CHAPTER 23

Male Infertility

Phil Vu Bach
Peter N. Schlegel

Introduction

Infertility, defined as the inability to conceive after 12 months of regular, unprotected intercourse, affects 8 million couples in the United States, of which up to 50% have a male contributory factor.[1,2] Overall, up to 12% of men of reproductive age worldwide suffer from male infertility.[3] Fortunately, the past 50 years has seen a tremendous increase in our understanding of male infertility and has paved the way for novel diagnostic and therapeutic strategies to help this cohort of infertile patients. In particular, the advent of advanced reproductive technologies such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) has enabled men, for whom fatherhood could be achieved previously only through donor sperm or adoption, to now father biological offspring.

Currently, both the American Urological Association and the American Society for Reproductive Medicine advocate that the initial screening evaluation of the infertile couple include investigation of both partners in parallel.[4] In this chapter, we will provide an up-to-date outline of evaluation and treatment algorithms that guide the management of the infertile male.

Evaluation of Male Infertility

- *Initial screening evaluation of male infertility should include a thorough history, a physical examination, and two semen analyses.*
- *Semen analyses should be performed after 1 to 5 days of abstinence and be spaced at least 7 days apart.*
- *While not diagnostic of male infertility, semen analysis is a cornerstone in the evaluation of male infertility.*
- *Further investigations of male infertility are directed by the initial screening evaluation, which may be broken up into low semen volume, oligoasthenoteratospermia, or azoospermia.*
- *Endocrine evaluation of male infertility should include at least serum testosterone and follicle-stimulating hormone (FSH).*

When and On Whom to Perform an Evaluation of Male Infertility

An initial screening evaluation on both partners is recommended if a couple has not conceived a pregnancy after 12 months of regular, unprotected intercourse. Alternatively, an earlier evaluation is justified if the female partner is older than 35 years old, if either partner has a medical history or physical findings suggestive of decreased reproductive potential, or if either partner is concerned about the male's reproductive potential. Men who do not have a partner but who are concerned about their reproductive potential should also undergo an initial screening evaluation.

The goals of the evaluation of male infertility are to identify and treat correctable causes of male infertility that could then result in natural pregnancy, to guide treatment options in those for whom natural pregnancy is unlikely to occur, and to identify significant medical problems that are associated with infertility (Box 23.1).

Initial Screening Evaluation

The initial screening evaluation of the infertile male should include a detailed history and physical examination as well as a minimum of two semen analyses.

History and Physical Examination

A thorough reproductive history (Table 23.1) is a critical component of the initial screening evaluation of the infertile male and should cover coital frequency and timing, duration of infertility, prior fertility, developmental history and childhood illnesses (including hypospadias, congenital anomalies, and onset of puberty), current systemic illnesses (especially diabetes mellitus, cystic fibrosis, cancer, and infections), surgical history (with a focus on scrotal, pelvic, retroperitoneal, and inguinal surgeries), sexual history (with a history of sexually transmitted diseases), medications and allergies, and exposure to gonadotoxins (both chemical and environmental toxins, such as heat [Table 23.2]). Additionally, a family history of cryptorchidism, infertility, disordered sexual differentiation, or hypogonadism, and/or

Abstract

Male factor contributes up to 50% of all infertility cases, making the proper evaluation and management of male infertility a critical part of the care of the infertile couple. The evaluation of the infertile male aims to identify correctable causes of infertility that can guide therapeutic decision making for the infertile couple while also detecting significant medical problems related to infertility. The management of male infertility involves a combination of lifestyle, medical, and surgical strategies, and with the advent of advanced reproductive techniques, even the most severe male factor infertility can often be successfully overcome.

Keywords

Male infertility
semen analysis
azoospermia
oligospermia
ejaculation
vasal reconstruction
sperm retrieval
ART

Table 23.1 Important Parts of the Male Infertility History

Infertility history
- Duration
- Prior pregnancies
  - Current versus previous partner
  - Outcome
- Prior fertility evaluation

Sexual history
- Coital frequency and timing
- Erectile function
- Use of lubricants

Past medical history

Developmental history
- Cryptorchidism
- Puberty
- Testicular pathology (e.g., trauma or torsion)
- Hypospadias

Medical history
- Diabetes mellitus
- Neurologic disease (spinal cord injury, multiple sclerosis)
- Fevers or infections (urinary, sexually transmitted, tuberculosis, prostatitis)
- Cancer and treatment (chemotherapy or radiation)
- Genetic disease (Klinefelter, cystic fibrosis)

Surgical history
- Genital (orchidopexy, testicular trauma, vasectomy)
- Pelvic (herniorrhaphy, prostatic, bladder neck)
- Abdominal/retroperitoneal

Family history
- Infertility
- Cryptorchidism
- Disorders of sexual differentiation
- Midline defects
- Cystic fibrosis

Medications

Social history
- Recreational drugs (smoking, alcohol, marijuana, cocaine)
- Environmental/occupational exposure (pesticides, radiation, heavy metals, heat)

Box 23.1 Significant Medical Conditions That May Present as Male Infertility[84,85]

Adult polycystic kidney
Brain tumors
Cystic fibrosis
Diabetes
Hemochromatosis
Hypopituitarism
Klinefelter syndrome
Multiple sclerosis
Pituitary adenoma
Prostate cancer
Retroperitoneal tumors
Spinal cord tumors
Testis cancer
Thyroid disease
Urinary tract infection

Table 23.2 List of Agents and Factors With Potential Adverse Impact on Male Fertility

Medications
- Gonadotoxic agents
  - Antibiotics
  - Nitrofurantoin
  - Erythromycin
  - Tetracycline
  - Gentamycin
  - Chemotherapeutic agents
  - Alkylating agents (cyclophosphamide, ifosfamide)
  - Cisplatin
  - Actinomycin D
  - Marijuana
  - Alcohol
- Androgen production inhibitors
  - Spironolactone
  - Ketoconazole
  - Cimetidine
  - Flutamide
  - 5 alpha reductase inhibitors
- Ejaculatory dysfunction
  - Alpha-blockers
  - Lithium
  - Antipsychotics
  - Tricyclic antidepressants
  - Valproic acid
  - Phenytoin
  - Selective serotonin reuptake inhibitors
- Hypothalamus-pituitary-gonadal axis inhibitors
  - Testosterone
  - Anabolic steroids
  - Monoamine oxidase inhibitors
  - Phenothiazines
  - Diethylstilbestrol
  - Digoxin
  - Alcohol
  - Opioids
- Sperm toxic agents
  - Nicotine
  - Calcium channel blockers
  - Sulfasalazine

Environmental
- Heavy metals (lead)
- Pesticides (dibromochloropropane)
- Heat
- Bisphenol A
- Organic solvents
- Ionizing radiation

a social history with frequent alcohol, tobacco, or recreational drug use may suggest potential etiologies for male infertility.

A general physical examination with an emphasis on the genitalia can also provide important information. Upon initial inspection, note should be taken of obesity, secondary sex characteristics, hair distribution, and gynecomastia. Specific examination of the genitalia should include the phallus, which should be examined for hypospadias, penile curvature, and plaques that may interfere with proper semen deposition within the vagina. Both testes should be examined for size, consistency, and the presence of masses. Eighty-five percent of testicular volume is made up of seminiferous tubules in which spermatogenesis occurs, and testicles smaller than the normal adult size of 20 mL (or 4 cm × 3 cm) may be associated with impaired spermatogenesis.[5]

Careful attention should be paid to the presence, consistency, and nodularity of the epididymides, which may help to identify obstruction and/or infection, while palpation of both vasa deferens can diagnose vasal agenesis, atresia, or injury. More specifically, congenital bilateral absence of the vas deferens (CBAVD) is a clinical diagnosis that can be made on physical examination. Palpation of both spermatic cords in the supine and standing positions both with and

without Valsalva enables the diagnosis of varicocele, which is also a clinical diagnosis. Scrotal ultrasound may be used to confirm the diagnosis of varicocele, but those subclinical varicoceles found only on ultrasound (and not on physical exam) are unlikely to be clinically relevant.[6,7] Finally, a digital rectal exam may help identify dilated seminal vesicles, ejaculatory duct cysts, or utricular cysts that may contribute to obstructive etiologies of male infertility.

Semen Analysis

Along with a thorough history and physical examination, semen analysis has long been the pillar upon which male infertility is evaluated and managed. While an abnormal semen analysis (with the exception of azoospermia) cannot delineate between fertile and sterile, abnormal semen quality is associated with decreased chances of natural conception.[8]

To account for the large degree of biological variability between semen samples, at least two semen analyses should be performed. Patients should be given specific instructions regarding the need for 2 to 5 days of abstinence prior to undergoing semen analysis with the two semen analyses preferably spaced at least 1 week apart.[9] The semen sample can be collected either by masturbation into a specimen cup or by intercourse with the use of a special semen collection condom that does not contain any spermatotoxic agents. In particular, lubricants should be avoided. If a specimen cannot be produced at the laboratory for analysis, it should be kept at room or body temperature during transport and delivered to the laboratory for analysis within 1 hour. Further delays can affect semen and sperm parameters, such as sperm motility, which decreases dramatically after 2 hours.

Parameters examined in routine semen analysis can be broken up into macroscopic and microscopic parameters. Key macroscopic parameters include semen volume, viscosity, color, pH, and coagulation/liquefaction; key microscopic parameters include sperm count/concentration, sperm motility, and sperm morphology. After analyzing the semen analyses of 1859 new fathers from eight countries across three continents, the World Health Organization (WHO) established the normal reference ranges for most of the key parameters of semen analysis (Table 23.3).[10] To establish the reference ranges, the WHO applied a one-sided lower reference limit of the 5th percentile to the semen parameters of the 1859 new fathers. While this methodology does provide lower thresholds for semen parameters in fertile men, it fails to answer the more relevant clinical question of which specific semen parameters and cutoffs are able to delineate between male fertility and subfertility. Efforts to identify specific semen parameters that can distinguish between male fertility and subfertility have instead found that while semen parameters are associated with fecundity, neither sperm concentration, morphology, nor motility could be considered diagnostic of infertility either alone or in combination.[8,11] Rather than a direct diagnostic test of male infertility, the semen analysis should instead be considered an important contributor to the overall picture of male fertility.

Table 23.3 WHO (5th Edition) Reference Values for Semen Analysis[10]

Semen Analysis Parameter	Reference Value
Ejaculate volume	1.5 mL
Sperm concentration	15 million sperm/mL
Sperm count	39 million sperm/ejaculate
Total motility	40%
Total progressive motility	32%
Sperm morphology	4% normal (strict criteria)
Sperm viability	58%
Sperm agglutination	Absent
White blood cells	<1 million leukocytes/mL

Further Investigations and Complete Evaluation

Results from the initial screening evaluation of male infertility may be normal or abnormal. Men with unremarkable reproductive histories and normal semen analyses are highly unlikely to harbor male infertility, and an in-depth assessment of potential female factors should be undertaken. However, if any abnormalities are detected on the initial screening evaluation of male infertility, further investigations that constitute the complete evaluation (often driven by the specific abnormalities detected) are required.

Endocrine Evaluation

While a specific endocrine cause of impaired sperm production is identified in only 2% of men with male factor infertility, an endocrine evaluation is still indicated in men with abnormal semen analyses (especially in those with sperm concentrations less than 10 million/mL), abnormal sexual function, or findings suggestive of endocrinopathy.[4,12] At minimum, an endocrine evaluation for male infertility should include serum FSH and morning testosterone levels. A low serum testosterone level (<300 ng/dL) should prompt the testing of a second morning serum testosterone level alongside serum LH and prolactin levels.[13] The importance of obtaining a second morning serum testosterone level should not be understated since gonadotropins and testosterone are typically released in a pulsatile manner, and testosterone levels commonly demonstrate a physiologic decline over the course of the day. The characteristic hormone profiles for various etiologies of male infertility are described in Table 23.4. In particular, while normal FSH levels (≤7.6 IU/L) do not guarantee normal spermatogenesis, elevated FSH levels often indicate an abnormality with spermatogenesis.[14]

Low Semen Volume

- *Low semen volume may be attributable to ejaculatory dysfunction, hypogonadism, ejaculatory duct obstruction, or CBAVD.*
- *An endocrine evaluation, postejaculatory urinalysis, and transrectal ultrasound (TRUS) can help identify the cause of low semen volume.*

Postejaculatory Urinalysis

The presence of low semen volume (<1.0 mL) should prompt a systematic algorithm to delineate the cause (Fig. 23.1). Potential etiologies for low semen volume include improper collection, CBAVD, hypogonadism, ejaculatory dysfunction, and ejaculatory duct obstruction. In men with normal serum

Table 23.4 Characteristic Hormone Profiles for Various Etiologies of Male Infertility

Condition	Testosterone	FSH	LH	Prolactin
Normal	Normal	Normal	Normal	Normal
Primary testicular failure				
Hypospermatogenesis	Normal/Low	High	High/Normal	Normal
Maturation arrest	Normal	Normal	Normal	Normal
Sertoli cell only	Low	Very high	High	Normal
Hypogonadotropic hypogonadism	Low	Low	Low	Normal
Hyperprolactinemia	Low	Normal/Low	Low	High
Klinefelter syndrome	Low	Very high	High	Normal

FSH, Follicle-stimulating hormone; *LH*, luteinizing hormone.

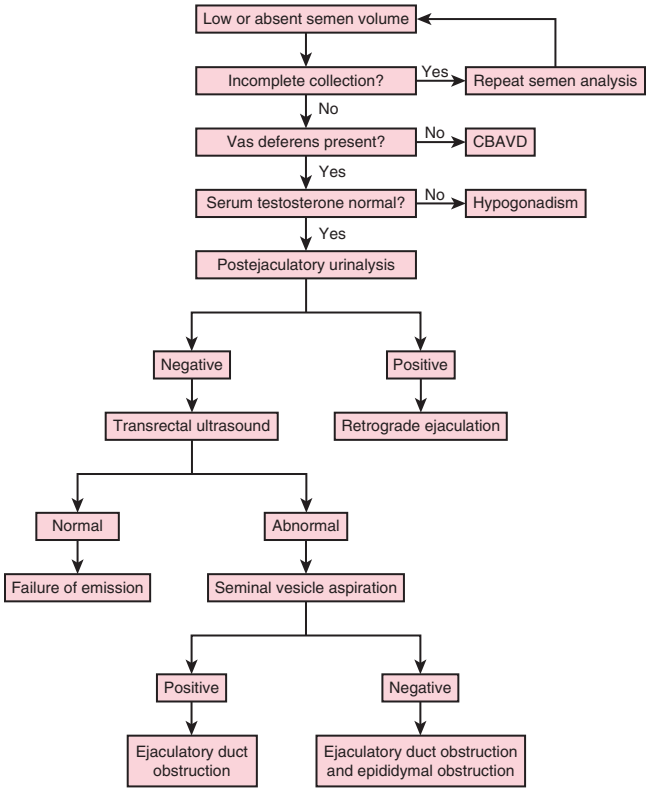

FIGURE 23.1 Algorithm for evaluation of men with low/absent semen volume. *CBAVD*, Congenital bilateral absence of the vas deferens.

testosterone levels and palpable vasa deferentia, a postejaculatory urinalysis should be performed to rule out retrograde ejaculation. The presence of a greater sperm count in the urine specimen pellet postejaculation following centrifugation is indicative of retrograde ejaculation.[15]

Transrectal Ultrasound

The absence of seminal fructose or a seminal pH less than 7 may suggest absence/atrophy of the seminal vesicles or ejaculatory duct obstruction. The diagnostic tool of choice for ejaculatory duct obstruction is TRUS. The presence of midline cysts, dilated seminal vesicles (anterior-posterior diameter >1.5 cm), or dilated ejaculatory ducts (>2.3 mm) on TRUS is suggestive, but not diagnostic, of complete or partial ejaculatory duct obstruction.[16,17] If dilated seminal vesicles are seen on TRUS, TRUS-guided seminal vesicle aspiration may be performed to confirm the diagnosis (with simultaneous cryopreservation of any sperm found).[18] Patients with unilateral absence of the vas deferens and low volume azoospermia may have a variant of CBAVD and should undergo genetic screening for cystic fibrosis transmembrane conductance regulator (CFTR) before TRUS. Forty percent of men with CBAVD and a negative CFTR screen will demonstrate renal anomalies and should be additionally screened with abdominal ultrasound. On the other hand, those with CBAVD and a positive CFTR screen rarely exhibit renal anomalies and do not warrant abdominal ultrasound.[19,20] Men with detectable CFTR mutations should undergo thorough genetic counseling prior to any fertility treatment.

Oligospermia/Asthenospermia/Teratospermia

- *Oligoasthenoteratospermia may be caused by varicocele, genetic abnormalities, immunologic infertility, or gonadotoxic exposures.*
- *Genetic testing comprises primarily of karyotype and Y-microdeletion testing and is indicated in men with severe oligospermia or nonobstructive azoospermia (NOA).*

Infertile men may demonstrate abnormalities in sperm concentration (oligospermia), motility (asthenospermia), and/or morphology (teratospermia), which are often seen together. Potential causes for these abnormal semen parameters include endocrinopathies, genital tract infections, immunologic antisperm antibodies (ASA), varicoceles, and genetic abnormalities (Fig. 23.2).

Semen Leukocytes

Genital tract infection or inflammation may result in the presence of leukocytes in the semen, which can negatively affect sperm motility and function via the overproduction of reactive oxygen species. Since both leukocytes and immature germ cells appear as "round cells" on microscopy, differentiating between the two types of cells can be tricky, but can be accomplished using cytologic staining or immunohistochemistry.[21] Those with pyospermia (>1 million leukocytes/mL) should be evaluated further to rule out or treat genital tract infection or inflammation. Since 83% of semen cultures in asymptomatic infertile men with pyospermia are positive with multiple organisms, the workup should

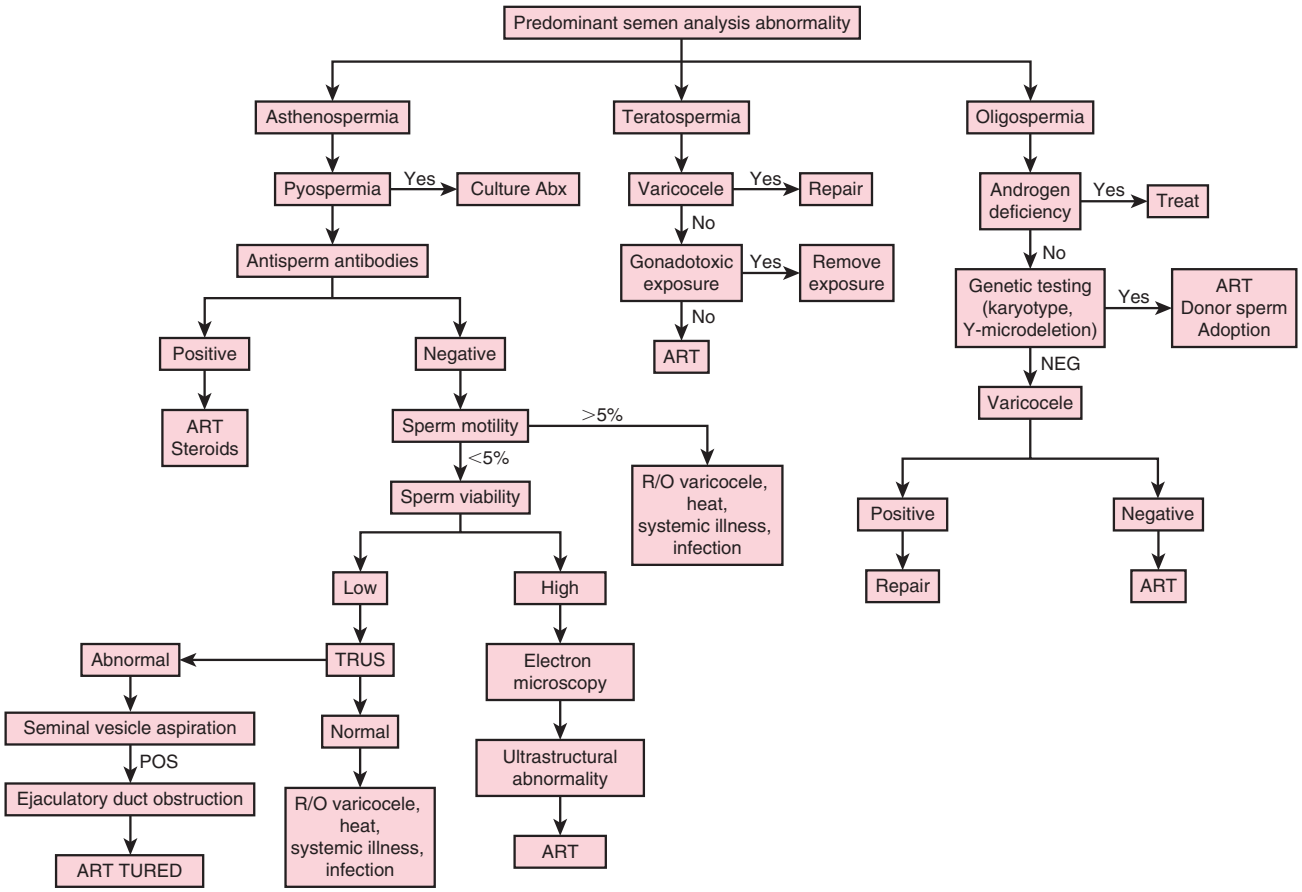

FIGURE 23.2 Algorithm for the evaluation and management of men with oligoasthenoteratospermia. *ART*, Assisted reproductive technique; *NEG*, negative; *POS*, positive; *TRUS*, transrectal ultrasound; *TURED*, transurethral resection of the ejaculatory ducts.

include an examination of expressed prostatic secretion for leukocytes instead, as well as a urethral culture for *Chlamydia* and *Mycoplasma*.[22]

Antisperm Antibodies

Patients with isolated asthenospermia or sperm agglutination may be bound by ASA, which are a rare cause of male infertility that can form following a breach of the blood-testis barrier after vasectomy, trauma, torsion, biopsy, or testicular cancer. ASA, which are not routinely tested for, can be found in the serum or seminal plasma via indirect antibody agglutination assays or directly bound to the sperm via a direct immunobead test. ASA are considered significant if over 50% of sperm are bound by ASA.[23] Since the presence of ASA correlates with spermatogenesis, the detection of serum ASA also may be clinically useful in differentiating azoospermic men with obstructive etiologies versus those with nonobstructive etiologies without the need for a diagnostic testicular biopsy.[24] Azoospermic men with positive ASA are more likely to have an obstructive etiology.

Genetic Testing

Genetic abnormalities can cause problems with sperm production or transport, and men with severe oligospermia (sperm concentration <5 million/mL) or NOA should be worked up for genetic abnormalities (Table 23.5).[4] In addition to the previously discussed CFTR mutations, karyotypic chromosomal abnormalities and Y-microdeletions are of concern. In total, genetic abnormalities are estimated to account for 15% to 30% of male infertility, though the overwhelming majority of these abnormalities have yet to be discovered or understood.[25]

Chromosomal abnormalities are more common in infertile men, with the prevalence of chromosomal abnormalities inversely proportional to sperm count. About 10% to 15% of azoospermic men harbor chromosomal abnormalities compared to 5% of men with severe oligospermia and <1% of men with normal sperm concentrations.[26-28] The most common chromosomal abnormality in infertile men is 47,XXY (Klinefelter syndrome), although inversions and balanced translocations are more prevalent in infertile men compared to fertile men.[28]

Deletions of clinically relevant sections from the azoospermia factor regions (AZF) on the long arm of the Y chromosome (Yq11) are found in up to 17% of men with NOA or severe oligospermia.[29] These Y-microdeletions can be categorized by their specific locations, which are prognostic of their ultimate impact on spermatogenesis and infertility. Men with deletions in the AZFa or AZFb regions are azoospermic with a near 0% chance for successful sperm retrieval.[30] In contrast, men with deletions in the AZFc region may have severe oligospermia, while 65% to 75% of those with azoospermia produce sufficient sperm for testicular sperm extraction (TESE) and for use in ICSI.[30]

Table 23.5 Common and Known Genetic Abnormalities in Male Infertility[86-88]

Genetic abnormality	Phenotype	Frequency
Chromosomal abnormality		
Klinefelter syndrome (47,XXY)	• Nonobstructive azoospermia, sperm retrieval rate up to 65% at microTESE • Hypogonadism	1:500 of newborn males
47,XYY	• Often phenotypically normal with variable sperm counts (normoozospermia to azoospermia)	1:1000 of newborn males
46,XX male	• Azoospermia with Sertoli-cell only testicular histopathology	1:20,000 of newborn males
Chromosomal translocations/ inversions	• Autosomal inversions can result in phenotypically normal males, but with oligospermia or azoospermia • Robertsonian translocations can cause recurrent miscarriage and/or offspring with genetic abnormality	1:600–1:1000 of newborn males
YCMD		10%–15% of men with severe oligospermia or NOA
AZFa	• Azoospermia and Sertoli-cell only pattern on testicular histopathology • Sperm retrieval rate of 0% at microTESE	2%–5% of YCMD
AZFb	• Azoospermia and uniform maturation arrest pattern on testicular histopathology • Sperm retrieval rate of 0% at microTESE	13%–16% of YCMD
AZFc	• Severe oligospermia to azoospermia • Sperm retrieval rate of up to 75% at microTESE	60%–75% of YCMD
Combination deletions	• Azoospermia with very poor sperm retrieval prognosis if AZFa or AZFb regions involved	10%–14% of YCMD
Single gene mutations		
CFTR gene mutations	• OA due to congenital bilateral absence of vas deferens • Clinical cystic fibrosis may also have chronic pulmonary obstruction/infection and pancreatic insufficiency	1:25 carriers, 1:2500 of live births
Kallman syndrome (*KAL1* and *FGFR1*)	• Hypogonadotropic hypogonadism • Range of testicular histopathology with recovery of spermatogenesis following hormonal treatment	1:30,000 of live births
AR gene mutations	• Varies depending on severity of AR deficiency • Female phenotype and Sertoli-cell only in AR negative or low AR patients • Male phenotype with infertility for AR positive patients • Intact spermatogenesis for abnormal AR patients	1:60,000 of live births
INSL3-LGR8	• Cryptorchidism	4%–5% of newborn males

AR, Androgen receptor; *microTESE*, microdissection TESE; *NOA*, nonobstructive azoospermia; *OA*, obstructive azoospermia; *TESE*, testicular sperm extraction; *YCMD*, Y-chromosome microdeletions.

Sperm DNA Fragmentation

Given the limitations of the conventional semen analysis in detecting male infertility, the use of sperm DNA fragmentation testing has grown in popularity as a diagnostic and prognostic tool, especially in the setting of recurrent pregnancy loss either by natural or assisted means. Sperm DNA damage is rarely seen in fertile males, but it can be found in 8% of infertile men with normal semen analyses, and in 17% of infertile men with abnormal semen analyses.[31] Sperm DNA damage may include intrinsic causes, such as abnormalities in DNA compaction and protamine deficiency, or extrinsic causes, such as heat, gonadotoxins, varicocele, smoking, and radiation. There are multiple assays available to measure sperm DNA fragmentation, including direct assays like Comet gel electrophoresis and terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate-nick end labeling (TUNEL), and indirect assays, such as sperm chromatin structure assay (SCSA) and sperm chromatin dispersion (SCD or Halo). As a relatively recent addition to the armamentarium of tools to investigate male infertility, our understanding of sperm DNA fragmentation remains incomplete and its use is not yet routine. However, while not yet definitive, the evidence does suggest a role for sperm DNA fragmentation in predicting IVF and ICSI outcomes, with elevated sperm DNA fragmentation appearing to be more closely associated with poor reproductive outcomes in IVF than in ICSI.[32-34] More specifically, sperm DNA fragmentation may be useful in helping couples decide which assisted reproductive technique (ART) modality to pursue in order to maximize their chances of conception.

Other Genetic Anomalies

While close to 2300 genes have been implicated in spermatogenesis, our understanding of their causative roles in male infertility is still in nascent stages.[35] However, advances in techniques, such as next-generation whole exome or whole genome sequencing, single nucleotide polymorphism (SNP) arrays, and array comparative genomic hybridization analysis, have dramatically helped to improve our understanding of these other genetic abnormalities that contribute to male infertility by enabling the study of numerous genes in parallel. In particular, investigation of asthenoozospermic men with primary ciliary dyskinesia has enabled the identification of new genetic abnormalities that impair the axoneme's structure and function *(DNAI1, DNAI2, DNAAF1/LRRC50, DNAAF2/Ktu, LRRC6, ZMYND10, CCDC40)*.[36]

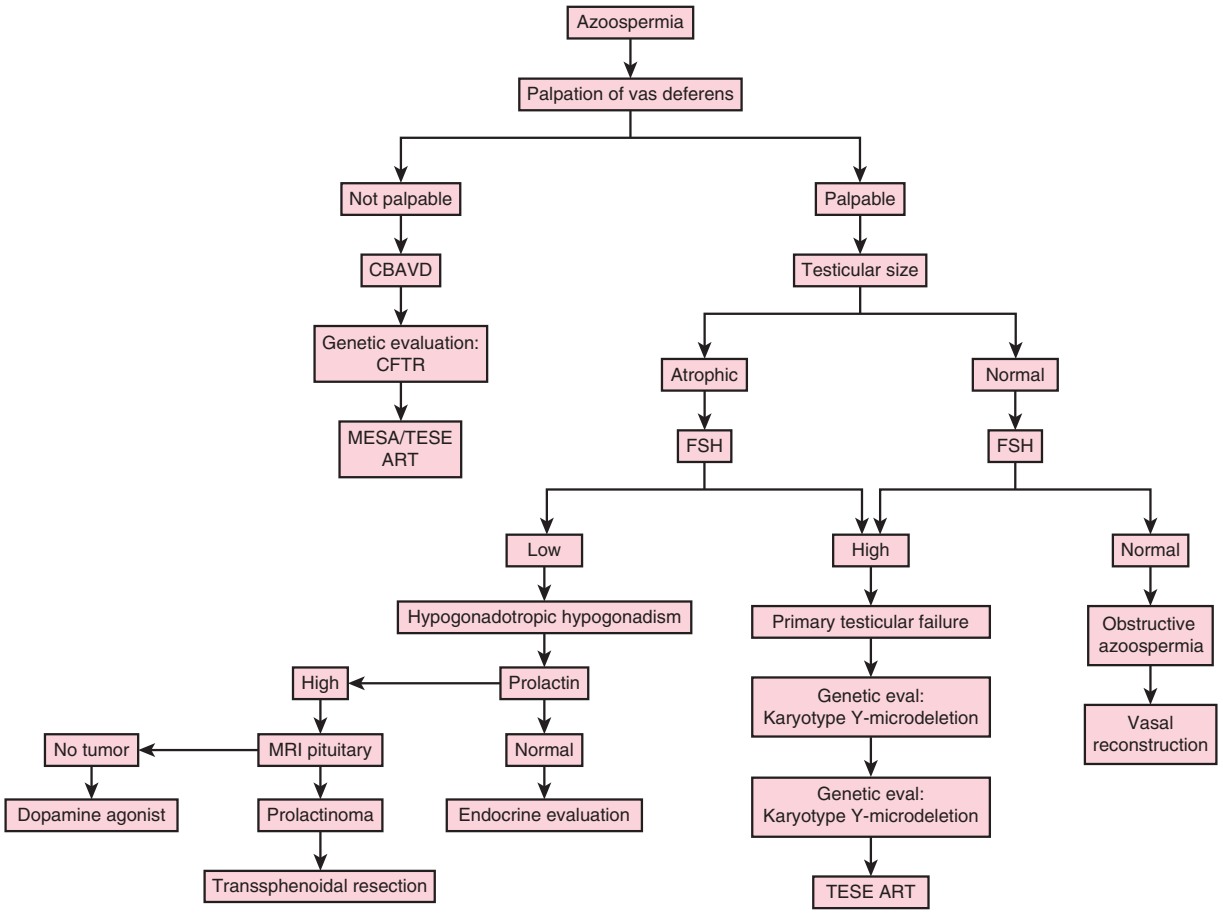

FIGURE 23.3 Algorithm for the evaluation and management of men with azoospermia. *CBAVD*, Congenital bilateral absence of the vas deferens; *CFTR*, cystic fibrosis transmembrane conductance regulator; *FSH*, follicle-stimulating hormone; *MESA*, microsurgical epididymal sperm aspiration; *MRI*, magnetic resonance imaging; *TESE*, testicular sperm extraction.

Other genes known to cause male infertility include the X-linked *KAL1* and the autosomal *FGFR1*, which both result in idiopathic hypogonadotropic hypogonadism (HH), or Kallman's syndrome when also associated with anosmia.[37] Genes causing teratoozospermia include *Aurora kinase c*, which has been found to cause macroozospermia, particularly in North African men, and *SPATA16*, *PICK1*, and *DPY19L2*, which have been shown to cause globoozospermia.[38,39]

In addition to the aforementioned single gene mutations, promising work is occurring in the field of epigenetics, or the regulation of gene expression without modification of the gene sequence. Investigation of various epigenetic processes, such as DNA methylation, post-translational histone modification, chromatin remodeling, and microRNAs, may help unlock the etiology behind many cases of male infertility that are currently classified as idiopathic, and may identify new diagnostic and therapeutic strategies for the management of male infertility.

Azoospermia

- *The critical distinction that needs to be made in the evaluation of azoospermia is obstructive versus NOA.*

A complete lack of sperm in the ejaculate can be caused either by obstructive etiologies (i.e., ductal obstruction) or by nonobstructive etiologies (i.e., testicular failure), which represents the critical distinction that needs to be made in the evaluation of men with azoospermia. Using many of the investigations outlined in Fig. 23.3 provides the information necessary to make the diagnosis that will drive the ultimate management of the azoospermic male. In rare equivocal cases where a testicular biopsy is needed to differentiate obstructive from NOA, it should be performed in the operating room with the surgeon ready to proceed immediately either to reconstruction of the male reproductive tract or to sperm retrieval.

Management of Male Infertility

- *Potentially effective lifestyle modifications for male infertility include counseling on coital practices, avoidance of spermatotoxic lubricants, smoking cessation, obesity reduction, and decreased exposure to wet heat.*
- *Men should discontinue their use of anabolic steroids or exogenous testosterone.*

Lifestyle Modifications

Counseling on coital practices, including the appropriate frequency and timing of intercourse and the avoidance of potentially spermatotoxic lubricants, may be an important

and productive intervention for many patients. If required, rather than using many of the commercially available lubricants, Pre-Seed, canola oil, and raw egg white appear to be sperm-friendly coital lubricants.[40,41]

Men using anabolic steroids or exogenous testosterone should be informed of the deleterious impact these medications have on spermatogenesis via inhibition of the pituitary-gonadal hormone axis, and counseled to discontinue their use. Similar warnings should be given to men using other medications or recreational drugs known to hinder spermatogenesis (see Table 23.2). Smoking, which is linked to decreased semen quality that results in decreased fecundity and lower success rates even with assisted reproduction, should be strongly discouraged.[42-44] Since obesity is associated with decreased semen parameters, weight loss should be encouraged.[45-47] Increased physical activity, which has been shown to improve semen parameters, but not necessarily clinical pregnancy or live birth rates following infertility treatment, should be encouraged.[48]

Routine exposure to wet heat via saunas, hot tubs, or hot baths should be discouraged as it can increase intratesticular temperature and transiently hinder spermatogenesis and sperm quality.[49,50] While an excellent form of aerobic exercise, bicycling may negatively affect semen parameters due to the increased scrotal temperature associated with scrotal compression against the saddle.[51] Men who biked more than 1.5 hours per week had 34% lower sperm concentrations than those who did not bike.[48] Of note, given that the spermatogenic cycle is typically 60 to 76 days long, recovery from a spermatogenic insult may take up to 3 months to resolve.[52]

Hormone Optimization

- *Men with low serum testosterone should be treated with medications that will not inhibit the hypothalamic-pituitary-gonadal axis, such as selective estrogen receptor modulators (SERM) or gonadotropins.*
- *Men with excess estrogen levels may benefit from treatment with aromatase inhibitors.*

Treatment of diagnosed hormonal abnormalities to optimize sperm production should occur before more invasive strategies are undertaken. Treatable endocrinopathies include hyperprolactinemia, hypothyroidism, and congenital adrenal hyperplasia. Men with low serum testosterone (<300 ng/mL) should be managed with agents that will increase serum testosterone without suppressing the hypothalamic-pituitary-gonadal axis, such as a SERM or human chorionic gonadotropin (hCG). A recent meta-analysis reviewing the use of SERM (clomiphene or tamoxifen) in infertile men with oligo and/or asthenoteratoozospermia showed an association between SERM use and increased pregnancy rates (odds ratio: 2.42; $P = 0004$) with no significant differences in complication rates between the treated and the control groups.[53] Men with HH may benefit from treatment with both hCG to induce testosterone production and FSH to stimulate spermatogenesis.[54-56] Another treatment option for men with HH and a functioning pituitary gland is with pulsatile gonadotropin-releasing hormone (GnRH).[56] Patients with excess estrogen levels manifested by low serum testosterone (<300 ng/mL) and decreased testosterone/estradiol ratios (<10) should be treated with an aromatase inhibitor (such as anastrozole, 1 mg PO daily), which increases circulating testosterone and decreases estradiol to enhance intratesticular testosterone levels and improve spermatogenesis.[57-59]

Ejaculatory Dysfunction

- *Retrograde ejaculation may be treated with sympathomimetic medications or with bladder harvest of sperm for use in ART.*
- *Men with anejaculation may be treated with penile vibratory stimulation (PVS) or rectal probe electroejaculation (EEJ).*

Retrograde ejaculation diagnosed on post-ejaculatory urinalysis can be treated with sympathomimetic medications to promote closure of the bladder neck at ejaculation or with bladder harvest of sperm for use in ART. Anejaculation, or lack of ejaculation, can occur in men with pelvic nerve damage from diabetes mellitus, retroperitoneal surgery, multiple sclerosis, spinal cord injury, or psychosocial causes. The use of PVS or rectal probe EEJ can help to procure a semen sample containing sperm for use with ART. In particular, PVS, which often does not require general anesthesia, works best in men with complete spinal cord injuries above T10, with up to 86% of patients able to achieve ejaculation with PVS.[60,61] On the other hand, only 0% to 15% of men with spinal cord injuries below T10 were able to achieve ejaculation with PVS.[60,62] In men with anejaculation from other etiologies or after failure with PVS, EEJ is preferred and can produce ejaculation in 92% of men with anejaculation from spinal cord injury.[60] Of note, since both PVS and EEJ can cause autonomic dysreflexia in men with spinal cord injuries at or above T6, blood pressure monitoring and premedication with nifedipine should be considered.[63] If these techniques fail, then surgical sperm retrieval with ART can be employed to circumvent the inability to ejaculate.

Ejaculatory Duct Obstruction

- *The ideal management for men with ejaculatory duct obstruction is sperm retrieval and ART, although those opposed to ART may be managed with transurethral resection of the ejaculatory ducts (TURED) or transurethral ejaculatory duct dilation.*

Ejaculatory duct obstruction is suspected in men with azoospermia, severe oligospermia, and/or asthenospermia with low semen volume, at least one palpable vas deferens, low semen pH, and negative semen fructose. Once confirmed, ejaculatory duct obstruction can be managed via TURED or transurethral dilation of the ejaculatory ducts, with 65% of men having significant and durable improvements in semen quality (Fig. 23.4).[64] Potential complications of transurethral management of ejaculatory duct obstruction can occur in 20% to 26% of patients and may include epididymitis, urine reflux into the excurrent ducts, and retrograde ejaculation.[64,65] Given the high complication rates associated with TURED for the management of ejaculatory duct obstruction, it should be reserved for patients who are counseled regarding its risks, and who are unwilling to undergo IVF.

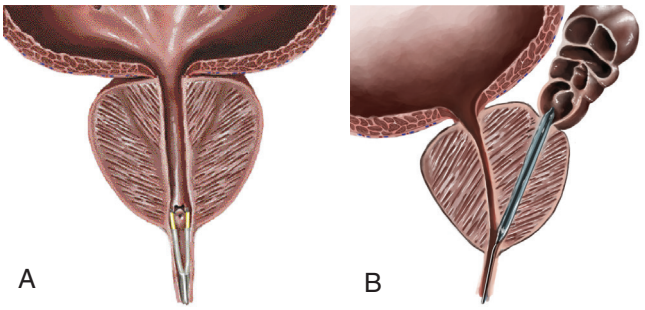

FIGURE 23.4 Techniques for transurethral resection of the ejaculatory ducts (A) and transurethral dilation of the ejaculatory ducts (B), which can be used to relieve ejaculatory duct obstruction. *(Figure courtesy Vanessa Dudley.)*

Pyospermia

- *Pyospermia should be treated with antibiotic therapy only after culture confirmation of bacterial infection.*

Pyospermia associated with a bacteriological infection should be managed with an appropriate course of culture-specific antibiotics. However, without concrete evidence of bacteriological infection, the management of pyospermia is controversial, though a limited course of a broad-spectrum antibiotic, such as doxycycline or trimethoprim-sulfamethoxazole, along with frequent ejaculation, has been shown to decrease semen leukocyte concentration.[66,67]

Immunological Infertility

- *ASA may be bypassed using ICSI, but also can be managed with long-term steroid therapy.*

Since the presence of ASA is often associated with obstruction of the genital tract, any lesions should be sought out and corrected. In men with persistent ASA, the management focuses on two broad strategies: immunosuppression or ART. Immunosuppression can be achieved using 6 to 9 months of corticosteroid therapy, which results in consistent reductions in antibody titers and in pregnancy rates ranging from 6% to 50%.[68] The potential complications of long-term steroid therapy are severe and must be accounted for prior to the initiation of immunosuppression.[69] Semen also can be either processed in the laboratory in an attempt to remove ASA prior to intrauterine insemination (IUI) or injected directly into an oocyte with ICSI. Due to the potentially significant complications of long-term steroid therapy and the advent of ART, only patients with an objection to IVF should be offered steroid therapy.

Varicocele Repair

- *There is no benefit to repairing subclinical varicoceles.*
- *The repair of clinical varicoceles is controversial, but recent evidence suggests an improvement in pregnancy rates after repair.*
- *Microsurgical inguinal or subinguinal repair is the technique of choice for varicocele repair.*

The decision on whether or not to repair clinical varicocele in the subfertile male remains controversial, although

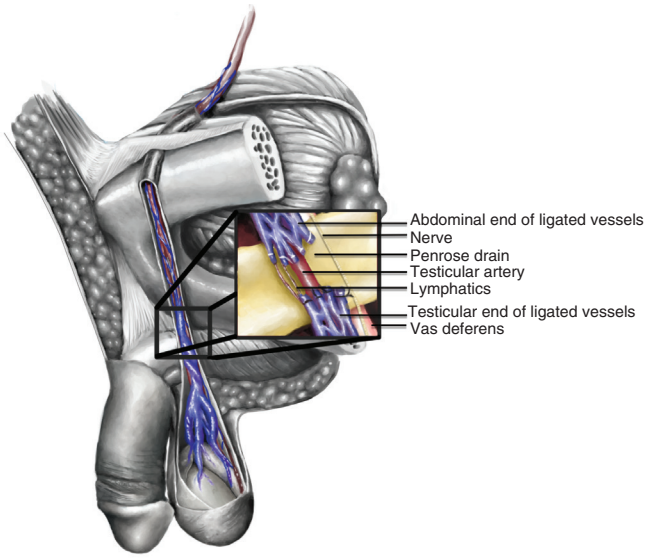

FIGURE 23.5 Representation of spermatic cord following completion of microsurgical varicocelectomy. All internal and external spermatic veins are ligated and divided, leaving only the testicular artery, vas deferens, deferential vessels, lymphatic channels, and nerves. *(Figure courtesy Vanessa Dudley.)*

growing evidence suggests a beneficial role for varicocele repair in this population. Meta-analyses trying to answer the question of the impact of varicocele repair on male fertility have been fraught with heterogeneity that makes it difficult to draw definitive conclusions. However, a recent Cochrane subgroup meta-analysis, which excluded studies of men with normal semen analyses and/or subclinical varicoceles, suggests an association between varicocele repair and improved pregnancy rates.[70] In particular, the evidence suggests that 30% to 50% of infertile couples who are candidates for only ART due to low semen quality may improve to the point of being able to downstage the level of ART needed to conceive or even to enable natural conception following varicocele repair.[71] Currently, the American Society for Reproductive Medicine guidelines suggest varicocele repair for two patient populations: adolescents with reduced ipsilateral testicular size, and the infertile couple in which the man has a clinical varicocele, an abnormal semen analysis, and a partner with normal or correctable fertility.[72] On the other hand, the question of whether to repair subclinical varicoceles is less controversial, with the evidence suggesting minimal benefit to the repair of these varicoceles.[73]

Many techniques for varicocele repair exist, including microsurgical subinguinal or inguinal, open subinguinal or inguinal, retroperitoneal, laparoscopic, percutaneous radiographic embolization, and sclerotherapy. While the success rates between the various techniques are similar, there are differences in the rates of complications, such as hydrocele and recurrence (Table 23.6). A meta-analysis from 2009 suggested that microsurgical varicocele repair (Fig. 23.5) was the gold standard for varicocele repair with both the lowest rate of hydrocele (0.4%) and of recurrence (1%).[74]

Vasal Reconstruction

◆ *Obstructive azoospermia (OA) may be treated with vasal reconstruction with either vasovasostomy or vasoepididymostomy.*

The most common etiology for OA is vasectomy, though it can also result from iatrogenic injuries (especially after inguinal hernia repair) and idiopathic causes. Of the 7% of American men who report having had a vasectomy, 20% also report a desire for future children.[75]

At the time of vasal reconstruction, if distal and proximal patency is confirmed, then a vasovasostomy is performed, in which the two cut ends of the vas deferens are anastomosed (Fig. 23.6). About 70% to 97% of men are likely to have a return of sperm to the ejaculate following vasovasostomy with pregnancy rates ranging from 38% to 93%.[76,77] However, if there is suspicion of secondary epididymal obstruction, then a vasoepididymostomy is performed instead, with the abdominal vas deferens anastomosed to the epididymis (Fig. 23.7). Also, 30% to 90% of men will have a return of sperm to the ejaculate following vasoepididymostomy with subsequent pregnancy rates ranging from 20% to 50%.[78] Due to the delicate nature of both surgeries, almost all vasal reconstructions are performed microsurgically.

Table 23.6 Summary of Varicocele Repair Techniques[89,90]

Technique	Hydrocele formation (%)	Recurrence rate (%)
Open retroperitoneal	6.4–10	7–35
Open conventional inguinal	7.3	0–37
Laparoscopic retroperitoneal	0–9.4	2.2–6.1
Microsurgical inguinal/ subinguinal	0.2–1.6	0–3.0
Radiographic	0	2–24

Assisted Reproductive Techniques

◆ *ART are the last line in the management of the infertile male.*

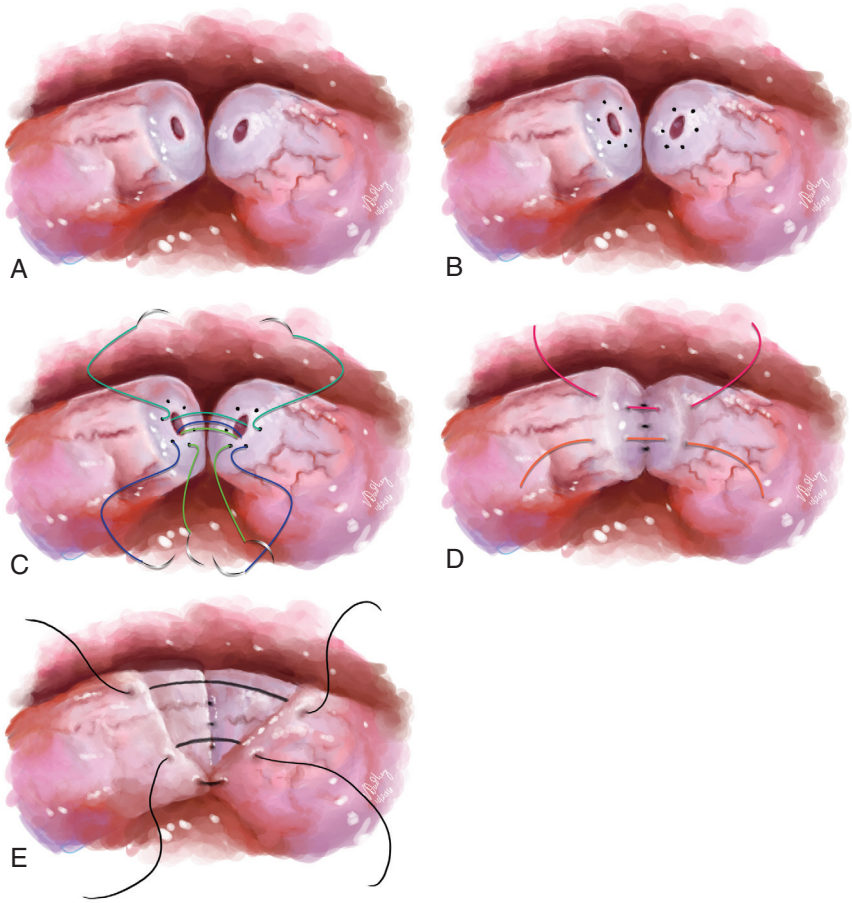

FIGURE 23.6 **Vasovasotomy.** Microsurgical anastomosis of patent abdominal and testicular vasal ends in three layers using 10-0 and 9-0 nylon sutures. (A) Approximation of testicular and abdominal ends of the vas deferens. (B) Microdot placement to assure accurate needle placement. (C) Mucosal layer suture placement. Note that this layer should be full thickness to avoid having sutures prevent apposition of muscular edges (shown as partial thickness for demonstration purposes). (D) Muscular sutures with 9-0 placed between mucosal layer sutures. Note this suture should not penetrate mucosal layer. (E) Adventitial sutures should be mattressed around the perivasal vessels to secure hemostasis. 6-0 Polypropylene can be used for this layer. *(Figure courtesy Vanessa Dudley.)*

- *Different types of ART are recommended for men with differing severities of infertility: IUI for those with moderate infertility, IVF for severe infertility, and ICSI for extreme infertility.*
- *Sperm can be retrieved from men with NOA using microdissection TESE.*

For men in whom the aforementioned lifestyle, medical, and surgical strategies fail, ART is the final step. ART can be subdivided into IUI, IVF, and ICSI (see Chapters 31 and 32). From the male perspective, deciding which ART strategy is the most appropriate to use depends primarily on the level of impairment as defined by the number of sperm that can be retrieved (Fig. 23.8). Men with total motile sperm concentrations above 5 million/mL in the ejaculate, those with immunological infertility, and those with anatomic problems precluding sperm delivery (such as hypospadias) are candidates for IUI. Men with a total motile sperm concentration of 500,000 to 5 million/mL either surgically retrieved or in the ejaculate are suitable candidates for IVF, while those with total motile sperm concentrations below 500,000/mL should consider ICSI, which theoretically requires only one single viable sperm to produce a pregnancy.

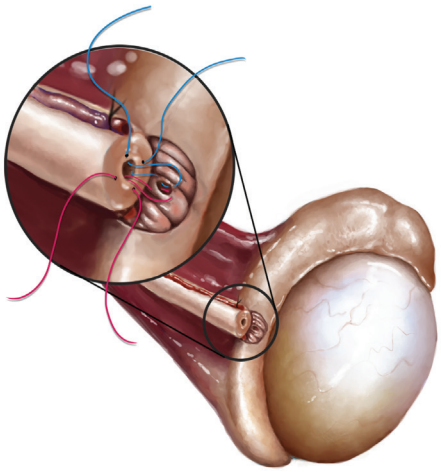

FIGURE 23.7 Vasoepididymostomy. Microsurgical anastomosis of abdominal vas deferens to epididymal duct using longitudinal end-to-side intussusception technique. *(Figure courtesy Vanessa Dudley.)*

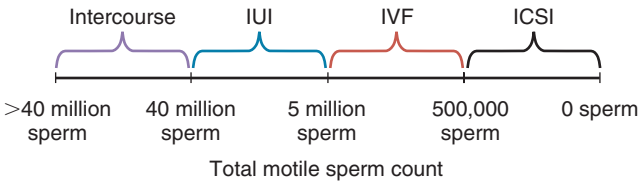

FIGURE 23.8 Level of assisted reproduction recommended for varying degrees of male subfertility based on total motile sperm count. *ICSI,* Intracytoplasmic sperm injection; *IUI,* intrauterine insemination; *IVF,* in vitro fertilization.

For men with iatrogenic OA, vasal reconstruction has been found to be a more cost-effective management strategy than ART, with the value proposition more dependent on female age and fertility potential than on obstructive interval.[79,80] Ultimately, the decision of whether to pursue vasal reconstruction or ART in men post-vasectomy will vary with each couple and will rely on factors such as female age/fertility potential, desired number of children, and willingness to undergo IVF. In short, couples in which the maternal fertility potential is less than 1 year should favor ART, while those in which that potential is greater than 1 year and/or who desire multiple children should favor vasal reconstruction.

Sperm Retrieval

The goal of sperm retrieval is to obtain a maximal amount of viable sperm for use in ART while minimizing the amount of damage to the reproductive tract. Different techniques are available for use in men with OA and for those with NOA (Table 23.7). In men with OA, sperm can be successfully retrieved in almost all patients from the vas deferens via vasal aspirate; from the epididymis via either percutaneous epididymal sperm aspiration or microsurgical epididymal sperm aspiration; and/or from the testicle via either testicular sperm aspiration (TESA) or TESE.

On the other hand, men with NOA present a much greater challenge, with traditional sperm retrieval rates of only 25% to 50%. Because of the poor sperm production in men with NOA, sperm can often be retrieved only from the testicle. Variations of TESE that have been developed to improve the success rate of sperm retrieval for use in ICSI in men with NOA include microdissection TESE (microTESE), in which an operating microscope is used to identify and remove fuller seminiferous tubules within the testicle that are more likely to harbor spermatogenesis (Fig. 23.9).[81] MicroTESE, which results in the removal of much less testicular tissue than TESE, has resulted in both an improvement in sperm retrieval rates (Table 23.8) and a decrease in complication rates when compared to TESE.[82] Other strategies that have been developed include fine-needle aspiration mapping, in which multiple diagnostic fine needle aspirations are systematically taken in a bid to create a map of spermatogenesis locations within the testis that can be used to direct future TESA or TESE at the time of ICSI.[83]

Conclusion

With male factor contributing to 50% of infertility, the appropriate and concurrent management of the male is critical. While the evaluation of the infertile male aims to identify correctable causes of infertility that can guide therapeutic decision making for the infertile couple, it can also detect significant medical problems related to infertility. The management of male infertility involves a combination of lifestyle, medical, and surgical strategies, but with the advent of ICSI and surgical sperm retrieval techniques, even the most severe male factor infertility often can be successfully overcome.

Table 23.7 Summary of Sperm Retrieval Techniques for Men with OA[91-93]

Procedure	Anesthesia	Sperm retrieval rate	Advantages	Disadvantages
Vasal aspiration	General/regional	100%	Most mature sperm	Requires delicate microsurgical reconstruction of vasotomy
PESA	Local	80%–100%	Office procedure Minimal recovery	Hematoma May not retrieve adequate sperm Can induce epididymal obstruction
MESA	General/regional	95%–100%	High likelihood of obtaining adequate sperm May perform simultaneous reconstruction	Requires operating room and microsurgical skills
TESA	Local	52%–100%	Office procedure Minimal recovery	Hematoma May not retrieve adequate sperm
TESE	General/regional	100%	Fast procedure No microsurgical skills required	Risk of testicular atrophy and hypofunction Requires operating room More invasive and longer recovery

MESA, Microsurgical epididymal sperm aspiration; *PESA*, percutaneous epididymal sperm aspiration; *TESA*, testicular sperm aspiration; *TESE*, testicular sperm extraction.

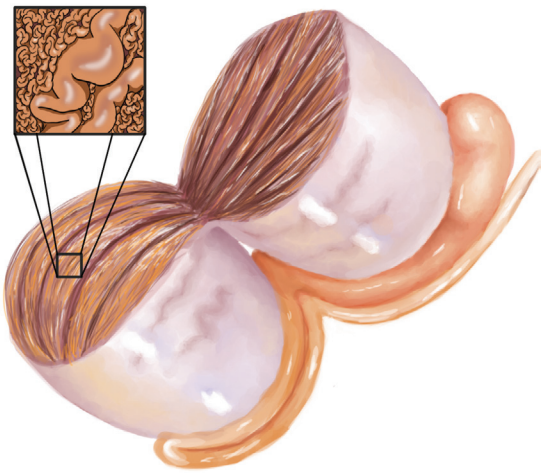

FIGURE 23.9 **With microdissection testicular sperm extraction, once the testicle is opened along its mid-equatorial plane, seminiferous tubules that harbor intact spermatogenesis can be identified and retrieved because they contain more cells and are therefore larger and more opaque than those without spermatogenesis.** *(Figure courtesy Vanessa Dudley.)*

Table 23.8 MicroTESE Sperm Retrieval and Pregnancy Rates for Various Azoospermia Patient Cohorts[94]

Patient condition	Sperm retrieval rate (%)	Pregnancy rate (%)
AZFc deletion	72 (39/54)	46
Klinefelter syndrome	65 (100/155)	40
Cryptorchidism	64 (116/181)	50
Post-chemotherapy	48 (55/114)	40
All patients	56 (794/1414)	48

microTESE, Microdissection TESE; *TESE*, testicular sperm extraction.

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