Male Infertility

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Contents

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Key Points

- Referral to reproductive urologist facilitates a complete workup and holistic care for men having difficulty conceiving.
- Adherence to a guideline-based approach reduces unnecessary tests and maximizes patient outcomes.
- The intensity of workup and management should be tailored to the reproductive potential of the partner and the severity of any identifiable pathology.
- Male infertility is associated with early mortality, and men with infertility should receive a thorough clinical evaluation with an emphasis on identifying other comorbidities and providing longitudinal care.

11.1 Introduction

For many couples with infertility, the inability to conceive a child can be one of the most emotionally taxing events of their lives. Roughly one in six couples worldwide suffer from infertility [1], and within these couples, up to 33% of cases are due to an isolated male factor, and an additional 20% of couples have combined male and female factors [2, 3]. Thus, roughly half of all couples with infertility may benefit from male evaluation and treatment. Worryingly, these statistics may be compounded by emerging data suggesting that sperm counts may be falling globally for unknown reasons [4]. Indeed, mammalian spermatogenesis is an exquisitely complex process requiring the most diverse proteome [5] of any tissue in the human body and lasting nearly 3 months from spermatogonia to mature spermatozoa. While the physiology of spermatogenesis has become increasingly well understood [6], the pathology underlying impaired spermatogenesis and sperm dysfunction in many subfertile and infertile men remains elusive, and 60% of all men who present with male infertility and undergo thorough workup will have no identifiable underlying cause [7]. Even more concerning is the emerging data supporting a link between male infertility and mortality [8], suggesting that early evaluation may provide not only a benefit for reproductive purposes but for overall health as well.

In the current chapter, we will briefly summarize the current state-of-the-art diagnosis and management of male infertility, with a particular focus on the emerging psychosocial effects and the importance of a thorough general medical examination to assess for comorbidities.

Clinical Vignette

A 35-year-old man presents with a chief complaint of infertility with his 30-year-old partner for 18 months. He has never caused a pregnancy to his knowledge. He denies any history of undescended testicles or hernia repair. He does report a left-sided scrotal fullness that worsens throughout the day and resolves by morning. He and his wife are wondering if there is any testing or treatment necessary to improve their chances of having a child.

11.2 The Psychological Impact of Male Infertility

While the emotional toll and societal stigma of female factor infertility have been the subject of increasingly insightful research efforts including the development of standardized instruments such as the FertiQoL [9] and female infertility stigma [10] instruments, comparatively little work has been completed on the male side. Nevertheless, it is clear that the inability to father a child contributes significant stress and decreases in quality of life for infertile men. Men receiving a diagnosis of male infertility experience significant increases in distress and rates of psychiatric comorbidities which persist even after receiving treatment [11]. Infertility is associated with significant decreases in sexual function, which can compound challenges with conception

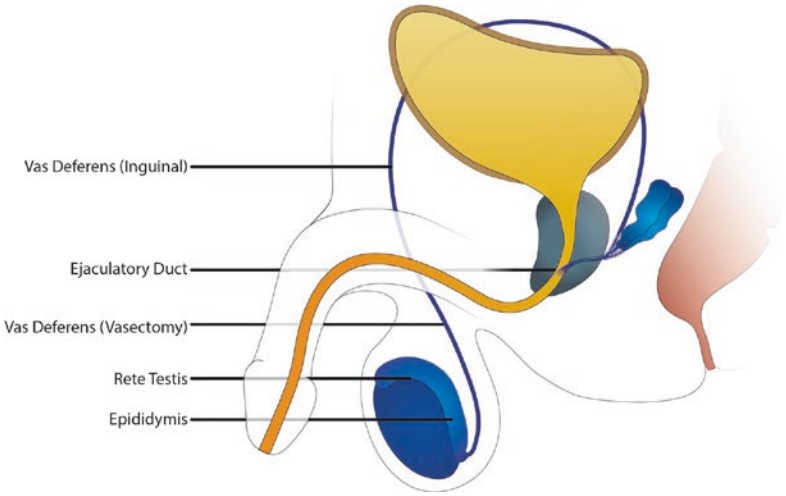

Fig. 11.1 List of locations along the male genitourinary tract for obstructive azoospermia

[12]. These symptoms are often minimized, perhaps due to the social stigma surrounding infertility. While only 5% of men with male infertility self-reported psychiatric illness, testing revealed a prevalence of almost one in three men [11]. Perhaps this reflects the deeply ingrained societal stigma surrounding infertility. Even more disturbingly, one in five couples treated for infertility have experienced thoughts of suicide [13]. Taken together, these findings suggest that further research is necessary to better understand which men are at greatest risk for mental health deterioration and may benefit significantly from referral for counseling or pharmacologic therapy.

11.3 Categorization of Male Infertility

Male infertility can be broadly categorized in several different ways. First, primary male infertility refers to men who have never successfully initiated a clinical pregnancy, while secondary male infertility refers to men who have previously caused a pregnancy but subsequently have difficulty [14]. Next, male infertility can be caused by either obstructive or non-obstructive etiologies. Obstructive etiologies, characterized by normal spermatogenesis but impaired sperm delivery, include ejaculatory duct obstruction, congenital absence of the vas deferens, epididymal obstruction due to infection, prior vasectomy, or inguinal hernia repair causing vasal obstruction (Fig. 11.1). Non-obstructive etiologies represent a failure of the testicle to generate sperm due to genetic, hormonal, environmental, or iatrogenic causes. Finally, it is important to distinguish idiopathic male infertility, which refers to men with poor semen quality for unexplained reasons, and unexplained male infertility, which describes men with male factor infertility in the absence of aberrations in semen analysis parameters [15].

Semen concentration provides another useful tool to characterize infertile men. Men with normal sperm counts are deemed to be within the normal range set by the World Health Organization (WHO) in the most recent 2009 guidelines [16]. These men are designated as "normospermic" if they have a semen concentration of >15 million sperm/mL. Men with semen concentrations between 5 and 15 million/mL are labeled as oligospermic, and men with <5 million/mL are termed severely oligospermic. If only rare sperm are seen, this is called cryptospermia. Finally, if no sperm are identified despite extensive efforts, the condition is termed azoospermia. Beyond merely sperm counts, semen analysis can also provide more narrow diagnoses. Men with abnormal sperm motility are termed

asthenospermic, and men with abnormal sperm morphology are termed teratospermic. These terms can also be combined; for example, a man with poor sperm counts, low morphology, and poor motility is deemed to have oligoasthenoteratozoospermia (OAT).

A subset of men with male infertility can be described according to their hormonal axis aberrations. The hypothalamic-pituitary-gonadal (HPG axis) describes the relationship between gonadotropin-releasing hormone (GnRH) and the hypothalamus providing a stimulus to the pituitary to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH stimulates the Sertoli cells, which are required for normal spermatogenesis, and LH stimulates Leydig cells to produce testosterone. Testosterone then feeds back negatively to complete the control loop. Men with primary testicular failure usually exhibit elevated FSH and LH but decreased T and low sperm counts. In contrast, men with decreased levels of both pituitary and testicular hormones are said to have hypogonadotropic hypogonadism or secondary testicular failure.

11.4 A Guideline-Based Approach for Diagnosis and Management of Male Infertility

Despite the complexities and nuances involved with the management of male infertility, there are two current standardized guidelines available for clinician use. The American Urological Association (AUA) and American Society for Reproductive Medicine (ASRM) recently released a joint series guideline encompassing the basic diagnosis and management of male infertility [17, 18]. In addition, the European Association of Urology (EAU) released independent guidelines for male infertility in 2012. Many of the statements in these two resources closely coincide. Both, for example, recommend concurrent male and female evaluation. Both recommend the use of the WHO standards for semen analysis interpretation, and both recommend at least two semen analyses be performed. There are, however, some differences in treatment approaches, including recommendations regarding medical therapy for men with male infertility. Taken together, these documents represent an evidence-based strategy for the index patient with male infertility and should be implemented in the workup and management of most patients.

11.5 The Importance of a Comprehensive Male Factor Workup

Frequently, couples begin their workup for infertility through reproductive endocrinology, and men undergo a basic semen analysis and are referred to urology only if this demonstrates significant abnormalities. Emerging data, however, suggests that 15% of men with male factor infertility have normal semen parameters [15], underscoring the importance of evaluation by a male reproductive specialist even in the absence of semen analysis abnormalities. In addition, there is a growing body of literature supporting the strong link between systemic disease and male factor infertility. There are now several reports describing an epidemiological link between male infertility and early mortality [8, 19]. A recent meta-analysis [19] showed that infertile men have a 1.6-fold higher risk of dying than fertile men, and this hazard ratio climbs to over 2 in azoospermic men. While the exact cause for this linkage is unknown and likely multifactorial, it implies that spermatogenesis may represent the "canary in the coalmine" and an early harbinger for morbidity in an otherwise asymptomatic man.

11.6 Infertility and Comorbidities

Infertility and Hypogonadism There is a clear linkage between subfertile men and hypogonadism. This may be due to the fact that normal spermatogenesis is reliant upon high levels of intra-testicular testosterone. Similarly, conditions such as cryptorchidism may lead to abnormal sperm production and abnormal tes-

tosterone production by Leydig cells. Hypogonadism has been shown to predispose men to decreased libido, erectile dysfunction, decreased lean body mass, depression, and poor bone health [20]. In addition, testosterone levels within the testicle are up to 125 times higher than in the circulation, and this elevated level is key for proper spermatogenesis [21]. While the exact relationship between these two testicular functions is difficult to fully describe, the two processes (spermatogenesis and hormone synthesis) are clearly intimately linked and must be addressed concurrently in men with poor testicular function.

Pituitary Masses Roughly 16% of men with erectile dysfunction and 11% of men with subfertility will be found to have elevated prolactin [22]. Many of these men will be found to have a sellar mass that may be either functional (e.g., prolactin-secreting or FSH-/LH-secreting) or nonfunctional. In fact, the prevalence of prolactinomas in men with infertility is approximately 350-fold higher than the general population [23]. As a result, it is important to consider prolactin measurement in select men with infertility and screen for symptoms of sellar mass.

Infertility and End-Stage Renal Disease (ESRD) Men suffering from renal failure are at significant risk for infertility for a multitude of reasons. Uremia itself appears to impair spermatogenesis and sperm function via direct and indirect hormonal effects. Men with chronic kidney disease typically present with oligoasthenoteratozoospermia (OAT) and a > 50% decrease in most semen parameters [24]. These changes appear to be directly correlated with the duration of hemodialysis. Most of these parameters will improve following renal transplantation, though a significant proportion of men will remain azoospermic [25].

Klinefelter Syndrome Klinefelter syndrome (47, XXY) is a common genetic syndrome affecting roughly 1 in 1000 life male births and commonly presents in adulthood with primary infertility. Physical examination may reveal gynecomastia, mild cognitive dysfunction, sparse body and facial hair, and decreased lean muscle mass. Genital exam will universally demonstrate prepubertal-sized firm testicles usually associated with primary testicular failure and hypogonadism. Proper identification and management of men with Klinefelter syndrome is important for avoiding the untoward effects of hypogonadism and simultaneously maximizing fertility capacity using assisted reproduction technology (ART). Even with aggressive management and early surgical sperm retrieval, however, only 50% of men will be found to have sperm.

Infertility and Cystic Fibrosis While the link between mortality and infertility remains poorly understood, the link between infertility and other comorbidities is quite strong. Approximately 1 in 1000 men have congenital bilateral absence of the vas deferens (CBAVD), and this population accounts for roughly 1% of all men presenting for infertility workup [26]. Mutations in the cystic fibrosis transmembrane region (CFTR) family of genes are found in roughly 90% of men with CBAVD [27]. When suspected by an experienced urologist during physical examination, these men should undergo kidney ultrasound to rule out a solitary kidney, CFTR gene testing, and referral to pulmonology for further management. In addition, the partner of these men should be screened, and couples should be counseled on the genetic implications of their condition should they choose to proceed with assisted reproductive technology. In contrast, congenital unilateral absence of the vas deferens (CUAVD) is less commonly associated with CFTR mutations but should still be evaluated using a similar algorithm.

11.7 Obtaining a History of the Infertile Male

Obtaining a thorough history is a vital step to identifying potential causal factors in men with infertility.

First, age is an important factor to consider as fertility diminishes over time. Despite this, however, roughly 80% of men in their fifth to seventh decades of life maintain normal semen parameters [28]. Assessment of prior pregnancies or children with a current

or prior partner will distinguish men with primary from secondary infertility.

Men should be queried for the length of unprotected intercourse and the use of conception strategies (e.g., ovulation kits, calendar-based approaches, basal body temperature, etc.). While seemingly superfluous, it is also important to confirm with couples that they are participating in penetrative intercourse and that ejaculation occurs.

Ideally, the female partner will be present at the consultation to provide an accurate partner history and encourage a coordinated workup and treatment discussion. This should include assessment of menstrual pattern, prior pregnancies with this or another partner, and consent to coordinate care with the reproductive endocrinology team when appropriate. Partner age is a critical component to assess, as this can directly dictates the intensity of therapy for men whose partners are nearing menopause.

A developmental history including assessment for cryptorchidism, hypospadias, posterior urethral valves, or other congenital genitourinary anomalies will identify key risk factors for poor testicular function. Assessment of the age of puberty is also important. Delayed puberty can be seen in men with Kallmann syndrome, Turner syndrome, hypogonadism, and men with pituitary masses and hyperprolactinemia. Aside from these diagnoses, men with subjectively delayed puberty appear to have worse semen parameters and a 25% decrease in semen concentration [29].

Infectious etiologies are a common cause of infertility and account for up to 15% of cases [30]. Recent illness is also an important factor to discuss, as a single febrile illness reduces sperm concentration by one third [31]. A discussion of sexually transmitted disease history is also indicated, as prior gonorrhea or chlamydia infection can result in obstruction of the epididymis and obstructive azoospermia [32].

Next, providers should strive to capture a thorough genitourinary surgical history including prior scrotal surgery, urethral instrumentation to assess for possible strictures, and history of retroperitoneal surgery as a risk factor for retrograde ejaculation. As many as 27% of infertile men who underwent inguinal hernia repair as a child will go on to develop vasal obstruction [33]. Thus, particular focus should be given to assessing for a history of hernia repair including age of intervention and type of repair (e.g., with or without mesh).

A minority of men will report an oncologic history, most commonly testicular cancer and some hematologic malignancies. Thorough documentation of malignancy type and treatments (including specific chemotherapeutic or radiation treatments) can elucidate important gonadotoxic exposures. Numerous agents are detrimental to spermatogenesis including alkylating agents (e.g., cyclophosphamide), cisplatin, and dactinomycin [34].

Environmental exposures can cause significant decreases in sperm counts and are primarily centered around exposure to gonadotoxic agents such as pesticides [35] . Heat is also a significant environmental exposure risk factor and can be applied by hot tubs [36] or laptops [37]. Smoking is a significant risk factor for subfertility and appears to decrease sperm concentration, total motile count, and oxidative stress [38].

Scrotal trauma is an often-forgotten cause of infertility. Men with a history of high-impact sport activities such as football can develop hypogonadism and erectile dysfunction [39]. Repetitive low-impact activities such as cycling may also have a detrimental effect [40], though the literature in this area remains mixed [41].

Finally, countless medications have been implicated in male infertility. For a full list, the reader is referred to ◘ Table 11.1 and to several recent reviews on the topic [42, 43].

11.8 Physical Examination of the Infertile Male

The physical exam remains a critical aspect in the evaluation of the infertile or subfertile male. Assessment of body habitus, presence of secondary sex characteristics, and gynecomastia should be performed. Abdominal exam may reveal surgical incisions from prior

Table 11.1 List of medications suspected or proven to cause male infertility

Category	Subcategory	Drugs	Pattern	Strength of evidence
Alpha-blockers		Tamsulosin, Silodosin	Retrograde ejaculation or anejaculation	Strong
Analgesics	Opioids	Oxycodone	Decreased libido, ED, concentration	Strong
		Methadone	Hypogonadism, decreased motility	Strong
		Tramadol	Decreased count, motility	Strong
Antacids	H2 blockers	Cimetidine, famotidine, ranitidine	Decreased sperm counts for cimetidine only	Weak
	Proton pump inhibitors	Lansoprazole, Omeprazole, Pantoprazole	Modestly decreased sperm counts	Weak
Antibiotics	Nitrofurantoin	Macrobid, macrodantin	Decreased motility	Weak
	Tetracycline	Doxycycline, Minocycline, tigecycline	Decreased viability and motility	Weak
Antihypertensives	ACE Inhibitors	Captopril, enalapril, lisinopril	Decreased motility	Weak
	Beta-Blockers	Atenolol, Carvedilol, Metoprolol	Decreased motility	Weak
	Calcium channel Blockers	Amlodipine, nifedipine, Verapamil	Decreased motility and capacitation	Weak
	Diuretics	Spironolactone	Decreased motility	Weak
Anti-inflammatory drugs		Colchicine	Decreased concentration	Weak
		Sulfasalazine	Decreased concentration, motility, morphology	Weak
Chemotherapeutics	Alkylating Agents	Cyclophosphamide, chlorambucil	Cytotoxic to spermatogonia	Strong
	Mitotic Inhibitors	Vinblastine	Cytotoxic to spermatogonia	Strong
Hormonal Therapies	Androgens	Testosterone	Azoospermia	Strong
	Antiandrogens	Bicalutamide, flutamide	Erectile dysfunction, decreased libido	Strong
	5-ARIs	Dutasteride, Finasteride	Decreased concentration, semen volume	Strong
	GnRH analogs	Leuprolide, goserelin	Erectile dysfunction, decreased libido	Strong

(continued)

Table 11.1 (continued)

Category	Subcategory	Drugs	Pattern	Strength of evidence
Immunosuppression	Antimetabolites	Azathioprine, Mycophenolate	Decreased motility, teratogenic	Weak
	mTOR inhibitors	Everolimus, sirolimus	Decreased concentration, motility, teratogenic	Weak
	Steroids	Prednisone	Minimal effect on sperm	Strong
Psychiatric medications	Phenothiazines	Chlorpromazine	Increased prolactin, decreased motility	Weak
	SSRIs	Fluoxetine, Paroxetine	Decreased counts and motility	Weak
		Lithium	Decreased motility	Weak
Radiation (pelvic)			Spermatogonia toxicity	Strong

inguinal hernia repair raising suspicion of vasal obstruction in the appropriate clinical context. Close attention is then paid to the genital exam which is often best performed in the standing position. Evaluation of testicular size can be performed with the use of an orchidometer or by subjective assessment by an experienced provider. The consistency of the testis is important to assess, as men with testicular failure may have soft testes, whereas a testicular mass will be firm and irregular. The epididymis should be palpated for tenderness, which may suggest epididymitis, or masses such as epididymal cysts (spermatoceles). Epididymal fullness can be appreciated on obstructed men. The presence or absence of the vas deferens is critical to identify men with vasal agenesis. The presence and grade of varicocele should then be noted, again with the patient in the standing position and with a Valsalva maneuver. Varicoceles are graded on physical exam as follows: Grade 1 varicocele is palpable only with Valsalva maneuver, Grade 2 varicocele is palpable without Valsalva, and Grade 3 is visible. Evaluation of meatal location, Tanner stage, and penis size may be important particularly in men with history of hypospadias and congenital hypogonadotropic hypogonadism, respectively. If the patient is of appropriate age, a rectal exam should be performed to assess for prostate masses.

11.9 Semen Analysis

Basic Semen Analysis The cornerstone of male fertility workup is the basic semen analysis. According to WHO guidelines [16], men are instructed to abstain from ejaculation for between 2 but not more than 7 days prior to providing a specimen. Specimens should be collected in a clean fashion without the use of saliva or most commercially available lubricants, both of which can negatively impact semen parameters [44]. Men should be educated on the importance of a complete collection, as a "split collection" where the initial or terminal portion of the specimen is lost can underestimate the true semen concentration significantly.

Following collection, the semen sample should be processed in a consistent manner by experienced technicians. While semen has a remarkable ability to buffer pH, a value of less than 7.0 is often associated with obstruction due to the loss of fructose-rich alkaline fluid from the seminal vesicles. Volume should typically exceed 1.5 mL in a normal specimen, and volumes lower than this should raise

concern for obstruction or retrograde ejaculation. It is important to note that vasal obstruction does not cause decreased ejaculate volume, as the testicular contribution to the ejaculate volume is only a fraction of the total ejaculated volume.

Semen concentration is perhaps the most versatile basic semen analysis parameter, as this provides a key measure of fertilizing ability. When combined with percentage of motile sperm and total volume, the total motile sperm count (TMSC) can be calculated. In subfertile men, TMSC of >5 million per mL is sufficient for intrauterine insemination (IUI), whereas values less than this are typically best managed with IVF or ICSI.

Many labs now perform computer-aided semen analysis (CASA) in addition to or in some cases in place of manual counts. These platforms use high-throughput digital imaging and analysis software to determine semen concentration, motility, and several other parameters including linearity and velocity. While these systems provide relatively consistent data, most literature suggests equivocal results to manual analysis [45, 46], and there is little evidence suggesting that these expanded parameters provide additional clinical utility.

Leukocytospermia Assessment Semen should be examined for the presence of round cells, which can represent either immature sperm precursor cells or white blood cells. If positive, samples are typically assessed using the myeloperoxidase test. Men with positive leukocytospermia testing should be further assessed for underlying etiologies including smoking and the presence of occult infection, which can be empirically treated using doxycycline [47].

DNA Fragmentation The fidelity of sperm DNA is critical to the successful generation and propagation of a human embryo, and as such the field of male infertility has spent considerable effort into studying assays to assess DNA fragmentation. Numerous assays have been developed including TUNEL, sperm chromatin structure, and sperm chromatin dispersion assays [48]. Despite its theoretical importance, clinical implementation of the data from these assays has proved to be difficult and is limited to specific clinical scenarios such as recurrent pregnancy loss or unexplained infertility. Furthermore, treatment of elevated DNA fragmentation primarily relies on antioxidant therapy or – in the setting of ART – collection of testicular sperm, which may relieve some of the accumulated DNA damage from elevated oxidative stress exposure in ejaculated sperm.

Oxidative Stress It is thought that the root cause of DNA damage in sperm is the presence of elevated oxidative stress. Measurement of oxidative stress can be accomplished via numerous assays including reactive oxygen species measurement using luminol chemiluminescence [49], total antioxidant capacity [49], and direct measurement of the oxidation reduction potential [50].

Viability Testing In cases of severely compromised motility and oligospermia or cryptospermia, sperm viability testing provides an attractive tool to confirm that sperm are alive and can be used successfully for intracytoplasmic sperm injection (ICSI). Some of the most common tests used for this purpose include the eosin-nigrosin stain [51], the hypoosmotic swelling test [52], and the laser-assisted detection tests [53].

Antisperm Antibodies Some semen specimens demonstrate significant sperm agglutination, which can be due to the presence of antisperm antibodies (ASA) from prior trauma or scrotal surgery [54]. These can be measured using the IgG-mixed antiglobulin reaction (MAR) test [55]. If identified, men with ASA can be treated with a host of approaches including immunosuppression, sperm washes, and sperm purification, and/or ICSI can be utilized depending on the clinical scenario [56].

Capacitation Assays The need for sperm to be able to penetrate the zona pellucida and enter the egg, as is necessary in traditional in vitro fertilization, has largely been supplanted by advances in ICSI. As such, the role for capacitation assays has been largely diminished, and these tests are now rarely performed.

11.10 Laboratory Workup

Bloodwork A typical laboratory workup performed in conjunction with semen analysis includes assessment of the HPG axis via measurement of follicle-stimulating hormone and testosterone, both of which are mandatory in men with impaired libido, erectile dysfunction, oligozoospermia or azoospermia, atrophic testis, or abnormal physical exam findings such as testicular atrophy [17]. If hypogonadism is identified, prolactin and luteinizing hormone should also be checked to assess for primary or secondary hypogonadism [18].

Genetics Genetic evaluation for the infertile male is typically reserved for men with severe oligospermia or azoospermia, recurrent pregnancy loss, or men with consanguinity or known syndrome or other high-risk populations. This involves a karyotype to assess for additional chromosomes or macroscopic insertions/deletions. Y-chromosome microdeletion (YCMD) is a special case whereby small deletions within the long arm of chromosome Y in one of three azoospermic factor (AZF) regions (AZFa, AZFb, or AZFc). While men with AZFa and AZFb have not been shown to have sperm on surgical interrogation, up to 75% of men with isolated AZFc mutations will have foci of spermatogenesis and thus should undergo surgical sperm retrieval [57]. While hundreds of single nucleotide polymorphisms have been identified and reported in the literature [58], the clinical utility in routinely assessing for these remains unproven. Finally, CFTR mutation testing is indicated in men with suspected CBAVD or CUAVD. If positive, the female partners should also be tested. All patients with a genetic abnormality on testing should be offered genetics counseling.

11.11 Imaging

Imaging can be a useful adjunctive tool in the diagnostic workup of the infertile male. Physical exam along with laboratory testing and semen testing can often provide sufficient diagnostic information; however in certain circumstances, imaging may be useful. Scrotal ultrasonography is the most commonly utilized imaging modality in this context. Ultrasonography can assess testicular volume, testicular echogenicity, presence or absence of varicocele in the setting of difficult physical exam as well as testicular mass, and epididymal anatomy. Clinicians might order scrotal ultrasonography if the physical exam is challenging or further anatomic information about the scrotal contents is desired. Transrectal ultrasonography can be a useful tool in the setting of obstructive azoospermia to evaluate for dilated seminal vesicles and ejaculatory ducts as well as prostatic utricle or Wolffian duct cysts. In patients with elevated prolactin, cranial MRI is indicated. Lastly, vasography can be performed intra-operatively to evaluate for distal genital tract obstruction in anticipation of operative repair.

11.12 Management

Medical Management of Male Infertility In many cases of oligozoospermia, medical interventions are sufficient to improve sperm parameters and cause a pregnancy. Men who are smoking should be counseled on the importance of cessation, particularly if associated with leukocytospermia. The importance of a healthy diet and healthy body composition also cannot be overstated. Antioxidants and vitamins are also often recommended to decrease oxidative stress, but the evidence for this approach is weak at best. Nevertheless, the risk to this approach appears to be quite low, and for oligozoospermic men with limited options for intervention, this can be considered.

HPG Axis Manipulation for Hypogonadism There are several indications for the treatment of infertile men with medications designed to modulate the HPG axis. Men with hypogonadism but with relatively normal pituitary hormone levels may benefit from treatment, but prescribing these men traditional testosterone replacement therapy is strictly contraindicated due to its suppression of spermatogenesis. Instead, selective estrogen

receptor modulators (SERMs), aromatase inhibitors, or human chorionic gonadotropin (hCG) can be prescribed. SERMs such as clomiphene citrate are mixed agonist/antagonists of the estrogen receptor which exert their effects by increasing GnRH pulse frequency and thus increasing FSH and LH levels. Aromatase inhibitors such as anastrozole work by limiting the conversion of androgens to estrogen. This class of medications is particularly helpful in obese men with elevated estradiol levels. Finally, recombinant hCG can also provide a safe way to increase testosterone in men desiring fertility.

HPG Axis Manipulation for Hypogonadotropic Hypogonadism In cases of hypogonadotropic hypogonadism (e.g., Kallmann syndrome), men desiring fertility should be referred to endocrinologists or male infertility specialists. The most common regimen used in these men consists of initial treatment with hCG and recombinant FSH to restore testicular function.

HPG Axis Manipulation for Idiopathic Subfertility The role for hormonal manipulation in the subfertile man with normal testosterone levels remains controversial. Many providers will consider a trial of off-label clomiphene in these men with the intention of optimizing sperm parameters for natural conception. Similarly, there is evidence supporting medical management in patients with non-obstructive azoospermia (NOA) prior to sperm retrieval to optimize sperm yeilds [59].

11.13 Surgical Management of Male Infertility

TURED For men with ejaculatory duct obstruction, transurethral resection of the ejaculatory ducts (TURED) can restore normal ejaculation volumes and thereby improve fertility. In this procedure, a transrectal ultrasound is performed and the dilated seminal vesicles aspirated for sperm preservation purposes. Many providers then inject methylene blue to provide visual feedback for the subsequent resection [60]. The cystoscope with working element of choice (cold knife, hot knife, hot loop, button, etc.) is then inserted and used to resect the verumontanum until blue efflux is noted. Outcomes are modest but favorable, with 83% of men experienced increased semen volume and 63% of men demonstrating increased semen concentration [61].

Varicocelectomy For men with a clinical varicocele and subfertility or varicocele-related pain, surgical varicocelectomy can be offered. For a detailed review on the management options for varicocele, the reader is referred to a recent systematic review [62] and Cochrane review [63] on the subject. Briefly, varicocelectomy can be accomplished with either surgical or endovascular intervention. Surgical approaches include laparoscopic, retroperitoneal, inguinal, and subinguinal approaches. Regardless of the approach used, success rates are high and range from 75% to 90%. Complications include hydrocele and varicocele recurrence. Testicular loss is exceedingly rare and should be mentioned as a complication.

Despite its well-described role and high prevalence in infertile men, outcomes for fertility purposes remain contentious. On the one hand, Abdel-Meguid [64] conducted a randomized controlled trial and found an odds ratio for pregnancy of 3.0 for varicocelectomy compared to observation. This corresponds to a number needed to treat of 5.3. A Cochrane review subsequently confirmed the benefit of varicocelectomy, but the number needed to treat for this analysis was much higher at 17.

Diagnostic Testicular Biopsy Outside of concern for malignancy or carcinoma in situ, the role for diagnostic testicular biopsy in the infertile male is limited [65]. Most men with azoospermia can usually be correctly categorized as obstructive or non-obstructive based upon a thorough history, semen analysis, and laboratory workup. In cases where the diagnosis for obstruction is equivocal, diagnostic testicular biopsy can be considered to ensure whether spermatogenesis is present prior to a more-involved reconstruction operation. Another viable option for these patients is testicular

sperm extraction with cryopreservation for both diagnostic and therapeutic purposes.

Surgical Sperm Retrieval For men with little to no sperm in their ejaculate, surgical sperm retrieval offers the ability to retrieve sperm directly from the epididymis or the testicle. The specific procedure indicated is dependent upon numerous factors including the etiology of azoospermia (obstructive or non-obstructive), patient anatomy, procedure setting, and management goals. For men with prior vasectomy who wish to father a child and would prefer IVF over surgical reconstruction, percutaneous epididymal sperm aspiration (PESA) using a narrow-gauge needle passed repeatedly into the dilated epididymis offers a minimally invasive approach with good success rates. The use of the operating microscope to target individual tubules is termed a microsurgical epididymal sperm aspiration (MESA) [66]. This procedure can increase yield but requires surgical delivery of the testicle and microsurgical expertise and is less commonly performed. A percutaneous testicular sperm aspiration (TESA) is another for men with obstructive azoospermia, but success rate is typically lower [67]. Non-obstructive azoospermic men are typically managed using surgical testicular sperm extraction (TESE) or microdissection testicular sperm extraction (microTESE or mTESE). This procedure requires surgical delivery of the testicle followed by incision of the tunica albuginea and sharp removal of a portion of the testicular parenchyma and tubules. The use of an operating microscope provides the ability to identify islands of tubules that visually appear to contain spermatogenesis without necessitating large quantities of parenchymal excision, which may lead to hypogonadism. The overall success rates for mTESE are reasonably good for men with NOA and typically hover around 50–60% [68]. Unfortunately, the only factor consistently shown to predict success rates is surgical pathology, which is typically not available preoperatively.

Vasectomy Reversal While the surgical nuances of vasectomy reversal are beyond the scope of this chapter, it is important for clinicians to recognize that vasectomy reversal is an operation commonly performed by urologists with specialty training in male infertility and offers excellent (>90%) technical success rates in most situations. Men with short interval between vasectomy and reversal (<15 years) can commonly be reconstructed using a vasovasostomy, while men with longer intervals or evidence of upstream obstruction at the time of reconstruction may require the more technically challenging vasoepididymostomy.

Conclusions

Male infertility is a broad clinical topic that accounts for roughly half of all cases of infertility, and the inability to conceive a child often conveys significant anxiety and stress for men suffering from this condition. Men with suspected or confirmed infertility should be evaluated and treated by a physician with expertise in reproductive health who can navigate the numerous diagnostic and therapeutic nuances associated with treating this vulnerable population of men.

Clinical Vignette (Cont'd)

After obtaining a thorough history, a physical exam reveals the presence of a left grade 3 varicocele. Semen testing shows oligozoospermia with a semen concentration of 10 million per mL and decreased motility of 20%. He is counseled on management options and elects to proceed with microscopic subinguinal varicocelectomy. Postoperatively, his semen concentration improves to 20 million, and his motility normalizes to 50%. He and his wife successfully conceive 5 months later and subsequently have a healthy baby girl.

11.14 Review Questions

1. What percentage of couples with infertility has a male component as the primary or contributing cause?
   A. 10%
   B. 25%
   C. 50%
   D. 75%

2. What is the traditional cutoff for sufficient sperm number to perform intrauterine insemination?
   A. One million nonmotile sperm
   B. One million motile sperm
   C. Five million nonmotile sperm
   D. Five million motile sperm
3. Which Y-chromosome microdeletion is associated with successful surgical sperm retrieval?
   A. AZFa
   B. AZFb
   C. AZFc
   D. None of the above

11.15 Answers

1. C
2. D
3. C

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