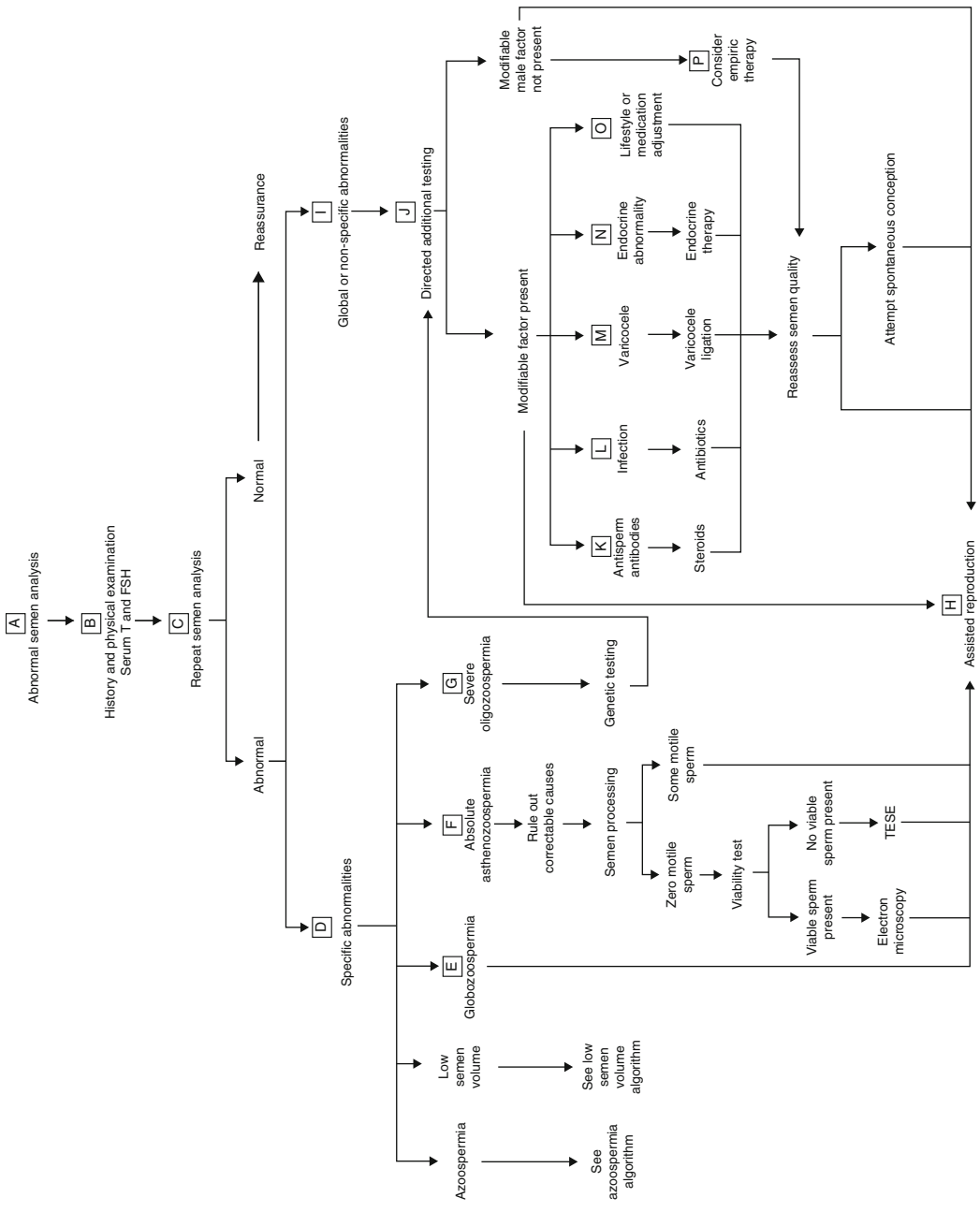
Chapter 1
Abnormal Semen Analysis



J.P. Mulhall et al., *Clinical Care Pathways in Andrology*, DOI 10.1007/978-1-4614-6693-2_1,

Interpretation of semen analysis (SA) results is an important skill for any clinician who cares for men with subfertility or testicular dysfunction. Confirmed SA abnormalities indicate the presence of male factor infertility, which occurs in 40–60% of subfertile couples, and guides subsequent evaluation and management. Male factor infertility is important to identify because it may be amenable to medical or surgical therapy, and because it may be the presenting symptom of occult health-threatening conditions such as hypogonadism or testicular cancer. Moreover, some causes of severe male factor infertility such as Y chromosome microdeletions and chromosomal translocations are genetically transmissible and may threaten the health or fertility of the patient's potential offspring. Semen analysis should be performed according to standard protocol published by the World Health Organization (WHO). Each sample should be collected after an ejaculatory abstinence period of 2–5 days. Samples should be collected in wide-mouthed, sterile containers, maintained as close as possible to body temperature, and analyzed within 1 h. The semen sample is allowed to liquefy and is examined under wet mount light microscopy. The main parameters analyzed are ejaculate volume, pH, sperm concentration (sperm per mL), total sperm number (sperm per total ejaculate), sperm motility (% of sperm with any motility and % of sperm with forward progressive motility), and sperm morphology (% of morphologically normal sperm). Abnormalities of semen parameters are typically described using standard nomenclature (Table 1.1) based upon reference values published by the WHO (Table 1.2).

(A)

In 1999 and 2010 the WHO published the only widely used, accepted reference limits for interpretation of the semen analysis (Table 1.2). It is important to understand that the WHO reference limits do not reflect "normal" or "average" values and do not have a validated relationship with subfertility. The 1999 reference limits were the result of expert consensus, while the 2010 reference limits were defined as the statistical 5th percentile value for each SA parameter derived from an international population of fertile men. The WHO reference limits should not be used as strict criteria to define the presence or absence of male factor subfertility, but rather should serve as a useful guide during the evaluation of each individual patient. Correctable male factors may be present in some men whose semen parameters are within the WHO 2010 normal reference range, and such men may benefit from treatment.

(B)

The initial evaluation of men with an abnormal semen analysis should include a detailed medical history (Table 1.3), a directed physical examination (Table 1.4), and measurement of serum testosterone (T), and follicle stimulating hormone (FSH). The serum T and FSH levels may indicate the presence of medically important and treatable endocrine dysfunction. FSH is a crude but reasonable marker of the level of spermatogenesis. The higher the level the more likely spermatogenesis is impaired. FSH levels higher than 8 IU/L are concerning for primary testicular dysfunction.

(C)

Significant intra-individual variation in semen parameters is common and at least two semen samples should be analyzed for each patient. It is preferable that the samples are collected over more than

1 cycle of spermatogenesis (2 months apart), particularly if systemic illness or gonadotoxin exposure has occurred. Analysis of a third semen sample may be informative if significant discrepancy exists between the two samples.

(D)

Some semen analysis abnormalities indicate the possibility of specific underlying etiologies and warrant-specific diagnostic testing and clinical management. These abnormalities include azoospermia, low semen volume, globozoospermia, absolute asthenozoospermia, and severe oligozoospermia (sperm concentration <5 million per mL, isolated or in combination with other semen analysis abnormalities).

(E)

Globozoospermia refers to the very rare (<1 in 1,000 semen analyses) condition in which all sperm are round-headed due to absence of the acrosome. Globozoospermia is easily diagnosed by an experienced andrologist during standard light microscopic evaluation, and may be confirmed if desired by sperm electron microscopy. Fertilization and biological paternity are only possible by intracytoplasmic sperm injection (ICSI), which is thought to be safe but is only effective in some cases.

(F)

Absolute asthenozoospermia refers to the rare condition (1 in 5,000 semen analyses) in which 100% of sperm in freshly ejaculated semen are immotile. This finding indicates one of the three possible underlying conditions: live sperm that are immotile because of ultrastructural flagellar defects, live sperm with unexplained (idiopathic) immotility, and dead sperm (necrozoospermia). The group of patients with ultrastructural defects includes patients with immotile-cilia syndrome and Kartagener's syndrome (immotile cilia syndrome plus situs inversus). The first step in the evaluation of absolute asthenozoospermia is to search for correctable factors such as genital tract infections, latex condom exposure, prolonged abstinence from ejaculation, and more rare conditions such as partial ejaculatory duct obstruction. If no correctable factors are identified, or if the condition persists after the correctable factor is addressed, the next step is semen processing by centrifugation, density gradient sperm selection, sperm incubation, and extensive sperm search. Identification of any motile sperm obviates the need for further specific testing, and the patient should be evaluated as is suggested for patients with "global or non-specific abnormalities." Sperm viability testing is indicated if motile sperm cannot be identified after semen processing. The commonly used sperm viability assays test sperm membrane function and include the eosin-nigrosin test (live sperm exclude the red eosin dye whereas dead sperm do not) and the hypo-osmotic swelling test (live sperm swell when placed in hypo-osmotic solution whereas dead sperm do not). Sperm electron microscopy may be considered (if available) to evaluate for sperm ultrastructural defects when viable sperm are found. In such cases, reproduction is possible by ICSI, which may be optimized by use of sperm selection techniques to identify viable sperm for oocyte microinjection. Genetic counseling is recommended to inform the patient of the risks of absolute asthenozoospermia, infertility, and associated health problems (such as recurrent pulmonary infections due to immotile cilia syndrome) in potential offspring. If no viable sperm are

found, the diagnosis is necrozoospermia. This condition may result from sperm death that occurs in the testis or epididymis due to infection, oxidative stress, hyperthermia, gonadotoxin exposure, systemic illnesses, or sometimes advancing age. In some cases viable sperm may be surgically retrieved from the testis and used for ICSI.

(G)

Y chromosome microdeletion testing and peripheral blood karyotyping are indicated in all men with severe oligozoospermia (i.e., sperm concentrations <5 million/mL). Genetic defects are detectable in 10–15% of such patients and are important to identify because of their prognostic relevance, possible overall health implications, and in some cases transmissibility to conceived offspring. The most commonly detected abnormalities in this population are Y chromosome microdeletions involving a region of the Y chromosome known as the AZFc (azoospermic factor C) region. Complete or partial AZFc deletions have variable effects on sperm production that range from severe oligozoospermia to azoospermia, and have no other known clinical sequelae. Diagnosis enables genetic counseling prior to assisted reproduction, which is critical because Y chromosome microdeletions are transmitted to all male offspring who inherit the abnormal Y chromosome. Other genetic abnormalities detected in severely oligozoospermic men include sex chromosome abnormalities (particularly classic or mosaic Klinefelter's syndrome, 47,XXY or 46,XY/47,XXY) and autosomal anomalies such as translocations and inversions. Patients with any karyotype abnormalities should undergo genetic counseling prior to assisted reproduction. Pre-implantation genetic diagnosis is indicated in some cases to reduce the risk of aneuploidy in offspring.

(H)

Assisted reproduction may be the only option for achievement of biological paternity for men with severe deficits in semen quality. ICSI is an advanced reproductive technology during which a single sperm is directly injected into a single oocyte under microscopic guidance. ICSI is an alternative to conventional in vitro fertilization, during which thousands of sperm are placed in the oocyte's microenvironment (together in a Petri dish) but must fertilize the oocyte without assistance. The development of ICSI in the early 1990s revolutionized the treatment of severe male factor infertility by enabling successful reproduction with surgically retrieved testicular sperm or functionally impaired ejaculated sperm.

(I)

The majority of subfertile men exhibit mild to moderate abnormalities in one or more semen analysis parameters and can generally be evaluated with the same diagnostic algorithm. This includes patients with isolated or combined oligozoospermia, teratozoospermia, and asthenozoopsermia (absolute asthenozoospermia and globozoospermia, however, require more specific evaluation, see "E" and "F").

(J)

Additional testing is helpful in some cases of poor semen quality and should be directed by the initial evaluation (history, physical examination, serum T, serum FSH, semen analysis). The goal of additional diagnostic testing is to identify or confirm the presence of treatable male factors that are not readily apparent from the initial evaluation. Indications for commonly used tests and methods for interpretation of their results are presented in Table 1.5.

(K)

Testing for anti-sperm antibodies should be considered when isolated asthenozoospermia or sperm agglutination (microscopic attachment of motile sperm to one another) are present on semen analysis. Anti-sperm antibodies can inhibit sperm transit through the female reproductive system and may interfere with sperm survival and/or oocyte fertilization. The most clinically important assays examine semen for the presence of antibodies bound to sperm. The clinical significance of serum anti-sperm antibodies in the male is less clear. Some experts advocate treatment of anti-sperm antibodies with systemic corticosteroids. Described protocols include cycled treatment with 40–80 mg of daily methylprednisolone on menstrual cycle days 1–10, and continuous treatment with 2–3 mg of daily dexamethasone for 9–13 weeks. However, this approach has not been prospectively validated and patients must be warned about the rare but serious side effect of aseptic bone necrosis. Other experts advocate treatment of affected subfertile couples with ICSI, which is not significantly affected by anti-sperm antibodies.

(L)

Infections of the male genital tract may have significant adverse effects on semen quality or sperm function. Although the value of antimicrobial testing in asymptomatic subfertile men is controversial and not supported by robust evidence, many experts advocate treating any positive cultures that are detected. The goals of therapy are to resolve any symptoms of infection that are present, to ameliorate the theoretical adverse effects of infection on semen quality and sperm function, and to avoid transmission of infection to the female partner.

(M)

Varicocele refers to the presence of abnormally dilated spermatic cord veins and is the most common correctable cause of male subfertility, found in 35–40% of cases. A large body of evidence that includes several meta-analyses and randomized controlled prospective trials has shown that varicocele has a negative impact on male fertility, and that varicocele treatment improves both semen quality and pregnancy outcomes. Nonetheless, considerable controversy persists about the value of varicocele treatment due to significant methodological flaws in most of the existing literature. The American Urological Association and the American Society for Reproductive Medicine advocate varicocele treatment in men with palpable varicoceles, impaired semen quality, and documented subfertility, who have a female partner with normal fertility or correctable infertility. The best treatment modality

is microsurgical varicocelectomy, which has lower recurrence and complication rates and yields greater improvements in semen quality than radiographic embolization or non-microsurgical surgical ligation.

(N)

Treatable endocrine abnormalities are the cause of only a small percentage of male subfertility cases. In most cases, treatment of the endocrine abnormality yields significant improvements in semen quality and often enables unassisted conception. Hypogonadotropic hypogonadism may be treated with gonadotropin replacement therapy. Deficiences in LH can be corrected by administration of human chorionic gonadotropin (hCG) injections (1,000–3,000 IU IM or subcutaneously three times per week). FSH deficiency is treated with injectable recombinant FSH (100–150 U three times per week). Treatment is typically highly effective but often requires prolonged gonadotropin replacement. Prolactin secreting pituitary tumors may be treated medically (Carbegoline 0.125–1.0 mg twice weekly) or surgically. Finally, although endocrine therapy is largely ineffective for primary testicular failure, patients with abnormally low (<10) serum testoserone:estradiol ratios may benefit from treatment with an aromatase inhibitor (anastrazole 1 mg daily, testalactone 100–200 mg daily, or letrazole 2.5 mg daily).

(O)

High dietary intake of fruits, vegetables, and whole grains has been recently linked to improve sperm function; and high intake of meat and potatoes may be associated with higher sperm concentrations. Chronic heavy alcohol use can impair the hypothalamic-pituitary axis, and acute alcohol ingestion directly interferes with sperm morphology. Moderate or social alcohol ingestion, however, is not associated with male subfertility. Cigarette smoking and marijuana smoking have been consistently associated with low sperm concentration, low motility, and poor morphology. Chronic scrotal heat exposure, most commonly including frequent use of hot tubs or saunas, impairs testicular function. Medications that may adversely affect semen quality are listed in Table 1.6.

(P)

Empiric therapy for male subfertility is advocated by some experts when no modifiable male factors are present. Although such treatments are supported only by limited evidence, semen quality and reproductive outcomes may improve significantly in appropriately selected patients. Antioxidant therapy and estrogen receptor modulation are the two most commonly utilized strategies. Oral antioxidants for which at least one study has demonstrated a benefit include coenzyme Q, vitamins C and E, carnitine, glutathione, N-acetylcysteine, and selenium. Clomiphene citrate (CC) is the most commonly used estrogen receptor modulator, which is used to drive testicular function by decreasing negative feedback exerted by estradiol at the pituitary, thereby increasing gonadotropin production. Due to its mechanism of action, CC is thought to work best in patients with low to normal serum LH levels.

Table 1.1 Semen analysis nomenclature

Term	Definition
Azoospermia	Clinical state in which sperm are not detectable by microscopic analysis of the pellet derived from centrifugation of a semen sample
Oligozoospermia	Clinical state in which the sperm concentration or total number of sperm are below the lower reference limits published by the World Health Organization (WHO)
Asthenozoospermia	Clinical state in which the percentage of sperm with any motility or the percentage of sperm with forward progressive motility are below the lower reference limits published by the WHO
Teratozoospermia	Clinical state in which the percentage of sperm with normal morphology are below the lower reference limits published by the WHO or below reference ranges for strict (Kruger) criteria
Oligoasthenoteratozoospermia	Clinical state in which oligozoospermia, asthenozoospermia, and teratozoospermia are simultaneously present
Necrozoospermia	Clinical state in which 100% of ejaculated sperm are immotile and proven to be dead by viability testing
Globozoospermia	Rare variant of teratozoospermia characterized by round-headed spermatozoa that lack acrosomes and are therefore incapable of fertilization without intracytoplasmic sperm injection
Leukocytospermia	Descriptive term indicating the presence of an abnormal concentration (>1 million/mL) of white blood cells in semen

Table 1.2 Semen analysis reference limits published by the World Health Organization in 1999 and 2010

Semen analysis parameter	WHO 1999 reference limits	WHO 2010 reference limits
Semen volume	≥2.0 mL	≥1.5 mL
pH	≥7.2	≥7.2
Total sperm number	$\geq 40 \times 10^6$ per ejaculate	$\geq 39 \times 10^6$ per ejaculate
Sperm concentration	$\geq 20 \times 10^6$ per mL	$\geq 15 \times 10^6$ per mL
Total motility	N/A	≥40%
Progressive motility	≥50%	≥32%
Sperm morphology	≥14% normal forms by WHO criteria	≥4% normal forms by strict criteria

Table 1.3 Important points to elicit in the medical history of patients with an abnormal semen analysis

Medical history	Interpretation
Developmental history, including testicular descent	Delayed puberty suggests congenital problems with androgen synthesis or action
	Cryptorchidism is often associated with poor sperm quality
Fertility history	Prior spontaneous conception suggests acquired (secondary) infertility
Partner's reproductive history and status	Guides treatment selection
Current or prior medical conditions, including sexually transmitted infections (STI)	Malignancy and hypogonadism may be associated with poor semen quality
	STIs may cause semen analysis abnormalities
Current or prior gonadotoxin exposure	May impair sperm production
Prior scrotal events including epididymitis, orchitis, and testicular torsion	Prior scrotal events may be associated with poor semen quality
Prior scrotal, inguinal, retroperitoneal, or pelvic surgery	Raises the possibility of iatrogenic injury to the male excurrent ductal system that could impair sperm transit or delivery
Medication use, including anabolic steroids	Current or prior immunosuppressive or antineoplastic therapy (chemotherapy, radiation therapy, hormonal therapy) may cause poor semen quality
	Anabolic steroid use is a common cause of poor semen quality
Symptoms of hypogonadism	Profound hypogonadism may be associated with poor sperm production

Table 1.4 Important points during physical examination of patients with an abnormal semen analysis

Physical Examination	Interpretation
Body habitus and hair distribution	Tall stature and long limbs and/or a gynecoid habitus suggest hypogonadism during development (long limbs result from delayed epiphyseal closure)
	Decreased body and/or facial hair suggest hypogonadism
	Very large muscles may suggest anabolic steroid use
Visual fields	Visual field deficits may be associated with pituitary tumors and hypogonadotropic hypogonadism
Gynecomastia	Gynecomastia indicates imbalance in the testosterone:estradiol ratio, which may occur in Klinefelter syndrome, Leydig cell tumors, germ cell tumors, and obesity
Spermatic cord examination	Varicoceles are the most commonly identified abnormality in subfertile men and are diagnosed on physical examination
Epididymal examination	Epididymal tenderness suggests epididymitis
	Epididymal induration suggests obstructive lesion
Testicular examination	Small or soft testicles suggest testicular dysfunction
	Testicular tumors are more common in sub-fertile men, may cause subfertility, and are detected by physical examination
Penile examination	Urethral discharge suggests STI

Table 1.5 Explanation of adjunctive tests useful in the evaluation of abnormal semen analysis

Test type	Specific test	Indications	Interpretation
Blood work	Luteinizing hormone (LH)	Abnormal serum testosterone	Distinguishes between central and testicular hypogonadism
	Follicle stimulating hormone (FSH)	Abnormality in sperm concentration	Indicator of spermatogenesis potential of the testes
	Estradiol	Abnormal serum testosterone Gynecomastia	Possible benefit of aromatase inhibitor therapy if testosterone:estradiol ratio <10
Microbiological testing	Semen culture, urethral swab, or culture of expressed prostatic secretions	Signs or symptoms of urethritis, prostatitis, or epididymitis Controversial role in asymptomatic patients	Treatment indicated for symptomatic patients with positive cultures
Semen testing	Semen peroxidase stain	>1 million round cells per mL on semen analysis	Distinguishes leukocytes in semen from immature germ cells
	Anti-sperm antibody testing	Isolated asthenozoospermia Sperm agglutination	Treatment may be indicated for sperm-bound antibodies detected in semen
Imaging	Scrotal ultrasonography	Indeterminate or difficult physical examination	May detect varicoceles or testicular pathology
	Transrectal ultrasonography	Low semen volume	Detects ejaculatory duct obstruction
Urinalysis	Post-orgasm urinalysis	Low semen volume	May detect retrograde ejaculation

Table 1.6 Medications associated with male infertility

Medication	Mechanism
Anabolic steroids	Direct gonadotoxicity, endocrine effects
Anti-androgens	Endocrine effects, sexual dysfunction
Anti-psychotics	Endocrine effects (hyperprolactinemia)
Cimetidine	Direct gonadotoxicity, endocrine effects
Erythromycin, gentamycin, neomycin	Direct gonadotoxicity
Chemotherapeutic agents	Direct gonadotoxicity, endocrine effects
Finasteride	Endocrine effects (the 1 mg dose of finasteride used for male pattern baldness has not been shown to affect fertility)
Nitrofurantoin	Direct gonadotoxicity, endocrine effects
Selective serotonin reuptake inhibitors	Direct gonadotoxicity, endocrine effects
Spironolactone	Endocrine effects
Testosterone	Direct gonadotoxicity, endocrine effects

Suggested Reading

Male Infertility Best Practice Policy Committee of the American Urological Association, Practice Committee of the American Society for Reproductive Medicine. Report on optimal evaluation of the infertile male. Fertil Steril. 2006;86(5 Suppl 1):S202–9.

Male Infertility Best Practice Policy Committee of the American Urological Association, Practice Committee of the American Society for Reproductive Medicine. Report on varicocele and infertility. Fertil Steril. 2004;82 Suppl 1:S142–5.

Practice Committee of American Society for Reproductive Medicine in collaboration with Society for Male Reproduction and Urology. The management of infertility due to obstructive azoospermia. Fertil Steril. 2008;90(5 Suppl):S121–4.

Showell MG, Brown J, Yazdani A, Stankiewicz MT, Hart RJ. Anti-oxidants for male subfertility. Cochrane Database Syst Rev. 2011;1(1):CD007411.

Sokol RZ. Endocrinology of male infertility: evaluation and treatment. Semin Reprod Med. 2009;27(2):149–58.

Stahl PJ, Stember DS, Schlegel PN. Interpretation of the semen analysis and initial male factor management. Clin Obstet Gynecol. 2011;54(4):656–65.

World Health Organization. WHO laboratory manual for the examination and processing of human semen. 5th ed. Geneva: World Health Organization; 2010.

Zini A, Boman JM. Varicocele: red flag or red herring? Semin Reprod Med. 2009;27(2):171–8.