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Evaluation and Diagnosis of Male Infertility

INTRODUCTION

It is well known that the motivation to have children and the formation of a new family unit are essential components of the individual instinct for existence and well-being. Fertility problems may represent a stressful situation to the individual’s life with important negative psychological consequences. The experienced clinician should realize and comprehend the burdensome bearings and frustrated mood of the infertile individual. Most adults are prompted to discuss their sexual issues and behaviors if the interview is conducted in a respectful, confidential, professional and nonjudgmental way.

In the last decades, extraordinary advances have been achieved in the field of male infertility. Significant progress has been made regarding both diagnostic and treatment techniques. Novel tests have been incorporated to the andrological armamentarium. Today, it is possible to correctly classify some cases which were previously believed to be idiopathic. The initial evaluation of common infertility complaint comprises the meticulous history taking, as well as conducting a thorough physical examination along with proper laboratory and imaging studies as needed.

DEFINITION AND EPIDEMIOLOGY OF MALE INFERTILITY

The infertility is defined as failure of the couples to conceive after 12 months of unprotected regular intercourse. Infertility is broadly classified into primary infertility, when the male partner has no previous history of fertility, and secondary infertility, when there was previous man’s history of successful impregnation of a woman. Subfertility refers to a reduced but not unattainable potential to achieve pregnancy, while sterility is denoted by permanent inability to induce or achieve pregnancy. Fecundity, on the other hand, indicates the capability of a given male or female to produce live births.

Epidemiology studies indicate that 13–15% of couples face difficulties to conceive. Approximately 8% of men in reproductive age seek medical assistance for fertility-related problems. Isolated male factor infertility, and its combination with female problems accounts for more than 50% of the couples’ inability to conceive. The male...
Section 2  Male Factor Infertility

factor is purely responsible for 20% of infertile couples, while it is contributory in another 30–40% of infertility.6

The World Health Organization defines male factor infertility as the presence of abnormalities in the semen analysis, or the presence of sexual or ejaculatory dysfunction.7 However, modern andrology has revealed that normal semen testing does not guarantee fecundity, and unraveled the predictive power of normal semen to induce natural pregnancy is about 60%.8 The introduction of novel sperm function testing is revolutionizing the criteria of diagnosis and definitions of male infertility.

Recent reports indicate that sperm counts of men from certain regions of the world have significantly deteriorated. Remarkable differences in sperm production have been detected among men from different countries in Europe and the United States of America. Differences are also seen in individuals of different regions within the same country. Moreover, there is a noticeable epidemiologic increase in the incidence of testicular cancer and urogenital anomalies.9-12 These observations cause public concerns particularly with regard to the implication of environmental factors and modern life habits.13-15 Some authors claim that the buildup in the prevalence of infertility among men may be attributed to increased prevalence of obesity.16-18 Others factors may also be implicated in the apparent rising prevalence of male infertility problems such as exposure to cell phones radiation19 and certain endocrine disruptors.20

PATHOPHYSIOLOGY, ETIOLOGY AND CLASSIFICATION OF MALE INFERTILITY

The male reproductive system consists of the testes, accessory glands and the ductal system for sperm transport. The seminal ducts constitute the pathways for sperm transport, and it includes the efferent ductules and rete testis, epididymis, vas deferens, ejaculatory ducts and urethra. The accessory sex glands include the seminal vesicles, prostate and bulbourethral glands (Figures 1 and 2).

The testes perform two important functions: spermatogenesis and steroidogenesis. Daily sperm production is about 40 million and declines progressively with aging. Recent data suggests that the duration of spermatogenesis is less than 60 days instead of 70 ± 4 days as previously thought for over 40 years.21 As such, the sperm production of an individual actually represents the result of influencing biological, physical and occupational factors, which acted within the past 2 months from ejaculation. Steroidogenesis and hormone production is another essential testicular function. The hormonal milieu that regulates spermatogenesis depends on complex coordinated interaction between the testes, pituitary gland and hypothalamus that form the hypothalamic-pituitary-gonadal (HPG) axis (Figure 3).

The storage and maturation of spermatozoa occur in the epididymis. However, the maturation process is exclusively completed within the female reproductive tract. Spermatozoa transit throughout the epididymis for

Figure 1  Schematic illustration of the male reproductive organs
about 12 days. The epididymides are in continuity with the vasa deferentia, which in turn join the emerging ducts from the seminal vesicles to form the ejaculatory ducts. They enter the prostate, a gland responsible for production of a fluid enriched with zinc, citric acid, acid phosphatase and proteases that contributes to liquefaction and accounts for approximately 0.5 ml of the ejaculate. The seminal vesicles produce an alkaline fluid with prostaglandins and fructose that composes 1.5–2.0 ml of the seminal fluid. Both seminal vesicles and vasa deferens have a common embryologic origin. As such, when congenital bilateral absence of vasa deferens (CBAVD) is diagnosed, it is often associated with seminal vesicles hypoplasia/agenesis. This is an important aspect in the differential diagnosis of azoospermia. In CBAVD, diminished or no fructose can be found in the seminal fluid and, hence, volume is low (< 1 ml). Under normal conditions, spermatozoa are stored in the epididymides rather than the seminal vesicles. At the time of ejaculation, ductal and epididymal muscle contractions under sympathetic stimulation conduct the spermatozoa towards the prostatic urethra where they join fluids excreted by the prostate, and form the semen. Periurethral muscle contraction is responsible for expelling semen out. Interference in any of these steps may lead to male infertility. Herein, the pathophysiological mechanism involved is dependent on which organ or regulatory system is afflicted.

Male infertility causes may range from simple, reversible and correctable causes to uncorrectable ones. Such conditions may be inherited or acquired. The factors affecting male fertility status can be divided into four major categories: disorders in sperm production, sperm transport and sperm function constitute the essential causes of male infertility. The fourth category is represented by “infertility of unknown origin”, a condition in which male infertility has aroused spontaneously, or from an obscure or unknown cause. This category accounts for 37–58% of the cases, and it is divided into two major subtypes: idiopathic and unexplained male infertility. Idiopathic male infertility is the cause of about 30% of male infertility, and it is characterized by unexplained reduction in semen quality with no previous history associated with fertility problems, and having normal findings on physical examination and endocrine laboratory testing. The term “unexplained male infertility”, on the other hand, is reserved for infertile men with infertility of unknown origin with normal semen profile, and in whom female infertility factors have been ruled out. This category accounts for 6–27% of male infertility, and it strongly depends on how exhaustive evaluation of the patient is done. Table 1 depicts the etiologic classification of male infertility.

The most commonly observed abnormality in infertile men seeking evaluation is varicocele followed by obstruction and cryptorchidism. Table 2 shows the distribution of the causes of male infertility in tertiary care infertility center. It should be noted, however, that the frequency distribution of primary infertility causes is different from secondary infertility causes in which varicocele accounts for 70–80% of the cases, followed by infection of genital tract.


Section 2  Male Factor Infertility

Figure 3  Schematic representation of the components of the hypothalamic-pituitary-testicular axis and the endocrine regulation of spermatogenesis. Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are secreted by the pituitary gland in response to hypothalamic gonadotropin releasing hormone (GnRH). While FSH acts directly on the germinal epithelium, LH stimulates secretion of testosterone by the Leydig cells. Testosterone stimulates sperm production and also feeds back the hypothalamus and pituitary to regulate GnRH secretion. FSH stimulates Sertoli cells to support spermatogenesis and to secrete inhibin B that negatively feedback FSH secretion.

GOALS AND THE PROPER TIMING FOR FERTILITY EVALUATION

Generally, the proper timing for an infertile couple to seek medical advice is after 12 months of regular intercourse. However, immediate attention must be given if any risk factor for infertility is present, such as history of infertility with another partner, cryptorchidism, orchitis and advanced female age either more than or equal to 35 years. Advanced paternal age is not only associated with a decline in the fecundity potential but also with
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1. Disorders affecting sperm production
   i. Hypothalamic and pituitary causes
      a. Lack of gonadotropin-releasing hormone secretion
         • Kallmann’s syndrome
         • Isolated hypogonadotropic hypogonadism
         • Midline facial defects
         • Congenital syndromes such as Prader-Willi syndrome, Laurence-Moon-Biedl syndrome
      b. Lack of luteinizing hormone (LH) secretion
         • Fertile eunuch syndrome
         • Isolated LH deficiency
   c. Isolated follicle-stimulating hormone (FSH) deficiency
   d. Pituitary disease
      • Tumors
      • Infiltrative disorders
      • Infarction
      • Radiation
      • Hyperprolactinemia
      • Endocrinopathies-induced alterations in pituitary gland responsiveness, such as thyroid dysfunction, glucocorticoid excess, exogenous androgens or estrogens
   ii. Testicular causes
      a. Vascular causes: torsion, varicocele
      b. Infection: mumps, orchitis
      c. Genetic and congenital causes
         • Congenital causes
           — Cryptorchidism
           — Anorchia
           — Polyorchidism
           — Microorchidism
         • Genetic causes
           — Chromosomal aneuploidy and structural defects
           — Gene defects
           — Y chromosome microdeletion
   d. Medications
   e. Castration, testicular trauma
   f. Systemic diseases
   g. Environmental factors

2. Disorders affecting sperm transport
   i. Congenital
      a. Bilateral absence of vas deferens
      b. Unilateral absence of the vas
      c. Prostatic/ejaculatory duct cysts
   ii. Acquired
      a. Iatrogenic (surgical procedures)
      b. Infection
      c. Trauma

3. Disorders affecting sperm function
   i. Immune infertility
   ii. Reactive oxygen species and oxidative stress
   iii. Sperm DNA damage
   iv. Fertilization defects
      a. Zona pellucida binding
      b. Hyperactivation
      c. Acrosome reaction
      d. Fusogenic ability
   v. Immotile cilia syndrome

4. Infertility of unknown origin
   i. Idiopathic
   ii. Unexplained

Table 1  Etiologic classification of male infertility

<table>
<thead>
<tr>
<th>Category</th>
<th>Numbers</th>
<th>Percentage</th>
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<tr>
<td>Varicocele</td>
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<td>21.9</td>
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<tr>
<td>Infectious</td>
<td>72</td>
<td>2.5</td>
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<tr>
<td>Hormonal</td>
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<td>1.9</td>
</tr>
<tr>
<td>Ejaculatory dysfunction</td>
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<td>1.0</td>
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<td>Systemic diseases</td>
<td>11</td>
<td>0.4</td>
</tr>
<tr>
<td>Idiopathic</td>
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<td>10.0</td>
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<td>Normal/Female factor</td>
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<td>Immunologic</td>
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<td>1.9</td>
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<td>Obstruction</td>
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<td>12.5</td>
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<tr>
<td>Cancer</td>
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<td>345</td>
<td>11.9</td>
</tr>
<tr>
<td>Total</td>
<td>2,875</td>
<td></td>
</tr>
</tbody>
</table>

Source: ANDROFERT, Campinas, São Paulo, Brazil
increased incidence of miscarriage and inheritance of genetic diseases such as Down’s syndrome as well as autism and schizophrenia.\textsuperscript{35-40} The yearly decline in sperm parameters has been estimated to be 0.03 ml for volume and 0.7\% for motility.\textsuperscript{41} The probability of having abnormal sperm counts increases with age. It is 5\% at age 30 years, 15\% at age 50 years and 50\% by age 80 years.\textsuperscript{41} As such, the impact of paternal age on male fertility cannot be underestimated. Current recommendations for immediate evaluation include men with advanced paternal age, i.e. more than 45 years, because their fertility potential may be compromised.

The essential goals of male evaluation for infertility encompass the detection of both correctable and uncorrectable causes. The uncorrectable male infertility can be managed by using assisted conception or donor insemination. The identification of genetic and/or chromosomal abnormalities are crucial for proper counseling not only regarding the chances of conception but also for the health of offspring. Evaluation of males complaining of infertility may also identify underlying health-threatening medical pathologies such as endocrinopathies and malignancies.\textsuperscript{42}

**APPROACHING THE SUBFERTILE MALE**

The basic evaluation of men with infertility complaint includes a detailed history, a thorough physical examination and at least two semen analyses. Additional laboratory and imaging testing may be ordered according to the initial findings. The role of the urologist in the management of the subfertile male cannot be underestimated. Whenever possible, he/she is responsible for diagnosing, counseling and treating the existing cause. When no specific treatment is available, the urologist is still responsible for referring the patient to a specialized assisted reproductive technology (ART) center, or for extracting the male gametes from the testicles or epididymides as a member of the ART center’s multiprofessional team.

**History**

The physician’s tasks during the medical interview are to address the patient’s concerns, and to conduct scientific, courteous and nonjudgmental interview. A comprehensive medical history encompasses all aspects of the male’s development from pregnancy to adult life. In Table 3, a comprehensive questionnaire for interviewing a male patient with infertility complaint is provided.
**Descriptive Elements**

Male age, duration of infertility, primary vs. secondary infertility, as well as age and fertility status of the female partner have prognostic and diagnostic significance. Advanced male or female age and longstanding history of infertility are negative factors for fecundity. The secondary infertility carries a better prognosis than the primary infertility. The secondary male infertility is often associated with correctable causes such as varicocele, infection or ejaculatory problems. A history of early miscarriages, or occurrence of fetal genetic abnormalities may suggest a male factor contribution.43,44

The female partner’s history of having successful pregnancies and live births renders male infertility more likely. Female age is the most important single variable influencing the outcome in assisted reproduction.45 Nevertheless, it is now commonplace to see couples delaying family planning due to professional and economic reasons. This delay mainly jeopardizes the female fertilizing potential. There is a 50% reduction in fecundity in woman aged 35 years compared to those aged 25 years.45

**Sexual and Coital Aspects**

Although sexual and coital factors account for only 5% of infertility causes, it is mandatory to analyze these factors, as they may be the sole cause of the problem.46 It is preferable to discuss these issues with both partners at the same interview, as this will help to disclose the misapprehension undertaken by the partners regarding the physiology of fertilization.

The clinician should address the concept of fertility window, and the importance of frequent and well-timed intercourse. Surprisingly, many couples have infrequent intercourse due to life stressors and irregular working hours, and are unaware of the importance of timed intercourse. The fertility window is defined as the 6-day period within the menstrual cycle when intercourse most likely results in a conception. It is estimated to range from 5 days before ovulation to the day of ovulation for normogonadotropic women.47,48 The highest probability of a successful pregnancy can be anticipated if intercourse occurs 1 to 2 days prior to ovulation.49,50

This phenomenon is based on short duration of human ovum longevity and survival that is estimated to be fewer than 16 hours.50,51 On the other hand, human sperm can survive for up to 6 days in well-estrogenized cervical mucus.52 This relatively protracted longevity and survival creates an adequate sperm reservoir for fertilization.

Therefore, it is advisable for couples to have intercourse every other day during the 6 days fertile window. Sperm counts are at their maximum after 5 days of ejaculatory abstinence. After that, sperm motility declines. Consequently, it is also advisable to abstain from ejaculation, not longer than 5 days, when attempting to conceive. Woman with regular menstrual cycle can estimate the fertile period by using basal body temperature and calendar calculations. However, these methods are both inaccurate and unreliable. The best methods to prospectively identify the entire fertile window for the purpose to achieve pregnancy would be either the fertility charting of vaginal discharge, or the elevation in urinary estrogen or luteinizing hormone (LH) surge.51

The former identifies the changes in vaginal discharge that correspond with high ovarian hormones and can roughly estimate the fertile window. The latter method identifies the rises in urinary estradiol 3-glucuronide (E3G) and urine LH surge, and can prospectively predict the 3–6 days fertile window before ovulation and the day of ovulation.51

Nonetheless, the best advice for women with unknown fertile window is to have intercourse at a frequency of two to three times a week during the whole menstrual cycle. Unfortunately, some couples find it more stressful and intricate to adhere to frequent schedule of intercourse than to timely assured fruitful intercourse.

A detailed sexual history is also a valuable tool to identify sexual dysfunction problems. A decreased libido may be caused by complex interaction of social, emotional, psychological and hormonal factors. The decreased libido may also be the only sign of hypogonadism, which results in erectile dysfunction (ED) and decrease in the sexual drive. Although erectile dysfunction may be attributed to psychogenic problems, endocrinopathies such as hypogonadism, diabetes, hypothroidism and hyperprolactinemia may also be involved.

The incidence of ED increases with age; it is 52% in men of age between 40–70 years old, and about 2–27% in men less than 40 years old.53,54

Though the recommendation to increase the frequency of intercourse in the fertile window is evidence-based, no specific coital technique is praised. Whatever the position is, the ejaculated sperm in the proximal vagina can find the way to the oviduct within five minutes.55 Consequent to increased coital frequency, vaginal dryness may direct the women to use vaginal lubricants. However, commercially available water-based lubricants are toxic to sperm. These lubricants may either induce poor sperm motility or chromatin damage and, correspondingly, loss of fertilizing potential of sperm.56 Among the lubricants available in the market, hydroxyethyl cellulose-based lubricant was shown to have the lowest damaging effects on sperm motility and chromatin integrity.57 Natural lubricants, such as saliva, vegetable oils (canola, vegetable, olive, safflower
and peanut), as well as glycerin and petroleum jelly cause mild decrease in sperm motility.56,58

**Ejaculatory Disorders**

Natural fertilization requires successful deposition of semen into the proximal vagina. Therefore, ejaculatory dysfunction can interfere with this process and may render a male infertile. The patient should be asked about volume of the ejaculate during coitus and masturbation. Low semen volume may be attributed to either congenital or acquired obstructive lesion of the genital tract, male hypogonadism or due to retrograde ejaculation. Anejaculation, on the other hand, is a complete absence of antegrade and retrograde ejaculation and is caused by defective seminal emission from seminal vesicles, prostate and the ejaculatory ducts into the posterior urethra. This condition is usually associated with intact orgasm, and its etiology is related to neurogenic or drug induced effect.59 Anejaculation should be differentiated from anorgasmia, which is a psychological disorder characterized by failure to attain orgasm and is usually associated with anejaculation.60 The prevalence of premature ejaculation among subfertile males is reported to be around 50%.61 However, premature ejaculation seems to be related to the stress imposed by the infertility condition rather than to be a primary cause.

**Pediatric and Developmental Contribution**

The questionnaire about childhood and pubertal development includes prenatal exposure to certain dietary, pharmaceutical and environmental factors that may lead to congenital urogenital anomalies, disordered hormonal milieu and even altered semen parameters. In utero exposure to diethylstilbestrol, a medication that has been banned from the market several years ago, leads to appearance of epididymal cyst, cryptorchidism and altered semen quality in the male offspring.62 History of parental infertility or the mother being subjected to any infertility medical treatment may render a male infertile. The patient should be asked about volume of the ejaculate during coitus and masturbation. Low semen volume may be attributed to either congenital or acquired obstructive lesion of the genital tract, male hypogonadism or due to retrograde ejaculation. Anejaculation, on the other hand, is a complete absence of antegrade and retrograde ejaculation and is caused by defective seminal emission from seminal vesicles, prostate and the ejaculatory ducts into the posterior urethra. This condition is usually associated with intact orgasm, and its etiology is related to neurogenic or drug induced effect.59 Anejaculation should be differentiated from anorgasmia, which is a psychological disorder characterized by failure to attain orgasm and is usually associated with anejaculation.60 The prevalence of premature ejaculation among subfertile males is reported to be around 50%.61 However, premature ejaculation seems to be related to the stress imposed by the infertility condition rather than to be a primary cause.

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The childhood history of congenital and acquired genitourinary disorders should also be taken into account. Cryptorchidism is the most common genitourinary disorder and affects about 1–3% of term infants. However, its prevalence among infertile men is 9.4%.71-73 If cryptorchidism is treated by orchidopexy at an early age, there will be higher chance of maintenance spermatogenesis.74 Though men with unilaterally repaired cryptorchidism have variable semen parameters; their paternity rate seems to be similar to that of general population.75 However, in those with bilaterally repaired cryptorchidism a 35–53% decrease in the paternity rates (compared to the general population) is observed, with high incidence of disordered semen parameters such as oligozoospermia (31%) and azoospermia (42%).76 Other rare urogenital anomalies such as microorchidism, polyorchidism, vanishing testis, prune belly syndromes, posterior urethral valve and bladder extrophy are well known causes of impairment of male fertility potential.

Inquiries should also include questions about accidental and surgical trauma to the testes during childhood as well as about pediatric hernia repair, which is associated with 0.8–2% risk of injury to the inguinal or retroperitoneal vas deferens.77 Unilateral vas injury may remain unnoticed in the presence of normally functioning contralateral testis and contralateral patent seminal duct. Bilateral pediatric hernia repair, particularly with the use of mesh, forms the highest risk of clinically evident vas injury and male infertility.78 History of testicular torsion, whether treated by orchidopexy or orchiectomy can lead to abnormal semen analysis in 30–40% of the affected patients.79

Now, mumps orchitis during childhood is rare because of the widely conducted vaccination program. Prepubertal mumps orchitis has not been found to affect testicular function.80,81 However, recent reports have raised concern about an increased incidence of postpubertal mumps orchitis after the age of 15 years.82 Mumps of postpubertal onset is associated with orchitis in 25% of cases,83 and in approximately 10–30% of cases, bilateral testicular involvement is documented.84 Mumps orchitis can lead to subfertility in 13% and 30–87% of patients with unilateral and bilateral testicular involvement, respectively.84,85

The age of puberty onset is of paramount importance as it reflects the proper interaction and the integrity of the HPG axis. Most males reach pubertal development at age 11–12 years.86 Constitutional delay of puberty is the most common cause for such condition and is usually confirmed by positive family history, delayed bone age and low or normal gonadotropins.86 Nevertheless, this delay may be attributed to primary testicular failure.
such as Klinefelter syndrome, partial androgen resistance or other acquired causes, or secondary to hypothalamic or pituitary dysfunction. There are many acquired and congenital causes of hypothalamic and pituitary dysfunction such as Kallmann’s syndrome, Prader-Willi syndrome, Laurence-Moon-Biedl syndrome, idiopathic hypogonadotropic hypogonadism and pituitary tumors. Conversely, precocious puberty, which is characterized by appearance of secondary sex features before 9 years of age, is either caused by premature activation of HPG axis (true precocious puberty) or excessive sex steroid production (incomplete precocious puberty). True precocious puberty may cause testicular enlargement and normal spermatogenesis so early that a boy at age of 4 years can father children. However, boys with incomplete or pseudoprecocious puberty may have pubic hair and penile enlargement, but no testicular enlargement or production of sperm. Such condition is often caused by adrenogenital syndrome, a form of congenital adrenal hyperplasia, or Leydig cell hyperplasia or tumors. In pseudoprecocious puberty, there is excessive production of androgens, which suppress gonadotropins production. Therefore, there is a lack of stimulatory factor of testicular development and sperm production despite the virilized effects of androgens.

Most men may not memorize the exact timing of their puberty unless there is a marked delay or premature onset. While some of these conditions may respond to hormonal manipulation, others are resistant to hormonal therapy and more aggressive therapies such as sperm retrieval and assisted reproductive techniques may be needed.

**Surgical Aspects**

Certain surgical procedures in the vicinity of male reproductive organs may inadvertently injure these organs. Surgery in the pelvis, retroperitoneum, scrotum and groin may cause impairment in the male reproductive potential. Ejaculatory and erectile dysfunctions are known complications of retroperitoneal lymph node dissection, deep radical pelvic surgery, bladder neck reconstruction surgery and spinal surgery. Transurethral resection of the prostate and bladder neck incision are often complicated by retrograde ejaculation. Bilateral open or laparoscopic adult inguinal hernia repair, particularly with use of knitted mesh, may result in bilateral vas deferens injury and azoospermia. The prevalence of such condition is estimated to be 0.3%. However, the unilateral injury may go unnoticed if the contralateral testis function and vas deferens are normal. Moreover, inguinal herniorrhaphy may contribute to testicular atrophy in 5% of cases. On the other hand, scrotal surgery for hydrocele and epididymal cyst may injure scrotal vas deferens, epididymal tubules and testicular arteries precipitating vasal and epididymal obstruction as well as testicular atrophy. Considering all these fertility related surgical complications may help to find the cause, direct specific diagnostic investigations and thereby restore fertility potentials.

**Medical Aspects**

Medical history of urologic and systemic diseases in infertile men may be related to the infertility problem. Recurrent attacks of urinary tract, sexually transmitted infections (STI) and mixed accessory gland infections have all been linked to male infertility. Infected urine is associated with and constitutes a risk factor for genital tract infections. The STI are commonly caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Ureaplasma urealyticum*, human immunodeficiency virus (HIV) and other less common microorganisms. Urethral stricture, epididymo-orchitis and postorchitis decline in testicular function are well recognized complications of STI. *Ureaplasma urealyticum* can have deleterious effects on sperm motility and DNA condensation leading to poor fertilization potentials. Moreover, recent reports have shown that *Chlamydia trachomatis* infection is often detected in infertile men. *Chlamydia trachomatis* may attach to the spermatozoa and causes impairment in sperm motility, and DNA integrity as well as acrosome reaction (AR) insufficiency. Mixed accessory gland infection (MAGI), which is a syndrome characterized by a chronic inflammatory process that involves the prostate, seminal vesicles or epididymides, is also caused by the same organisms causing STI such as gonococci, *Chlamydia* and gram-negative bacteria. This syndrome is found in about 10% of infertile men, and it is characterized by leukocytospermia, increased reactive oxygen species and high concentrations of inflammatory cytokines. Symptoms suggestive of MAGI, such as urethral discharge, pain and/or pus or blood associated with the ejaculate, should be taken in consideration.

Human immunodeficiency virus is one of the STI that impairs male fertility by multiple mechanisms. Orchitis, hypogonadism, enhanced oxidative stress, oligozoospermia and even azoospermia have been described in association with HIV infection. Some men with autosomal dominant polycystic kidney disease may have low semen volume, oligozoospermia, asthenozoospermia and even impaired fertilization potential. Systemic medical diseases, such as renal insufficiency, liver cirrhosis and endocrinopathies such as thyroid dysfunction, Cushing syndrome and diabetes, are all associated with gonadal dysfunction and disordered spermatogenesis. Men with a history of galactorrhea,
headache and impaired vision may have prolactinoma. Gastrointestinal diseases, such as celiac disease, inflammatory bowel diseases and other malabsorption syndromes, are associated with delayed puberty, hypogonadism and impaired semen quality.103,104

Some respiratory diseases and male infertility may have common genetic origin. More specifically, some syndromes may cause chronic nasal polyps and sinus-pulmonary infections and sperm transport problems such as Young’s syndrome that is associated with obstruction of the epididymides and vasa deferentia due to ininspissated secretions; cystic fibrosis which is associated with congenital bilateral absence of the vas deferens; and ciliary dyskinesia syndromes that are characterized by immotile sperm. Other respiratory diseases may affect the fertility potential through centrally induced hypogonadotropic hypogonadism state such as sarcoidosis and obstructive sleep apnea.105,106 Furthermore, chronic obstructive airway disease may cause pubertal delay and hypogonadism either through hypoxia, or corticosteroid-induced hypogonadotropic hypogonadism.107 Men with active pulmonary tuberculosis may also have gonadal hormonal dysfunction attributed to central mechanism.108

Male infertility is also common in sickle cell anemia, presumably, due to intratesticular ischemia.109,110 Prolonged fever may cause reversible impairment in semen quality.111 Malignancy and its treatment, such as radiotherapy and chemotherapy, may also be a risk factor for male infertility due to transient or permanent alterations in sperm production and, less commonly, androgen insufficiency. Testicular cancer, Hodgkin’s disease and acute leukemia are the most common malignancies in young adult patients. Men with testicular cancer may be oligozoospermic in 50% and azoospermic in 10–15% of cases before receiving any treatment.112 Some specific clinical features have genetic relations with male infertility such as anosmia (Kallmann’s syndrome), deafness (deafness-infertility syndrome), early cataract (myotonia dystrophica), bronze discoloration of the skin (hemochromatosis), muscle weakness (myotonia dystrophica, mitochondrial disease) and certain birth marks or scaling skin (X-linked ichthyosis).

**Use of Medication**

Drugs and medications may undermine male reproductive function in various ways. Personal use of drugs and medications must be thoroughly elucidated. There are four mechanisms explaining their impact on male fertility:

1. By acting as direct gonadotoxins such as chemotherapy agents,
2. Through alterations in the hormonal control of testicular function such as exogenous anabolic steroids,
3. Inflicting erectile and ejaculatory dysfunction such as beta-blockers and alpha-blockers, or
4. Mitigating libido such as psychotherapeutic medications and recreational drugs.113 Table 4 presents a comprehensive list of medications and drugs related to fertility impairment.

**Inherited and Familial Aspects**

Genetics play essential role in male subfertility. Therefore, exploring the personal history of certain inherited diseases that may affect the reproductive function as well as the family history of involuntary male childlessness are essential components of male fertility evaluation. The retrieved information from such enquiries may shed a light on the genetic etiology of male infertility.

Personal history of cystic fibrosis, Kallmann’s syndrome, Klinefelter’s syndrome, myotonia dystrophica, Kartagener’s syndrome, or adult onset polycystic kidney disease may explain the etiology of childlessness in infertile men. History of recurrent miscarriages may also indicate male chromosomal abnormalities or DNA integrity defects.

The queries about family history must disclose the fertility status of men in the family pedigree of three generations that include first-degree relatives such as father, brothers as well as paternal and maternal uncles. Some studies detected familial clustering of cases of male subfertility due to known genetic, or even due to undiscovered genetic etiology. A single study has shown that 11.8% of 621 couples have involuntary childlessness in at least one first-degree and second-degree relatives on the husband side.114 Another study demonstrated that men with impaired semen quality, reported higher incidence of subfertility among their brothers than that reported by male relatives of normozoospermic infertile men.115

Moreover, the husband’s family history of multiple births defects also raises the concern about chromosomal disorders. Husband’s parental consanguinity is also considered a risk factor for genetic male infertility.

**Environmental Factors and Occupational Exposure**

The worldwide rising incidence of male infertility has been recently attributed to environmental toxicants. Exposure to these harmful factors must be assessed such as excessive heat from saunas and hot tubs, use of pesticide and organic solvents, radiation from X-rays or from excessive use of cell phone and heavy metals intoxication such as lead or cadmium.

Certain occupations constitute a hazard for male reproductive health. The foundry and steel workers, specialized welders, and bakers reported to have
heat-induced decline in semen quality. Sedentary occupations have claimed to increase scrotal temperature and affect the testicular function. Other occupations, including exposure to organic solvents, such as painters, printers, dyes manufacturers are also considered hazardous to male reproductive health.

Cigarette smoking history should be verified, and the patient should be encouraged to quit smoking. As smokers have higher incidence of testicular atrophy, altered semen parameters and sperm function, as well as sperm with oxidative DNA damage and chromosomal aneuploidy.\textsuperscript{116} Alcohol, on the other hand, should be taken in

<table>
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<tr>
<th>Medication</th>
<th>Gonadotoxic</th>
<th>Altered HPG axis</th>
<th>Decreased libido</th>
<th>Erectile dysfunction</th>
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</tbody>
</table>

HPG: hypothalamic-pituitary-gonadal axis; MAOIs: monoamine oxidase inhibitors; (+) means that the medication has an effect; (–) means that the medication has no effect.
Section 2  Male Factor Infertility

Moderation because alcohol may suppress testosterone production and consequently impair spermatogenesis. Lastly, obesity and malnutrition must be considered as both can have detrimental effect on male reproductive function. Such conditions may result in deficiency of vitamins and micronutrients which impairs the highly active biological process of spermatogenesis.

Female Factor Infertility

A comprehensive female evaluation by the gynecologist is an essential step in the integral evaluation of the infertile couple.

Physical Examination

General Aspects

Initially, the physical examination must be performed in a warm room and the patient is asked to undress and stand with his arms outstretched. This position enables the physician to measure the patient’s height, weight and arm span as well as to observe abnormal body hair distribution, abnormal body habitus, muscular hypotonic posture, fat distribution and skin pigmentation. Physical signs of hypogonadism depend on age of onset in relation to puberty. Prepubertal hypogonadism onset is characterized by eunuchoidism (arm span exceeds body height by more than 5 cm) due to delayed closure of the epiphyseal plates in long bones with sparse facial, pubic and axillary hair distribution pattern. In contrast, postpubertal hypogonadism (adult onset) may not affect the anthropometric measurements; however, decline in the muscle bulk and bone mass with loss of beard and pubic hair, and thinning of facial skin may be visible. Both conditions affect skin color and texture, due to poor development of androgen-dependent sebaceous gland, resulting in dryness, wrinkling and pallor of the skin. Although testicular and penile size may not be affected to a great extent in adult onset, hypogonadism, preadolescent hypogonadism usually culminates in infantile gonads and penis.

Although rare, particular attention should be paid to the diagnosis of specific inherited syndromes that negatively impact the male reproductive potential. Such conditions include Prader-Willi syndrome, which is characterized by obesity, hypogonadism, short stature, skin hypopigmentation and muscle hypotonia, and Laurence-Moon-Biedl syndrome featured by obesity, mental retardation, and retinitis pigmentosa.

The physical examination of head and neck includes testing for smell, visual field defects, midline craniofacial abnormalities and thyroid enlargement. Anosmia is one of the presenting features of Kallmann’s syndrome. Blurred vision and visual field loss are signs of pituitary and intracranial tumors. The combination of galactorrhea, visual field defects and infertility is suggestive of prolactinoma. Thyroid dysfunction is accompanied by relative androgen deficiency and impairment of spermatogenesis.

Chest is examined for the presence of gynecomastia and galactorrhea. The signs of chronic sinopulmonary infections, in association with male infertility, may reveal underlying genetic syndromes such as cystic fibrosis, Young’s syndrome and Kartagener’s syndrome.

Abdomen is meticulously inspected and palpated to detect signs of chronic liver diseases, such as liver enlargement, and splenomegaly or signs of polycystic kidney diseases.

Genitalia

The genital examination, including digital rectal examination, should be carried out. The inguinal and genital regions must be carefully inspected, in order to identify scars from previous surgical interventions, such as hydrocele correction, inguinal hernia repairs and surgery for undescended testicle. They may account for damage to the testicle blood supply and to the vas deferens. The genital examination may reveal the presence of a hypospadiac urethral meatus, pathological curvature of the phallus or active sexually transmitted disease. These factors may ultimately result in misplacement of spermatozoa inside the vaginal vault following ejaculation.

Testis volume can be estimated with the aid of an orchidometer or can be measured by using a pachymeter (Figure 4A). A normal sized adult testicle should have a length of 4 cm and a width of 2.5 cm resulting in a volume around 20 ml. They should present with firm consistency. Eighty-five percent of the testicular parenchyma is involved with spermatogenesis. There is no lower limit for testicular volume to exclude the presence of spermatoza. As such, testicle size cannot be relied on as a clinical marker to preclude a trial of sperm retrieval.

Bilateral testicular atrophy may be caused by primary or secondary testicular failure. When serum testosterone is low, seminal fluid is often of small volume as well. Endocrine workup helps to distinguish both conditions. High follicle-stimulating hormone (FSH) levels accompanied by normal or low testosterone levels imply primary testicular failure. These patients should be offered genetic evaluation for chromosomal abnormalities and Y chromosome microdeletions. The combined low serum FSH and testosterone levels suggest hypogonadotrophic hypogonadism, particularly, if bilateral atrophic testicles are present. In this scenario, serum LH is often low. These men should undergo cranial imaging and serum prolactin measurement to exclude pituitary gland disease as in Kallmann’s syndrome.
The epididymides have to be evaluated according to their size and consistency as well. The obstructed epididymis is augmented and ingurgitated (soft). A healthy epididymis free of trauma, infection or obstruction should be firm. Partial regression of an epididymis may represent a scenario of CBAVD. The vasa are easily palpable inside the posterior aspect of the spermatic cord as a distinct, firm, round, “spaghetti-like” structure. Unilateral or bilateral congenital absence of the vasa results in oligozoospermia or azoospermia, respectively. Narrowing areas of the vasa deferentia may represent an infection or traumatic sequelae.

Absence of the vasa deferentia or vasal agenesis is a clinical diagnosis and does not depend on any complementary imaging study. However, 25% of men with unilateral vasal agenesis and about 10% of those with CBAVD also have unilateral renal agenesis and should undergo an abdominal ultrasound to identify this condition.\(^\text{120}\)

Each spermatic cord has to be inspected to assess volume and consistency and to detect existing lipomas or varicocele.

Varicocele may be identified by physical examination with the patient standing in a warm room.\(^\text{121}\) A physical examination alone provides a sensitivity and specificity of approximately 70%.\(^\text{122}\) Varicoceles diagnosed by this method are termed “clinical” and may be graded according to the size. Valsalva maneuver may reveal differences in blood volume in each cord. Internal spermatic veins and cremasteric veins are filled up, whenever the patient stands. In varicocele patients, a venous dilation exists and may be enhanced during Valsalva maneuver. Large varicoceles (grade III) are varicose veins seen through the scrotal skin (Figure 5). Moderate varicoceles (grade II) and small-sized varicoceles (grade I) are dilated veins palpable without and with the aid of the Valsalva maneuver, respectively.\(^\text{123}\)

No standardized diagnostic method has been defined for the identification of varicocele.\(^\text{124}\)

Lastly, digital rectal examination should assess the pelvic muscle tone in cases of suspected erectile dysfunction and detect any palpable masses including prostatic cysts that may obstruct the ejaculatory ducts.

**Investigation**

This initial workup consists of semen fluid analysis. Additional testing may be needed depending on the results of semen analysis or the information obtained by history and physical examination.
**Section 2  Male Factor Infertility**

**Seminal Fluid Analysis**

Semen is basically composed of spermatozoa and secretory fluid of the accessory sex glands. The seminal analysis is considered as the cornerstone of the laboratory evaluation, although it is not a sperm functional test. It provides information of the functional status of the germative cells, epididymides and accessory sexual glands. Semen analysis is of great value on the male initial investigation and its results are often taken as a surrogate measure of male fecundity and pregnancy risk. Reference intervals for values of semen parameters from a fertile population may provide data, on which prognosis of fertility or diagnosis of infertility can be extrapolated. Therefore, it is recommended that evaluation should be undertaken in a specialized andrology laboratory and should be analyzed by well-trained technicians under rigorous quality control standards.

Nonetheless, the prognostic value of semen components such as sperm number, motility and morphology, as surrogate markers of male fertility, is confounded in several ways; the fertility potential of a man is influenced by sexual activity, the function of accessory sex glands and other defined, as well as yet unrecognized conditions. Routine semen analysis itself has its own limitations, and does not account for putative sperm dysfunctions such as immature chromatin or a fragmented DNA. Results from at least two, preferably three separate semen analyses must be obtained before a definitive conclusion can be drawn, as wide biological variability may exist within the same individual. The interval between the semen analyses is arbitrary and is generally recommended to be 1–2 weeks. Ejaculatory abstinence should be a minimum of 2 days to a maximum of 7 days, ideally 2–3 days. Longer abstinence periods lead to higher ejaculatory volume and increased spermatozoa quantity, but motility is usually decreased. The specimen is generally collected by masturbation inside a sterile recipient with a wide opening in order to avoid spillage outside the container that otherwise can be misinterpreted as hypospermia. The collection should be preferentially done in a proper collection room and no lubricant should be used. If collected at home, the specimen should be brought to the laboratory within 30 minutes, and should be kept close to the body in an effort to maintain physiological temperature during transportation. The specimen must be identified and allowed to liquefy for 30–60 minutes before analysis is undertaken. Routine semen analysis should include:

- Physical characteristics of semen, including liquefaction, viscosity, pH, color and odor
- Specimen volume
- Sperm count
- Sperm motility and progression
- Sperm morphology
- Leukocyte quantification
- Fructose detection in cases where no spermatozoa is found especially if the total volume is less than 1 ml.

The criteria used for normality according to the World Health Organization (WHO) have been recently updated, as shown in Table 5. Approximately 2,000 men from eight countries, whose partners had a time-to-pregnancy of either less than or equal to 12 months, were chosen as individuals to provide reference distributions for semen parameters. One-sided lower reference limits (the fifth centile) were generated and have been proposed to be considered the cutoff limits for normality (Table 5). Apart from the total sperm number per ejaculate, the limits of these newly released reference values are lower than the previously presented ones but are in agreement with recent observations on the seminal profile of fertile men.

The morphometric description of spermatozoa, according to the strict criteria described by Kruger et al., was definitely incorporated in the new WHO guidelines. The low proportions of normal spermatozoa, as defined by those selected in endocervical mucus, inevitably produce very low reference limits for a fertile population. With this method, similar low values of 3–5% normal forms have been found by others to be optimal cutoff values to discriminate fertile from infertile men, whose spermatozoa were used for in vitro fertilization, and in spontaneous

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**Figure 5** Photograph of a large left grade III varicocele that can be seen through the scrotal skin (Reprinted with permission from Esteves SC, Miyaozka R, Agarwal A. An update on the clinical assessment of the infertile male. CLINICS 2011;66(4):691-700)
Interpretation of the reference ranges requires an understanding that they merely provide a description of the semen characteristics of recent fathers. The reference limits should not be overinterpreted to distinguish fertile from infertile men accurately, but they do represent semen characteristics associated with a couple’s achieving pregnancy within 12 months of unprotected sexual intercourse; as such, the limits provide only a standardized guide regarding a man’s fertility. None of these values were able to solely distinguish fertile and infertile men, although morphology was suggested to be the most important. The coexistence of more than one altered seminal parameter significantly increases the risk for infertility. A man’s semen characteristics need to be interpreted in conjunction with his clinical information. The reference limits provided by the WHO manual are from semen samples initiating natural conceptions. As such, they may indicate whether a man would need infertility treatment, but they should not be used to determine the nature of that treatment.

Leukocyte count should also be added to the routine semen analysis. Leukocytospermia (> 1 million leukocytes/ml of semen) incidence in infertile men vary between 3% and 23% and has been correlated with clinical and subclinical genital infections, elevated levels of reactive oxygen species, antisperm antibodies and deficient sperm function. Neutrophils predominate among the inflammatory cells and may be both identified and quantified through different methods and coloring techniques. The Endtz test is one of the most used as it is a simple and low-cost option to detect the presence of peroxidase within neutrophils.

In azoospermic patients, diagnosis must be confirmed by lack of any spermatozoa on centrifuged seminal fluid on two separate occasions at high powered microscopic field evaluation. The WHO recommends centrifugation for 15 minutes at 3000g or greater. Azoospermia with low ejaculate volume (< 1.0 ml) not related to hypogonadism or CBAVD can be caused by ejaculatory dysfunction, although the most common cause is ejaculatory duct obstruction (EDO). When suspected, EDO can be confirmed by assessing seminal pH and fructose as normal seminal vesicle secretions are alkaline and contain fructose.

### Endocrine Evaluation

Endocrine evaluation should be performed in the following scenarios:
- Sperm concentration less than 10 million/ml
- Erectile dysfunction
- Hypospermia (semen volume < 1ml)
- Signs and symptoms of endocrinopathies or hypogonadism

The minimal evaluation includes serum FSH and total testosterone. They reflect germ cells and Leydig cells status respectively. If testosterone level is low, a second analysis will be recommended along with free testosterone, LH, estradiol and prolactin measurements. Isolated FSH elevation is usually indicative of severe germ cell damage. Elevated FSH and LH levels associated with

### Table 5

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<tr>
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<td>&lt; 1.0 × 10⁶/ml</td>
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*Lower reference limit obtained from the lower fifth centile value
† Grade a = rapid progressive motility (> 25 μm/s); grade b = slow/sluggish progressive motility (5–25 μm/s); Normal = 50% motility (grades a + b) or 25% progressive motility (grade a) within 60 min of ejaculation
§ Arbitrary value
³ No actual value given, but multicenter studies refer to > 14% (strict criteria) for in vitro fertilization
“Normal shaped spermatozoa according to Tygerberg (Kruger) strict criteria
Section 2  Male Factor Infertility

Low-normal or below-normal testosterone levels imply diffuse testicular failure which may have a congenital (e.g. Klinefelter syndrome) or acquired cause. Comitant low levels of FSH and LH may implicate hypogonadotropic hypogonadism. This may also be congenital, or secondary to pituitary diseases. In these cases, a complete workup of pituitary function is recommended including serum measurement of adrenocorticotropic hormone, thyroid-stimulating hormone, growth hormone and brain magnetic resonance. Gonadotropin values within normal range suggest extraluminal obstruction in azoospermic subjects. However, patients with sperm maturation arrest and 10% of those diagnosed with Sertoli-cell-only syndrome may present with nonelevated hormonal measurements. Serum estradiol measurement should be done in obese patients and in those presenting with gynecomastia or hypogonadism. Infertile patients, in whom testosterone to estradiol ratio is less than 10, can harbor significant but reversible seminal alterations. Vaucher et al. suggested that hyperestrogenism secondary to a higher conversion of testosterone into estradiol in Klinefelter syndrome patients inhibits testosterone production via a negative feedback pathway and may indicate overexpression of aromatase CYP19 in the testis at a molecular level. As such, there would be scientific rationale for use of aromatase inhibitors in Klinefelter syndrome patients.

In azoospermic men with normal ejaculate volume, a FSH serum level greater than twice the upper normal limit is reliably diagnostic of dysfunctional spermatogenesis and, when found, diagnostic testicular biopsy is usually unnecessary although no consensus exists in this matter. If FSH level is normal, a unilateral biopsy on the larger testis may be recommended as there is no guarantee of normal spermatogenesis.

Hyperprolactinemia is a rare cause of infertility in healthy men and is more commonly related to erectile dysfunction and pituitary diseases. These men may present micropituitary or macropituitary prolactin-secreting adenomas. Serum prolactin must be determined in infertile men with a complaint of concomitant sexual dysfunction or in those who have clinical or laboratory evidence of pituitary disease. Although hormonal alterations may be present in approximately 10% of men who undergo investigation, clinically significant dysfunctions affect less than 2% (Table 2).

Genetic Evaluation

Genetic factors commonly associated with male infertility include chromosomal aberrations, genetic mutations and Y chromosome microdeletions. Chromosomal aberrations are assessed through peripheral blood lymphocyte culture and Giemsa band staining (G band karyotyping). Genetic mutations and Y chromosome microdeletions assessments are also performed by analysis of peripheral blood sampling. DNA is amplified using polymerase chain reaction technique. Table 6 summarizes the indications and recommended tests for genetic evaluation.

Chromosomal abnormalities can be found in about 6% of infertile men and its prevalence inversely correlates with sperm count. Azoospermic men can present chromosomal alterations in as much as 16% of cases. Sex chromosomal aneuploidy (Klinefelter syndrome; 47,XXY) is the most frequent chromosomal disorder present in infertile men and is generally associated with hypotrophic or atrophic testicles, elevated serum FSH levels and azoospermia, although spermatogenesis can be differently affected in patients with a mosaic karyotype (46,XY/47,XXY).

The mutation of the cystic fibrosis gene located on the long arm of chromosome 7 is the most commonly found genetic mutation. According to the extension of the mutation, cystic fibrosis can be manifested at its full clinical presentation (an autosomal recessive potentially fatal disease) or in a mild form, where congenital bilateral absence of the vasa deferentia exists and affects approximately 1.3% of infertile men. Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations compromise the development of Wolffian ducts derived structures (efferent ducts, epididymides and vasa deferentia) and may even be implicated in seminal vesicles hypoplasia or agenesis, and unilateral renal agenesis. Approximately 80% of men presenting with CBVAD have a CFTR mutation. As the diagnostic methods routinely used are not 100% sensitive, a man with CBVAD should be assumed to harbor a CFTR mutation. Genetic testing should be offered to female partners to exclude the possibility of these being carriers (approximately 4% risk) before using their husband sperm for assisted conception. Genetic counseling should be offered after genetic testing. Recent data suggest that azoospermic men with idiopathic obstruction and those presenting the triad of chronic sinusitis, bronchiectasis and obstructive azoospermia (Young’s Syndrome) have an elevated risk for CFTR mutation.

The long and short arms of Y chromosome are respectively related to spermatogenesis and testicle development. The Y chromosome region related to infertility is named azoospermia factor (AZF) locus. The AZF locus can present complete or partial microscopic deletions, isolated or in combination, and in nonoverlapping subregions called AZFa, AZFb, AZFc and AZFd (Figure 6). These subregions contain multiple genes controlling different steps of spermatogenesis.
Chapter 3  Evaluation and Diagnosis of Male Infertility

The most common Y chromosome deletion in infertile men is the one affecting the deleted in azoospermia (DAZ) gene located in AZFc region. Severe oligozoospermia or azoospermia can be seen in such cases. Y chromosome microdeletions can be found in 6% of men presenting with severe oligozoospermia (< 1 million/ml) and 15% of those with azoospermia. For sperm counts between 1 million/ml and 5 million/ml, the detection rate drops down to 1.7%. Detection of Y chromosome microdeletions provides predictive information on the success of obtaining spermatozoa from the testicle for intracytoplasmic sperm injection (ICSI). AZFa and AZFB microdeletions present as azoospermia and are associated with germ cell aplasia and maturation arrest, respectively. In such cases, sperm retrieval attempt is not indicated because the chances of finding testicular sperm are unlikely. In case of AZFc...
Section 2  Male Factor Infertility

use for subclinical varicocele diagnosis is controversial, as several studies demonstrated no clinical benefit from surgical treatment in this situation. When there is doubtful physical examination such as in obese patients or difficulty to assess the contralateral side of a clinically detectable varicocele then ultrasonography is useful, as correction of a subclinical varicocele concomitant to a clinical contralateral one might be justified in this scenario. The commonly accepted color-Doppler ultrasonography criterion for varicocele (maximum vein diameter of 3 mm or greater) has a sensitivity of about 50% and specificity of 90% compared to physical examination. A pencil-probe Doppler (9 MHz) stethoscope is an inexpensive tool that may aid in the diagnosis of the varicocele. The patient is examined in the upright position, and a venous “rush” representing blood reflux is heard with or without the Valsalva maneuver (Figure 4B). Although simple and easily performed in the office, Hirsh et al. demonstrated that more than 50% of men without clinical varicoceles exhibited a Valsalva maneuver Doppler-positive reflux. None of these adjunctive diagnostic methods can differentiate between clinical and subclinical varicoceles. The significance of a positive test result using any of these adjuvant techniques in infertile men remains uncertain.

Urinary tract ultrasonography is indicated to evaluate renal status in patients diagnosed with CBAVD. Renal agenesis may be present in 10% of patients with CBAVD and 25% of those with unilateral absence of vas deferens.

Magnetic resonance imaging: Use of magnetic resonance imaging (MRI) in infertility investigation has gained importance in the recent years. Situations such as varicocele, EDO, seminal vesicle agenesis and undescended testis are male infertility related conditions and can be incidentally seen. Pelvic MRI helps to clarify in detail pictorial changes initially seen at TRUS (Figure 7). Moreover, MRI has traditionally been used to exclude cranial pathologies manifested by hormonal changes including low testosterone levels, low serum LH and FSH values, and high prolactin level.

There is evidence of the optimized usefulness of pituitary MRI in men with hypogonadism when prolactin levels are greater than twice the normal range or when there are worrisome symptoms suggesting intracranial abnormality (headache, visual disturbances, diffuse metabolic derangements and other). In general, pituitary abnormalities can be identified in 25% of hypogonadal men. Of these, however, empty sella and pituitary nonfunctional microadenomas require no specific treatment and make one wonder about the cost-effectiveness of their diagnosis.

Imaging

Transrectal, scrotal and renal ultrasonography: The indications for transrectal ultrasonography (TRUS) include:

- Low semen volume (< 1.5 ml)
- Abnormal digital rectal examination
- Ejaculatory disorders (anejaculation, hematospermia, painful ejaculation)

It allows for evaluation of the distal extraductal system (seminal vesicles and ejaculatory ducts). Ejaculatory duct obstruction (EDO) EDO may be congenital or acquired, and present either as complete or partial obstruction. The characteristic feature of EDO in TRUS is the enlargement of the seminal vesicles; however visualization of cysts at the level of ejaculatory ducts may coexist. When CBAVD is diagnosed, TRUS can reveal abnormalities at the level of seminal vesicles such as hypoplasia or agenesis. A recent study has suggested that combination of scrotal and TRUS may not only distinguish obstructive from NOA but also determine the etiologic classification of obstructive azoospermia (OA). In this condition, ultrasonographic anatomic abnormalities are more commonly seen than in NOA patients (92.2% vs 2.8%, p < 0.001). Sensitivity, specificity and accuracy of combined assessment in discriminating between OA and NOA were 95.3%, 97.2% and 96.0%, respectively. Seminal vesicle aspiration and seminal vesiculography may be performed under TRUS guidance and may help to establish the diagnosis of EDO. In azoospermic men, finding of a large number of sperm in the seminal vesicle aspirate, strongly suggests EDO. Concomitant seminal vesiculography can determine the site of obstruction.

The indication for scrotal ultrasonography is to evaluate palpable nodules or testicular masses. Its
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Nuclear magnetic resonance spectroscopy has been recently proposed as a possible tool to identify metabolic signatures associated with various histological states in infertile men. Based on ex vivo analysis of testicular biopsy specimens, concentrations of 19 tissue metabolites were acquired and then reassessed in men with a diagnosis of NOA. A singular pattern could be determined for two testis histological states: normal and Sertoli-cell-only syndrome. Proliferating germ cells are related to high phospholipid synthesis and with elevated phosphocholine. Normal spermatogenesis spectroscopic pattern presents high peaks of phosphocoline as opposed to Sertoli-cell-only syndrome. Further research in this area may aid in the identification of a distinct metabolic signature for sperm existence sites, regardless of testis histopathology.157

**Vasography:** It is indicated in selected cases of obstructive azoospermia. It can also be performed when there is reason to suspect of unilateral obstruction (e.g. previous surgical intervention) in severe oligozoospermic men with a hypotrophic contralateral testis. Vasography and seminal vesiculography are usually undertaken by scrotal or transrectal routes, but can also be performed transurethrally or perineally. The contrast solution flows through vas deferens, seminal vesicles and ejaculatory duct delineating the anatomy and allowing for identification of obstructive segments. The presence of sperm on microscopic analysis of the fluid recovered from vas deferens and seminal vesicles indicates distal obstruction and rules out testicle or epididymal obstruction. Currently, isolated diagnostic vasography is not recommended, but may be performed concomitantly with surgical approach for obstruction resolution.

**Sperm Function Laboratory Testing**

In 10–20% of infertile couples who undergo basic investigation, all diagnostic workup will yield normal results and couples will be etiologically classified as having unexplained infertility. Additional tests have been developed in order to identify functional disorders and other sperm abnormalities, which are not addressed in conventional semen analysis. Some of them are only utilized as research tools (computer-assisted semen analysis, acrosome reaction, oxidative stress evaluation using chemiluminescence, hamster egg sperm penetration test, hemizona assay).158 Others, such as antisperm antibodies and sperm DNA fragmentation have been implemented in clinical practice. The clinical indications of these highly specialized tests are unexplained male infertility or idiopathic male infertility with recurrent failure on multiple in vitro fertilization (IVF)/ICSI cycles. A brief overview of sperm function test are provided below.

**Antisperm antibodies:** Risk factors for antisperm antibodies (ASA) formation include genital infections, testicular trauma or surgical biopsy, cryptorchidism, testicular damage secondary to excessive heat exposure and obstruction of extratesticular ductal system (e.g. vasectomy). Antisperm antibodies can alter sperm motility and sperm-oocyte interaction. The immunobeads test is commonly used for antibodies detection and consists in using human anti-immunoglobulin antibody-coated polyacrylamide beads that are capable to detect IgA and IgG, the two most clinically important immunoglobulin subtypes associated to immunological infertility.159 It precisely detects antibodies in serum and seminal plasma or bound to sperm surface. The rates of sperm bound to beads above 50% are considered clinically significant and may cause dysfunctional motility, vitality and capability for egg interaction.127 The detection of antibodies in the serum and seminal plasma are of limited value as antibodies to sperm are the most likely to induce functional alterations.

**Sperm DNA fragmentation testing:** Sperm DNA fragmentation seems to be one of the most important causes of reduced fertility potential.160 Advanced paternal age, inadequate dietary intake, drug abuse, pesticide environmental exposure, tobacco use, varicocele, medical disease, scrotal hyperthermia, air pollution, genital inflammation or infectious diseases can be cited as possible causes; some of which are reversible. Fragmentation
Section 2  Male Factor Infertility

can be secondary to internal factors such as apoptosis and oxidative stress (a pathophysiological mechanism secondary to a high concentration of free radicals), or external factors such as the presence of leukocytes. Assessment of sperm DNA integrity is indicated in the following situations:
- To investigate infertility in men presenting normal semen analysis as determined by conventional methods
- Cases of recurrent spontaneous abortion
- To aid determining the most appropriate reproductive assisted technology when necessary.

Abnormally fragmented sperm DNA can be found in 5% of infertile men with normal semen analyses and 25% of infertile men with abnormal semen analyses, but is rarely seen in fertile men. Assays to evaluate sperm chromatin/DNA integrity can be divided in three groups: (a) sperm chromatin structural probes using nuclear dyes (e.g. microscopic acridine orange test (AOT), sperm chromatin structural assay (SCSA), aniline blue test (AB), chromomycin-A3 (CMA3) and toluidine blue (TB), (b) tests for direct assessment of sperm DNA fragmentation (e.g. terminal deoxynucleotidyl transferase mediated dUTP nick end labeling assay (TUNEL) and single-cell gel electrophoresis assay (COMET), and (c) sperm nuclear matrix assays (e.g. sperm chromatin dispersion test). TUNEL technique seems to be one of the most adequate as it offers the possibility to precisely identify all existing endogenous breaks in sperm DNA. It combines both enzymatic and immunohistochemical techniques for direct observation of DNA fragmentation using a fluorescence microscope or flow cytometry. Elevated sperm DNA fragmentation rates significantly diminish the chances for natural or assisted pregnancy.

Reactive oxygen species: It has been shown that 40–88% of nonselected infertile patients have high levels of seminal reactive oxygen species (ROS). Moreover, 11% of normozoospermic infertile men have higher ROS levels and reduced total antioxidant capacity (TAC) levels normozoospermic infertile men have higher ROS levels have a physiological role for capacitation, hyperactivation and AR. Defective ZP-binding sperm is present in approximately 15% and 25% of subfertile men with normal and abnormal semen analyses, respectively.

Two tests of sperm binding to the human zona which have been described:
1. The hemizona assay
2. The sperm-zona binding ratio test.

In the former, a single zona is bisected and each zona half is incubated with control and tested sperm suspensions. In the latter, a complete zona is incubated with equal numbers of motile spermatozoa from control and test populations, each labeled with a different such as vitamin C and taurine, chain-breaking antioxidants such as alpha-tocopherol and ROS-metabolizing enzymes such as superoxide dismutase and those of the glutathione cycle, but very little catalase. Imbalance between the oxidants load and natural antioxidant defense system is called oxidative stress or oxygen paradox.

The most often used methods for detecting ROS in an andrology setting are divided into two major categories:
1. Direct methods such as chemiluminescence and flow cytometry
2. Indirect methods such as the colorimetric one.

Chemiluminescence uses probes such as luminol to detect ROS. Luminol can penetrate the cell and react with intracellular reactive oxygen species; in addition, extracellular ROS exhibit chemiluminescence when mixed with an appropriate oxidizing agent. This property is due to the formation of unstable endoperoxide, which ultimately breaks down with the release of light. The emitted light photons are converted to an electrical signal and measured by luminometer, with ROS generation being measured as counted photons per minute (cpm). The normal range is < 0.2 X 10^6cpm per 20 million spermatozoa. Intracellular ROS can also be measured by flow cytometry using different fluorescent probes such as 2,7’-dichlorofluorescin-diacetate and hydroethidine that react with ROS to emit a red fluorescence. The colorimetric technique is also widely used for indirectly quantifying ROS. It is based on the principle of spectrophotometry and measures lipid peroxide end products, mainly malondialdehyde, lipid hydroperoxides and isoprostanes.

Sperm-zona pellucida binding: Sperm binding to the zona pellucida (ZP) is attributed to the presence of complimentary binding sites or receptors on the surface of both gametes; Human ZP3 (hZP3) is believed to be the primary ZP receptor for capacitated acrosome-intact sperm binding. Sperm binding to ZP3 induces a signal transduction cascade within the spermatozoon, involving multiple proteins that lead to the AR. Defective ZP-binding sperm is present in approximately 15% and 25% of subfertile men with normal and abnormal semen analyses, respectively.

Two tests of sperm binding to the human zona which have been described:
1. The hemizona assay
2. The sperm-zona binding ratio test.
fluorescent dye. In each case, the number of spermatozoa from each population bound per whole or half zona is counted and the number of test sperm expressed as a ratio of that of the control.

**Acrosome reaction:** The AR is defined as the process of fusion of sperm plasma membrane with outer acrosomal membrane leading to release of exocytotic proteolytic enzymes (acrosine and hyaluronidase) in response to sperm-ZP binding. ZP3 is considered the natural stimulus for the AR, which leads to the proteolytic dissolution of the ZP. Artificial stimuli used *in vitro* to challenge the AR are calcium ionophore A23187 and progesterone. Defective AR of clinical significance are: (i) AR prematurity, which is defined as high level of spontaneous AR (> 20% of spermatozoa exhibiting spontaneous AR), and (ii) AR insufficiency, which is defined as poor responsiveness to AR stimulants (when < 15% of spermatozoa responded to the ionophore A23187 challenge). Both conditions are associated with poor fertilization capacity on conventional IVF treatment. Under normal conditions, > 15% AR in response to ionophore treatment is expected. Various techniques are used for visualizing the human sperm acrosome, including lectins, monoclonal antibodies or the triple stain. Replicate (minimum two) slides must be scored for each determination, with at least 100 spermatozoa counted per slide.

The frequency of spermatozoa exhibiting defective ZP induced AR (ZPIAR) is high in subfertile men with idiopathic oligozoospermia (65%) and severe teratozoospermia (62%, strict normal sperm morphology < 5%), but low 25% in normozoospermic subfertile men. Sperm from men with unexplained infertility may be able to bind to the zona but unable to induce the AR, ultimately resulting in reduced sperm-ZP penetration and failure of fertilization. Patients with this condition usually have a long duration of unexplained infertility and normal semen analysis, and have zero or low rates of fertilization with standard IVF. The diagnostic feature is that very low proportions of sperm undergo AR after binding to the ZP. However, those patients achieve high fertilization and pregnancy rates with ICSI.

Although the exact mechanisms of defective AR are unknown, defective ZPIAR is more likely to be related to major structural defects of the sperm head, such as small or abnormal acrosomes, or associated abnormalities in the overlying plasma membrane in severe teratozoospermic subfertile men. In normozoospermic men, it has been shown that the seminal zinc concentration as a decapacitating factor was significantly higher in men with defective ZPIAR.

**Sperm penetration testing:** The ability of the equatorial region of the acrosome-reacted human sperm to fuse with the vitelline membrane of the oocyte is tested by using the sperm penetration assay (SPA) also known as the zona-free hamster oocyte penetration test. Although this test does not assess sperm-ZP binding it measures the spermatozoos’s ability to undergo capacitation, AR, fusion and penetration through the oolemma, and decondensation within the cytoplasm of an oocyte. The ZP is removed from a hamster oocyte, which is then incubated with human spermatozoa. In its original description, sperm penetration ability is scored by calculating the percentage of ova that are penetrated; normal sperm are able to penetrate 10–30% of hamster ova. Recent refinement of this test includes the incubation of sperm in a more potent capacitating media that allow the majority of ova to be penetrated; scores are obtained by calculating the number of subfertile sperm that penetrate each ovum compared to fertile controls. Several studies have evaluated the ability of the SPA to predict success or failure of IVF. Normal SPA results are predictive of fertilization by conventional IVF. Nonetheless, semen samples which fail to fertilize hamster ova usually are unable to fertilize human ova. Although the SPA is considered a research tool, it may be of clinical value for men with unexplained infertility with poor fertilization rate on IVF.

**Postejaculatory Urine Examination**

Postejaculatory urine (PEU) examination inspects for the presence of sperm to diagnose retrograde ejaculation. It helps to differentiate from other causes of hypospermia (volume < 1.5 ml) such as specimen collection issues, hypogonadism, EDO and congenital bilateral absence of the vas deferens.

**Testis Biopsy**

Testis biopsy is indicated in selected cases of azoospermia or severe oligozoospermia to distinguish obstructive from nonobstructive cases. Histopathology results may reveal normal spermatogenesis, hypospermogenesis, germ cell maturation arrest, germ cell aplasia (Sertoli-cell-only syndrome), tubular sclerosis or a combination of these conditions. Biopsy can be performed by percutaneous or open approaches. Intraoperative imprint technique may yield information regarding testicular cytology including the presence of spermatogenesis or Sertoli-cell-only syndrome; however, this method is limited to provide a specific and detailed morphological assessment. In cases biopsies are obtained for diagnostic purposes only, the authors’ technical choice is to perform the procedure...
either percutaneously or using the "window" open technique without testis delivery from the scrotum. Specimens should be placed in an appropriate fixative solution such as Bouin's fixative, Zenker's fixative or glutaraldehyde; formalin should not be used. In cases of NOA, histology results provide important prognostic information on the chances to retrieve spermatozoa to be used in ART. However, as spermatogenesis is often limited and focal in NOA patients who harbor sperm production, it is recommended that biopsy is undertaken preferentially in assisted reproduction specialized centers to allow for immediate fresh sample examination and sperm cryopreservation for future ICSI, and avoiding the need of repeated procedures.

**Algorithms for Evaluation and Diagnosis**

A detailed medical history, physical examination, semen analyses and complementary tests, as appropriate, are the key to correctly diagnose and to define the better treatment strategies. In Figures 8A and B, we present algorithms summarizing what should be considered when assessing the infertile male.
Figures 8A and B  Algorithms for the workup of the infertile male. (A) Algorithm to be considered on initial evaluation; (B) Algorithm for the male patient presenting with azoospermia on semen repeated analyzes (Adapted from Esteves SC, Miyaoka R, Agarwal A. An update on the clinical assessment of the infertile male. CLINICS 2011;66(4):691-700, with permission from the Editor)

REFERENCES

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