62]

Role of Supplements

Antioxidants are known to have protective effects against oxidative stress, which have been demonstrated in patients with sperm DNA damage and reduced motility, which lead to male infertility. The most studied antioxidants are vitamins E and C, coenzyme Q10, and selenium. A meta-analysis comparing seven small, randomized trials concluded a possible increase in live birth rates in those men taking antioxidants, but the investigators also concluded that this was based on low-quality evidence. Therefore, there remains a need for larger randomized control trials to evaluate the role of antioxidants in male infertility.[63]

Treatment options for patients with obstructive azoospermia include epididymal or testicular sperm retrieval for IVF/ICSI or surgical reconstruction. Both conventional and microdissection TESE are safe and effective options for patients eligible for sperm retrieval procedures.[64] Patients with nonobstructive azoospermia are less likely to benefit from sperm retrieval with success rates of about 50%. Therefore, men with nonobstructive azoospermia should be counseled on the options of donor sperm insemination or adoption.[65]

Varicoceles, or dilations of the pampiniform plexus venous vasculature within the spermatic cord, are present in healthy men about 15% of the time and in men with abnormal SA about 25% of the time.[6] Varicoceles can be repaired surgically or microsurgically, and surgical management is recommended for men with infertility with clinical varicoceles (grades 1–3), abnormal SA, and/or unexplained infertility with a female partner with no suspicion of female factor infertility. Varicocele repair can decrease sperm DNA fragmentation rates and reactive oxygen species. Livebirth outcomes following ART procedures are better for couples with male partners who received varicocele repair before ART.[66] Pregnancy and live birth rates have been shown to be 1.76-fold and 1.69-fold higher for men treated with varicocelectomy before ART, respectively.[66] Varicocele repair also seems to improve semen parameters, specifically sperm motility and total count.[67]

SUMMARY

Fertility evaluation should proceed in parallel for both male and female members of a couple to optimize fertility outcomes. Male factor infertility can be due to several

causes and should be initially evaluated with a thorough history, physical examination, adequate SA, and when indicated, endocrine profile analysis. Abnormal SA findings include azoospermia (which warrants further workup to differentiate between obstructive and nonobstructive etiologies), asthenospermia, oligospermia, and teratozoospermia. Depending on the etiology of the male patient's etiology, assisted reproductive techniques may be offered to support the couple in their family planning goals. Given the complexity of managing patients with male infertility, OB/GYN providers should also leverage the expertise of reproductive urologists in evaluating and managing male factor infertility.

CLINICS CARE POINTS

- Initial infertility evaluation should include a parallel assessment of both female and male factor infertility.
- Evaluation of male infertility should include a thorough history, physical examination, and semen analysis, with high-quality semen analysis requiring at least two assessments spaced ideally at least 2 weeks apart.
- Men with infertility and/or abnormal semen parameters should be counseled on possible associated conditions and health risks associated with their reproductive condition.
- Patients should be counseled that the risk factors and causes for male infertility are incompletely understood and that new data are emerging to support future recommendations regarding the evaluation and management of male factor infertility.

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