

# Clinical Management of Male Infertility

Giorgio Cavallini  
Giovanni Beretta  
*Editors*

 Springer

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Paolo Turchi, Giovanni Beretta, and Giorgio Cavallini

The clinical management of couple infertility suffers from a way of thinking still widely diffused today among those working in the field, who often consider the understanding of the male factor of infertility too vague and its remedies not yet supported by solid scientific evidence. Consequently it often happens that couples are initiated directly to assisted reproduction techniques (ART), even in the presence of a male factor, undiagnosed or untreated [1, 2]. Unilateral handling of reproductive care, according to this common way of thinking, should provide the couple with the best chances of procreation. In fact, there are four strong reasons to favor bilateral management of the infertile couple, including an assessment of the male.

Firstly, infertility should be considered a disease. It can be an expression of sometimes serious disorders not yet diagnosed at the time of the search for pregnancy [3, 4]. A comprehensive male infertility evaluation may allow to detect significant disease(s) that otherwise would have remained undiagnosed if the evaluation of the male factor were limited to seminal examination only. Recent studies have suggested that male infertility may be associated with reduced longevity [5] and that male factor infertility is an increased risk factor for certain malignancies [6, 7]. Furthermore, the condition of an infertile male can cause psychological and marital stress [8–10]. Quantifying this risk, it has been estimated that for every 15 couples evaluated, in 1 couple (6 %) the male partner has a significant medical condition [11].

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These figures highlight the concept that not to provide infertile males with an appropriate diagnostic evaluation should be regarded as an error and/or omission by the physician and a missed opportunity, objectively difficult to justify.

Secondly, a correct andrologic diagnostic workout may unveil infertility factors in about 70 % of infertile males [12]. Many of such factors are correctable or treatable, with the perspective ideally to allow the couple to spontaneously conceive, but also to have better chances of success when exposed to ART [13–16].

Thirdly, scientific evidence suggests that considering the high cost, success rates, and possible side effects of ART, early efforts to improve male fertility appear to be an attainable and worthwhile primary goal. The main results obtained concern evidence-supported indications regarding other causes of male infertility, and their early detection and treatment [17].

Lastly, it should be appreciated that the modern andrologist is no longer a specialist acting according to personal experience and common sense only. Scientific evidence and ensuing clinical guidelines are in fact today available. The skills of the andrologist today encompass internal medicine, endocrinology, seminology, microbiology, molecular biology surgery, and genetics. Pertinent scientific societies, according to the available peer reviewed literature, have produced guidelines, recommendations and diagnostic/therapeutic algorithms. Such advances in the andrologic field allow today infertile males to be properly evaluated and potentially treated, making the andrologist the male infertility specialist that is equipped with the latest medical knowledge.

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Paolo Turchi

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## 2.1 Definition

Infertility is defined by the World Health Organization (WHO) as “a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse” [1]. Infertility can also be defined on the basis of demographic considerations, such as “an inability of those of reproductive age (15–49 years) to become or remain pregnant within 5 years of exposure to pregnancy” [2] or as “an inability to become pregnant with a live birth, within 5 years of exposure based upon a consistent union status, lack of contraceptive use, non-lactating and maintaining a desire for a child” [3]. The WHO also defines infertility from an epidemiologic perspective: “women of reproductive age (15–49 years) at risk of becoming pregnant (not pregnant, sexually active, not using contraception and not lactating) who report trying unsuccessfully for a pregnancy for 2 years or more.” No definition considers male infertility as a specific condition, and in only one, contained in the 5th edition of the WHO *Laboratory Manual for the Examination and Treatment of Human Sperm*, has the male factor been cited: “Infertility is the inability of a sexually active, non-contracepting couple to achieve pregnancy in 1 year. The male partner can be evaluated for infertility or subfertility using a variety of clinical interventions, and also from a laboratory evaluation of semen” [4]. In this statement, reference is made to the need for a comprehensive evaluation of the infertile male.

Once considered a disorder of inconvenience, infertility has been classified as a disease in the US regulatory Americans with Disabilities Act [5]. Indeed, infertility in women was ranked the fifth highest serious global disability (among rural populations younger than 60 years) [6]. This change of view also applies to men. A disease is any deviation from or interruption of the normal structure or function of any

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part, organ, system, or combination thereof of the body that is manifested by a characteristic set of symptoms or signs. Based on this definition, male infertility meets these criteria [7] and thus should accordingly, be considered a disease.

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## 2.2 Epidemiology

While most studies agree that infertility affects approximately 15–20 % of all couples [8–11], data relating to male infertility are more uncertain. An epidemiologic study of male infertility in fact presents a clinical problem because fertility is a couple-related concept and male fecundity (i.e., his biological capacity to reproduce) is a component of the fertility rate. Both male and female partners make an independent contribution to a couple's fertility, but the outcomes of fertility are only fixed in terms of pregnancy rate or births. It is often difficult to determine which partner makes the greatest contribution to a couple's disease, and this difficulty is a feature of infertility, in which there are no pathognomonic findings to confirm a diagnostic certainty. This difficulty is also an important limitation of epidemiologic studies, in which the male factor is often undervalued and underestimated.

Epidemiologic studies of male infertility are also severely limited by several other factors. First, traditionally the couple's infertility is addressed by evaluating the woman while male diagnostics is often confined to a semen analysis. Semen quality and quantity are the most widely used biological markers of male fertility and are a source of essential information in assessing the fertility of a couple, but they correlate with indices of subfertility, such as time to pregnancy (TTP), in addition to sexual activity and several other conditions [12]. Semen analysis is poorly predictive of the male fertility status, mainly giving information about the status of the male genital tract and, thus, only indirect indications of potential male fertility. Moreover, semen analysis is an operator-dependent examination and has a high coefficient of variability [13]. Classification of the male condition of fertility/infertility based on the seminal characteristics is an influential factor that limits the understanding of the problem. Furthermore, male infertility is not a specific disease subject to documentation as is, for example, a prostate cancer, which is easily detectable within large-scale databases. In addition, it is usually evaluated and treated in the private outpatient setting, and clinical data are not stored in the public health system databases. Therefore, quantifying the actual burden of the male component is often impossible. The consequence is a lack of data with which to track diagnoses and treatments of a disease, and difficulty in quantifying its causes and frequency. Another factor limiting the understanding of the epidemiologic problem, and which contributes to the loss of data related to male infertility, is the frequent use of empiric treatments of male factor infertility, such as the *in vitro* fertilization (IVF) that primarily treats the female partner. In general, IVF programs require that an exact cause is assigned for the woman, whereas the male factor is classified only as present or not present. When a male cause is reported, it is almost always based only on seminal data without undertaking a clinical assessment, making data partial and generic [14, 15].

## 2.3 Incidence

The majority of studies examining the incidence and prevalence<sup>1</sup> of male infertility have been conducted in specific geographic regions. In these studies, the incidence of male factor infertility varied considerably depending on the region considered. For example, a study conducted in Siberia reported female and male factors to account for 52.7 % and 6.4 %, respectively [10], whereas a Nigerian study revealed a high prevalence of male infertility [16]. In this study, male factor infertility was estimated at 42.4 % whereas female factors were estimated at 25.8 %. In 20.7 % of couples, both partners were affected. Sexual promiscuity and sexually transmitted diseases (and inadequate treatment) have been implicated in the high rate of male factors [16]. Epidemiologic studies are numerous but, even considering all the data available today, none is able to define the incidence of male infertility. Male factor infertility can vary widely based on geography (e.g., Siberia vs Nigeria) and inherent risk factors. Evaluating existing literature, a component of male factor infertility may range widely, from 6 to 50 %, with many groups estimating 30–50 % [17–20]. Perhaps the only consistent aspect found in the scientific literature is that male infertility is variable with a multitude of contributory factors (race, country, geography, socioeconomic variables, environmental and occupational exposures, the fertility of the partner, and so forth), many of which require further research to be better characterized. To understand the approximation of these data it should be re-emphasized, however, that the true extent of male infertility is probably underestimated because of the frequent lack of assessment of the male in the diagnostic workup of infertile couples. Eisenberg et al. [21] have evaluated the frequency of evaluation of male infertility using data from the National Survey of Family Growth, and have found that 18–27 % of men in infertile couples were not evaluated. Overall, these data suggest that male factor infertility is a significant component of global infertility and needs better quantification, using population-based studies conducted on a large scale, to help physicians fill these gaps in understanding.

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## 2.4 Classification

The nosology of male infertility, despite the growing attention it receives from medical research, is still difficult to define. On the one hand a growing burden of the male component of the infertile couple is described, with studies reporting a decline in male fertility over the years [22–25]. On the other hand, except for some specific causes of infertility such as cryptorchidism and genetic causes, other infertility factors, such as varicocele or genitourinary tract infections, often remain hypothetical and are not investigated. Male infertility therefore continues to be classified as being due to poor semen quality (oligozoospermia, asthenozoospermia, or teratozoospermia alone or in

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<sup>1</sup>Incidence is defined as the number of new cases of a disease in a specific population at risk over a specific period of time. Prevalence is defined as the total number of cases of disease (both old and new) present in a specified population at a single point in time.

combination) of unknown causes, which does not contribute to increased knowledge about the etiology [26]. A correct clinical evaluation of the infertile male would, instead, identify an infertility factor in 60–70 % of cases (Table 2.1). In 30–40 % of cases, no cause of male infertility can be found; these men, affected by oligoasthenoeratozoospermia syndrome, might be defined as having idiopathic male infertility.

**Table 2.1** Male infertility causes and associated factors, and percentage of distribution in 10,469 patients

Diagnosis	Unselected patients ( <i>n</i> = 12,945)	Azoospermic patients ( <i>n</i> = 1,446)
<i>All</i>	100 %	11.2 %
Infertility of known (possible) cause	42.6	42.6
Maldescended testes	8.4	17.2
Varicocele	14.8	10.9
Sperm autoantibodies	3.9	–
Testicular tumor	1.2	2.8
Others	5.0	1.2
Idiopathic infertility	30.0	13.3
Hypogonadism	10.1	16.4
Klinefelter syndrome (47, XXY)	2.6	13.7
XX male	0.1	0.6
Primary hypogonadism of unknown cause	2.3	0.8
Secondary (hypogonadotropic) hypogonadism	1.6	1.9
Kallmann syndrome	0.3	0.5
Idiopathic hypogonadotropic hypogonadism	0.4	0.4
Residual after pituitary surgery	<0.1	0.3
Others	0.8	0.8
Late-onset hypogonadism	2.2	–
Constitutional delay of puberty	1.4	–
General/systemic disease	2.2	0.5
Cryopreservation due to malignant disease	7.8	12.5
Testicular tumor	5.0	4.3
Lymphoma	1.5	4.6
Leukemia	0.7	2.2
Sarcoma	0.6	0.9
Disturbance of erection/ejaculation	2.4	–
Obstruction	2.2	10.3
Vasectomy	0.9	5.3
Cystic fibrosis (congenital bilateral absence of vas deferens)	0.5	3.1
Others	0.8	1.9

From Jungwirth et al. [27] and Thonneau et al. [26]

**Table 2.2** Classification and distribution of the causes of male infertility

Pretesticular	5–10 %
Testicular	65–75 %
Post-testicular	10–20 %

**Table 2.3** Main factors associated with male infertility

Cryptorchidism
Genetic causes
Varicocele
Testicular tumors
Testicular trauma
Genitourinary tract infections (testis, epididymis, prostate, seminal vesicles)
Iatrogenic causes (surgery, chemotherapy, radiotherapy)
Systemic diseases
Twisting of the spermatic cord

**Table 2.4** Main risk factors associated with male infertility

Age
Lifestyle
Cigarette smoke
Substances abuse (alcohol, cannabis derivatives, opioids)
Sedentary lifestyle/obesity
Scrotal temperature (clothing, underwear, occupational exposure to heat, regular sauna)
Exposure factors and/or toxic environmental/occupational
Family history of infertility and/or recurrent poliabortivity

When we consider male factor infertility, we imply a series of possible causal factors divided into pretesticular causes (inadequate stimulation of the testis by gonadotropin), testicular causes (diseases of the testis), and post-testicular causes (seminal tract obstructions, ejaculatory disorders, erectile dysfunction) (Table 2.2). As almost none of the causes can be considered a definitive factor of infertility, it is preferable to define each condition as a male infertility associated factor whenever a clinical evaluation of the infertile male is performed (Table 2.3). In addition, many risk factors are associated with a worsening of semen quality (Table 2.4), which is attracting great attention and should be considered in the process of collecting the medical history, but for which, at present, the scientific evidence is not sufficiently strong.

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## 3.1 Is Sperm Analysis an Indicator of Male Infertility?

Sperm analysis is an important fertility test for infertile couples, and it is suggested that this test be performed before any treatments even if a female problem has been resolved. It is unacceptable to subject a woman to medical procedures and tests without knowing the status of her partner's semen. Semen analysis has long represented the standard test for evaluating male fertility and remains a cornerstone; however, it is a poor predictor of fertility [1].

The World Health Organization (WHO) guidelines on sperm analysis are based on percentiles, which in turn are based on a group of men who fathered children in a time window of 1 year or less. The lower acceptable numbers represent the fifth percentile of this group. In other words, fewer than 5 % of the men who fathered a child in the past year had semen parameter measurements below these cutoffs. This implies that having better or worse numbers does not necessarily mean that a man will or will not be able to father a child. The semen parameters are merely guidelines to consider when investigating the potential causes of infertility.

Diagnosis is important in the management of male infertility, but “infertility” in itself is not a diagnosis but a symptom, like pain. Sperm analysis is only the first step; all male patients with abnormal sperm should have a full clinical history taken and should undergo a complete clinical examination.

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In general, a man is asked to abstain from any ejaculations for 3 to 5 days before the test. In the laboratory it is important to use a cup, provided by the lab, because some materials are toxic to spermatozoa; if the sperm is obtained at home the sample should be brought to the laboratory within approximately 1 h.

The sperm analysis must include the evaluation of both macroscopic and microscopic parameters; if found to be abnormal, the test should be performed on multiple ejaculates before characterizing a man as infertile [2].

The biological variation of seminal parameters further diminishes the clinical significance of the most recent WHO reference values.

Data indicate that there are variations in semen parameters between men in different geographic regions and even between samples from the same individual [3, 4].

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## 3.2 Macroscopic Parameters

Semen is made up of more than just sperm; in fact, less than 5 % of semen consists of sperm. Healthy semen includes fluid from the testes, the seminal vesicles, the prostate gland, and the bulbourethral glands.

*Normal ejaculate* is between 1.5 and 6 mL of fluid. Absence of seminal fluid after orgasm (*aspermia*) occurs in males with diabetic neuropathy, following surgical procedures, or after the intake of sympatholytic drugs. In some of these cases, because the nervous plexus is damaged, there may be retrograde ejaculation into the bladder, and an examination of the postejaculatory urine should be conducted.

*Volume* <1.5 mL (*hypospermia*) may be due to the loss of a portion of the ejaculate during collection, incomplete orgasm, or incorrect abstinence. pH <7.0 may indicate absence of seminal vesicles or obstruction/subobstruction of the ejaculatory ducts. If pH is >8.0, this may indicate hypogonadism with accessory gland impairment, inflammation, or intake of narcotics.

*Appearance* and *semen color* seem to be insignificant in assessing sperm fertilization potential.

A translucent aspect can denote the absence of spermatozoa, whereas an opaque sample may indicate the absence of sperm cellular components. Red color may indicate an excessive number of erythrocytes (*hematospermia*) and yellow color the presence of jaundice.

When semen is ejaculated it is thick and gelatinous, to help it adhere to the cervix. The semen eventually liquefies within 20–30 min of ejaculation. *Absence of coagulation* denotes possible obstruction or agenesis of seminal vesicles with secondary lack of secretions. *Delayed liquefaction* may indicate a problem with the prostate, the seminal vesicles, or the bulbourethral glands, also known as the male accessory glands.

*Viscosity* is another parameter that is considered abnormal if the length of a thread exceeds 50 mm; in these cases there is low sperm motility and the sperm transportation can be compromised.



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### 3.3 Microscopic Parameters

#### 3.3.1 Sperm Concentration

Sperm count is in millions per milliliter of semen. Normal samples have more than 15 million spermatozoa per milliliter.

The cutoff of 15 million spermatozoa/mL has been suggested in 2010 by the WHO as the lower normal value for sperm concentration in an ejaculate. Normal semen has more than 39 million in the whole ejaculate [5].

In a study evaluating two semen specimens from each of the male partners in 765 infertile couples and 696 fertile couples, subfertile men had sperm concentrations of  $<13.5 \times 10^6/\text{mL}$  [6].

Another study that evaluated 166 male factor infertility patients and 56 proven fertile donors has suggested the concentration of  $31.2 \times 10^6/\text{mL}$  as a prognostic factor for fertility status [7].

On the other hand, the literature describes significant overlap in threshold sperm concentration between fertile and infertile men.

Oligozoospermia, a low sperm concentration, is indicated when sperm concentration falls below  $5\text{--}10 \times 10^6/\text{mL}$ , and may be due to the loss of a portion of the ejaculate, partial obstruction of the genital tract, drugs, or genetic abnormalities. Other factors include the use of various medications, such as aspirin or nitrofurantoin, and excessive heat exposure.

Azoospermia, the absence of spermatozoa, may be caused by complete obstruction of sperm transport, hypogonadism, and iatrogenic causes (chemotherapy),

or idiopathic factors that are most probably genetic in origin. In these cases, the semen analysis must be repeated with cytocentrifugation of the sample to confirm the azoospermia [8].

### 3.3.2 Sperm Motility

Spermatozoa are graded according to their ability to swim.

Sperm that swim in a progressive manner are graded as having rapid or sluggish motility.

Sperm motility is considered as compromised if the percentage of progressive motility falls below 32 % and total (progressive + nonprogressive) motility is below 40 % within 60 min of sample collection [5]. Asthenozoospermia, the presence of low sperm motility, can occur as a result of prolonged time to processing of collected samples. Containers may be toxic to the sperm, and sample exposure to extreme temperature or sunlight can determine asthenozoospermia. A long period of abstinence can also be a cause of poor sperm motility. Other causes include axonemal deformities of spermatozoa, leukocytes, and idiopathic factors. Asthenozoospermia is also most commonly seen with antisperm antibodies. The observation of sperm clumping combined with low sperm motility is a further indication of the presence of antisperm antibodies [9].

The presence of severe asthenozoospermia necessitates an investigation of sperm viability and identification of necrozoospermia (nonviable spermatozoa).

A *vitality test* is suggested when the number of immotile sperm is >60 %. This is a staining technique that identifies whether the immotile sperm are dead or just immotile, and is reported as percentage vitality. The normal value is 58 % or above.

### 3.3.3 Sperm Morphology

The shape and size of the sperm are assessed on a stained preparation. The 2010 WHO guidelines encourage the use of Kruger's strict criteria, based on the research of Kruger and Menkeveld [10].

In men whose partners are able to conceive within 12 months, a lower normal value of 4.0 % has been suggested for morphologically normal spermatozoa [5].

Debate is still ongoing regarding the morphologic criteria that should be used and which one offers the most predictive power for in vivo and in vitro fertility.

In advocating the use of the strict criteria, the WHO suggests >4 % as a cutoff point for correlation with positive in vitro fertilization (IVF) outcomes [11].

It is important to note that other studies have found the strict criteria to be of less value in predicting IVF outcomes [12].

### 3.3.4 Non-Sperm Cellular Components

Immature germ cells are present in oligozoospermia, where the ejaculates usually have low sperm counts.

**Table 3.1** Distribution of values for semen parameters from men whose partners became pregnant within 12 months of discontinuing contraceptive use [5]

Parameter (units)	<i>N</i>	Centile								
		2.5	5	10	25	50	75	90	95	97.5
Semen volume (mL)	1,941	1.2	1.5	2.0	2.7	3.7	4.8	6.0	6.8	7.6
Sperm concentration (10 <sup>6</sup> per mL)	1,859	9	15	22	41	73	116	169	213	59
Total sperm number (10 <sup>6</sup> per ejaculate)	1,859	23	39	69	142	255	422	647	802	928
Progressive motility (PR, %)	1,780	28	32	39	47	55	62	69	72	75
Non-progressive motility (NP, %)	1,778	1	1	2	3	5	9	15	18	22
Immotile spermatozoa (IM, %)	1,863	19	22	25	31	39	46	54	59	65
Normal forms (%)	1,851	3	4	5.5	9	15	24.5	36	44	48
Vitality (%)	428	53	58	64	72	79	84	88	91	92

Special attention should be given to the concentration of leukocytes in the seminal ejaculate. Leukocytes are normally present in the seminal fluid, but a concentration above  $1 \times 10^6/\text{mL}$  is considered abnormal [5]. A higher than normal white blood cell (WBC) count is known as leukocytospermia, which may indicate infection. However, some men may have leukocytospermia without any active infection or male fertility impairment. In fact, anywhere from 5 to 20 % of men tested may be found to have leukocytospermia. A positive correlation has been observed between leukocyte count and the total count of microorganisms in semen samples. An optimal sensitivity/specificity ratio appears at  $0.2 \times 10^6$  WBC/mL semen [13] (Table 3.1).

The excessive presence of leukocytes may be detrimental to spermatozoa, owing to their excessive production of reactive oxygen species (ROS) and cytotoxic cytokines [14].

The presence of erythrocytes is not always indicative of reproductive tract abnormality, while the presence of microorganisms is an indication of genital tract infection [15].

### 3.4 Sperm Function Tests

Semen analysis is mainly used to estimate male fertility potential, but clinical research has shown that normal semen analysis might not reflect defects in sperm function. Sperm function testing is used to determine if the sperm have the capacity to reach and fertilize oocytes. A variety of tests is available to evaluate different aspects of these functions [16, 17].

Our knowledge of the molecular mechanisms regulating sperm function continues to grow, as do the opportunities for new diagnostic tests; for example, recent studies emphasize the importance of nuclear DNA integrity and compaction [18–20].

### 3.4.1 Test of Sperm Capacitation

Capacitation is a series of structural and biochemical changes that spermatozoa go through to be able to fertilize an oocyte.

All processes take place in the female genital tract, but with capacitation media can be induced in vitro. It is thought to have a role in preventing the release of lytic enzymes until spermatozoa reach the oocyte. One of the signs of capacitation is the display of hyperactivation by spermatozoa. At present, the clinical value of sperm capacitation testing remains to be determined [21].

### 3.4.2 Testing for Antibody Coating of Spermatozoa

It has been known for more than 100 years that an immune response can be generated against the antigens present on the surface of spermatozoa. The presence of anti-sperm antibodies can be suggested on the basis of excessive sperm agglutination. Antibodies may block the penetration of cervical mucus by spermatozoa, or prevent sperm binding and penetration of zona pellucida.

Immunologic protection to sperm antigens are provided by the tight junctions of Sertoli cells forming the blood-testis barrier.

The antigenic capacity of semen can be ascribed to the fact that spermatogenesis begins during puberty, when the immune system is able to respond to antigenic stimulations. The spermatozoon evokes an immune response when exposed to the systemic immune defense system under conditions whereby this barrier gets disrupted and leads to the formation of antisperm antibodies, such as testicular torsion, vasectomy, and testicular trauma [9].

Two current methods of detecting antibodies bound to the surface of motile sperm are the Mixed Agglutination Reaction assay (MAR test; only for immunoglobulin G) and the immunobead-binding assay (for immunoglobulins A, G, and M).

A positive finding of >50 % motile sperm with attached beads is considered to be clinically significant [22, 23].

### 3.4.3 Tests of Sperm DNA Damage

DNA damage is interconnected with poor semen parameters, e.g., low sperm concentration, low motility, and high levels of reactive oxygen species. Fertilization in mammals involves the direct interaction of the sperm and the oocyte, fusion of the cell membranes, and union of male and female gamete genomes. Although a small percentage of spermatozoa from fertile men also possess detectable levels of DNA damage, which is repaired by oocyte cytoplasm, there is evidence to show that the spermatozoa of infertile men possess substantially more DNA damage and that this damage may adversely affect reproductive outcomes [24, 25]. There appears to be a threshold of sperm DNA damage, which can be repaired by oocyte cytoplasm

(ie, abnormal chromatin packaging, protamine deficiency), and beyond which embryo development and pregnancy are impaired [26, 27].

#### 3.4.3.1 Direct Tests

- (a) Terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end-labeling (TUNEL) assay
- (b) DNA oxidation measurement

#### 3.4.3.2 Indirect Tests

- (a) Sperm chromatin structure assay (SCSA)
- (b) Sperm chromatin dispersion assay
- (c) Sperm fluorescence in situ hybridization analysis (FISH)

Overall, even if there are some data to suggest that sperm DNA damage is associated with poor pregnancy outcome after standard IVF, there is no significant relationship between sperm DNA damage and fertilization rate or pregnancy outcomes at IVF or IVF/intracytoplasmic sperm injection [5, 28–31].

According to the Practice Committee of the American Society for Reproductive Medicine, significant intraindividual variations exist for the sperm chromatin structure assay, making precise conclusions problematic [32].

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## 3.5 Conclusions

Semen analysis is essential in estimating male fertility, but is not a direct measure of it. Abnormalities in the semen analysis can occur for numerous reasons, such as incomplete collection by the patient. Illness, fever, stress, and various medications can also affect sperm quality.

Confirmation of a true sperm problem requires at least a second test. Each variable alone is not a suitable predictor of the fertility status, and has to be considered in the context of the other parameters and the clinical setting.

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Edoardo S. Pescatori

Whenever a couple has not conceived after 1 year of unprotected intercourse, both partners should undergo a thorough medical examination. An earlier evaluation is suggested in the presence of a known male (i.e., history of cryptorchidism) or female (i.e., age over 35 years) infertility risk factor or if a man wishes to know his fertility potential [1].

The justification for male evaluation by an andrologist relies on the fact that a male factor is solely responsible in about 20 % of infertile couples and is contributory in another 30–40 % [2, 3]. It is presently recommended that, to categorize infertility, both partners should be investigated simultaneously [4]. The goals of a male evaluation for infertility are to identify causes of infertility that after correction could allow natural conception, to identify causes of infertility that after correction could increase the chances of success of assisted reproduction technologies (ARTs), and to explore underlying conditions that, in addition to being related to infertility, could pose a risk for the man's health.

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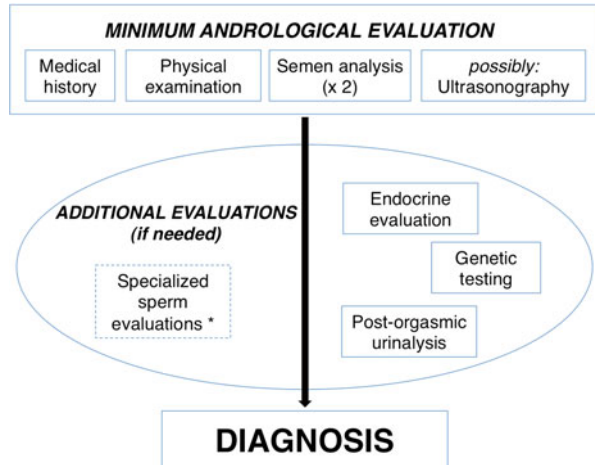
## 4.1 Andrologic Evaluation for Male Infertility: The Initial Office Visit

The minimum andrologic evaluation for male infertility should include a complete medical history, physical examination, and the evaluation of at least two semen analyses [1]. The physical evaluation is usually complemented by the ultrasonographic evaluation of the scrotal content and, if indicated, the prostate. All of these tests can be carried out during a single andrologic office visit. Additional

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**Fig. 4.1** Andrologic workup flow chart: \*specialized sperm evaluations are presently considered experimental (WHO)



investigations may be appropriate, should specific problems emerge at the initial office visit. These tests chiefly comprise endocrine evaluation, genetic testing, post-orgasmic urinalysis, and specialized sperm evaluations (Fig. 4.1). The components of the andrologic office visit are detailed here.

### 4.1.1 Medical History

The medical history should investigate all possible causes that may affect the fertility potential of the man. The following areas should be addressed.

#### 4.1.1.1 Reproductive History

Did the man under investigation formerly induce pregnancy or pregnancies with the present or other partners? If so, this would suggest that medical attention be focused more on the present female partner. Should a history of spontaneous abortions be present, this should direct one's attention to sperm DNA evaluations.

#### 4.1.1.2 Occupational History

Professions at risk of affecting fertility, such as direct and prolonged exposure to high temperatures (e.g., kitchen work) and exposure to gonadotoxic agents (e.g., pesticides), should be noted. According to the specific agent, fertility may improve after 1–2 spermatogenetic cycles (3–6 months) after discontinuation of exposure.

#### 4.1.1.3 Lifestyle Risk Factors

Smoke [5–7], excessive alcohol [8] and coffee [9] intake, recreational drugs [10], elevated body mass index (BMI) [11, 12], and low physical activity [13] also have been linked to impaired male fertility; modifying such risk factors may have a positive impact on male fertility.

**Fig. 4.2** Prader orchidometer



#### **4.1.1.4 Andrologic History**

The possible occurrence of the following conditions should be investigated: undescended testis and age of orchiopexy, testis torsion and outcome, former inguinoscrotal surgery such as for inguinal hernia repair, former prostate surgery, pubertal/prepubertal mumps-related orchitis, pubertal development, anosmia, former neoplasia and related treatments, current and recent medications, current and recent genitourinary symptoms or infections, and recent episodes of high fever.

#### **4.1.1.5 Sexual History**

The patient should be asked about libido, quality of erection, intercourse frequency, ejaculation, and possible sexual distress related to reproductive difficulties or timed sex.

### **4.1.2 Physical Examination**

In the man evaluated for infertility, physical examination is more informative by far than in the woman: male genitalia are external and easily evaluated, even without the aid of ultrasonography. Moreover, the main male sexual accessory gland, the prostate, can be digitally palpated through the anus.

The andrologic physical evaluation should comprise: evaluation of secondary sexual characteristics, presence of (pseudo-)gynecomastia, penis inspection with attention to location of the external urethral meatus, and digital rectal examination of the prostate.

A detailed evaluation of the scrotal content is of paramount importance. Testes should be assessed for bilateral presence, location (in place, vs retained, vs ectopic), size (according to Prader orchidometer; Fig. 4.2), consistency, and presence of nodules. Epididymides should be evaluated for their presence, possible dilatations, and associated cysts. Bilateral presence of deferent ducts should be ascertained. The presence of varicocele, and its grading [14], should be sought while in orthostasis (Fig. 4.2).

**Table 4.1** Distribution of values at 5th and 50th centiles for semen parameters from men whose partners became pregnant within 12 months of discontinuing contraceptive use (WHO)

Parameter	(Units)	Centile	
		5th	50th
Semen volume	(mL)	1.5	3.7
Sperm concentration	(10 <sup>6</sup> /mL)	15	73
Total motility (PR + NP)	(%)	40	61
Normal forms	(%)	4	15

*PR* progressive motility, *NP* nonprogressive motility

### 4.1.3 Semen Analysis

Semen analysis is the cornerstone of the laboratory evaluation of the infertile male, and helps to define the severity of the male factor [1]. The 2010 World Health Organization (WHO) *Laboratory Manual for the Examination and Processing of Human Semen* details the present standards of semen analysis and the related laboratory protocols [15], and every laboratory performing semen analyses should comply with such standards.

In general, laboratory reports of semen analysis define values within normal as those values that do not fall below the lower reference limit (fifth centile). When critically evaluating sperm analysis reports, it should be remembered that the fifth centile indicates values below which only 5 % of the observations of fertile men will fall, and not the average values of fertile men whose partners had a time to pregnancy of 12 months or less [15]. Table 4.1 lists the latest WHO sperm parameter reference values of the 5th and 50th centiles, with the aim of providing the reader with a more critical interpretation of sperm analysis.

It should always be remembered that semen parameters within the 95 % reference interval do not guarantee fertility; nor do values outside these limits, in isolation from other clinical data, necessarily indicate male infertility or abnormality: a man's semen characteristics need to be interpreted in conjunction with his clinical information [16] (Table 4.2).

### 4.1.4 Ultrasonography Evaluation of Testes and Prostate

Usually the andrologic physical evaluation of the male is complemented by ultrasonographic evaluation of scrotal content and, if indicated, the prostate.

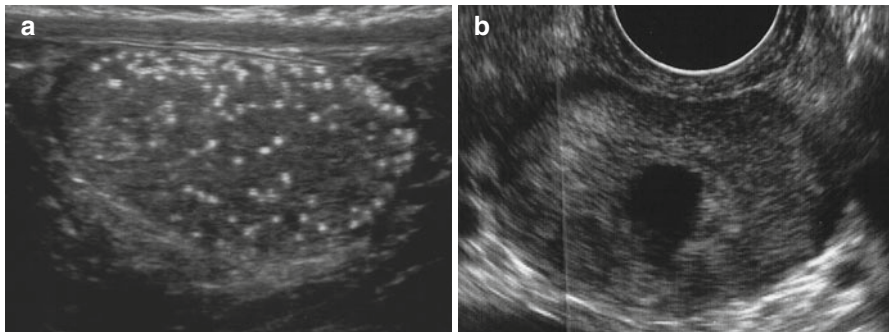
Testis sonography adds useful information regarding the structure of testicular tissue (Fig. 4.3a: microlithiasis), the possible presence of nonpalpable tumors, accurate definition of testes volumes, details of epididymis, and varicocele definition (using Doppler ultrasonography performed while in orthostasis).

If there are clues of obstructive pathology, a transrectal ultrasonogram may unveil an intraprostatic obstructive cyst (Fig. 4.3b). Obstructive intraprostatic cysts should be suspected in the presence of reduced semen volume or even azoospermia, normal-sized testes with distended epididymis, and ejaculatory discomfort/pain.

**Table 4.2** Some examples of medical history, physical examination, semen analysis data, and possible underlying pathology

Medical history	Physical examination	Semen analysis	Suspected
Former prostate surgery	–	Reduced/absent sperm at orgasm	Retrograde ejaculation
Anosmia/delayed puberty	Cryptorchidism	–	Kallmann syndrome
Inguinal hernia repair	Distended epididymis	Oligospermia	Deferent ischemic damage
Low libido	Altered sexual characters	OAT	Hypogonadism
Low libido	Small firm testes	Azoospermia	Klinefelter syndrome
Postpubertal parotitis	Small soft testes	Azoospermia/cryptozoospermia	Postviral testicular damage
–	Varicocele	OAT	Causal role of varicocele
Pain at ejaculation	Prostatic tender “nodule”	Low semen volume	Obstructive intraprostatic cyst
–	Small testes	Normal volume, azoospermia	Nonobstructive azoospermia
–	Distended epididymis	Low volume, azoospermia	Obstructive azoospermia
Recent fever	Painful epididymis	Two million WBC/mL OAT	Infection

OAT oligoasthenoteratospermia, WBC white blood cells

**Fig. 4.3** Possible ultrasonographic findings (a): testicular microlithiasis; (b): intraprostatic obstructive cyst

## 4.2 Andrologic Evaluation for Male Infertility: Additional Investigations

Some elements gathered during the initial andrologic office visit may prompt further diagnostic workup. The more frequent aspects of additional investigation are endocrine status, genetic testing, postorgasmic urinalysis, and specialized sperm evaluations.

**Table 4.3** Simplified endocrinologic differential diagnoses in the presence of altered sperm analysis

FSH	LH	TT	Interpretation
>	>	<	Primary hypogonadism: the problem is the testis
<	<	<	Secondary hypogonadism: the problem is hypothalamus/hypophysis
>	N	N	Possibly: maturation arrest, germinal aplasia, genetic causes
N	N	N	Nonendocrine causes vs functional hypogonadotropic hypogonadism

*FSH* follicle-stimulating hormone, *LH* luteinizing hormone, *TT* total testosterone, *N* normal

## 4.2.1 Endocrine Evaluation

It is appropriate to perform an endocrine evaluation whenever medical history and physical findings suggest an endocrinopathy, in the presence of a low sperm count, and if there is concomitant sexual dysfunction. Gonadal activity relies on the pituitary input provided by luteinizing hormone (LH) and follicle-stimulating-hormone (FSH). Although a minimum initial hormonal evaluation consists of FSH and total serum testosterone, the concomitant assessment of LH, prolactin, and estradiol permits one to obtain a more comprehensive picture of the endocrine status of the patient (Table 4.3).

## 4.2.2 Genetic Testing

When nonobstructive azoospermia or severe oligozoospermia (sperm count  $<10 \times 10^6/\text{mL}$ ) is present, karyotype assessment and a search for microdeletions of the long arm of the Y chromosome are recommended [17]. When bilateral or unilateral congenital absence of the vas is detected, and in the presence of obstructive azoospermia or severe oligozoospermia (sperm count  $<10 \times 10^6/\text{mL}$ ), screening for CFTR mutations is strongly advised [17]. If anosmia has been identified during medical history taking, and even more so if associated with azoospermia, KAL1 gene screening is recommended, with the aim of detecting the X-linked variety of Kallmann syndrome [18].

## 4.2.3 Postorgasmic Urinalysis

This test is indicated in men with low-volume or absent ejaculation at orgasm. The presence of any sperm in a postejaculatory urinalysis in these cases is suggestive of retrograde ejaculation.

## 4.2.4 Specialized Sperm Evaluations

### 4.2.4.1 Reactive Oxygen Species

Reactive oxygen species (ROS) are generated by both seminal leukocytes and sperm cells; although they have a normal physiological role in capacitation and



acrosome reaction, if in excess they can interfere with sperm function by peroxidation of sperm lipid membranes, and induce DNA damage in both the nuclear and mitochondrial genomes [19]. Chemiluminescent procedures may be used to measure ROS production and the redox activity of human spermatozoa.

#### 4.2.4.2 Sperm Chromatin Assessments

Several methods have been used to test the normality of sperm chromatin and DNA. At present the most used tests are the TUNEL test (terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling), the COMET assay (single-cell gel electrophoresis), and the SCD (sperm chromatin dispersion) test. The results of these tests are correlated with each other [20] and with sperm morphology, motility, and viability [2].

Although sperm chromatin assessments are often advocated in cases of inability to conceive by intercourse, intrauterine insemination, in vitro fertilization (IVF), and IVF using intracytoplasmic sperm injection, it is still controversial as to whether there is any relationship between the results of these tests and the specific reproductive problems [2].

Of note, currently both ROS determinations and sperm chromatin assessments are considered research procedures [2].

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### 4.3 Thinking of the Man, Not Only of the Sperm: Potentials of Infertility Male Workup to Detect Underlying Abnormalities and Risk Factors for Male Health

It has been recently reported that infertile men are overall less healthy than fertile men [21, 22] and that poor semen quality may be a biomarker of general health, associated with worse survival [22].

While the above studies refer chiefly to comorbidities are not typically related to male infertility, two specific conditions more prevalent in infertile men are directly linked to male fertility: testicular germ cell tumors and elevated BMI. Testicular cancer has a 20-fold greater incidence in infertile men than in men with normal fertility [23], and semen parameters of men affected with testis tumor are altered in comparison with healthy controls [24]. Elevated BMI is in turn known to negatively correlate with sperm density [25], sperm motility, and sperm chromatin integrity [26].

Two other risk factors for poor male fertility, namely cigarette smoke [5] and low physical activity [25], though not more prevalent in the infertile male population, are worth mentioning because, along with elevated BMI, they are also well-known cardiovascular risk factors.

The andrologic evaluation of the infertile man has the extra benefit of opening a window on the general health of the man besides his fertility, with the potential to discover life-threatening conditions such as testis cancer, and to identify cardiovascular risk factors which, if corrected, may positively affect the health quality and survival of affected men (Table 4.4).

**Table 4.4** Life expectancy, principal conditions, and risk factors more prevalent in infertile men/men with poor semen parameters, versus fertile men

Conditions	Reference
Increased mortality <sup>a</sup>	[22]
Testicular germ cell tumors	[23, 27–29]
Colorectal cancer	[30]
Melanoma	[30]
Prostate cancer	[30]
Cardiovascular disorders	[21]
Pulmonary diseases	[21]
Connective tissue disorders	[21]
Liver diseases	[21]
Diabetes mellitus	[21]
Body mass index	[21]

<sup>a</sup>Increased mortality was due to a wide range of diseases and not particularly diseases related to lifestyle or socioeconomic status

#### 4.4 When to Refer, How to Refer: Key Elements of the Referral Letter

At the conclusion of the andrologic diagnostic workup, the management of the male patient will depend on both the outcome of the workup itself and the possible presence of female infertility risk factors, including advanced female age (>35 years). If a female factor is present, priority should be given to a male treatment strategy that does not delay access to assisted conception programs.

The possible scenarios are summarized in Table 4.5.

As outlined in Table 4.5, a frequent outcome of the andrologic workup is a referral for assisted conception. When this occurs, it is important to write an appropriate referral letter to the assisted reproduction colleagues to adequately summarize the situation regarding the male partner.

Recently, an Italian panel of andrologists and gynecologists proposed a schematic referral letter, aimed to synthetically provide the ART physicians with all the key clinical information concerning the male partner [31]. These five sections of the proposed referral letter are outlined here.

1. *Heading*: This section should report the name and age of both partners
2. *Reason for referral*. This section should summarize the male reproductive history: for how long the man has tried to conceive with the present partner, and possible formerly induced pregnancies (and related outcomes) with the present and, if pertinent, previous partners. Furthermore, results of the male diagnostic evaluation should be summarized: nontreatable male factor infertility versus potentially treatable male factor infertility but suspect/presence of female factor infertility, versus unexplained infertility
3. *Summary of male workup*: Diagnostic conclusions (i.e., varicocele, hypergonadotropic hypogonadism, etc.)

**Table 4.5** Management priorities of the infertile couple, according to workup outcomes

MFI	FFI	Management
+, treatable	–	Male treatment + reassessment
+, treatable	+	Male treatment + parallel referral to ART
+, not treatable	+/-	Referral to ART
– (unexplained infertility)	+/-	Referral to ART

*MFI* male factor infertility, *FFI* female factor infertility, *ART* assisted reproduction treatment

4. *Indications on how to improve sperm quality*: For example, removal of identified risk factors (cigarette smoke, elevated BMI, etc.), specific treatments that may parallel ART (e.g., varicocele correction, genital inflammation treatment)
5. *Special notes, in case of azoospermia*: Type of azoospermia (obstructive vs nonobstructive), results of performed genetic testing, and suggestion on the most appropriate sperm retrieval procedure, in light of the specificity of the case

### Conclusions

Male andrologic workup is mandatory when addressing a couple's reproductive difficulties. The presence of ejaculated sperm, even if sperm values are not below the lower recommended WHO thresholds, should not prevent the male from being evaluated by means of medical history, physical examination, and, possibly, ultrasonography.

Male investigation can allow identification of conditions and risk factors which, when corrected, may improve the chances of both spontaneous conception and success with ART. Furthermore, male andrologic workup may unveil underlying conditions that pose a previously unknown risk for male health.

The extent of male diagnostic investigations must be always appraised in light of the possible presence of female factor infertility.

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## 5.1 Introduction

The male factor of couple infertility is associated with impaired spermatogenesis in the majority of cases. Because spermatogenesis is a complex process that develops immature stem cells into mature gametes, it is obvious that, independent of the etiology of infertility, there exist harmful agents that are able to exacerbate every cause of infertility. Birth is the intended product of intercourse between a heterosexual couple and subsequent conception, so knowledge of the male partner's fertility conditions is mandatory before an andrologist prescribes any therapy. For this reason a general therapeutic approach to male infertility exists, independent of the cause that generates infertility. This general approach involves evaluation of the therapeutic measures that should be used for all infertile men.

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## 5.2 Sperm Analysis

Male fecundity (defined as the potential male capability to induce pregnancy, independent of female conditions) is related to sperm count. However, this relationship is hyperbolic and achieves a plateau at about  $30 \times 10^6$  spermatozoa/mL, 50 % class A motility, and 14 % typical forms (strict criteria) [1–3]. Thus in attempting to improve couple fertility, the more severe the dyspermia, the more crucial is its therapy.

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### 5.3 Female Age

Initially, extensive international data showed fairly consistent age-related risks of Down syndrome live births in different ethnic groups [4]: approximately 1 in 1490 at age 20–24 years, 1 in 200 at 35 years, 1 in 60 at 40 years, and 1 in 11 at 49 years. The observed trisomic births, however, were soon found to be only the tip of the iceberg. Older women have an extremely high rate of pregnancy loss of both chromosomally normal and abnormal conceptions, and increased rates of spontaneous abortions occur at ages similar to those of Down syndrome births. Moreover, spontaneously aborted conceptions that are chromosomally abnormal are mostly trisomic [5].

The reproductive timeline for women is complex. A woman is born with all the oocytes she will ever have, and only 400–500 are actually ovulated [6]. As the number of oocytes declines, a woman's menstrual cycle shortens, infertility increases, and menstrual irregularity begins 6–7 years before the menopause. Increasing age increases a woman's time to pregnancy. When under the age of 30, a woman's chances of conceiving may be as high 71 %; when over 36, it may only be 41 % [7]. The chances of becoming pregnant and being able to maintain a pregnancy are also affected. Matorras et al. reported that in a population of women, the number of infants born begins to exponentially decrease after the age bracket of 35–39 ( $n=89,287$ ) [8]. The odds of becoming pregnant and maintaining a pregnancy are believed to be connected to numerous factors, including euploidy and dehydroepiandrosterone [9].

These data imply that correction of male fertility should be performed in relation to female age, reserving correction of less severe dyspermias for couples whose female partner is younger than 35 years, with the exception of couples who refuse assisted reproduction. Further correction of dyspermias in couples whose female partner is older than 40 is a non sequitur.

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### 5.4 Diet

Sperm morphology and motility are linked to dietary intake of vitamin C, cryptoxanthin, carotenoid, and lycopene [10, 11]. Consuming a diet rich in carbohydrates, fiber, folate, and lycopene, in addition to fruit and vegetables, correlates with improved semen quality [12]. Consuming lower amounts of both proteins and fats are more beneficial for fertility [13]. In other words, the Mediterranean diet improves male (and female) fecundity [14].

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### 5.5 Smoking Habits

Men who smoke before or during attempts to conceive risk decreasing their fertility (odds ratio 1.6) in comparison with nonsmokers [15]. Men who smoke tend to have a decrease in total sperm count, density, and motility, normal sperm morphology,

and semen volume [16, 17]. Smoking may reduce the mitochondrial activity in spermatozoa, and lead to a decreased fertilization capacity [18]. Smoking also can affect the DNA integrity of the sperm, with several studies noting an increase in DNA damage [19].

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## 5.6 Caffeine

It is likely that caffeine intake does not affect spermatogenesis [20].

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## 5.7 Alcohol

In men, alcohol consumption has been linked with many negative side effects such as testicular atrophy, decreased libido, and decreased sperm count [17, 21, 22]. It is likely that sperm count decreases because of a link between alcohol, oxidative stress, and infertility. Oxidative stress has been found to systematically increase with alcohol consumption [23].

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## 5.8 Stress

Stress is defined as mental/emotional tension resulting from a poor/absent compliance to a life situation.

Stress, whether physical, social, or psychological, is a prominent part of any society. Infertility itself is stressful, owing to the societal pressures, testing, diagnosis, treatments, failures, unfulfilled desires, and even fiscal costs with which it is associated [17].

Males who experienced more than two stressful life events before undergoing infertility treatment were more likely to be classified below World Health Organization standards for sperm concentration, motility, and morphology [24]. Stress has a significant impact on sperm density, total sperm count, forward motility, morphology, and DNA fragmentation [24, 25]. Stress and depression are thought to reduce testosterone and luteinizing hormone pulsing [24, 26]. Coping with various lifestyles also affects fertility. It was reported that actively coping with stress, such as being assertive or confrontational, may negatively affect fertility. These data indicate that planning sex in accordance with ovulation day(s) should be ruled out [27–29].

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## 5.9 Exercise

Physically active men who exercised at least three times a week for 1 h typically scored higher in almost all sperm parameters in comparison with those who participated in more frequent and rigorous exercise [30, 31].

## 5.10 Illicit Drugs

Studies of the effects of illegal drugs on human fertility have been scarce because of ethical considerations, and also subject to under-reporting and bias attributable to the characteristics of the population being studied, such as low socioeconomic status or improper prenatal care [32]. The use of illicit drugs appears to have a negative impact on fertility.

### 5.10.1 Marijuana

Marijuana acts both centrally and peripherally to cause abnormal reproductive function. Marijuana contains cannabinoids, which bind to receptors located on the vas deferens and inhibit its motility. In males, cannabinoids have been reported to reduce testosterone released from Leydig cells, modulate apoptosis of Sertoli cells, decrease spermatogenesis, decrease sperm motility, decrease sperm capacitation, and decrease acrosome reaction [33].

### 5.10.2 Cocaine

Cocaine is a stimulant of both the peripheral and central nervous systems that causes vasoconstriction and anesthetic effects. It is thought to prevent the reuptake of neurotransmitters [34], possibly affecting behavior and mood. Long-term users of cocaine claim that it can decrease sexual stimulation; men found it harder to achieve and maintain erection and to ejaculate [35]. Cocaine has been demonstrated to adversely affect spermatogenesis, which may be due to increases in serum prolactin and decreases in serum total and free testosterone [36, 37].

### 5.10.3 Opiates

Opiates represent another large group of illicit drugs. Opiates such as methadone and heroin are depressants that cause both sedation and decreased pain perception by influencing neurotransmitters. In men taking heroin, sexual function became abnormal and remained so even after cessation [38]. Sperm parameters, most noticeably motility, also decrease with the use of heroin and methadone [37, 39].

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## 5.11 Radiofrequency Electromagnetic Waves (Cell Phones)

Several studies demonstrate negative effects of radiofrequency electromagnetic waves generated by cell phones on sperm count. Cell phone usage has been linked with decreases in progressive motility of sperm, decreases in sperm viability, increases in reactive oxygen species, increases in abnormal sperm morphology,



and decreases in sperm counts [40–42]. One study evaluating 52 men demonstrated that those who carried a cell phone around the belt line or hip region were more likely to have decreased sperm motility in comparison with those who carried their cell phones elsewhere or did not carry one at all [42].

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## 5.12 Male Fertility and Longevity

Stress, alcohol, prohibited drugs, smoking habit, Mediterranean diet, and physical exercise are all linked to life expectancy and sperm count. This chapter elucidates why sperm quality can be used as an index of good health and longevity in males [43].

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## 5.13 Residual Fertility

Residual fertility is defined as the probability of a couple to conceive after a period of desiring a child. The longer the period, the lower is the residual fertility (ie, possibility to conceive naturally), even in the case of a correct therapeutic approach and an increase in sperm count [44].

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## 6.1 Definition

*Azoospermia* is defined as the complete absence of sperm in the ejaculate even after centrifugation. Yet even a patient with rare nemasperms after centrifugation in the seminal fluid test is erroneously considered *azoospermic*. This latter condition is instead more correctly defined as *cryptozoospermia*. Instead, severe *oligospermia* is considered a sperm count less than 5 millions/ml. *Azoospermia* must also be differentiated from *aspermia*, which is, instead, the complete absence of seminal fluid emission during orgasm. In this situation the causes are very different and depend on defects of the bladder neck and urethral and ejaculatory ducts system (retrograde ejaculation, urethral stricture, neurological alterations) [1].

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## 6.2 Epidemiology and Classification

Approximately 15 % of couples are unable to procreate after a year of unprotected intercourse and are therefore defined *infertile*. An isolated male factor is present in about 20–30 % of these cases, while in another 20–30 %, there is an association between the male and female factors [2]. Therefore, approximately in half of the cases of couple infertility is the male factor present. The prevalence of azoospermia is approximately 1 % among the general male population and ranges between 10 and 15 % among infertile men [3].

The different types of azoospermia are commonly classified in two large groups: obstructive azoospermia (OA) caused by an obstruction of the passage of sperm

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along the seminal pathways and secretory or non-obstructive azoospermia (NOA) due to a sperm production deficit. The latter can then be subdivided into pre-testicular and testicular according to whether the problem derives from an alteration of the hypophysary hormonal system which stimulates spermatogenesis (very rare condition) or from damage intrinsic to the testis (more frequent condition). The prevalence of OA and NOA regarding the total of the different types of azoospermia is very variable according to authors and geographical areas. In countries or cultures where vasectomy is very diffused as a contraception system, a prevalence of slightly higher OA (40 %) [4] can be seen compared to countries, like Italy, where this is rarely done (25–30 %) (Franco G. 2008, unpublished data). It is clear, therefore, that on the whole, the NOAs constitute the majority of the different types of azoospermia (60–75 %). As will be seen in this chapter, even OA and NOA prognosis is rather different and more favourable to OA.

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## 6.3 Aetiology

### 6.3.1 Obstructive Azoospermia

Obstructive azoospermia is usually classified according to the location of the obstruction (Table 6.1).

#### 6.3.1.1 Testicular Obstruction

The isolated form, with total absence of spermatozoa in the epididymis and normal spermatogenesis, is an extremely rare condition, more often due to a congenital malformation (complete detachment of testicle from epididymis, vasa efferentia and rete testis atresia). The form associated with patchy epididymal obstruction with the presence of some epididymal tubules containing spermatozoa is more frequent and usually due to an acquired post-phlogistic base.

#### 6.3.1.2 Epididymal Obstruction

Obstruction usually happens in the epididymis. It affects about 30–67 % of azoospermic men with normal serum FSH values. The congenital form of it most often appears as bilateral agenesis of the vas deferens (CBAVD), which is associated with a cystic fibrosis gene mutation in 82 % of cases. This form is often correlated to the absence of the distal part of the epididymis (body and tail) and to the agenesis or atresia of the seminal vesicles. Other congenital forms include Young's syndrome which

**Table 6.1** Obstructive azoospermia: obstruction location

Testicular obstruction (often congenital, extremely rare)
Epididymal obstruction (post-flogistic, postvasectomy, congenital, Young's syndrome)
Vas deferens obstruction (congenital: partial or complete aplasia; iatrogenic: vasectomy, hernioplasty)
Ejaculatory duct obstruction (cysts, post-flogistic stenosis)

typically is associated with chronic pulmonary infections, normal spermatogenesis and dilation of the head of the epididymis which is full of spermatozoa and amorphous matter, with the absence of spermatozoa in the epididymal corpus region. Among the acquired forms, the most frequent are the obstructions from sexually transmitted infections (gonococcus, chlamydia) and the postvasectomy obstructions from blow-out of the epididymal tubule due to secondary hyperpressure.

### 6.3.1.3 Vas Deferens Obstruction

The most common cause of congenital obstruction is vas deferens agenesis, almost always associated with the cystic fibrosis gene mutations. In Italy, it has been calculated that about one out of three cases of obstructive azoospermia is caused by vas deferens agenesis. The most frequent form is the complete bilateral one in which the vas cannot be palpated by physical examination, but conditions of partial or unilateral atresia can be observed in which at least one vas deferens or a section of it can be palpated. Unilateral complete or partial aplasia is associated with irregularities of the ejaculatory ducts with to contralateral renal agenesis in 80 and 26 % of cases, respectively.

In the countries where vasectomy is widespread, the most common cause of acquired obstruction is represented by vasectomy as a contraception method. In the United States, almost 500,000 vasectomies are performed per year and approximately 2–6 % of the patients require a conversion (from 10 to 30 thousand reversals/year). In Italy, vasectomy is rarely used; therefore, it is a very less frequent cause of obstruction. Even inguinal hernioplasty surgery can induce vas deferens obstruction via accidental direct damage of it or of its blood supply during surgery. Fibroblastic reaction induced by contact with the polypropylene of the mesh can also determine delayed vas obstruction.

### 6.3.1.4 Obstruction of the Ejaculatory Ducts

This represents almost 10 % of the obstructive forms of azoospermia and can be congenital (cyst, atresia) or acquired (post-flogistic or dysfunctional).

The utricle, Mullerian and Wolffian cysts are localized in the prostate between the ejaculatory ducts and can be communicating or noncommunicating with the semen pathways and normally cause obstruction by compressive phenomena and lateralization of the ejaculatory ducts themselves. Postinflammatory obstructions, decisively more rare, are secondary to acute, subacute or chronic prostatovesiculitis. When complete, the ejaculatory duct obstructions are associated with a reduced volume of seminal fluid (<1.5 ml) with reduction or absence of fructose, acid pH and dilatation of the seminal vesicles.

## 6.3.2 Non-obstructive Azoospermia

The non-obstructive forms of azoospermia (secretory) are usually classified according to their cause (Table 6.2). In almost all cases, the cause is at the gonad level (*testicular cause*), while very rarely, only in the case of hypogonadotropic hypogonadism is

**Table 6.2** Non-obstructive forms of azoospermia: aetiological classification

1. Idiopathic
2. Genetic
3. Cryptorchidism
4. Testicular torsion
5. Orchitis (viral or bacterial)
6. Varicocele
7. Chemo- or radiotherapy, medicines, toxics
8. Hypogonadotropic hypogonadism

azoospermia attributed to an alteration of the hypophysary gonadotropin secretion (*pre-testicular cause*).

### 6.3.2.1 Idiopathic

Unfortunately, in almost half of the non-obstructive types of azoospermia, it is difficult to pinpoint the cause connected to the condition, and therefore we speak about an idiopathic or unknown cause. Many of these situations probably have a base of genetic defects which are still unknown, congenital aberrations or a previous unknown exposition to gonadotoxins.

### 6.3.2.2 Genetic

Karyotype aberrations can be recognized in 10–15 % of azoospermia cases. *Klinefelter's syndrome* is characterized by the presence of a supernumerary X chromosome (47 XXY). One male out of 600 is affected. The patients manifest small and hard testicles, gynecomastia, azoospermia and high levels of gonadotropins. The only possible therapy is testicular sperm extraction (TESE) for intracytoplasmic sperm injection (ICSI). Apparently the best probabilities of success are in younger patients in whom spermatogenesis may not be entirely compromised.

Thanks to recent techniques of molecular biology (PCR), it has been possible to demonstrate that almost 5–10 % of azoospermic patients are carriers of a *microdeletion of chromosome Y*. This is characterized by alterations of the genes localized in the AZF region (azoospermia factors a, b and c) which have a determining role in spermatogenesis. The complete deletion of the AZFa and AZFb loci is always associated with the absence of spermatozoa in the testicles and therefore with a worse fertility prognosis [5, 6].

### 6.3.2.3 Cryptorchidism

Cryptorchidism is the undescend of one or both testicles into the scrotum, often linked to a development deficit of the testicles and their ligament connections. In 8 % of cases the testicle remains in the abdomen, in 70 % in the inguinal canal and in 20 % in the pre-scrotum. The greater the degree of retention, the more serious the testicular dysfunction; there is an absence of germinative cells in 20–40 % of testicles in the inguinal or pre-scrotum region and in 90 % of testicles in the intra-abdominal location. In the case of bilateral cryptorchidism, the probability of infertility is 50–90 %, while in the case of monolateral forms, the probability is 20–70 %. Azoospermia caused by cryptorchidism is almost always due to

alterations of spermatogenesis connected to the testicular dysgenesis syndrome or due to damage caused by the elevated temperature the retained testicle is exposed to, in particular when not operated on immediately (before 1–2 years of age). Other possible causes of azoospermia are epididymal aberrations often associated with the cryptorchid testicle (didymo-epididymal detachment of testicle from epididymis) which could theoretically cause an obstructive-based azoospermia or mixed secretory-obstructive azoospermia.

#### **6.3.2.4 Testicular Torsion**

Testicular torsion can result in azoospermia in the case of bilateral torsion, in monorchid patients or when contralateral testicle is already compromised by other conditions.

#### **6.3.2.5 Orchitis**

The parotitis virus can be responsible for orchitis in almost 30 % of affected patients, above all in the post-puberty age, with bilateral interest in 10–30 % of cases. As a result of the infection, an atrophy or permanent testicular hypotrophy can occur with consequent azoospermia. The introduction of the anti-parotitis vaccination has made this event rare. Other bacterial and viral infections or infections from other microorganisms can cause non-obstructive azoospermia from direct damage of spermatogenesis. These germs, however, more frequently cause epididymitis which determine a condition of obstructive azoospermia.

#### **6.3.2.6 Varicocele**

The relationship between varicocele and azoospermia is still a matter for discussion. According to most authors, the two conditions could be coexistent only, but for others there is a direct correlation between them. On the basis of this, some suggest the treatment of varicocele which can lead to the reappearance of spermatozoa in the ejaculate, particularly in the presence of a histological pattern of a late maturation arrest or hypospermatogenesis [7].

#### **6.3.2.7 Exposure to Drugs, Toxic Substances and Radiation**

Chemotherapy can exercise a negative effect on spermatogenesis. The most affected cells are the spermatogonia and spermatocytes up to the preleptotene stage. The type of drug, its dosage and patient age at time of treatment assume a relevant importance. It seems that alkylating agents and procarbazine are the most toxic for the testicles. During chemotherapy many patients become azoospermic with elevated levels of serum FSH, but the majority of them recover a normal spermatogenesis months or years afterwards. Instead, in other patients, azoospermia is permanent. Also radiation exposure plays a negative role on spermatogenesis; in fact, spermatogonia and spermatocytes are very sensitive to this. Lastly, many toxic substances can cause a serious reduction in spermatogenesis, leading to azoospermia.

#### **6.3.2.8 Hypogonadotropic Hypogonadism**

This is a very rare cause of azoospermia (less than 1 % of cases), even if it is the only condition treatable with medical therapy. In hypogonadotropic hypogonadism



the alterations of the hypothalamus or the pituitary gland compromise the correct release of gonadotropins, determining seminal alterations that extend to cases of azoospermia. The Kallmann syndrome is characterized by hypogonadotropic hypogonadism associated with anosmia. An insufficient secretion of GnRh from the hypothalamus with consequent gonadotropin reduction and secondary testicular insufficiency is recognized as the cause of this syndrome. A delayed puberty is a pathognomonic sign. In this condition testicles are usually very small, under 2 cm in longitudinal diameter. Other pathologic conditions affecting the hypophysis diseases such as ischaemia, tumours or infections can cause hypogonadotropic hypogonadism. The Prader-Willi syndrome is characterized by hypogonadism, obesity, muscular hypotonia, mental retardation, reduced development of hands and feet and short stature. These patients have an FSH and LH deficit caused by an insufficiency of GnRh. Therapy for these types of hypogonadism is pharmacological with administration of gonadotropins sometimes associated with GnRh.

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## 6.4 Diagnosis

A careful and accurate andrological evaluation can immediately pinpoint the genesis of azoospermia: personal history, for example, can reveal previous cryptorchidism, testicle infections (orchitis, mostly from epidemic parotitis) or previous chemo- or radiotherapy treatments.

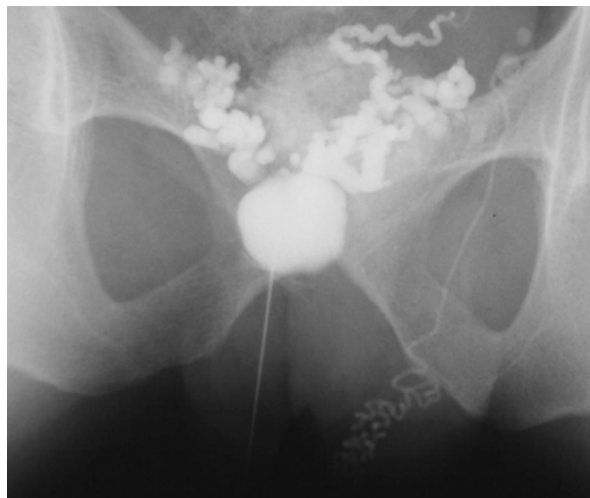
Particular attention is to be paid to:

- Family medical history (even reproductive)
- Personal reproductive medical history and alterations of the ejaculate
- Pathological personal medical history
  - Congenital aberrations (e.g. cryptorchidism)
  - Inflammatory diseases
  - Traumas
  - Inguinal-scrotal and pelvic surgery
  - Systemic diseases
  - Endocrinopathies
  - Chronic obstructive bronchopulmonary diseases
  - Drugs and chemo- and radiotherapy
  - Environmental and professional exposure to heat sources, radiations and toxics

Physical examination can reveal small testicles (<10 ml) with reduced consistence or eunuchoid look of the patient in NOA, while the presence of a normal testicular volume, or unpalpable vasa, will orient towards OA. Physical examination can also show the presence of a varicocele.

The seminal fluid exam can reveal the nature of OA/NOA via the evaluation of volume, pH and fructose. Serum levels of FSH and inhibin B supply further indications for the differential diagnosis between OA and NOA. In fact, an elevated

**Fig 6.1** Ultrasound-guided transperineal vesiculodeferentography with fine needle puncture of a median prostatic cysts communicating with the seminal tract



FSH value and a low inhibin B value certainly point to a NOA condition. Scrotum ultrasounds must always be done for the study of the testicle (volume, echogenicity) and epididymis (cribriform pattern suspect for obstruction) but also for the screening of testicular tumours, more frequently found in azoospermic subjects and, in general, in the infertile male. Scrotum echo Doppler or colour duplex scanning must be done in the presence of clinically evident varicocele. TRUS (transrectal ultrasound of the prostate) is recommended in cases of oligoposia, when obstruction of the ejaculatory ducts and agenesis of the vas deferens or seminal vesicles are suspected. As concerns genetic screening, karyotype and chromosome Y microdeletions screening must be done when NOA is suspected and in any case before assisted reproductive techniques (ART). On the other hand, cystic fibrosis gene mutations screening is advised for patients with suspected congenital obstruction but also for the partner, in order to verify the risk of development of cystic fibrosis in the newborn. The invasive diagnostic study, instead, is represented by testicular fine needle aspiration, open testicular biopsy and vasography and vesiculography, which can be performed transscrotally or transperineally via ultrasound-guided needle puncture of the distal seminal tract (Fig. 6.1).

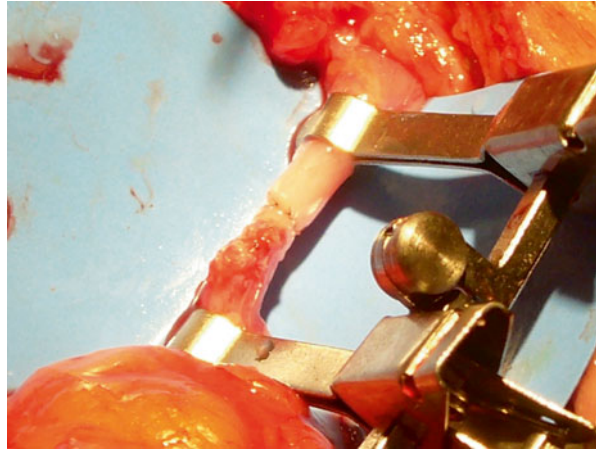
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## 6.5 Therapy

### 6.5.1 Obstructive Azoospermia

In obstructive azoospermia, when possible, recanalization of the seminal tract and restoration of spontaneous fertility are indicated. Obstruction location and characteristics and partner age influence the choice of treatment.

**Fig. 6.2** Microsurgical vasovasostomy in two layers according to Silber



- *Microsurgical recanalization of the proximal seminal pathways*

This treatment is indicated in case of azoospermia, confirmed by at least two recent spermograms and normal spermatogenesis at least on one side, documented by histology or testicular cytology. Microsurgical reconstruction (epididymovasostomy, vasovasostomy) should be indicated as the first therapeutic option in azoospermia due to epididymal or vasal obstruction. In the majority of patients, it consents the achievement of spontaneous pregnancies by avoiding ART techniques which carry high costs and invasivity to the female partner. In a recent revision of over 4,000 operated cases, Silber reports patency and pregnancy percentages after microsurgical reconstruction at, respectively, 96 and 81 % for vasovasostomy and 84 and 67 % for vasoepididymostomy [8]. The recent introduction of simpler microsurgical anastomosis techniques has further improved results (Figs. 6.2 and 6.3) [9]. When the female partner is older than 37 years, there is, instead, a priority indication for immediate ICSI. This might also be associated with a contextual microsurgical recanalization of the seminal tract.

- *Recanalization of the distal seminal tract*

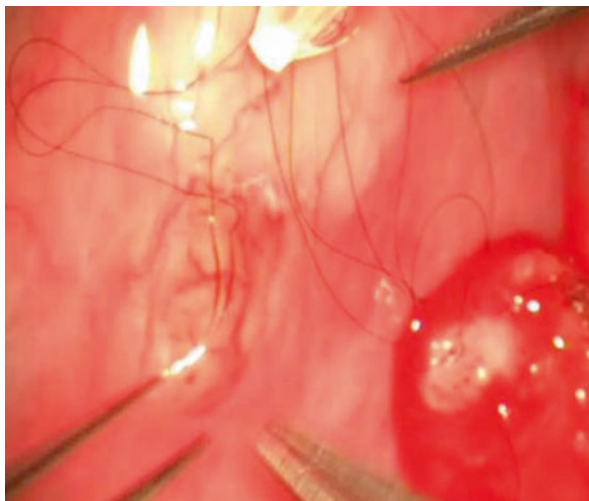
Endoscopic resection of the ejaculatory ducts (TURED) or obstructing prostatic cysts is the treatment of choice in distal obstruction. However, its indications have recently been reduced due to the introduction of less invasive techniques and the known possibility of negative postsurgical consequences such as urinary reflux in the seminal tract during micturition [10, 11].

In the presence of prostatic cysts obstructing the ejaculatory ducts but not communicating with the seminal pathways, a recanalization is possible with a minimally invasive approach of transperineal ultrasound-guided injection and sclerotization of the cysts with alcohol (TRUCA) [10, 11].

- *Sperm retrieval for ICSI*

When recanalization is not feasible, sperm retrieval and ICSI are indicated [12, 13].

**Fig. 6.3** Microsurgical terminolateral vasoepididymostomy (tubulovasostomy): simplified technique with invagination of the epididymal tubule according to Monoski



**Table 6.3** Retrieval techniques of male gametes and their acronyms

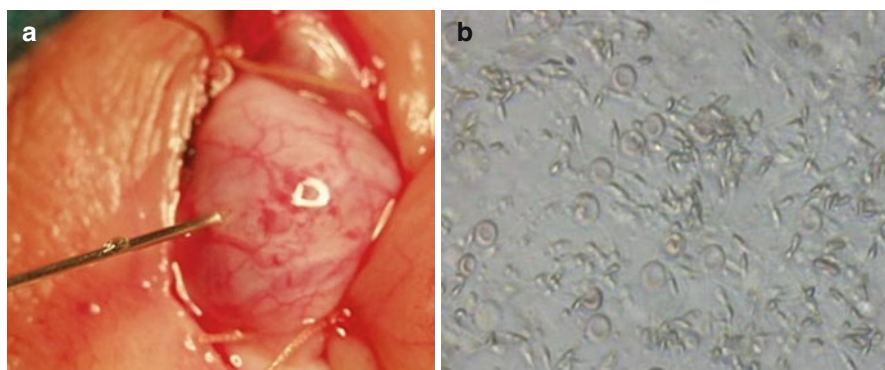
MESA	Microsurgical epididymal sperm aspiration
PESA	Percutaneous epididymal sperm aspiration
TESA	Testicular sperm aspiration
TESE	Testicular sperm extraction
MicroTESE	Microsurgical testicular sperm extraction

## 6.5.2 Non-obstructive Azoospermia

Except in the rare cases of hypogonadotropic hypogonadism which can be treated with medical therapy, in patients with NOA the only possible treatment is sperm retrieval for assisted reproductive techniques (ART).

### 6.5.2.1 Sperm Retrieval Techniques for ART

Sperm retrieval techniques with acronyms are listed in Table 6.3. There is general consensus that in the case of obstructive azoospermia any technique allows a sufficient sperm retrieval for ICSI [14–19]. In fact, by definition, in OA spermatogenesis is normal and sperm can be easily retrieved from the testicle or epididymis even with percutaneous techniques (TESA, PESA) [20, 21]. The original MESA technique is today rarely used because of its high costs and longer surgical times, but its simplification (Mini-MESA), introduced in 1996 [22–24], combines advantages and simplicity of percutaneous techniques with the precision and accuracy of microsurgical procedures. Using a small scrotal incision, the head of the epididymis is exposed and dislocated in the wound, anchoring it at the edges. The procedure continues with the direct puncture of the more dilated and whitish epididymal tubules with a TB syringe (Fig. 6.4). This technique allows one to obtain high counts of sperm and therefore facilitate cryoconservation of an adequate number of paillettes for subsequent ICSI cycles.



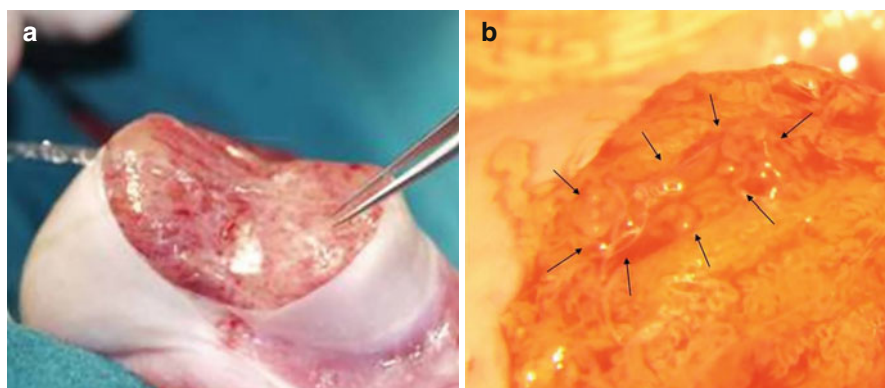
**Fig 6.4** Mini-MESA: (a) TB needle aspiration from the head of the epididymis, (b) sperm retrieval

TESA (or TEFNA, testicular fine needle aspiration) is the simplest percutaneous technique and in OA allows an immediate retrieval of sufficient spermatozoa for one or more ICSI cycles. With a 21G needle butterfly, the testicle is punctured, and with slight movements, testicular fluid is aspirated and sent to the lab for sperm search. PESA is a similar percutaneous technique but performed by inserting the needle into the head of epididymis in order to obtain a more sizeable and clean sperm retrieval compared to TESA. PESA is particularly indicated in congenital absence of the vas deferens. In TESE one or more open surgical biopsies are performed on one or both testicles. TESE is particularly indicated in NOA and when the percutaneous techniques have failed [38].

Many studies have compared ICSI results using freshly retrieved or frozen-thawed sperm, and the majority of these have concluded that there is no difference in terms of fertilization, implantation and pregnancy rates [25].

In NOA the standard treatment is represented by single or multiple TESE [36, 37]. In fact, success rate with percutaneous techniques is extremely low [26, 27]. Overall, in nearly 50–60 % of NOA patients, it is possible to retrieve spermatozoa with TESE [38–40]. Microsurgery has regained interest even in NOA after the introduction of the MicroTESE technique proposed by Schlegel et al. in 1999 [28]. With this technique, many authors have reported a higher rate of sperm retrieval, with less complications compared to multiple TESE [29–31, 36–40]. The technique is performed with an equatorial incision of the tunica albuginea and clam opening of the testicle. Using the magnification of an operating microscope, it is possible to spare the blood supply and to extract single seminiferous tubules with jeweller's forceps. This is done in different areas of the exposed parenchyma, trying to identify the more dilated tubules which more likely harbour sperm (Fig. 6.5).

Extracted tubules are then sent to the laboratory for the search of spermatozoa. The incision is then closed with microsurgical running suture. MicroTESE reduces the possibility of vascular lesions with a lower loss of tissue than multiple TESE. Furthermore, postsurgical pain is reduced due to lesser retraction of the tunica albuginea and consequent less compression of the testicular parenchyma [32].



**Fig. 6.5** (a) MicroTESE: atraumatic extraction of the seminiferous tubule with jeweller's forceps. (b) Dilated seminiferous tubules (*arrows* indicate an area of dilated seminiferous tubules)

However, recent reports have shown a reduction in serum levels of testosterone and an increase in LH and FSH after MicroTESE [33].

### A New “Stepwise” MicroTESE Approach

Following these considerations, we proposed a “stepwise” approach to MicroTESE in order to reduce invasivity and optimize results, particularly for those patients who did not have previous TESE or histology and whose chance of sperm retrieval is unknown or unclear. Under local anaesthesia (cord block and skin infiltration), a small (10 mm) scrotal window incision is performed and a single testicular biopsy (5 mm) is taken from the mid-portion of the testis and sent to the lab for sperm extraction together with a specimen for histology. If there is presence of sperm, the procedure is terminated and the wound closed. In case of absence of sperm, the scrotal incision is expanded, and the horizontal albuginea incision is also extended equatorially until the testicle is split open and MicroTESE performed. We believe that this approach can optimize the results and reduce the invasivity of sperm retrieval procedures. In fact, although MicroTESE has been shown to be less invasive than multiple TESE [34], a significant hormonal impairment has been described after one or more MicroTESE procedures [33].

Several questions concerning the sperm retrieval techniques in NOA are still being discussed. The possibility of programming the sperm retrieval procedure on the same day of ICSI, in order to use fresh sperm, has been taken into consideration by Verheyen et al. [35]. The authors conclude that there are no significant differences regarding the implant, embryo transfer and pregnancy rate after ICSI with fresh or cryconserved sperm, and therefore they propose, for all patients with NOA, a planned TESE for diagnostic and therapeutic aims, with cryoconservation of the retrieved spermatozoa followed by a differed ICSI. In this way a useless ovarian stimulation of the partner can be avoided in the case of failed sperm retrieval. The superiority of TESE over TESA in NOA has been confirmed by Hauser et al. in a study on the evaluation of the sperm retrieval rate after TESA and multiple TESE in 32 patients with NOA [26, 36–40].

In conclusion, in sperm retrieval techniques, the complexity of the clinical situations and the multiplicity of the therapeutic options presently available suggest the need for a correct evaluation and management of the azoospermic patient. An expert in the field, adequately trained and with competences both in male genital surgery and reproductive medicine, will be able to best carry this out.

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## 7.1 Definition and Classification

Varicoceles are abnormally dilated testicular veins (pampiniform plexus) in the scrotum, normally secondary to internal spermatic vein reflux. This common abnormality has implications such as pain and testicle discomfort, failure of testicular growth, and infertility.

Ambroise Pare defined this anatomic problem in 1550 as a tumor of dilated veins, “a compact pack of vessels filled with melancholic blood” [1]. A modern definition of varicocele is a pathologic dilation of the pampiniform plexus or of the cremasteric venous system that is sufficient to allow a retrograde flow of blood back into the venous system when the intra-abdominal pressure increases. Varicocele is a physical abnormality present in 11.7 % of men with normal semen analysis, 25.4 % of men with abnormal semen [2], approximately 25 % of the normal male population, and up to 40 % of men presenting with infertility; it occurs on the left side in as many as 98 % of patients [3].

The following classification of varicocele is useful in clinical practice:

- (a) Subclinical varicocele: Not palpable or visible at rest or during Valsalva maneuver but is demonstrable by scrotal ultrasonography and color Doppler examination
- (b) Grade 1: Palpable during Valsalva maneuver but not otherwise
- (c) Grade 2: Palpable at rest but not visible
- (d) Grade 3: Visible and palpable at rest [4, 5].

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## 7.2 Pathogenesis and Etiology

Presumably because of anatomic differences, varicoceles are much more common on the left side. The left internal spermatic vein empties into the left renal vein. It is much longer (6–8 cm) than the right spermatic vein, which drains into the vena cava. This process is thought to result in increased hydrostatic pressure, causing dilation and tortuosity of these vessels.

Although most men with varicoceles are able to father children, there is abundant evidence that varicoceles are detrimental to male fertility, but the exact association between reduced male fertility and varicocele is unknown. Different theories have been proposed to explain this possible association.

### 7.2.1 Heat

It has long been observed that even minor fluctuations in temperature can affect spermatogenesis and sperm function.

The scrotum is a temperature regulator for the testes, and varicocele can cause an increase in scrotal temperature and thus impair spermatogenesis. In 1973 Zorognotti and MacLeod were able to correlate the increase in intrascrotal temperature with impaired testicular function in varicocele patients [6]. Later, Lewis and Harrison (1979) also showed a correlation between varicocele, increased scrotal temperatures, and infertility [7]. Hyperpyrexia can also damage sperm production; this may be the way large varicoceles work, but it is difficult to understand how this could be the *modus operandi* of smaller varicoceles.

*Metabolites.* Because a varicocele may be caused by retrograde flow of blood from the renal and adrenal veins, in the left side this may contain toxic substances, perhaps a high concentration of catecholamines. In 1974 Comhaire and Vermeulen found the catecholamine concentration to be higher in the spermatic vein of varicocele than in a control group, implying that catecholamines in the pampiniform plexus lead to chronic testicular vasoconstriction and impaired spermatogenesis [8].

Data on the role of metabolites in the varicocele patient is controversial and inconclusive at present.

*Ischemia.* When markedly distended, especially in large varicoceles, the pampiniform plexus contains a large amount of venous blood that may be sufficient to impede the arterial input to the testis, lower the partial pressure of oxygen, and cause hypoxia. More work is required to substantiate this theory [9].

*DNA damage.* Varicocele is associated with increased sperm DNA damage, and this sperm pathology may be secondary to varicocele-mediated oxidative stress. Varicocelectomy can reverse this sperm DNA damage, as shown in several studies [10].

*Obstruction of the epididymis.* Varicocele, when vary large, may cause partial obstruction of the efferent ductules or of the epididymal duct itself, which can impair maturation of spermatozoa in epididymis and lead to motility disturbances [9].

### 7.3 Diagnosis

The first step to the diagnosis of varicocele is the medical history and physical examination of the patient in both standing and recumbent positions. Rarely will the male have an abnormal feeling or heaviness in the scrotum or have palpated the veins himself. In general, the classic varicocele will disappear in the lying position owing to venous decompression into the renal vein, whereas the varicocele secondary to cancer invasion of the renal vein will remain because of an anatomic block.

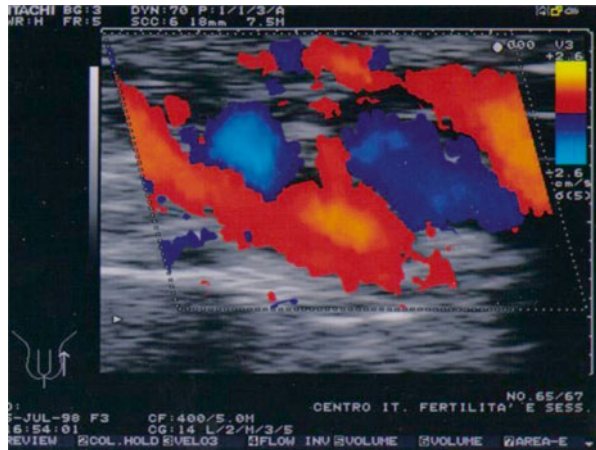
The presence and size of varicocele is most frequently diagnosed on testicular ultrasonographic examination (Fig. 7.1).

The reversal of bloody flow can be demonstrated using the Doppler facility (Fig. 7.2).

**Fig. 7.1** Ultrasonographic appearance of a large left varicocele



**Fig. 7.2** Color Doppler ultrasonogram of left varicocele



Venography is a much more invasive diagnostic method but provides a more detailed view of the varicocele, and also is used to determine the efficiency of a varicocele repair.

Scrotal ultrasonography and color-flow Doppler examination has replaced venography in most cases, and has proved especially useful in those patients so obese that accurate physical examination of the scrotum is impossible.

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## 7.4 Treatment

The clinical benefit of varicocele repair in improving fertility has not been firmly established, but several approaches can be used in the treatment of a varicocele [11].

*Open surgery.* Open surgical options include retroperitoneal, inguinal, and scrotal approaches, or laparoscopy.

In the *retroperitoneal high procedure* the spermatic vein is ligated at a point above the pelvic brim. With this approach it is not possible to examine any contribution to the varicocele made by the cremasteric venous system. The incidence of hydrocele with this procedure is 5–10 % [12]. Today this procedure is rarely used.

The *inguinal approach* requires incision in the anterior wall of the inguinal canal and the exposition of the cord; the vas and the artery are identified. Usually there are at least three or four veins that need ligation. There is a high possibility of missing out a branch of testicular vein; some surgeons use a microscope to identify all the vessels in the cord.

The *scrotal approach*. This procedure produces a very high incidence of hematoma, testicular atrophy, and arterial damage, and is no longer used [13].

*Laparoscopy.* In this approach the complete vascular bundle is diathermed, and for this reason has many unacceptable complications: injury to testicular artery and lymph vessels, intestinal and nerve damage, bleeding, pneumoscrotum, and wound infection [14].

In general, the risks of surgical varicocele repair are rare and usually mild, and include hydrocele, hematoma formation, wound infections, recurrence of varicocele, and, rarely, testicular atrophy [15, 16].

*Percutaneous embolization.* This procedure is performed under general anesthesia, is minimally invasive, and is accomplished by embolization of the refluxing internal spermatic vein or veins.

Occlusion of the vein can be performed in a number of different ways such as the use of solid devices, sclerosing agents, and fibrin plugs.

The success of these techniques can be checked by venography [17].

No single method has proven superiority over another as a cure for infertility. On comparing different surgical treatments of varicocele, Al-Kandari et al. showed no clear benefit in favor of any technique in relation to improving sperm parameters [18]. However, the microscopic inguinal approach seems to be associated with significantly less recurrence and potentially fewer complications such as hydrocele, but also requires more operating time and microsurgical training [5].

### 7.4.1 Medical Treatment

The presence of endocrine dysfunction suggests that certain patients with varicocele and low sperm counts have Leydig cell dysfunction; therefore, human chorionic gonadotropin (hCG) administration might stimulate the testosterone production and the seminiferous tubule activity [19].

Increased numbers of pregnancies have been reported with the use of hCG [20].

Pentoxifylline and antioxidants improve sperm quality in male patients with varicocele. Oliva et al. examined the effect of 12 weeks of daily oral administration of pentoxifylline with zinc and folic acid on the semen quality of 36 men with varicocele-associated infertility in an open, uncontrolled study. After 4 weeks of treatment, the proportion of morphologically normal sperm cells was significantly increased [21].

Although the work presented herein is interesting, the medical treatment in male patients with varicocele remains controversial.

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## 7.5 Discussion

Evers et al. came to the conclusion that clinical evidence supports the concept that there is an association between varicocele and male infertility, but that there is clear evidence showing that appropriate treatment improves a couple's chance of conception [22]. This meta-analysis has been criticized for including several biased heterogeneous studies [23].

Three controlled randomized studies found surgical repair in men with subclinical varicocele to be ineffective [24–26]. Moreover, in men with varicocele and normal semen analysis, no clear benefit has been shown after surgical treatment [27, 28]. For these reasons varicocele repair as a treatment for infertility is not indicated in patients with normal semen parameters or a subclinical varicocele.

In a recent meta-analysis of four randomized controlled studies of varicocelectomy in men with clinical varicocele, oligozoospermia, and otherwise unexplained infertility, a trend in favor of surgical correction was observed [29].

A recent study found an increase in motility of spermatozoa associated with postoperative pregnancy, irrespective of the method by which pregnancy was obtained [30].

However, when the male partner of a couple attempting to conceive has a varicocele, treatment may be considered when all of the following conditions are met:

1. The varicocele is palpable on physical examination of the scrotum
2. The couple has known infertility
3. The female partner has normal fertility or a potentially treatable cause of infertility
4. The male partner has abnormal semen parameters or abnormal results from sperm function tests [31];
5. Varicocele treatment is recommended for adolescents who have progressive failure of testicular development documented by clinical examination [32]

Varicocelectomy improves semen in up to 80 % of infertile men, but the degree of improvement is less clear. In patients with a low sperm count, total motile count varicocelectomy may be of benefit and may reduce the invasiveness of assisted reproductive technologies [33].

Surgical and medical treatment of varicocele is indicated in selected patients with infertility and in others with pain or important local symptomatology [34].

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## 8.1 Definition and Epidemiology

The main genetic factors involved in male infertility are chromosomal abnormalities. These abnormalities can be structural (e.g., deletions, duplications, translocations, inversions, etc.) or numerical (e.g., trisomy, tetrasomy, aneuploidy, etc.) [1, 2] and involve sex chromosomes (e.g., Klinefelter syndrome, 47,XXY) or autosomes (reciprocal translocations and Robertsonian translocations). The incidence of chromosomal aberrations in the general population is approximately 0.5–0.6 % [3–6]. About 1 in 150 babies is born with a chromosomal abnormality [7, 8]. Chromosomal abnormalities account for about 5 % of infertility in males, and the prevalence reaches approximately 15–20 % of the azoospermic males [9, 10] and 5–10 % of the oligozoospermic males [11]. Karyotype abnormalities are reported in 2–14 % of males presenting with infertility [12]. Klinefelter syndrome and Y-chromosomal microdeletions are the most frequent genetic cause of male infertility.

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## 8.2 Etiology

Chromosomal abnormalities are caused by *errors in the number or structure of chromosomes*. It is still unknown why these errors occur.

The *errors in the number of chromosomes* occur during cell division (mitosis and meiosis).

A chromosomal abnormality can also occur before fertilization.

Meiosis is the process of division of reproductive cells (with half the number of chromosomes, 23, haploid cell): eggs and sperms.

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If this process does not occur properly, the chromosomes do not segregate properly, and gametes, eggs, or sperms may end up with too few (monosomy) [13] or too many chromosomes (trisomy) [14].

Errors can also occur during mitosis, after fertilization, when the chromosomes are being duplicated during fetal development resulting in mosaicism: some cells with a typical number of chromosomes and some with an incorrect number of chromosomes.

The *errors in structure of chromosomes* can occur, usually before fertilization, and change the structure of one or more chromosomes. Usually, individuals with structural chromosomal abnormalities have a normal number of chromosomes, but a portion of a chromosome is missing, deleted or inverted, duplicated, misplaced, or exchanged with another part of another chromosome.

Chromosome abnormalities can be inherited from a parent, such as the translocation, or may also occur for the first time in an individual [15].

An important causal factor of chromosomal abnormalities is the *maternal age* (over 35 years) as the primary risk factor for nondisjunction during meiosis, which leads to the occurrence of trisomy 21 (Down syndrome) [16], trisomy 18 (Edward syndrome) [17], and trisomy 13 (Patau syndrome) [18].

The *paternal age* is less important as a causal factor of chromosomal abnormalities [19–21].

*Environmental factors* can cause chromosomal aberrations although there are few demonstrations [22–25].

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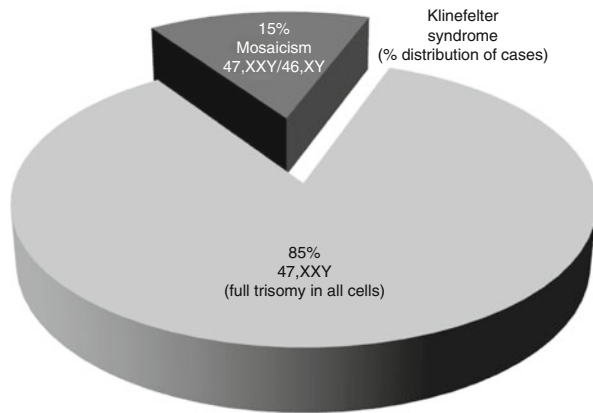
### 8.3 Pathology, Diagnosis, Therapy, and Prognosis

The majority of human chromosomal abnormalities occur in the autosomes. The most common autosomal abnormalities are trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome), trisomy 13 (Patau syndrome), partial deletion of the short arm of chromosome 4 (Wolf–Hirschhorn syndrome), and deletion of the short arm of chromosome 5 (cri du chat syndrome). Individuals with these autosomal abnormalities usually have multiple physical malformations, mental retardation, and relatively short lives. The most common sex chromosome abnormalities are Klinefelter syndrome, monosomy X (Turner syndrome), and fragile X syndrome. These sex chromosome abnormalities are slightly less common than autosomal abnormalities, and they are generally much less severe in their effects, and the first two are not associated with mental retardation.

However, for the purposes of this chapter the author has chosen to focus mainly on the most common chromosomal causes of infertility [26]:

- Numerical sex chromosome abnormality = 54 %
- Structural chromosomal aberrations: chromosomal translocations (autosomal translocation, 15 %; Robertsonian translocation, 8 %; sex chromosome translocation, 4 %), Y-chromosomal microdeletions, and CFTR gene deletions or duplications
- Others = 19 %

**Fig. 8.1** The Klinefelter's distribution



**Table 8.1** Klinefelter syndrome

Common clinical signs
Infertility (azoospermia or oligospermia)
Small testes
Hypergonadotropic hypogonadism
Gynecomastia
Tall height
Learning difficulties (children)
Long arms and legs
Shorter torso
Decreased facial and pubic hair (adults)
Psychosocial or behavioral problems

### 8.3.1 Klinefelter Syndrome (47,XXY)

Klinefelter syndrome (KS) is the most common numerical sex chromosome disorder in males caused by aneuploidy, affecting one in 660 newborn males [27]. This disease was described for the first time in 1942 [28].

KS is usually associated with the karyotype 47,XXY which may be in all cells (full trisomy) or in mosaic form (15 % of the cases, see Fig. 8.1) [29]. In KS mosaicism some of the cells only have an extra X chromosome (47,XXY/46,XY).

The extra X chromosome derives from nondisjunction during meiosis and may have a paternal (>50 %) or maternal (40–50 %) origin [29]; for the rest of the cases, the X chromosome is originated post-zygotically [30]. The only way to confirm the presence of an extra X chromosome is by a karyotype analysis of peripheral blood or on amniocytes or chorionic villi from prenatal specimens. Common signs and symptoms are small testes (bi-testicular volume <6 ml) [31], hypergonadotropic hypogonadism, gynecomastia, learning difficulties (children), azoospermia and decreased facial and pubic hair (adults), long arms and legs, and tall height (see Table 8.1). Most, but not all, patients affected by KS, are infertile with small

testicles, increased numbers of Leydig cells, tubular sclerosis, and interstitial fibrosis of varying degrees [32]. The physical manifestations of KS are often variable.

This syndrome generally causes spermatogenesis arrest at the primary spermatocyte stage, but occasionally later stages of sperm maturation are observed [33]. It has been estimated that 25 % of non-mosaic KS patients have sperm in their ejaculate [9]. Paduch (2008) reported that over 50 % of KS patients were not sterile [34]. Some recent studies have reported a reduction of life expectancy for KS patients by 1.5–2 years, with increased mortality due to different disorders: diabetes, lung cancer, breast cancer, non-Hodgkin lymphoma, cerebrovascular disease, vascular insufficiency of the intestine, and epilepsy [35, 36]. Klinefelter syndrome should first be suspected whenever a patient consults the doctor because of infertility. In this case these following tests should always be performed: karyotype analysis, semen count, and blood test to check hormone levels of follicle-stimulating hormone, luteinizing hormone, testosterone, and estradiol. Differential diagnoses for KS may include the following conditions: fragile X syndrome, Marfan syndrome, and Kallmann syndrome. With the introduction of the procedure intracytoplasmic sperm injection (ICSI), which consists of the use of sperm extraction from deep within the testicles of KS patients (non-mosaic), some 47,XXY men will have an increased chance of fathering a child [37–39]. Androgen replacement therapy in KS patients should begin in puberty to promote linear growth and secondary sexual characteristics and to permit the normal accrual of muscle mass, bone mineral content, and the adult regional distribution of body fat [40]. However, this treatment is ineffective for treating infertility, gynecomastia, and small testes. Treatment options include different routes of administration: transdermal, oral, and intramuscular injections. A gradual increase of dosage sufficient to maintain age-appropriate serum concentrations of testosterone, estradiol, FSH, and LH is recommended.

### 8.3.2 Structural Chromosomal Aberrations

- *Chromosomal translocations*
- *Y-chromosomal microdeletions*
- *CFTR gene deletions or duplications*

#### 8.3.2.1 Chromosomal Translocations

Chromosomal translocations are caused by the rearrangement of parts between non-homologous chromosomes.

There are two types of chromosomal translocations: reciprocal or Robertsonian translocations.

Reciprocal translocations occur when there is an exchange of chromosomal material between two different chromosomes. When translocations affect the non-sex chromosomes, they are called autosomal translocations. These translocations occur in 1 in 500 newborns and are the most commonly observed structural chromosomal anomalies in infertile men [26]. Reciprocal translocations can be inherited

from a parent, or they can appear *de novo*. Translocations are “balanced” when the chromosome material has been rearranged but no genetic material has been lost or gained. Balanced translocations do not usually impact on the growth or development of the individual involved. Nevertheless, carriers (parents) of balanced translocations (who are normal phenotypes) produce both balanced and unbalanced gametes with deletions and duplications of large pieces of the chromosomes involved. The child conceived by an unbalanced gamete inherits a rearrangement of the chromosomes with deletion and/or duplication of chromosome; this condition is known as an unbalanced translocation. Although carriers of balanced chromosomal translocations are phenotypically normal, they may experience reduced fertility, spontaneous abortions, or birth defects [41, 42].

Autosomal translocations negatively affect spermatogenesis due to disrupted meiotic pairing and segregation [43–45]. While translocations have no effect on other tissues, these aberrations can seriously impair spermatogenesis causing severe oligozoospermia or azoospermia [45, 46].

In the same way that occurs in other chromosomal translocations, any part of the sex chromosome may translocate to autosomes. Translocations affecting sex chromosomes have direct consequences on genes involved in spermatogenesis. Translocations between the Y chromosome and autosomes are rare and often cause abnormal spermatogenesis and infertility [47, 48]. The possible mechanisms for reduced fertility due to sex chromosome translocation are the altered gene loci or altered formation of sex vesicle during meiosis.

Translocations involving a sex chromosome and an autosome cause infertility more easily than translocations involving autosomes.

When translocations involve acrocentric chromosomes, these aberrations are called Robertsonian translocations.

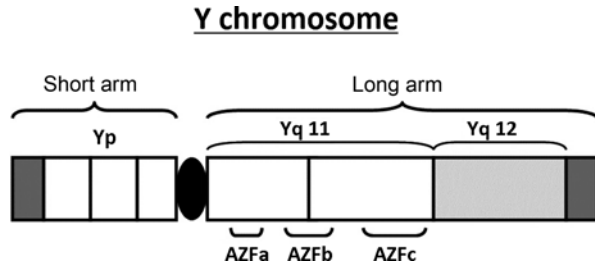
Robertsonian translocations involve only these chromosomes and specifically chromosomes 13, 14, 15, 21, and 22. This type of translocation originates from a centric fusion of two acrocentric chromosomes.

When two chromosomes fuse at the centromere (centric fusion), the result is a Robertsonian translocation. Robertsonian translocation is the most frequent structural chromosomal abnormality in humans, and it occurs in around 1 in 1,000 live births [49]. Balanced Robertsonian translocations do not usually impact on the growth or development of the individual involved. Nevertheless, carriers (parents) of Robertsonian translocations, as with reciprocal translocations, can have reproductive effects, when the child receives the translocation in an unbalanced form. Robertsonian translocations can cause various degrees of sperm alteration (oligospermia or azoospermia) [50, 51]. Robertsonian translocations are more common in oligozoospermic and azoospermic men, with rates of 1.6 and 0.09 %, respectively [52].

Robertsonian translocations involving chromosome 21 are found in 5 % of patients with Down syndrome [53].

Preimplantation genetic diagnosis (PGD) by fluorescence in situ hybridization (FISH) is recommended for a Robertsonian translocation and may be useful for couples who opt for assisted reproductive techniques [26].

**Fig. 8.2** Schematic representation of human Y chromosome



### 8.3.2.2 Y-Chromosomal Microdeletions (Y Chromosome-Related Azoospermia)

The Y chromosome is the smallest human chromosome and contains many of the genes that are necessary for spermatogenesis and the development of testes. Y-chromosomal microdeletions, which span several genes and remove one or more of them, are able to cause various spermatogenic defects. Y-chromosomal microdeletions are determined by submicroscopic deletions on the Y chromosome (Yq11 region) (see Fig. 8.2), and these alterations are not large and visible by conventional cytogenetic methods. After the Klinefelter syndrome, Y-chromosomal microdeletions are the most frequent genetic cause of male infertility [54, 55]. These gene deletions have been attributed to intrachromosomal homologous recombination within unstable amplicons clustered within the AZF region (azoospermia factor region) [56]. Y chromosome-related azoospermia is the most frequent structural chromosomal anomaly associated with failure in sperm production. The incidence of this anomaly is 15–20 % in men with idiopathic azoospermia and 7–10 % in men with idiopathic severe oligozoospermia [57]. Y-chromosomal microdeletions are extremely rare in infertile males with a sperm concentration >5 million/ml. Generally, Y-chromosomal microdeletions are “de novo” events and are estimated to occur in one in 2,000–3,000 males [58–61]. Infertile men with Y-chromosomal microdeletions usually have no visible symptoms, although some have small testicles and/or cryptorchidism. The first association between azoospermia and deletions of the long arm of the Y chromosome was demonstrated by Tiepolo (1976) [62].

Microdeletions most frequently occur on the long arm of the Y chromosome, Yq 11 region. An important area of interest on Yq is the AZF region that contains genes involved in germ cell development. This region contains three subregions: AZFa, AZFb, and AZFc [63] (see Fig. 8.2).

Gene deletions in this region cause various spermatogenic and infertility phenotypes [64]. Severe infertility or azoospermia is manifest when AZFa, AZFb, or AZFc is singly, or in combination, deleted from the genome. AZFc deletions are the most common form of Y-chromosomal microdeletions and account for approximately 58.3–69 % of reported microdeletions [65–67], followed by deletions of the AZFb region (14 %) and deletions of the AZFa region (6 %) [67]. Zhang et al. reported these incidence rates of several possible combinations of AZF region microdeletions [68]: AZFa=1.7 %, AZFb=12.5 %, AZFc=64.2 %, AZFb+c=20.0 %, and AZFa+b+c=1.7 %.

AZFc deletions are usually associated with low levels of sperm in the ejaculate or azoospermia (about two-thirds of individuals) [69]. Transmission of Y-chromosomal AZFc microdeletions could potentially result in the development of sexual ambiguities and Turner stigmata (45,X0) [70, 71]. Microdeletions of AZFa are associated with the complete Sertoli-cell-only (SCO) syndrome and azoospermia, while microdeletions of AZFb or AZFc result in a variable clinical and histological phenotype, ranging from the SCO syndrome to oligozoospermia [72–74]. AZFb+c deletions usually produce no testicular sperm. When AZF-deleted sperms are used for *assisted reproductive techniques* (ART), fertility defects in male offspring are inevitable [65]. Classical Y-chromosomal microdeletions do not confer a risk for cryptorchidism or testicular cancer [74, 75]. If complete AZFa or AZFb microdeletions are detected, micro-testicular sperm extraction (TESE) is not indicated because this technique is very time consuming—it is extremely difficult to find sperm cells [74]. Microdeletion analysis using PCR helps determine the frequency and site of gene deletion and thus the testicular phenotype. Yq microdeletion analysis (AZF screening) is generally carried out by multiplex polymerase chain reaction (PCR) amplifying AZFa, AZFb, and AZFc loci in the q arm of the Y chromosome [76]. The analysis of Y-chromosomal microdeletions permits to establish a diagnosis and to formulate a prognosis, in men with idiopathic infertility presenting with azoospermia or severe oligospermia with sperm concentrations <5 million/ml [77]. AZF screening is important before varicocelectomy because infertile men carrying a Yq microdeletion will most likely not benefit from the surgical procedure [77]. In case of diagnosis of Y-chromosomal microdeletion, a genetic counseling is mandatory (especially for the ART candidates) to provide information about the risk of conceiving a son with impaired spermatogenesis.

### 8.3.2.3 Mutations in the CFTR Gene

Congenital bilateral absence of the vas deferens (CBAVD) is an important disorder characterized by agenesis of the vas deferens, and it affects about one in 1,000 male individuals [78]. It is an important cause of sterility in men, approximately 2 % of infertility cases [79], and it accounts for 6 % of cases of obstructive azoospermia (OAZ) [80].

Genetic mutations in the cystic fibrosis transmembrane conductance regulator gene (CFTR) are responsible for CBAVD and cystic fibrosis (CF). The CFTR gene is located on the long (q) arm of human chromosome 7 at position 31.2 [81] (see Fig. 8.3).

CFTR gene mutations are responsible in about 95 % of men with CBAVD [82].

Cystic fibrosis is the most frequent severe autosomal recessive genetic disorder in the Caucasian population, affecting about 1 in 2,500 live births [83]. The most frequent clinical manifestations of CF are chronic obstruction and infection of the respiratory tract and often exocrine pancreatic insufficiency. About 98 % of male CF patients are infertile as a result of CBAVD [84, 85]. The CFTR gene encodes for a membrane protein that also influences the formation of the ejaculatory duct, seminal vesicle, vas deferens, and distal two-thirds of the epididymis.

**Fig. 8.3** Location of the CFTR gene on human chromosome 7



Genetic mutations in the CFTR gene (deletions or duplications) lead to the low function of CFTR resulting in the production of viscous secretions (dehydration of mucus secretions) that obstruct the lumen of airways, sweat glands, gastrointestinal tract, pancreatobiliary ducts, sinuses, and reproductive tissues [86].

CBAVD may also occur as an isolated form of genital disorder without clinical CF symptoms (incomplete genital form of CF) [87]. Patients with this phenotype of CF, previously considered a distinct genetic entity, have an increased frequency of CFTR gene mutations [88, 89]. CFTR gene mutations were detected in some patients with congenital unilateral absence of the vas deferens (CUAVD); this condition could be an incomplete form of CBAVD [89]. CUAVD is a rare condition and has an incidence of 0.5–1 % in the male population [90]. CUAVD was found to occur twice as frequently on the left than on the right side [91]. Whereas in some of CUAVD patients the condition is associated with mutations in the CFTR gene, in other patients this congenital anomaly is probably caused by other factors [88]. Men with CUAVD may be normally fertile [88]; in these males there is a high incidence of ipsilateral renal agenesis [92]. CUAVD is interesting because of its association with renal anomalies and CFTR gene mutations [92]. Renal imaging and cystic fibrosis (CF) screening were recommended to all



patients with CUAVD or CBAVD. In fact unilateral renal agenesis is also possible in CABVD patients with an incidence of about 10 %, mostly seen in patients without CFTR gene aberrations [93].

Screening for CFTR mutations is recommended in the following conditions:

- Azoospermic male with a semen volume of < 1.5 ml and pH less than 7.0
- Individuals with a family history of CF or CFTR mutations
- Males with CBAVD or CUAVD
- Patients with chronic or idiopathic pancreatitis
- Reproductively active individuals or couples
- Couples who opt for ART (assisted reproductive techniques) for determining the risk of transmitting CFTR mutations to the offspring

### 8.3.3 Prader–Willi Syndrome

Prader–Willi syndrome (PWS) is a rare genetic disease which occurs equally in both sexes and all races.

PWS was first described in 1956 [94] and has a prevalence about of one in 50,000 newborns [95–98].

This syndrome is characterized by severe muscular hypotonia, hyperphagia, obesity, hypogonadism, mental retardation, and short stature. This condition is caused by the absence of paternal expression of imprinted genes localized in the 15q11-q13 region [94, 99]. However, the following are possible genetic subtypes [100]: paternal deletion of chromosome 15q11-q13 (type I or II), 75 %; maternal uniparental disomy (UPD), 24 %; imprinting center defects (ID), 1 %; and translocation <1 %.

Delayed and incomplete pubertal development is documented in almost all PWS patients. Manifestations of hypogonadism in infancy include micropenis and/or cryptorchidism (80 %) in males [101, 102]. Hypogonadism was generally considered to be of hypothalamic origin [102–105].

DNA methylation analysis is the only technique, which can both confirm and reject the diagnosis of this syndrome [86]. A prenatal diagnosis could be suspected in cases of reduced fetal movement and polyhydramnios [106]. In a family who previously had a child with PWS (with an imprinting defect), the man with a deletion has a 50 % chance of fathering a baby with PWS again [100]. At present there are no reports of paternity in PWS [100].

A possible therapeutic program should include:

- Obesity management with institution of a low-calorie, well-balanced diet, with regular exercise and rigorous supervision
- GH treatment in children to improve growth during childhood
- Hormonal treatment for induction, promotion, or maintenance of puberty
- Management of behavioral and psychiatric problems

### 8.3.4 Angelman Syndrome

Angelman syndrome (AS) is a rare condition caused by deletion on the mother's chromosome 15. The incidence is one in 12,000–20,000 births [107–109]. Angelman syndrome is a rare neurological disorder characterized by developmental delay, significant intellectual disability, difficulties with speech development, seizures, uncontrolled limb and body movements, motor impairment, spontaneous laughter, EEG abnormalities, and epilepsy [110]. Anomalies of the head and face are common, including microcephaly, macrostomia, maxillary hypoplasia, mandibular prognathism, deeply set eyes, and widely spaced teeth. Males and females with Angelman syndrome achieve puberty normally, with normal secondary sexual characteristics. However, there has been no documented case of reproduction in a male with Angelman syndrome [110]. A successful reproduction has been reported in only one case of female with Angelman syndrome [110].

DNA methylation analysis identifies approximately 80 % of individuals with AS. If the DNA methylation analysis is abnormal, the next step is FISH or array CGH analysis [111].

For completeness, other very rare forms of male infertility caused by genetic disorders [79] are listed at the end of this chapter:

- Myotonic dystrophy (DM)
- Kallmann syndrome
- Immotile cilia syndrome
- Noonan syndrome
- Denys–Drash syndrome (DDS) and Frasier syndrome
- Androgen insensitivity syndrome
- Polycystic kidney disease (with multiple cysts in the liver, kidneys, epididymis, and seminal vesicles)
- Usher's syndrome

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# Male Idiopathic (Oligo) ± (Asthen) ± (Terato)-Spermia

# 9

Giorgio Cavallini

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## 9.1 Definition

Male idiopathic (oligo)±(asthen)±(terato)-spermia (iOAT) is defined as a defective spermatogenesis of obscure etiology and is regarded as undetectable using common laboratory methods [1]. iOAT can be classified from a clinical point of view as isolated asthen±teratospermia (no alteration in sperm concentration), moderate iOAT (sperm concentration  $<20 \times 10^6/\text{mL}$ ), or severe iOAT (sperm concentration  $<5 \times 10^6/\text{mL}$ ) [2].

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## 9.2 Epidemiology

iOAT affects approximately 30 % of infertile men and is one of the most common causes of infertility [1]. It is likely that its prevalence is increasing, in association with the progressive declining sperm count in men today [3].

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## 9.3 Etiology

Descriptions of reputed causes of iOAT have at least two biases. Two patterns whose alterations are linked to male infertility with normal sperm parameters have been described: DNA damage and alterations of polymerase mitochondrial gamma gene (*POLG*) [4–6] (see Chap. 10). The sum of the percentages of patients with different causes of iOAT gave a result much higher than 100 %. This finding implies that the causes overlap, that the primary cause (if any) of iOAT is still unknown, and/or that more than one cause is needed to affect sperm patterns. The most likely hypothesis

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is the first; it has been demonstrated that iOAT sufferers comprise at least two different populations of infertile men [7].

### 9.3.1 Age

There is evidence that sperm motility declines progressively after age 30 years, although there is less evidence that a similar decline in sperm volume and concentration may also occur in typical presentations [8, 9].

### 9.3.2 Noninflammatory Functional Alteration in Post-testicular Organs

Low seminal concentration of prostate-specific antigen, zinc, fructose, and prostatic acid phosphatase [10], and low seminal activity of neutral  $\alpha$ -glycosidase are linked to isolated asthenospermia in addition to increased viscoelasticity [11] and osmolarity of seminal plasma [12]. Alterations of epididymal methylation of spermatogenesis-specific genes have been suspected to be involved in the etiology of iOAT [13, 14]. Demethylation is critical for gene transcription.

### 9.3.3 Infective Agents

*Chlamydia trachomatis* (CT) and adenovirus (AV) infections have been regarded as being associated with iOAT; however, proof regarding the role of asymptomatic CT and/or AV infection in infertility is inconclusive [15, 16].

### 9.3.4 Genetic Factors

Approximately 10 % of rat genomes are specifically linked to spermatogenesis, and about 200 genes are regarded as critical for germ cell development [17]; this means that several genes might be involved in iOAT etiology. To be considered a key factor for iOAT, a gene must display all of the following characteristics: (1) it should be specifically expressed in the germ cell line, (2) its altered expression should be associated with iOAT; and (3) it should have an essential role in spermatogenesis [18]. Despite this restriction, several genes have been identified as causes of iOAT [19, 20]. (Diagenic) heredity and de novo mutations are the theoretical causes of the bad gene expression [1].

### 9.3.5 Mitochondrial Alterations

In asthenospermia, both mitochondrial membrane potential [21, 22] and DNA mitochondrial content [23, 24] are impaired.

### 9.3.6 Subtle Hormonal Alterations

A decreased luteinizing hormone (LH) pulse frequency has been found to occur in iOAT men whose amplitude parallels the severity of the disorder [25].

Molecular variants of LH have been associated with iOAT [26].

IOAT displays a shift toward lower testosterone (T) serum levels, lower calculated T index, and lower T/LH ratio, and a shift toward higher serum LH levels, higher 17- $\beta$ -estradiol (E2), and higher E2/T levels [27]. Increased E2 levels are postulated to contribute to the central suppression of gonadotropin production which, in turn, may decrease both T production and spermatogenesis [28]. E2 is derived mainly from the intratesticular and peripheral aromatization of androstenedione and T by aromatase, a product of the CYP19 gene. CYP 19A1 is a single-copy gene located on chromosome 15q21.2. Aromatase polymorphisms have been shown to affect various estrogen-dependent diseases in men and women. The most commonly studied aromatase polymorphism is the tetranucleotide Tyrosine-Tyrosine-Tyrosine-Adenine [TTTA] repeat polymorphism [TTTAn] present in intron 4 of the CYP 19A1 gene. This polymorphism is associated with the activity of the aromatase enzyme both in vivo and in vitro [29]. Higher numbers of TTTA repeats (>7 repeats) in the aromatase gene are associated with a negative relationship between obesity and sperm count. The effect of obesity on E2 and sperm count appears to be absent in men with fewer ( $\leq 7$ ) repeats [30].

### 9.3.7 Environmental Pollutants

Environmental pollutants are regarded as capable of deteriorating semen quality. Chapter 16 is specifically dedicated to this aspect.

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## 9.4 Pathogenesis

The aforementioned causes affect spermatogenesis. Impaired spermatogenesis leads to increased reactive oxygen species (ROS) and unbalanced germ cell apoptosis.

### 9.4.1 Increased ROS

ROS originate from the cellular physiologic metabolism of O<sub>2</sub> in aerobic conditions, and are mainly produced by leukocytes and immature gametes. Immature gametes are common findings in iOAT. ROS are short-lived chemical intermediates containing one or more electrons with unpaired spins. All spermatozoa structures can be attacked and denatured by ROS [1, 31], ultimately resulting in death and/or irreversible damage. Physiologic (low) levels of ROS exert critical function in normal sperm physiology, such as fertilizing ability (acrosome reaction,

hyperactivation, capacitation, and chemotaxis) and sperm motility; whereas increased ROS generation and/or decreased antioxidant capacity leads to the imbalance between oxidation and reduction in living systems, which is called sperm oxidative stress. This condition was widely considered to be a significant contributory factor to sperm DNA damage/apoptosis, lipid peroxidation, and reduced motility, which, in turn, increased the risk of male factor infertility/subfertility and birth defects [31].

### 9.4.2 Modified Apoptosis

Apoptosis (programmed cell death) is a physiologic mechanism aimed at achieving optimal Sertoli cell/gamete ratio and removing damaged gametes [32]. The range of stimuli that triggers this activity is impressively broad and includes various forms of electromagnetic radiation, environmental toxicants, heavy metals, and chemotherapeutic agents [33–37]. In addition, genetic perturbation of the germ cell line occurs through, for example, overexpression of SPATA17 [38] or androgen-binding protein [39], or deletion of key genes involved in the regulation of spermatogenesis [40–42]. The impression given is that if spermatogenesis is disrupted in any way, the germ cells tend to default to an apoptotic state. The stage of spermatogenesis when apoptosis is induced appears to be predominantly pachytene spermatocytes, and the Fas (fibroblast-associated death receptor)/Fas ligand and caspase systems seems to be the major mediators of this process [34].

## 9.5 Diagnosis

iOAT is commonly diagnosed by exclusion; the differential diagnosis is presented in Table 9.1.

**Table 9.1** Differential diagnosis of male infertility [2]

Reproductive failure mechanism		Methods of diagnosis
Chromosomal	X chromosome disorders	Objective examination, Y microdeletion detection, karyotype screening of cystic fibrosis, hormonal profiles, androgen receptor detection, semen analysis
	Y chromosome disorders	
	Autosomal disorders	
Developmental	Hypospadias	Clinical history, objective examination, semen analysis, scrotal echography
	Ductal obstruction	
	Didymal-epididymal interruption	

**Table 9.1** (continued)

Reproductive failure mechanism		Methods of diagnosis
Testicular pathology	Cryptorchidism	Clinical history, objective examination, semen analysis, scrotal echography
	Ectopic testicle	
	Retarded descent	
	(Floating testicle?)	
	Testicular tumors	
	Bilateral atrophy	
	Trauma	
	Testicular torsion	
Genital tract inflammation	Urethritis	Clinical history, objective examination, semen analysis, scrotal echography, urethral swab, urine analysis, sperm and urine cultural analysis
	Prostatitis	
	Epididymitis	
	Orchitis	
Varicocele		Objective examination, scrotal bilateral echo-color Doppler examination, semen analysis
Endocrine	Pituitary disorders	Hormonal profiles
	Hypothalamic disorders	Semen analysis
	Testicle disorders	
	Thyroid disorders	
	Adrenal gland disorders	
Iatrogenic	Surgery	Clinical history, objective examination, semen analysis
	Drugs	
	Radiation	
Sexually related causes	Erectile deficiency	Clinical history, semen analysis
	Disturbed ejaculation	
General diseases	Renal diseases	
	Liver diseases	
	Neurologic diseases	
	Gastrointestinal diseases	
	Hematologic diseases	
	Autoimmune diseases	
	Infectious diseases (AIDS)	
	Psoriasis	
Sarcoidosis		
	Diabetes	
Idiopathic oligoasthenoteratospermia		Semen analysis, exclusion criteria

## 9.6 Therapy

Therapy for iOAT is commonly regarded as empiric, because it is not possible in the current outpatient clinical setting to define the exact etiology of the spermatogenetic disorder of each iOAT patient. A number of therapies have been proposed, the most effective of which, according to author's experience and literature review, are reported here. Obviously these therapies might improve the sperm count in the majority of patients but not in all, and these therapies should be intended as symptomatic therapies: i.e., sperm count is improved as long as these therapies are administered, and decrease immediately after their suspension. Therapies should be administered for at least 3 months, because a stem cell requires about 61 days to achieve the final status of mature spermatozoon [43]. A rough therapeutic classification can be compiled on the basis of sperm analysis results.

### 9.6.1 Isolated (Asthen) ± (Terato)-Spermia

*Coenzyme Q10* 100 mg twice daily for at least 3 months. Coenzyme Q10 is a lipophilic antioxidant agent and should be administered after meals. Galenic preparations should use lipophilic excipients (e.g., cocoa butter) [44].

### 9.6.2 Oligo-Asthen-Teratospermia with Sperm Concentration $>5 \times 10^6/\text{mL}$

*L-Carnitine* 1 g twice daily; *acetyl-L-carnitine* 500 mg twice daily; *cinnoxycam* 30 mg, one tablet every 4 days after the main meal. These drugs are antioxidant agents [45, 46].

### 9.6.3 All Degrees of Dyspermia with Serum Follicle-Stimulating Hormone $<2 \text{ mIU/mL}$

Intramuscular *recombinant Follicle-Stimulating Hormone (FSH)* 100–300 IU every 2 days. FSH stimulates Sertoli cell function and spermatogenesis [47, 48].

### 9.6.4 All Degrees of Dyspermia with a low ( $<10$ ) T/E2 Ratio

These dyspermias have exhibited an increased sperm count after *letrozole* (2.5 mg/day) and/or *anastrozole* (1 mg/day) treatment. Nonobstructive azoospermic patients with T/E2 ratio  $<10$  also had their sperm count increased with letrozole and/or anastrozole treatment. Letrozole and anastrozole are members of a novel class of nonsteroidal, hormone-targeting agents used for breast cancer therapy. They reversibly inhibit the aromatase enzyme, which converts the androgen precursors in adipose

tissue to E2. Blocking of estrogen production has been shown to provoke increased gonadotropin and androgen levels in the blood and a parallel E2 decrease, resulting in spermatogenesis stimulation [49, 50].

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## 9.7 Prognosis

Prognosis is difficult to define in these patients, mainly because of the empiric nature of the therapies. However, antioxidant drugs and aromatase inhibitors significantly lower the number of couples that might require treatment with assisted reproduction to achieve a pregnancy [51].

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## 10.1 Definition

Infertility means not being able to get pregnant after a year of constant and unprotected intercourses [1]. Infertility and sterility are two very different concepts. Sterility is the permanent inability to reproduce. Infertility, on the other hand, can be either a permanent or temporary inability for fertilization to occur, because of one or more interfering factors [1]. In recent decades, the quality of the male semen compared to the 1999 classification by the World Health Organization (WHO) has become increasingly worse so that in 2010 (Table 10.1) normospermia was defined as having a sperm concentration  $\geq 15$  mil/ml, a progressive motility  $\geq 32$  %, and a morphology with a percentage of normal forms  $\geq 4$  % where for each parameter the percentile was identified, and where the minimum parameter corresponded to the 5th percentile, which meant that out of 100 people, 95 % had the best fertility parameters. In other words, just referring to the morphology, only 5 % of people had 4 % of fertile sperm in their normal form [2].

Obesity, defined as abnormal or excessive fat accumulation that presents a risk to health, has important effects on fertility [3].

Obesity is a multifactorial disease caused by energy imbalance between calories consumed and calories expended, resulting in the accumulation of body fat. The condition of obesity is defined using the body mass index (BMI) which is a biometric datum, expressed as the ratio between the individual's weight and the square of the height, and it is used as an indicator of ideal weight (Table 10.2) [4].

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**Table 10.1** Spermogram parameters by the WHO [2]

Spermogram parameters by the World Health Organization	1999 ed.	2010 ed.
Volume	≥2 ml	≥1.5 ml
Concentration	20 mil/ml	15 mil/ml
Ntot sperm cells	40 mil	39 mil
Total motility	≥50 %	≥40 %
Progressive motility	≥25 %	≥32 %
Morphology % normal	≥30 %	≥4 %
Vitality	≥50 %	≥58 %

**Table 10.2** The worldwide classification of the body mass index (BMI) [4]

Classification	BMI (kg/m <sup>2</sup> )	
	Main cutoff points	Additional cutoff points
Underweight	<18.50	<18.50
Critical thinness	<16.00	<16.00
Moderate thinness	16.00–16.99	16.00–16.99
Mild thinness	17.00–18.49	17.00–18.49
Normal weight	18.50–24.99	18.50–22.99 23.00–24.99
Overweight	≥25.00	≥25.00
Pre-obese	25.00–29.99	25.00–27.49 27.50–29.99
Obese	≥30.00	≥30.00
Obese class I	30.00–34.99	30.00–32.49 32.50–34.99
Obese class II	35.00–39.99	35.00–37.49 37.50–39.99
Obese class III	≥40.00	≥40.00

## 10.2 Epidemiology

Infertility is caused by male factors in 25.5 % of infertile couples [5]. Body mass index or BMI is a simple and widely used method for estimating body fat mass. The healthy BMI range varies with age and sex; obesity in children and adolescents is defined as a BMI greater than the 95th percentile. In children, obesity is more severe and shows an even distribution of the body fat mass, which involves the whole body, including the upper and lower limbs, normally excluded by the adult obesity which has a typical central arrangement. Obesity is one of the most common diseases among the industrialized countries where the incidence rates are increasing so much that according to the data of the WHO, 54 % of the adult population is overweight

**Table 10.3** Causal factors of couple's infertility [5]

Causal factors of couple's infertility	(%)
Male factor	25.5
Ovulatory endocrine infertility	16.9
Endometriosis	6.0
Male or female factor	17.3
Unexplained infertility	29.1
Others	5.3

and 25 % is obese [4]. Infertility, especially in the highly industrialized countries, contributes to the dramatic fall in the birth rate. Epidemiological studies in the USA sorted out that the male fertility has been gradually reduced in the industrialized countries since 1936 by recording a severe incidence of obesity. Over the past 70 years, the semen quality got worse, with an incidence in the male population between 15 and 18 % [3] (Table 10.3).

Numerous data in the medical literature confirm that the reduction in male fertility depends on nutritional factors [6–8]. There is an inverse correlation between BMI and the main hormones that mediate male fertility, where the obese have increased levels of estrogen and low levels of FSH, LH, inhibin B, and total and free testosterone [9–11]. Several studies confirm that the increase in BMI would refer to a reduction in sperm concentration (oligospermia), motility, and sperm morphology (asthenoteratospermia) and to an increase in nemaspermic DNA fragmentation (Table 10.4) [23–25].

### 10.3 Etiopathology

There is a close relationship between fertility and lifestyles [26]. As a matter of fact, the reduction of fertility in men is also connected to nutritional factors [6]. Energy intake in obese subjects is chronically larger than the energy expenditure, but the phenomena that give rise to this chronic alteration are not known. However, in humans, we can clarify the physiopathological mechanisms that regulate energetic homeostasis through constant regulation of body weight and balance between body fat and lean mass [27].

It has been reported that overweight and obese men have an up to 50 % higher rate of subfertility when compared to normal-weight men [21]. This effect persists even when confounding factors such as diseases, age, smoking, alcohol use, and obese female partner have been controlled [3]. Obesity is strongly linked to reduced spermatogenesis, poor quality of sperm, and a reduced percentage of normal sperm morphology [23]. Men's diets, in particular the amount and type of different fats they eat, could be associated with their semen quality. According to the results of a study [14], it has been found that men who ate omega-3 polyunsaturated fats (the type of fat often found in fish and plant oils) had better-formed sperm than men who ate less. A diet full of saturated fatty acids would cause a reduction in sperm count, while a diet rich in omega-3 fatty acids would

**Table 10.4** Scientific evidence between obesity and male infertility

Reports	Number of patients	People	Results/conclusion	Ratio BMI/infertility
Eisenberg et al. [12]	501	Couples from a longitudinal investigation on infertility and environment	No modified semen parameters No DNA fragmentation in the sperm cell	No
Jensen et al. [13]	701	Cross-sectional study of young men attending the military service	A high intake of saturated fats reduces the sperm concentration and total sperm count	Yes
Attaman et al. [14]	99	Men attending fertility clinic	A higher intake of omega-3 fats is positively related to sperm morphology	Yes
Fariello et al. [15]	305	Male patients of a cross-sectional study	Decreased progressive motility Increased sperm DNA fragmentation	Yes
Rybar et al. [16]	153	Men of infertile couples	No modified semen parameters	No
Martini et al. [17]	794	Male patients of a blind prospective study	Deleterious effects of obesity on seminal quality	Yes
Safarinejad [18]	160	Fertile and infertile men	A higher intake of omega-3 fats is positively related to semen parameters	Yes
Chavarro et al. [19]	483	Men of infertile couples	Hypospermia Reduction of sperm cell if BMI >35 DNA fragmentation in the sperm cell	Yes
Hofny et al. [20]	122	Only fertile and infertile obese men	Reduction in the sperm count and motility Increase of atypical sperm cells, sexual hormones alteration	Yes
Pauli et al. [21]	87	BMI 16.1–7.0kg/m <sup>2</sup>	Any meaningless correlations with sperm parameters, reduced fertility	Yes/no
Agbaje et al. [22]	56	Men with diabetes type 2	DNA fragmentation and reduction of the semen volume	Yes

contribute to a better sperm morphology. Men with a high intake of saturated fat have a 35 % lower total sperm count than men with a low intake and a 38 % lower sperm concentration [13]. A number of previous studies had investigated the link between BMI and semen quality, with mixed results (Table 10.4). The mechanisms by which obesity is associated with hypogonadism are mostly unknown, but it is likely that insulin or other hormonal factors released from the adipose tissue may have a role in regulating the production of pituitary LH [22]. In men, one of the main causes of infertility determined by obesity is closely related to the hyperactivity of aromatase, an enzyme which is present in high percentage in the so-called white adipose tissue, which converts testosterone into estradiol. The increase of estradiol concentration is proportional to the quantity of adipose tissue, and estrogens exert a negative feedback action on the pituitary secretion of both FSH and LH, the essential hormones for the normal growth and differentiation of sperm [28]. The white adipose tissue is also the main site of synthesis of leptin, a hormone which regulates the energetic stability and body weight by modulating the energy intake and expenditure at the level of the central nervous system. So an increase in fat mass, resulting from a caloric excess, corresponds to an increased secretion of the hormone on behalf of the adipose tissue. Leptin circulates in plasma at concentrations that parallel the amount of fat reserves. In obese males, androgen levels decline in proportion to the degree of obesity. When leptin is produced in exaggerate amounts, it can reduce the level of androgens, and as its receptors are found in the testicular tissue, this can have a direct effect on the functionality of the sperm [20].

Another characteristic of the adipose tissue that may interfere on male fertility is the increased production of resistin, a protein associated with insulin resistance. Plasma levels of this cytokine are increased in obese individuals [29]. Hyperinsulinemia is related to inhibition of spermatogenesis, and it also produces a deterioration of spermatid DNA, which causes not only a reduction in fertility but also a higher incidence of spontaneous abortions in female partners [22].

Obesity and diabetes mellitus are insulin-resistant states with different abnormalities in oxidative stress, protein glycation, and cellular processes that lead to impaired endothelial function, vascular inflammation, and hemostasis: processes which give rise to impaired function of the microcirculation [22]. A large body of scientific evidences indicates that overweight or obese men frequently suffer from erectile dysfunction (ED) which is a cause of infertility. Sedentary life, prolonged sitting, and fat deposition in the lower abdomen can reduce male fertility, likely through increased testicular temperature to the level of body core temperature [30].

An excessive intake of metabolizable food, especially carbohydrates and fats, subdues the individual to an oxidative stress with negative echoes on the reproductive area. In a healthy body there is a balance between the oxidative mechanisms and the antioxidant defenses. In normal conditions, the toxic potential of free radicals (ROS) is neutralized by a complex system of antioxidant factors that represents our physiological mechanism of defense. The relationship between oxidant factors and antioxidant defenses is the so-called oxidative

balance. Oxidative stress is, therefore, the expression of biological damage that occurs when the prooxidant factors (drugs, toxic substances, radiations, inflammations, etc.) exceed the endogenous antioxidant defenses (enzymes such as superoxide dismutase, coenzyme Q10, catalase, peroxidase, etc.) and the exogenous ones (antioxidants found in food). Obesity is a pathological condition which causes oxidative stress with increased ROS in sperm causing its decreased quality. During the last years, andrologists' interest on the diagnostics and treatment of male infertility has focused on the role of ROS in the pathogenesis of male infertility with harmful effects on sperm membrane rich in polyunsaturated fatty acids. The increased production of ROS and the related oxidative stress associated with obesity may be therefore responsible for the increased lipidic peroxidation damage to the sperm cell membrane [31, 32]. Not only the quantity but also the quality of food can have an effect on male fertility, and in recent years a lot of attention has been paid to the so-called endocrine-disrupting compounds, i.e., substances which have a structural similarity to the endogenous hormones, and therefore they are able to mime the hormones themselves, interacting with their transport proteins. A substantial number of environmental pollutants, such as polychlorinated biphenyls, dioxins, polycyclic aromatic hydrocarbons, phthalates, bisphenol A, alkylphenols, pesticides, and heavy metals (arsenic, cadmium, lead, mercury), have shown to interfere with endocrine function as they are released in the environment in different ways such as smoke, sewage, and careless use of pesticides with the direct release on the food. These substances can cause reproductive problems by reducing either the concentration of sperm or its quality [33].

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## 10.4 Diagnosis and Therapy

In this context, prevention has been of great importance in order to protect and preserve the fertility of the individual since childhood. Smoking, obesity or excessive thinness, different environmental substances, physical inactivity, and even unrestrained physical activity are some of the major risk factors capable of influencing the sexual and reproductive health of an individual [34].

In the first 2 years of life, a hyperalimentation can cause not only a hypertrophy of fat cells but can lead to hyperplasia that will develop to a sure adult obesity [35]. The best treatment of male infertility is the correct diagnosis. The andrologist, through a careful diagnostic process, can identify which is the most appropriate medical and/or surgical treatment for the infertile patient and has an important role in referring eventually the infertile couple to medically assisted procreation. Obesity is often associated with metabolic alterations (diabetes, hypertension, dyslipidemia, hyperuricemia) that are important cardiovascular risk factors which may have an impact on male sexual and reproductive health and in determining psychological disorders. Therefore, in the diagnostic algorithm of morbid obesity, it is essential to weigh the patient, to examine some

important parameters about his family history, to know his waist circumference and blood pressure, and to ask for a few diagnostic tests which are essential to a correct understanding of the problems [35]. Laboratory tests are of considerable importance to assess glucose tolerance and lipid and hormone profile as well as an assessment of the seminal fluid. In particular, it is necessary to evaluate the hypothalamic-pituitary-gonadal axis through the determination of FSH, LH, estradiol, and total testosterone and the examination of seminal fluid according to the WHO criteria of 2010 (Table 10.1) [17].

Once the patient's clinical history, state of health, behavior, and food habits have been pointed out, a therapeutic integrated path referring to the different pathologies will be started. Since obesity is an altered balance between energy consumption and caloric intake, dietary therapy and physical activity must become part of a rehabilitation program. Weight reduction (5–10 % of initial body weight) leads to benefits in terms of morbidity and mortality: it is shown that a lasting weight loss allows significant improvements of all the metabolic syndrome parameters, and in particular the reduction of visceral fat is associated with an improvement of the male reproductive function [35]. Moreover, a psychological evaluation is essential. Improving fertility can be a strong motivation for weight loss [36]. Dietary antioxidants may be beneficial in reducing sperm DNA damage, in infertile obese men [37].

In a male who suffers from obesity, diabetes, or metabolic syndrome, with a reduced fertility and hypogonadotropic hypogonadism, it is possible to evaluate a treatment with antiestrogens or aromatase inhibitors that, if properly prescribed, can improve the quantitative and qualitative characteristics of the seminal fluid. Antiestrogens have the ability to bind to estrogen receptors, both at the hypothalamic and the peripheral levels in a competitive manner, thus inducing an increase in plasma levels of gonadotropins and then of intratesticular testosterone [38]. The pharmacological effect on spermatogenesis should be manifested through increased concentrations of FSH, LH, and testosterone, although a direct effect on spermatogenesis cannot be excluded. The first used antiestrogen was clomiphene citrate, replaced by tamoxifen citrate in recent years [39]. Estradiol is derived from the conversion of testosterone, mediated by the aromatase system which occurs in the testicles and peripheral, especially in adipose, tissues. Testolactone, an inhibitor of aromatase, can improve the testicular function through two mechanisms: a decrease of the concentrations of estradiol and a stimulation of the secretion of gonadotropins from the pituitary through a block of the inhibitory feedback exerted by estradiol. Anastrozole, a selective inhibitor of aromatase, at a dose of 1 mg per day, and letrozole (2.5 mg/day) seem to be comparable to the testolactone for its effects on spermatogenesis [28].

The use of these molecules is interesting especially in patients with an altered testosterone/estradiol ratio, as occurs in obese subjects. Further studies will be necessary to evaluate the effectiveness of these drugs in the treatment of male infertility in the obese because of the small number of studied subjects.

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## 11.1 Definition

Unexplained male infertility (UMI) is defined as infertility whereby semen analysis is normal [1, 2]. Genetic defects are regarded as causes of UMI. Genetically compromised spermatozoa used in assisted reproductive technology (ART) have been associated with a wide range of abnormal embryo development [3]. A proper diagnosis of UMI is mandatory.

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## 11.2 Epidemiology

Failure to determine the cause of infertility occurs in 15 % of infertile couples, which therefore are possibly indicated as UMI [4].

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## 11.3 Etiology

Genetic abnormalities may be associated with UMI [1–3, 5–8] and can be categorized as follows: (1) chromosomal defects in the somatic cells; (2) gene mutations and polymorphisms in the somatic cells; (3) sperm chromosomal abnormalities; and (4) epigenetic disorders.

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### 11.3.1 Chromosomal Defects

Patients with chromosomal translocation may have different types of alteration of spermatogenesis: from normal spermatogenesis to inability to produce spermatogonia [9]. Chromosomal translocations occur when nonhomologous chromosomes exchange segments. Translocations can be balanced (in an even exchange of material with no genetic information extra or missing, and ideally full functionality) or unbalanced (where the exchange of chromosome material is unequal, resulting in extra or missing genes). Robertsonian translocations (RT) are among the most common balanced structural rearrangements in humans, and comprise complete chromatin fusion of the long arm of two acrocentric chromosomes. RT gives rise to one large metacentric chromosome and one extremely small chromosome that may be lost from the organism with little effect because it contains so few genes. The resulting karyotype in humans leaves only 45 chromosomes, as two chromosomes have fused together. RTs are relatively frequent, and affect fertility in 1 of every 1,000 men [10]. Carriers of RT may exhibit normal phenotype but be otherwise infertile because of more or less severe sperm abnormalities [11]. RT, however, may account for only few cases of unexplained infertility [12].

### 11.3.2 Gene Mutations

UMI includes mutations of cation channel of sperm (CatSper) and sperm mitochondrial genes. The diagnosis of gene mutations can be made only by molecular genetic testing.

#### 11.3.2.1 CatSper Gene

Voltage-gated calcium channels (CatSper 1–4) and H<sup>+</sup> are four pumps located in the principal part of the sperm flagellum. The action of CatSper in human spermatozoa can induce elevation of both intracellular pH and Ca<sup>2+</sup> required for sperm activation in the female reproductive tract (hyperactivation) [13, 14] which is positively correlated with the extent of zona pellucida binding, acrosome reaction, zona-free oocyte penetration, and fertilization capacity in vitro [15]. An abnormally low proportion of sperm exhibiting hyperactivation has been found in UMI associated with CatSper1 gene mutations. CatSper-related male infertility is inherited in an autosomal recessive manner [16].

#### 11.3.2.2 Sperm Mitochondrial Deoxyribonucleic Acid Mutations

Sperm mitochondria are located around the mid-segment in a helical arrangement containing mitochondrial deoxyribonucleic acid (mtDNA). mtDNA encodes 37 genes that regulate the Krebs cycle (oxidative phosphorylation). mtDNA is not protected by histones and physically associates with the inner mitochondrial membrane, where highly mutagenic oxygen radicals are generated by the respiratory chain [17, 18]. Thus mtDNA is more prone than nuclear DNA to mutations.

Mitochondrial DNA polymerase gamma (POLG) is a key reparative enzyme of mtDNA strands that encode for the POLG gene. The POLG gene is associated with UMI [19, 20].

### 11.3.3 Sperm Chromosomal Abnormalities

A threefold increase in the frequency of sperm aneuploidy is found in infertile men (approximately 3 %) in comparison with their fertile counterparts [21]. Sperm aneuploidy has been associated with severe sperm defects, UMI, recurrent miscarriage, failure of in vitro fertilization, and increased risk of chromosome abnormalities in newborns [21, 22].

### 11.3.4 Epigenetic Disorders

Epigenetics defines all types of molecular information (independent of DNA) transmitted from the spermatozoa to the embryo. The epigenetic regulatory mechanisms include, in theory: (1) centrosome; (2) DNA methylation; (3) histone modifications; (4) chromatin remodeling; and (5) role of RNA transcripts.

Histone covalent modifications are associated with several nuclear functions including transcriptional control, chromatin packaging, and DNA methylation. If abnormally modified, histones might impede normal embryogenesis [23, 24]. It is thought that assessments of DNA condensation/decondensation or fluorescent in situ hybridization of sperm chromosomes might be useful tools for these patients, although the poor reproducibility of tests raises doubts about their clinical usefulness [23, 24].

### 11.3.5 Germ Cell Splicing Factor

Alternative splicing of precursor messenger RNA (pre-mRNA) is common in mammalian cells and enables the production of multiple gene products from a single gene, thus increasing transcriptome and proteome diversity. Disturbance of splicing regulation is associated with many human diseases; however, key splicing factors that control tissue-specific alternative splicing remain largely undefined. In an unbiased genetic screen for essential male fertility genes in the mouse, the author's group identified the RNA-binding protein RBM5 (RNA binding motif 5) as an essential regulator of haploid male germ cell pre-mRNA splicing and fertility. This gene encodes several apoptosis-related proteins including *Caspase 2* [25], *FAS* receptor, and *c-FLIP* [26]. It has been suggested that RBM5 male germ cell splicing factor is one of the contributory factors in UMI [27].

### 11.3.6 Chromosome Heteromorphism

Certain regions in the genome are subject to heteromorphisms because of their repetitive DNA content. Chromosome localizations of these regions may be identified by several methods, each of which reveals typical staining patterns implying constitutional differences in heterochromatin [28]. The term heteromorphism is used synonymously with the polymorphism or normal variant. Common cytogenetic polymorphisms detected by G-banding are considered as heteromorphisms

**Table 11.1** Genetic tests in unexplained male infertility [30, 31]

Test	Objective	Specimen tested
Cytogenetic test	Assess number and appearance of chromosomes	Blood
Gene sequencing	Determine gene sequencing for mutations	Blood
Fluorescence in situ hybridization	Assess spermatozoa aploidy	Sperm
Microarray technology	Analyze copy number variations, gene expression levels, single-nucleotide polymorphisms, and mRNA transcripts pool expressed by sperm	Sperm, blood
Next-generation sequencing technologies	Detect DNA mutilation problems	Blood
Giemsa-trypsin banding (G-banding)	Detect chromosome polymorphism	Blood

and include heterochromatin regions of chromosomes 1, 9, 16, and Y, and also prominent acrocentric short arms, satellites, and stalks [29]. There seems to be an increased incidence, especially in UMI men, but the mechanism underlying this association needs to be elucidated [30].

## 11.4 Diagnosis

A series of tests can be used to identify genetic and epigenetic defects in UMI (Table 11.1) [30, 31]. Unfortunately, these tests are not routinely available. Despite being limited by the widespread use of ART, a cost-effective genetic evaluation should be considered as an integral part of the workup in UMI. POLG gene mutations can be detected using sequence analysis, and testing is clinically available ([www.transgenomic.com](http://www.transgenomic.com)).

## 11.5 Therapy

At present the only available therapy is ART. Of note, the prognosis for pregnancy by POLG gene alterations is good in cases treated with ART, as mtDNA is not transmitted to the offspring [11]. About one-half of the couples submitted to ART are affected by UMI. In the author's opinion frustration induced by infertility, notwithstanding laboratory examinations within the reference values, might play a critical role on the behavior of these couples.

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## 12.1 Definition

Inflammatory infertility occurs when male infertility is provoked by inflammation of the urogenital tract and might constitute a curable cause of infertility [1]. About 10–15 % of infertile men have genital tract inflammation. After exclusion of urethritis and/or bladder infection, a sperm leukocyte concentration of  $>10^6/\text{mL}$  indicates inflammation [2]. It was recently advocated that a high leukocyte count in prostate-specific materials, even in the absence of clear leukocytospermia, may be associated with male infertility/dyspermia [3]. A concentration of  $>10^3$  colony-forming units is significant for bacteriospermia [2].

Clinical studies raise doubts about whether inflammation of epididymis and didymis negatively affect male fertility when seminal duct obstruction is absent [4], leading to the suspicion that inflammation of the testicles exerts a poor influence on fertility. In fact, inflammation is one of the most important components of immune protection. On coming into contact with pathogen antigens, cells of the inflammatory response release signaling molecules (proinflammatory cytokines), which amplify the response by recruiting other macrophages and granulocytes to the infection site. To prevent inflammatory damage, another set of signaling molecules have the function of turning the signal off [5]. However, the disruption of immune response at the testicular level strongly affects spermatogenesis, indicating a protective role of the immune system in regard of fertility potential [6, 7].

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Further testicular macrophages play an important role in the balance between defense against invading microorganisms and “testicular immune privilege,” which serves to protect the neoantigens of the meiotic and haploid germ cells that appear during puberty after the establishment of self-tolerance. Although testicular macrophages exhibit many typical macrophage characteristics such as effective antigen presentation, phagocytic functions, and expression of Fc receptors and major histocompatibility complex class II receptor [8], they are more reminiscent of a type-2 macrophage displaying diminished proinflammatory responses and reduced capacity to induce T-cell activation [9].

Thus the majority of the so-called inflammatory infertilities are of prostatic origin, with epididymitis of marginal interest.

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## 12.2 Epididymitis

Acute epididymitis is divided into two classes [10, 11].

1. Sexually transmitted epididymitis (usually linked to urethritis), caused most often by *Neisseria gonorrhoeae* or *Chlamydia trachomatis*, occurs among sexually active adults younger than 35 years
2. Nonsexually transmitted epididymitis is often associated with urinary tract infections, and occurs more often in adults older than 35 or who have recently undergone urinary instrumentation procedures

A slight impairment of sperm forward motility might occur, which is completely recovered after appropriate antibiotic therapy [12]. Obstructive azoospermia after bilateral epididymitis can occur, although its prevalence is unknown.

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## 12.3 Prostatitis

### 12.3.1 Definition and Categorization

Prostatitis is a prostatic inflammation. About half of all men suffer from prostatitis symptoms during their life span [13, 14]. Prostatitis is classified according to five categories: acute prostatitis (category I), chronic bacterial prostatitis (category II), abacterial inflammatory prostatitis (category IIIa), abacterial noninflammatory prostatitis (category IIIb), and asymptomatic prostatitis (category IV) [15].

Chronic prostatitis increases the risk for benign prostatic hyperplasia and prostate cancer [16, 17], and may affect male reproductive health [18].

### 12.3.2 Etiology of Prostatitis

*Escherichia coli*, *Klebsiella* sp., *Proteus mirabilis*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *C. trachomatis*, and *Ureaplasma urealiticum* are the most common bacteria involved in bacterial prostatitis infections. The route of infection is urinary ascending or lymphatic transrectal [19].

### 12.3.3 Pathogenesis of Dyspermia Associated with Prostatitis

Most of the literature agrees that the existence of bacteria in the prostate is linked with asthenospermia and decreased male reproductive health [20]. Chronic prostatitis seems to affect sperm count mainly if associated with irritable bowel syndrome, because of dilation of the periprostatic venous plexus and increased temperature [21]. An increase in reactive oxygen species (ROS) from leukocytes [22] has been indicated as a further physiopathologic mechanism of dyspermia associated with prostatitis.

### 12.3.4 Diagnosis

Although several symptomatic indices for prostatitis have been developed, only the National Institutes of Health (NIH) Chronic Prostatitis Collaborative Research Network has produced a valid instrument for evaluation of symptoms of prostatitis: the NIH Chronic Prostatitis Symptom Index (NIH-CPSI). This index has nine items divided into three domains (pain, urinary symptoms, and quality of life), and is used as a tool for the diagnosis and follow-up of chronic prostatitis and chronic pelvic pain syndrome. Initially it was presented in English [23] (Table 12.1) and later also in Italian [24].

The prostate is tender, with various degrees of pain at objective examination. Urine culture and expressed prostatic secretion (EPS) represent the most important investigations for the diagnosis and categorization of prostatitis. EPS has been fully described by Mears and Stamey (Table 12.2) [25].

If prostatic biopsy is contraindicated [26], transrectal echography might be of some help when stones or abscess are suspected [27]. The efficacy of semen culture in the diagnosis and evaluation of chronic prostatitis remains unclear, and ejaculate culture is not recommended as a first line of diagnostic evaluation in these patients [28]. Increased seminal plasma elastase [1], interleukins (especially interleukin-6) [29], and ROS [1], in addition to decreased zinc, citric acid, fructose, phosphatase, and  $\alpha$ -glutamyltransferase [30], are regarded as biochemical signs of chronic prostatitis.

**Table 12.1** National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) [23]

Part a: National institutes of Health: classification system for prostatitis

Type	Classification	Definition
I	Acute bacterial prostatitis	Evidence of acute bacterial infection
II	Chronic bacterial prostatitis	Evidence of recurrent bacterial infection
III	A Chronic abacterial inflammatory prostatitis	White blood cells in semen, expressed prostatic secretions or VB3
	B Chronic abacterial non-inflammatory prostatitis	No white blood cells in semen, expressed prostatic secretions or VB3
IV	Asymptomatic inflammatory prostatitis	No symptoms, incidental diagnosis during prostate biopsy or presence of white blood cells in prostatic secretions during evaluation for others disorders.

Part b) NIH Chronic Prostatitis Symptom Index (NIH-CPSI).

Pain or discomfort.

1) In the last week, have you experienced any pain or discomfort in the following areas?

	Yes	No
a) Area between rectum and testicles (perineum)	1	0
b) Testicles	1	0
c) Tip of the penis (not related to urination)	1	0
d) Below your waist, in your pubic or bladder area	1	0

2) In the last week, have you experienced:

	Yes	No
a) Pain or burning during urination	1	0
b) Pain or discomfort during or after sexual climax (ejaculation)	1	0

3) How often have you had pain or discomfort in any of these areas over the last week?

0	Never
1	Rarely
2	Sometimes
3	Often
4	Usually
5	Always

4) Which number best describes your average pain or discomfort on the days that you had it, over the last week? 0 = no pain; 10 = pain as bad you can imagine.

0	1	2	3	4	5	6	7	8	9	10
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Urination

5) How often have you had a sensation of not emptying your bladder completely after you finished urinating over the last week?

0	Not at all
1	Less than 1 time in 5
2	Less than half time
3	About half time

**Table 12.1** (continued)

4	More than half time
5	Almost always

6) How often have you had to urinate again less than two hours after after you finished urinating over the last week?

0	Not at all
1	Less than 1 time in 5
2	Less than half time
3	About half time
4	More than half time
5	Almost always

Impact of symptoms

7) How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week?

0	None
1	Only a little
2	Some
3	A lot

8) How much did you think about your symptoms, over the last week?

0	None
1	Only a little
2	Some
3	A lot

Quality of life.

9) If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that?

0	Delighted
1	Pleased
2	Mostly satisfied
3	Mixed (about equally satisfied and dissatisfied)
4	Mostly dissatisfied
5	Unhappy
6	Terrible

Scoring the NIH-Chronic Prostatitis Symptom Index Domains.

Pain: Total of items 1, 2, 3 and 4 = .....

Urinary symptoms: Total of items 5 and 6 = .....

Quality of life impact: Total of items 7, 8 and 9.....

**Table 12.2** Mears and Stamey localization technique [25]

The test begins when the patient needs to void: drink 500 mL water, 30–60 min before the test

Four sterile containers are needed, named VB1, VB2, EPS, and VB3

Retract completely the foreskin

Cleanse the glans with sterile physiologic solution and dry the glans with sterile gauze

Urinate 10–20 mL in VB1

Urinate 200 mL in the toilet and without interrupting the stream urinate in VB2

The physician massages the prostate until several drops of prostatic secretion are obtained (EPS)

If no EPS could be collected during massage, a drop may be present at the orifice of urethra, and this drop should be taken with a 10- $\mu$ L calibrated loop and cultured

Immediately after massage the patients urinates 10–15 mL in VB3

### 12.3.5 Therapy

A full review of the therapy of prostatitis is presented on the Web site of the European Urological Association (EUA): [http://www.uroweb.org/guidelines/online-guidelines/?no\\_cache=1](http://www.uroweb.org/guidelines/online-guidelines/?no_cache=1) It should be noted that trimethoprim-sulfamethoxazole is contraindicated for the treatment of inflammatory infertility linked to prostatitis because this drug is toxic for male gametes (see the Chap. 15). The therapy of prostatitis is mainly aimed at resolving the symptoms (see the following paragraph), and from a reproductive point of view the goals are reduction/eradication of microorganisms in prostatic secretions and semen, normalization of sperm inflammatory parameters, and improvement of sperm count [1, 14, 31]. At present only antibiotic therapy is achieving these goals [1].

### 12.3.6 Prognosis of Prostatitis in Terms of Human Fertility

EUA guidelines indicate that antibiotic treatment often eradicates microorganisms but cannot reverse anatomic dysfunctions, and might improve sperm quality, which does not necessarily enhance the probability of conception [4].

These data are not surprising, because the relationship between male fecundity and sperm count is hyperbolic and achieves a plateau at about  $30 \times 10^6$  spermatozoa/mL, 50 % class A motility, and 14 % typical forms (strict criteria) [32–34]. Thus the more severe the dyspermia the more crucial is its therapy to improve couple fertility, and chronic prostatitis is seldom associated with severe dyspermia [4, 20, 21]. Furthermore, male fecundity is linked more to the quality of spermatogenesis than to sperm count [35, 36], and spermatogenesis is obviously not or poorly affected in the course of prostatitis. Despite these limitations to therapy, it is generally recognized that appropriate therapy for prostatitis should be performed to ensure, at the very least, symptom relief.

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## 12.4 Mumps Orchitis

Mumps orchitis is rare; however, because of its detrimental sequelae on sperm count it merits discussion here. Orchitis is a common complication of mumps in postpubertal men affecting about 20–30 % of cases (10–30 % of which are bilateral), often results in testicular atrophy, and occurs 1–2 weeks after parotitis [37].

The causes of testicular atrophy are not fully known. In the course of inflammation the tunica albuginea forms a barrier against edema, and the subsequent rise in intratesticular pressure leads to pressure-induced testicular atrophy [38]. Adamopoulos et al. found elevated luteinizing hormone (LH) levels and an exaggerated pituitary response to LH-releasing hormone (LHRH) stimulation in the acute phase of mumps orchitis. Basal testosterone concentrations returned to normal after several months, whereas mean basal follicle-stimulating hormone (FSH) and LH concentrations remained significantly increased at 10 and 12 months after the acute phase [39].

Mumps orchitis rarely leads to azoospermia, more frequently leading to various degrees of dyspermia [40]. Testicular sperm extraction is indicated in cases of azoospermia (even with high concentrations of FSH and LH), whereas no treatment has been proposed for dyspermia [41].

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## 12.5 Sperm DNA Fragmentation in Inflammatory Infertility: A Less Orthodox Point of View

Sperm DNA fragmentation (SDF) is the separation or breaking of DNA strands into pieces. Any form of DNA damage may result in male infertility. Sperm DNA integrity is essential for the complete transmission of genetic information, and is necessary for the normal fertilization and embryo growth in both natural and assisted conception [42, 43], but also for normal fetal development [44]. It has been reported that when 30 % or more of sperm DNA is damaged, natural pregnancy is not possible [45, 46]. Approximately 15 % of patients with male factor infertility have a normal semen analysis [47].

Increased sperm DNA fragmentation is frequently observed in males with normal semen characteristics. In fact, sperm DNA damage is found in 8 % of men with normal seminal parameters [48, 49]. Moreover, a significant proportion of males (8.4–23 %) diagnosed as unexplained infertile according to conventional semen analysis have high levels of sperm DNA fragmentation [50–53]. DNA integrity can be considered an effective monitor of normal male fertility potential [54].

High levels of sperm DNA fragmentation have been correlated with low fertility potential, failure to obtain blastocysts, hindrance in embryonic development, increased risk of recurrent miscarriages, reduced chances of successful implantation, and abnormal outcomes in the offspring [55–57].

Several etiologic factors have been associated with sperm DNA fragmentation: environmental conditions and cigarette smoking [58, 59], chemotherapy [60–62], irradiation [63, 64], cancer [65], varicocele [66, 67], leukocytospermia [68, 69], advanced paternal age [70–72], high fever [73], and chronic prostatitis [74–78]. Sharma et al. found the highest levels of ROS in semen of infertile men with prostatitis [79]. High levels of ROS mediate the DNA fragmentation commonly observed in spermatozoa of infertile men [80, 81]. Therefore, inflammations of the male genitourinary tract can adversely affect male fertility by causing sperm DNA damage.

Chronic prostatitis affects about 10–15 % of the male population [82]. In other studies the prevalence of prostatitis symptoms ranged from 2 to 9.7 % [83–85]. Prostatitis is the most frequent urologic diagnosis in males younger than 50 years [86]. It has been estimated that approximately 50 % of men will suffer from prostatitis during their lifetime [87]. A study of National Center for Health Statistics showed that about 25 % of outpatients evaluated for genitourinary problems suffered from prostatitis [88]. Males with a previous diagnosis of prostatitis had a 20–50 % risk for recurrent episodes [89]. A history of male genital inflammations, including prostatitis, epididymitis, and orchitis, occurs in 5–12 % of infertile men [90].

A study by El-Bayoumi et al. has revealed that prostatitis was the cause of infertility in 27.5 % of a sample of 375 infertile male patients [91]. A more recent study has shown chronic prostatitis as a cause of infertility in 39.1 % of 534 patients with male infertility [92].

Hu et al., in their recent (2013) study, have shown that chronic prostatitis significantly reduces sperm quality and male fertility, also highlighting a significant increase in sperm DNA fragmentation [76].

Considering that sperm DNA fragmentation is a frequent condition (due to various causes) and that chronic prostatitis is also very common and causes infertility in a high percentage of cases, one can deduce that sperm DNA damage is a frequent precondition for male infertility.

As sperm DNA fragmentation cannot be detected by routine molecular and cytogenetic methods, several assays have been developed to evaluate sperm chromatin/DNA integrity.

Some of these tests measure DNA damage directly, such as TUNEL (terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling assay) and COMET (single-cell gel electrophoresis) [93, 94]. Other tests (indirect) include SCSA (sperm chromatin structure assay) and the SCD test (sperm chromatin dispersion) [95, 96]. The SCD test and TUNEL assay are both effective in detecting sperm DNA damage; however, using bright-field microscopy, the SCD test appears to be more sensitive than TUNEL [97]. Sperm DNA fragmentation has now become a new biomarker for male infertility diagnosis [98].

There are several notable facts regarding the interpretation and evaluation of the results of these different methods, as follows.

**SCSA:** The pregnancy rates are significantly higher with DNA fragmentation index (DFI) below the thresholds of 30–40 % [99]. Other investigators have found that a DFI cutoff level of 30.27 % was able to discriminate infertile and fertile men [100];

**TUNEL:** A threshold value of 20 % sperm DNA fragmentation (SDF) has been suggested to distinguish between fertile men and infertile patients [54]. A more recent study has shown a cutoff value of 19.2 % that can differentiate infertile men with DNA damage from healthy men [101];

**COMET (alkaline test):** The risk of failure to achieve a pregnancy increases when SDF exceeds a prognostic threshold value of 52 % [102];

**COMET (neutral test):** When SDF exceeds a prognostic threshold value of 77.5 %, there is a high risk of pregnancy failure [103];

**SCD test:** Men with SDF greater than a diagnostic threshold of 22.75 have a high risk of infertility [103].

According to current knowledge, intake of antioxidants may be beneficial in reducing sperm DNA damage, particularly in men with high levels of DNA fragmentation [104]. It is also important to identify behaviors that may reduce sperm DNA damage, such as removing testicular gonadotoxins and/or hyperthermia, treatment of genital tract infections and chronic prostatitis, correction of varicocele, smoking cessation, and reducing radiation exposure [80, 104–109].

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## 13.1 Cryptorchidism

Cryptorchidism is the commonest congenital anomaly affecting the genitalia of newborn male infants.

The cause may be related to an intrinsic testicular defect or lack of maternal gonadotropins. Approximately 10 % of instances are bilateral. The most common location is at the external inguinal ring [1].

The testes normally descend into the scrotum at 7 months' gestation. The incidence of cryptorchidism therefore decreases with age: it is 30 % in premature infants, 3 % in newborns, 1.5 % at 1 month and 0.75 % at 1 year of age [1].

Most recent data reported that at 1 year of age, nearly 1 % of all full-term male infants have cryptorchidism [2].

A patent processus vaginalis is present in 90 % of patients, while inguinal hernia in 25 % [1].

The most useful classification of cryptorchidism is clinical, distinguishing into *palpable* and *non-palpable* testes [3].

The clinical management is decided by the location and presence of the testes:

- In the presence of *palpable* and retractile testes, the clinical approach should be initially conservative.
- In case of bilateral *non-palpable* testes, an immediate endocrinological and genetic evaluation is necessary.

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From the etiological point of view, we can distinguish two kinds of undescended testicle:

- Those in which the gubernaculum has gone “off course”, and we call them *ectopic testes*.
- Those in which the descent to the bottom of the scrotum has been incomplete, but “on course”. We call them “incompletely descended” or *dystopic testes*.

In case of *ectopic testicle*, it has to be searched into one of four possible locations:

- Inguinal, in the abdominal wall, near the external inguinal ring
- Perineal
- Penile, near the base of the shaft
- Crural, in the thigh

In case of *dystopic testicle*, it moves up and down and can be defined according to its range of movement as:

- Abdominal, when the testicle may move in and out of the internal inguinal ring
- Inguinal, when it moves along the inguinal canal
- Emergent, when it appears at the external ring
- High retractile, when it moves up and down but cannot be made to go to the bottom of the scrotum
- Low retractile, when it descends to the bottom of the scrotum only in particular conditions (warm bath, under general anaesthesia, hand traction)

Low retractile testes are essentially normal and will always end up in the scrotum with puberty [4].

Possible complications of undescended testis could be [4]:

- Torsion: a peritoneal sac is often associated with an undescended testicle, making it prone to torsion.
- Infertility: common only in case of bilateral undescended testicles, not with unilateral.
- Cancer: about one in ten testicular tumours is associated with undescended testicle.

### 13.1.1 Diagnosis

Physical examination is sufficient for differentiating between palpable and non-palpable testes. The groin region may be “milked” towards the scrotum to detect the possible attraction of the testis into the scrotum. A retractile testis can generally be brought into the scrotum until a cremasteric reflex will retract it into the groin again [5].

A unilateral, non-palpable testis and an enlarged contralateral testis suggest testicular absence or atrophy, but this should not avoid surgical exploration. An inguinal, non-palpable testis requires specific visual inspection of the femoral, penile and perineal regions in order to exclude an ectopic testis [3].

When no testicle can be felt on one side, it is often in the inguinal canal. The testicle is easily found with a computed tomography (CT) scan, even in the abdomen [4].

Diagnostic laparoscopy is the only examination that can reliably confirm or exclude an intra-abdominal, inguinal and absent/vanishing testis (non-palpable testis). Before carrying out laparoscopic assessment, examination under general anaesthesia is recommended because some, originally non-palpable, testes could be palpable under anaesthetic conditions [6].

### 13.1.2 Treatment

Although 90 % of testicles are in the scrotum at birth, the next 9 % do not descend until 12 months, after which no more do [4]. Treatment should be done as early as possible, around 1 year of age, starting after 6 months and finishing preferably at 12 months of age, or 18 months at the latest. The timing is driven by the final adult results on spermatogenesis and hormone production, as well as the risk for tumours [7, 8].

After puberty the chance of improving fertility is minimal, and the risk of cancer increases rapidly, but most young men wish to keep both testes. When an undescended testicle is found in a mature grown man, orchiectomy is the procedure that should be advised in view of the risks of malignancy [4].

#### 13.1.2.1 Medical Therapy

Taking into account the hormonal dependence of testicular descent, the use of human chorionic gonadotrophin (hCG) or gonadotrophin-releasing hormone (GnRH) is recommended, with maximum success rates of 20 %. However, it must be considered that almost 20 % of descended testes have the risk of reascending later [3].

In addition, the price that the patient will have to pay will be a premature puberty, with stunting of growth from early fusion of epiphyses [4].

A total dose of 6,000–9,000 U hCG (depending on weight and age) is given in four doses over a period of 2–3 weeks, along with GnRH, given for 4 weeks as a nasal spray at a dose of 1.2 mg/day, divided into three doses per day [3].

Medical treatment may be beneficial before surgical intervention (orchidolysis and orchidopexy) or afterwards (low intermittent dosages), in terms of increasing the chances of fertility in later life [9].

#### 13.1.2.2 Surgery

##### Palpable Testis

Surgery for a palpable testis includes orchidofuniculolysis and orchidopexy, via an inguinal approach, with success rates of up to 92 %. It is important to remove and dissect all cremasteric fibres to prevent secondary retraction [3].

Through a crease incision over the internal ring, the external oblique is opened, and the testicle is mobilized, taking care not to injure its artery or the vas deferens. The testicular vessels are followed up behind the peritoneum and mobilized medially by dividing fibrous bands. This allows the testicle to be placed in a sac between the dartos muscle and skin of the scrotum, without tension [4].

Associated problems, such as an open processus vaginalis, must be carefully dissected and closed. There should be no fixation sutures or they should be made between the tunica vaginalis and the dartos muscle. The lymph drainage of a testis that has undergone surgery for orchidopexy has been changed from iliac drainage to iliac and inguinal drainage (this is important in the event of later malignancy).

Scrotal orchidopexy can be considered in less severe case and when performed by surgeons with experience using that approach [3].

### **Non-palpable Testis**

Inguinal surgical exploration with possible laparoscopy should be attempted for non-palpable testes. There is a significant chance of finding the testis via an inguinal incision. In rare cases, it is necessary to search into the abdomen if there are no vessels or vas deferens in the groin. Laparoscopy is the best way of examining the abdomen for a testis. In addition, either removal or orchidolysis and orchidopexy can be performed via laparoscopic access [10].

For boys aged  $\geq 10$  years with an intra-abdominal testis, with a normal contralateral testis, removal is an option because of the theoretical risk of later malignancy. In pre-pubertal boys, an effort should be made to preserve the testis. The exact location of the testis should be provided by CT scan and confirmed by laparoscopy [4].

In bilateral intra-abdominal testes, or in boys younger than 10 years, a one-stage or two-stage Fowler-Stephens procedure can be performed. In the event of a two-stage procedure, the testicular vessels are laparoscopically clipped or coagulated proximally to the testis as a first step, to allow development of collateral vasculature [11].

Six months later, a second operation provides the mobilization of the testicle downwards into the scrotum, by which time it will have acquired a new blood supply from the artery to the vas and it is safe to divide the testicular vessels [4].

This second-stage procedure, in which the testis is brought directly over the symphysis and next to the bladder into the scrotum, can also be performed by laparoscopy. The testicular survival rate in the one-stage procedure varies between 50 and 60 %, with success rates increasing up to 90 % for the two-stage procedure. Microvascular autotransplantation can also be performed with a 90 % testicular survival rate. However, the procedure requires skilled and experienced surgeons [12].

*Ectopic testes* never find their way into the scrotum and require orchidopexy [4].



### 13.1.3 Prognosis

Although boys with one undescended testis have a lower fertility rate, they have the same paternity rate as those with bilateral descended testes. Boys with bilateral undescended testes have lower fertility and paternity rates.

Boys with an undescended testis have an increased risk of developing testicular malignancy. Screening both during and after puberty is therefore recommended for these boys [3].

Pre-pubertal orchidopexy may decrease the risk of testicular cancer, and early surgical intervention is indicated in children with cryptorchidism.

Boys with retractile testes do not need medical or surgical treatment, but require close follow-up until puberty [3].

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## 13.2 Testicular Torsion

Testicular torsion is one of the most common emergencies in urology. It may occur at any age, but is most common around puberty [4]. About one-half of instances occur during sleep. Although the cause is unknown, poor fixation of the testis within the tunica vaginalis (the so-called bell clapper deformity) is most often given as the origin [1].

It results in twisting of the spermatic cord and occlusion of the venous or arterial supply to the testis. It is a true vascular emergency that, if not treated within 3–4 h after onset of pain, causes a complete infarction of the testis, followed by its atrophy [1].

Clinical presentation entails a sudden onset of pain and swelling in the testicle. Patients often recall attacks of pain that come on and are relieved equally suddenly (a history of such warning attacks is sufficient reason to explore the testicle and fix it). On examination, the scrotum is tender, red and swollen, and it is seldom possible to distinguish testis from the epididymis [4].

The first classification classically distinguishes two forms [4]:

- *Extravaginal* torsion, rarely seen in newborn boys, in which the testicle has rotated on the spermatic cord and it is almost never possible to save the testis by untwisting it
- *Intravaginal* torsion, in which the tunica vaginalis may be unusually roomy even with a normally descended testicle, and the testis and epididymis can twist on a stalk (like a light bulb in its socket)

The differential diagnosis is from [4]:

- Mumps orchitis, which never attacks boys before puberty
- Epididymitis, which is often secondary to urinary infections

- Fat necrosis, occasionally seen in infants
- Cancer, which in older boys and men can present with inflammation
- Torsion of an appendix testis, which is difficult to be distinguished from torsion of the testis without exploration
- Incarcerated inguinal hernia

### 13.2.1 Diagnosis

No investigation should be allowed to delay surgical exploration. A Doppler or radioisotope scan may show absence of arterial circulation in the testicle but is justified only if it will not delay matters [4].

Generally, no harm results from scrotal exploration if epididymitis is found, but much harm can result from delay in treating testicular torsion [1].

### 13.2.2 Treatment

It is important to untwist the testicle before it dies from ischaemia [4]; therefore, the treatment depends on the interval from onset of pain to presentation in the emergency room.

Within 4 h of onset, manual detorsion under local anaesthesia of the testicular cord should be attempted (the testes twist towards the midline as seen from the feet). If manual detorsion is successful, elective bilateral orchidopexy is indicated within the next few days. If it is not successful, immediate surgical exploration is indicated [1].

If presentation is between 4 and 24 h from pain onset, immediate surgical exploration, detorsion and bilateral orchidopexy should be performed [1].

If more than 24 h have passed since onset of pain, surgical exploration is indicated, but preservation of testicular function is doubtful [1].

In these cases, orchiectomy and placement of a testicular prosthesis is the treatment of choice.

The testicle is explored through a transverse scrotal incision. The tunica vaginalis is opened and the testicle is untwisted. If there is any doubt about the viability of the testis, it can be incised to see if it still bleeds. All too often it is necrotic and must be removed [4].

In case of *torsion of the appendix testis*, tiny cysts are usually present at the upper pole, one on the epididymis (Wolffian duct origin) and the other on the testis (Mullerian duct origin). Apart from being of interest to embryologists either can twist on its stalk, exactly mimicking torsion of the testicle and equally requiring urgent exploration [4].

Because torsion occurs in about 10 % of cases on the other side, the other testicle should be fixed then or at a later operation.

### 13.3 Testicular Microlithiasis

Testicular microlithiasis (TM) is a relatively uncommon condition characterized by the presence of multiple, 1-mm to 3-mm foci of increased echogenicity distributed randomly in the testicular parenchyma, detected incidentally during scrotal ultrasound (US). Its incidence varies according to different reports: in healthy men, the incidence ranges between 1.5 and 5.6 % and in subfertile population between 0.8 and 20.0 % [13–15], but it increases over 50 % in patients with testicular cancer [16–18].

TM usually affects both testes, but may be unilateral and can be focal or diffuse.

The exact aetiology of TM is unclear. It is suggested that these calcified concretions within the lumen of seminiferous tubules originate from sloughing of degenerated intratubular cells and failure of the Sertoli cells to phagocytose the debris [19].

TM has been associated with several urological diseases, including testicular cancer (TGCT), intratubular germ cell neoplasia (ITGCNU), cryptorchidism (testicular dysgenesis), varicocele, Klinefelter's syndrome, hypogonadism and infertility.

The relationship between TM and infertility is not well understood even if decreased fertility could be expected because the majority of seminiferous tubules can be obstructed by intratubular calcifications. Infertile patients with TM may have significant reductions in sperm migrations and motility. However, although some authors have reported abnormal semen parameters in infertile men with TM, others have found no significant difference among infertile men with or without TM with no significant differences in sperm count, motility or morphology in terms of sperm function between infertile men with or without TM [13, 14, 17].

The clinical importance of TM is not well clarified: because they can often be observed in association with germ cell tumours, many authors suggest to consider them as a possible “marker” of testicular cancer and to perform a prolonged scrotal ultrasound follow-up of these patients in order to recognize possible testicular tumours.

However, still today, the debate continues because many of the observations who link TM and testicular cancer are based on retrospective series [20, 21].

Many studies report in fact the co-association between testicular tumour and TM, but few ones describe the actual risk of development of a testicular cancer after TM [22, 23].

Serter et al. identified TM in 53 of 2,179 (2.4 %) asymptomatic men (age 17–42 years), but none had testicular tumour [24]. Similarly, Peterson et al. reported TM in 84 of 1,504 asymptomatic men (5.6 %) and 1 man without TM who had TGCT; they concluded that testicular microlithiasis is a common finding in asymptomatic men that may not be related to testicular cancer [15].

DeCastro et al. [23] screened 1,504 healthy men (age between 18 and 35 years) and detected 84 cases of TM (5.6 % prevalence). Even if at 5-year follow-up one man had developed a TGCT (64 months after initial screening), implying increased risk of developing testicular cancer compared with the general population, the authors concluded that most men with TM would have not developed a testicular

cancer and that, for this reason, an intensive screening program for men with testicular microlithiasis is not cost-effective and would have done little to improve outcomes associated with testicular cancer [23].

Richenberg et al. performed a pooled analysis of literature data: a total of four patients (1 %; 95 % CI 0.4–2.6 %) among the 389 patients who were included in the study developed during the follow-up period a testicular cancer (median follow-up range 29–62 months).

Of these four patients, three had coexisting risk factors, one atrophied testis and two with previous history of testicular germ cell cancer. Excluding these patients from the final analysis, only one patient in 386 with TM and no coexisting risk factors developed cancer during follow-up (0.26 %; 95 % CI 0.05–1.45 %). They concluded that the literature reports a high association between testicular microlithiasis and testicular cancer, but that their meta-analysis did not suggest a causal link between microlithiasis and cancer. In the absence of additional risk factors, surveillance is not advocated, while in the presence of additional risk factors, surveillance with regular follow-up is recommended [25].

Recently Tan et al. [26] in their systematic review and meta-analysis summarized literature data about TM: management should depend on the clinical context. In healthy, asymptomatic individuals, the absolute risk of concurrent or interval TGCT or ITGCNU is very low. In patients who undergo scrotal ultrasound because of sub- or infertility, cryptorchidism or a personal history of germ cell tumour and for this reason already are at an elevated risk of testicular cancer, the presence of TM further increases the risk of a concurrent diagnosis of ITGCNU or germ cell tumours. In their pooled analysis, the estimated summary risk ratio was 8.5. However, even in the presence of risk factors, in contrast with other authors that recommend performing testicular biopsy [16], they suggest only to follow up these patients regularly.

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## 13.4 Testicular Trauma

Testicular trauma most commonly occurs in young men between 15 and 40 years. Testicular trauma may be the consequence of blunt or penetrating trauma [27].

### 13.4.1 Blunt Trauma

Blunt trauma to the scrotum can be responsible for testicular dislocation, testicular haematocele and testicular rupture, associated or not to scrotal haematoma.

*Testicular dislocation* is quite rare; it is more common in motor vehicle accidents and in these cases can be also bilateral. Possible sites with relative frequency are superficial inguinal 50 %, pubic 18 %, penile 8 %, canalicular 8 %, truly abdominal 6 %, perineal 4 %, acetabular 4 % and crural 2 %.

Traumatic dislocation of the testicle is treated by manual replacement and secondary orchidopexy. If primary manual reposition cannot be performed, immediate orchidopexy is indicated [28].

*Haematocele* can be treated conservatively if it is smaller than three times the size of the contralateral testis [27]. Larger haematoceles or growing ones in fact can require delayed surgery, because conservative treatment often fails. Early surgical intervention resulted in preservation of the testis in more than 90 % of cases compared to delayed surgery, which resulted in orchiectomy in 45–55 % of patients [29–31].

*Testicular fracture or rupture* may occur because of a traumatic compression of the testis against the inferior pubic ramus or symphysis, resulting in a rupture of the tunica albuginea testis, haemorrhage and extrusion of testicular contents into the scrotal sac.

The scrotum appears tender, swollen and ecchymotic, and the testis itself may be difficult to palpate. Ultrasound images show an irregular testicular outline, intra- and/or extra-testicular haematoma and heterogeneous testicular echotexture, with focal hyperechoic or hypoechoic areas in the testicular parenchyma corresponding to areas of haemorrhage or infarction [32].

In case of suspected testicular rupture, surgical exploration, with evacuation of haematoma, debridement of necrotic tissue and closure of the tunica albuginea, is indicated [31, 32].

### 13.4.2 Penetrating Scrotal Trauma

Penetrating trauma is usually due to gunshot wounds and less commonly to stab wounds, animal attacks and self-mutilation.

Testicular fractures and ruptures from penetrating injury are managed in the same way as are fractures and ruptures from blunt injury, with conservative debridement of non-viable tissue. Depending on the extent of the injury, primary reconstruction of the testis and scrotum can usually be performed. In patients with spermatic cord injury and complete vascular transection, immediate surgical exploration is mandatory with microvascular reanastomosis when possible.

When conservative surgical treatment is not possible, orchiectomy is indicated [27, 31, 32].

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## 13.5 Testicular Cancer

### 13.5.1 Introduction

Testicular cancer accounts for about 5 % of all urological tumours, with an estimated incidence of 3–10 new cases occurring per 100,000 males/per year in Western countries [33].

The recent widespread use of high-frequency ultrasonography (US) has led to an increasing number of incidentally detected small testicular masses [34] (STMs), defined as non-palpable and less than 25 mm in diameter, and intrascrotal masses,

**Table 13.1** Pathologic classification of testicular tumours

Germ cell tumours	Sex cord/gonadal stromal tumours	Miscellaneous nonspecific stromal tumours
Intratubular germ cell neoplasia	Leydig cell tumour	Ovarian epithelial tumour
Seminoma	Malignant Leydig cell tumour	Tumour of the collecting duct and rete testis
Spermatocytic seminoma	Sertoli cell tumour	Benign tumour of nonspecific stroma
Embryonal carcinoma	Malignant Sertoli cell tumour	Malignant tumour of nonspecific stroma
Yolk sac tumour	Granulosa	
Choriocarcinoma	Thecoma/fibroma group	
Teratoma	Incompletely differentiated or mixed sex cord tumours	
Tumours with more than one histologic type	Gonadoblastoma	

and more than 70 % of patients are diagnosed with stage I disease [35]; the early diagnosis and the good response to extreme chemo- and radiotherapy give an excellent cure rate to all the typology of testicular tumours [33].

Testicular tumours can be classified into three categories: germ cell tumours (90–95 %), cord stromal tumours and miscellaneous tumours (Table 13.1) [36].

### 13.5.2 Diagnosis of Testicular Cancer

Preoperative diagnosis of testicular cancer is based on identification of testicular nodules with the straight palpation of the testis and the exploration of inguinal lymph nodes that could be enlarged. The second step is *ultrasound (US) of both testes* and additional US of the retroperitoneum to screen for extensive retroperitoneal metastasis.

*Serum tumour markers*, both before and 5–7 days after orchiectomy (AFP and hCG) and LDH, should be always assessed [37]. A total body CT scan should be always carried out for detection of metastasis and retroperitoneal, mediastinal and supraclavicular nodes assessment.

The final diagnosis of testicular tumours is completed with the pathologic examination of the mass after inguinal exploration and orchiectomy with en bloc excision of the testis, tunica albuginea and spermatic cord. Organ-sparing surgery can be performed in some cases such as bilateral tumour [38] or solitary testes or incidental detection of STMs with intraoperative frozen section examination (FSE) of the mass [39].

## 13.6 Testicular Cancer's Staging System TNM (Table 13.2) [37]

### 13.6.1 Guidelines for the Treatment of Testicular Cancer

#### 13.6.1.1 Seminoma Stage I

The most recommended management option is surveillance, due to the low risk of recurrence rate (<6 %) [37]; radiotherapy is not recommended as adjuvant therapy. one cycle of carboplatin-based chemotherapy can be used as alternative to surveillance [40].

**Table 13.2** Testicular Cancer's Staging System TNM [37]

pT	<i>Primary tumour<sup>a</sup></i>
pTX	Primary tumour cannot be assessed
pT0	No evidence of primary tumour (eg, histologic scar in testis)
pTis	Intratubular germ cell neoplasia (testicular intraepithelial neoplasia)
pT1	Tumour limited to testis and epididymis without vascular/lymphatic invasion: tumour may invade tunica albuginea but not tunica vaginalis
pT2	Tumour limited to testis and epididymis with vascular/lymphatic invasion or tumour extending through tunica albuginea with involvement of tunica vaginalis
pT3	Tumour invades spermatic cord with or without vascular/lymphatic invasion
pT4	Tumour invades scrotum with or without vascular/lymphatic invasion
<i>N – Regional lymph nodes clinical</i>	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass $\leq 2$ cm in greatest dimension or multiple lymph nodes; none $> 2$ cm in greatest dimension
N2	Metastasis with a lymph node mass $> 2$ cm but $\leq 5$ cm in greatest dimension or multiple lymph nodes; any one mass $> 2$ cm but $\leq 5$ cm in greatest dimension
N3	Metastasis with a lymph node mass $> 5$ cm in greatest dimension
<i>pN – Pathologic regional lymph nodes</i>	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass $\leq 2$ cm in greatest dimension and $\leq 5$ positive nodes; none $> 2$ cm in greatest dimension
pN2	Metastasis with a lymph node mass $> 2$ cm but $< 5$ cm in greatest dimension; or $> 5$ nodes positive, none $> 5$ cm; or evidence of extranodal extension of tumour
pN3	Metastasis with a lymph node mass $> 5$ cm in greatest dimension

(continued)

**Table 13.2** (continued)

<i>M – Distant metastasis</i>			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
M1a	Nonregional lymph node(s) or lung		
M1b	Other sites		
<i>pM – Pathologic distant metastasis</i>			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
M1a	Nonregional lymph node(s) or lung		
M1b	Other sites		
<i>S – Serum tumour markers</i>			
Sx	Serum markers studies not available or not performed		
S0	Serum marker study levels within normal limits		
	<i>LDH, U/l</i>	<i>hCG, mIU/ml</i>	<i>AFP, ng/ml</i>
S1	<1.5×N and	<5,000 and	<1,000
S2	1.5–10×N or	5,000–50,000 or	1,000–10,000
S3	>10×N or	>50,000 or	>10,000

*LDH* lactate dehydrogenase, *N* upper limit of normal for the LDH assay, *hCG* human gonadotrophin, *AFP*  $\alpha$ -fetoprotein

<sup>a</sup>Except for pTis and pT4, where radical orchidectomy is not always necessary for classification purposes, the extent of the primary tumour is classified after radical orchidectomy; see pT. In other circumstances, TX is used if no radical orchidectomy has been performed

### 13.6.1.2 Non-seminomatous Germ Cell Tumour (NSGCT) Stage I

In this case the treatments depend on vascular invasion: in case of no vascular invasion (low risk of recurrence/metastasis), a long-term surveillance (at least 5 years) close follow-up is the recommended option [41]; an alternative adjuvant chemotherapy or nerve-sparing retroperitoneal lymph node dissection (RPLND) can be proposed; if RPLND shows nodal involvement, two courses of PEB (cisplatin, etoposide, bleomycin) chemotherapy are the best option.

In case of vascular invasion (pT2–pT4), the high risk of metastasis indicates chemotherapy with two courses of PEB [42] or an alternative surveillance or nerve-sparing RPLND [43] in patients not willing to undergo adjuvant chemotherapy.

If pathologic stage II is revealed at RPLND, further chemotherapy should be considered.

### 13.6.1.3 Metastatic Germ Cell Tumours GR

In case of low-volume NSGCT stage IIA/B with elevated markers, it should be treated with three or four cycles of PE; in case of tumours without marker elevation,



chemotherapy can be performed after histologic analysis with RPLND or biopsy 6 weeks after orchiectomy [44].

In case of NSGCT > stage IIC, three or four courses of PEB are the primary treatment of choice according to prognosis grade [44].

If serum levels of tumour markers are normal or normalizing, surgical resection of residual masses after chemotherapy in NSGCT is indicated.

Seminoma IIA/B can be treated with radiotherapy; chemotherapy can be used as a salvage treatment with the same schedule as for the corresponding prognostic groups of NSGCT.

In seminoma stage CS IIB, chemotherapy (4 × EP or 3 × PEB, in good prognosis) is an alternative to radiotherapy.

Seminoma stage ≥ IIC should be treated with primary chemotherapy according to the same principles used for NSGCT [45].

### 13.6.2 Testicular Stromal Tumours

Testicular stromal tumours are rare (<10 % of all testicular tumours); among a wide array of benign and malignant lesions, Leydig cell tumours and Sertoli cell tumours are the most common [46].

### 13.6.3 Leydig Cell Tumours

Leydig cell tumours represent 1–3 % of adult testicular tumours and 3 % in childhood [46, 47]. Only 7–10 % of them are malignant; no malignant tumours have occurred in the pre-pubertal population [47].

The clinical presentation usually is characterized by a painless enlarged testis but very often the diagnosis is incidental in course of testicular US; it is very often accompanied by hormonal disorders (80 % of cases) [48]. Nowadays, the good outcome of Leydig cell tumours treated by partial orchiectomy is widely demonstrated [47–49, 50], but the diagnosis of Leydig cell tumours is possible only often pathologic analysis, for this reason intraoperative FSE is mandatory [47]. In case of malignancy, orchiectomy and RPLND are the best options [46].

### 13.6.4 Sertoli Cell Tumours

They are rarer than Leydig cell tumours, accounting for 1 % of all testis tumours; malignancy is found in 10 % of cases. Clinical presentation is similar to Leydig cell tumours, such as frequency of incidental diagnosis [46].

Even in this case organ-sparing surgery with intraoperative FSE is a good option of treatment, but in case of histologic signs of malignancy, orchiectomy and RPLND are the treatment of choice [49].

### 13.6.5 Conclusions

The most common testis tumours derive from germ cells; nowadays the development of diagnostic allows their detection in an early stage.

The treatment of choice is orchietomy with excellent cure rates when it is performed in early stages.

In advanced stages a multidisciplinary therapeutic approach offers an acceptable survival rate. Follow-up schedules are mandatory to initial staging and treatment.

Testicular stromal tumours are rare and usually benign; they can be treated by organ-sparing surgery associated with intraoperative FSE. In case of malignancy, orchietomy and RPLND are the treatment of choice.

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Giorgio D. Piubello

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## 14.1 Definition

This chapter encompasses all spermatogenesis-altering conditions affecting the normal male endocrine balance. Such conditions can be caused by either testicular abnormalities (or other endocrine gland or pituitary-hypothalamus disorders) or the effect of exogenous substances (endocrine disruptors).

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## 14.2 Epidemiology

Male infertility is caused by endocrine alterations in 18–30 % of cases [1].

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## 14.3 Etiopathogenesis

### 14.3.1 Hypogonadisms

The development, endocrine function, and reproductive function of the gonads are regulated by the hypothalamic-pituitary-gonadal axis. In the hypothalamus, specialized neurons release pulses of gonadotropin-releasing hormone (GnRH), which modulates the secretion of gonadotropins from the pituitary gland. In turn, the anterior pituitary gland produces luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which stimulate steroid secretion and germ cell production in the testes. A complex interaction of endogenous inputs, chronobiological signals, and exogenous stressors regulates the whole process.

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**Table 14.1** Classification of male hypogonadism

Secondary hypogonadism (hypogonadism hypogonadotropic)
Panhypopituitarism
Failure of the gonadotrophic function of the pituitary
Isolated LH deficiency
Isolated FSH deficiency
Altered LH biological activity
Altered FSH biological activity
Primary hypogonadism (hypogonadism hypergonadotropic)
Congenital or acquired anorchidism
Cryptorchidism
Mumps orchitis
Genetic and developmental conditions: Klinefelter syndrome, androgen receptor, LH receptor and enzyme defects
Sertoli cell only syndrome
Radiation treatment or chemotherapy
Testicular trauma
Testicular torsion

Male hypogonadism is defined as a clinical situation presenting a deficit in the testicular function. This defect can be a consequence of a disorder first originating in the testis (primitive or hypergonadotropic hypogonadism) or can be caused by insufficient stimulation of pituitary gonadotropins in the testis (hypogonadotropic hypogonadism). This condition can in turn be due to a defect in the pituitary (secondary hypogonadotropic hypogonadism) or an alteration in the secretion of hypothalamic GnRH (tertiary hypogonadotropic hypogonadism). The classification of male hypogonadism is reported in Table 14.1.

Late-onset hypogonadism, a condition in which androgens decline with advancing age, is instead imputable to the hypothalamus-pituitary and/or the testes.

Isolated deficiencies of FSH and LH also have been reported. Subjects with the rare isolated LH deficiency show eunuchoid body habitus, large testes, and small-volume ejaculates containing few spermatozoa. Plasma testosterone is low while FSH levels are normal.

Isolated FSH deficiency is also a rare condition that allows normal virilization and testosterone levels, albeit with low levels of FSH and oligospermia or azospermia. Its cause may be an FSH  $\beta$ -subunit deficiency, an idiopathic genetic defect, or excess inhibin-B (idiopathic or resulting from a granulosa cell tumor).

### 14.3.2 Testicular Steroidogenesis Congenital Disorders

Hormone biosynthesis is carried out in both the adrenal cortex and the gonads. Many steps of this process are common to both, while others are only possible in the adrenal cortex. A congenital deficit of an enzyme of one of the steps of steroidogenesis

produces a deficit in the hormones of the next step, and an increase in the hormones of preceding steps.

A series of complex syndromes are produced by the lack of certain hormones, which should have been synthesized, and by the increase of their precursors in circulation.

The most common condition is reduced virilization in the male embryo (male pseudohermaphroditism). There are eight known enzymatic defects able to affect testosterone synthesis, the most frequent of which is 21-hydroxylase deficit, which accounts for 95 % of such defects.

### 14.3.3 Androgen Resistance Syndromes

Androgen resistance syndromes are caused by alterations of the androgen receptor or the 5 $\alpha$ -reductase enzyme, which hinder the androgenic action. Virilization defects shown by affected individuals are highly variable and have been classified according to five phenotypic variants, ranging from complete testicular feminization syndrome to simple, and sometimes slight, virilization defects. Spermatogenesis is absent or reduced, but can be normal in rare cases.

### 14.3.4 Other Endocrine Diseases

#### 14.3.4.1 Hyperprolactinemia

A chronic prolactin excess interferes with gonadic function, reducing testosterone levels and causing oligospermia. The mechanisms by which hyperprolactinemia inhibit testicular function are not yet fully verified, even though experimental data indicate that it is likely the result of a combined action at the pituitary-hypothalamic level (by reducing the GnRH/gonadotropic secretion) and at the testicular level (by interfering with testosterone synthesis and secretion). Spermatogenesis alterations are probably secondary with respect to the testosterone deficit, while it is unknown whether prolactin is able to act negatively at a tubular level.

A routine check of prolactin levels in asymptomatic infertile men is not recommended. In fact, mild increases in prolactin are of doubtful significance, as they may be caused by medications or several other medical conditions. Prolactin-secreting tumors are rare, with prolactin levels beyond 50 ng/mL appearing in adenomas larger than 1 cm [2].

#### 14.3.4.2 Thyroid Disease

Male infertility is more frequent in thyroid diseases, particularly in hyperthyroidism [3, 4]. Nonetheless, most men with thyroid abnormalities are not infertile, either before or after treatment. Thyroid abnormalities, if present, often lead to oligospermia rather than azoospermia. The following mechanisms have been proposed: alterations in sex steroid metabolism, testicular and pituitary developmental abnormalities, changes in sex hormone binding globulin (SHBG), and increased

levels of estradiol. Severe congenital hypothyroidism may cause global developmental abnormalities of the hypothalamic-pituitary-gonadal axis.

#### **14.3.4.3 Growth Hormone Alterations**

There are few data confirming a role of growth hormone (GH) in endocrine dysfunction in fertility [5]. In fact it is difficult to identify a reliable method of measuring GH secretion patterns that may relate to fertility. However, acromegaly may inhibit spermatogenesis [6].

#### **14.3.4.4 Hyperestrogenism**

High levels of estrogens caused by peripheral aromatization in adipose tissue, mainly in obese subjects, can inhibit pituitary function [7] and, therefore, spermatogenesis.

#### **14.3.4.5 Cushing Syndrome**

In Cushing syndrome, the glucocorticoid excess not only can suppress LH function but may also have a direct contributing role in affecting spermatogenesis and maturation arrest [8].

#### **14.3.4.6 Diabetes Mellitus**

Infertility rates in individuals with diabetes are higher than average (16 and 19.1 %, respectively, for primary and secondary infertility) [9]. Excessive weight, and obesity in particular, seem to be the leading contributors to infertility.

Three main dysfunctional mechanisms may be postulated to explain the sperm damage observed in diabetic patients: endocrine disorders, diabetic neuropathy, and oxidative stress. In insulin-dependent diabetes:

1. Leydig cell function and testosterone production decrease because of the lack of stimulatory effect of insulin on these cells
2. An insulin-dependent decrease in FSH reduces LH levels
3. The FSH decrease also reduces sperm output and fertility

As a result, in diabetic patients serum testosterone is decreased and gonadotropin levels are increased. Moreover, a steroidogenetic defect in Leydig cells can be observed.

### **14.3.5 Endocrine Disruptors**

Endocrine manipulation in male infertility starts with ruling out possible endocrine disruptors [10].

Micropollutants in the environment, in particular steroid mimetics (in water supplies, food sources, etc.), may contribute to an overall decline in male fertility.

The increasing use of phytoestrogen has also been claimed to contribute. In fact, many dietary supplements contain significant levels of plant phytoestrogens that mimic testosterone and estrogen.



## 14.4 Diagnosis

Clinical history and physical examination are the cornerstones of the diagnosis: penis and testis volume, weight, height, and secondary sexual characteristics should be evaluated. The occurrence of headaches, visual disturbances, bitemporal visual field losses, cranial nerve palsies, and cerebrospinal fluid rhinorrhea should also be investigated.

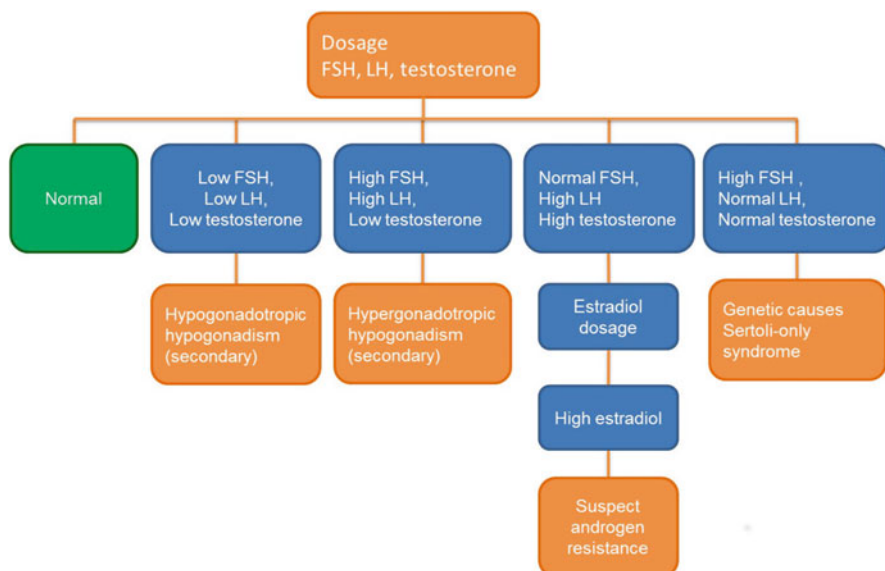
A small set of basal hormones (testosterone, LH, FSH, estradiol, SHBG, prolactin) is usually sufficient for diagnosis (Fig. 14.1) [11]. It should be remembered that FSH and LH are secreted in short pulses, and a single measurement may not be sufficient to clarify the diagnosis.

### 14.4.1 Dynamic Tests

Persistent borderline low hormonal values may be further evaluated with the GnRH stimulation test, the clomiphene stimulation test, and the human chorionic gonadotropin (hCG) stimulation test [12].

#### 14.4.1.1 GnRH Stimulation Test

This test is indicated in adult men with low testosterone levels and normal or low-to-normal gonadotropins. The patient receives GnRH 100  $\mu$ g intravenously. LH and FSH both are expected to rise, with a peak occurring between 15 and 60 min; LH increases threefold to sixfold while FSH increases about 20–50 % above the baseline.



**Fig. 14.1** Diagnostic flow chart of male hypogonadism

### 14.4.1.2 Clomiphene Stimulation Test

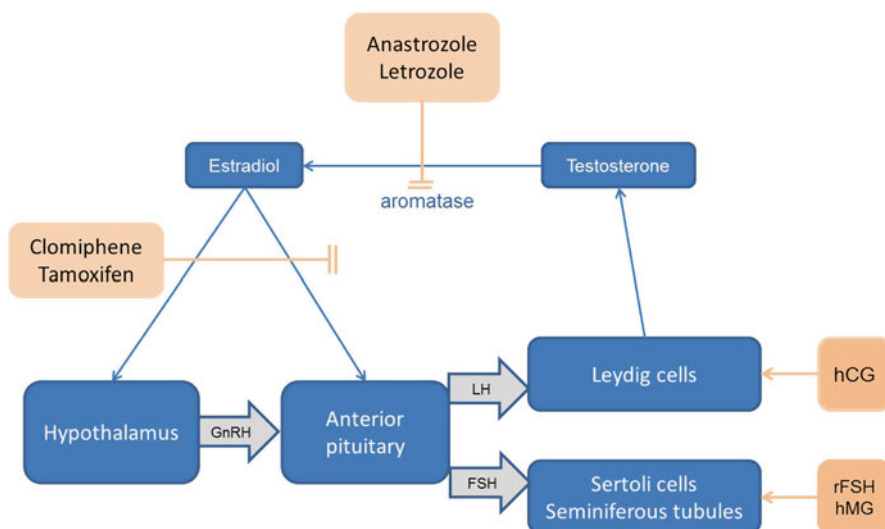
This test is indicated in suspected gonadotropin deficiencies. Clomiphene acts as an antiestrogen centrally and as a weak estrogen peripherally. The central antiestrogen effect, interrupting the negative feedback of estrogen on GnRH release, induces a rise in LH and FSH. The patient is treated for 5–7 days with 100 mg clomiphene citrate. A doubling of LH and a 20–50 % increase in FSH are considered normal.

### 14.4.1.3 Human Chorionic Gonadotropin Stimulation Test

The hCG stimulation test is indicated in adults, in the differential diagnosis of combined testicular and pituitary failure versus secondary hypogonadism. A single dose of hCG (5,000 IU intramuscularly) is administered, and testosterone values are measured at the baseline and every 24 h up to day 5. In adult hypogonadism the lack of an increase in testosterone after hCG suggests a lack of functioning testicular tissue. Conversely, a rise suggests an intact Leydig cell system. In gonadotropin deficiency with no primary testicular abnormality, the basal testosterone value should triple after hCG.

## 14.5 Therapy

Several sites can be influenced by selective drugs (Fig. 14.2).



**Fig. 14.2** Sites of action of drugs used for treating male hypogonadic infertility

### 14.5.1 Estrogen Receptor Modifiers

Both clomiphene and tamoxifen are selective estrogen receptor modifiers (SERMs); inhibiting estrogen receptor at the level of the pituitary, both FSH and LH levels increase. As a result testosterone increases, thus favoring sperm growth and maturation [13].

In hypogonadism and oligospermia, clomiphene is used as monotherapy [14]. Starting dose is 25 mg once daily; as clomiphene is normally available in 50-mg tablets, a starting dose might be 50 mg every other day. When testosterone remains low, clomiphene can be titrated up to 100 mg once daily.

Clomiphene has also been used on hypogonadic patients with azoospermia. Increases in testosterone in the testis may favor production of sufficient sperm in the ejaculate. Tamoxifen is used for the same indications [15], at a dosage of 10 mg once daily.

### 14.5.2 Aromatase Inhibitors

Anastrozole and letrozole are aromatase inhibitors, directly limiting estrogen feedback to the pituitary, thus increasing the production of FSH and LH [16]. Some men with severely defective sperm production have excessive aromatase activity, documented by low serum testosterone and relatively high estradiol levels. Aromatase inhibitors can increase endogenous testosterone production and serum testosterone levels. Treatment of infertile males with aromatase inhibitors has been associated with increased sperm production and return of sperm to the ejaculate in men with nonobstructive azoospermia.

Anastrozole (1 mg once daily) and letrozole (2.5 mg once daily) are used for impaired spermatogenesis, although this represents an off-label use.

Enclomiphene citrate [17] (an isomer of clomiphene) is in phase 3 trials for the treatment of hypogonadism infertility.

### 14.5.3 Gonadotropins

SERMs and aromatase inhibitors are effective and relatively inexpensive, and thus are used as first-line agents for the treatment of endocrine dysfunction in the hypogonadal infertile male.

However, in cases of severe hypogonadotropic hypogonadism, the LH homologue hCG is the gold standard for treatment [18]. hCG 2,000 IU subcutaneously, three times per week, is usually sufficient to achieve desired testosterone levels and induce spermatogenesis. Direct testosterone administration has proved to be ineffective [19, 20].

In congenital forms, a 6-month titration is often required to be followed by the use of recombinant FSH or an FSH analogue, human menopausal gonadotropin.

The usual dosage for both is 75 IU or 150 IU three times weekly, as the usual vial contains 75 IU. Even in acquired hypogonadotropic hypogonadism, however, combination hCG/FSH analogues may be more effective than hCG alone in stimulating spermatogenesis.

#### 14.5.4 Future Therapy

The new horizon of idiopathic male infertility treatment is personalized pharmacogenetic therapy.

Gene therapy is one of the frontiers of modern medicine. A viral vector can be used as a delivery device to reconstitute a key missing promoter sequence encoding a vital protein for cellular function. Unfortunately, little is known about the genetic loci involved in spermatogenesis. Moreover, it may be difficult to affect testis and/or spermatozoa with gene therapy without affecting the germline. The Sertoli cells, because of their special tolerogenic properties, may represent an ideal candidate for cell-based gene therapy.

Further possibilities are tissue grafting and spermatogonial stem cell transplantation.

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## 15.1 Introduction

There are surgical treatments and a number of chemotherapeutic agents and drugs commonly used in therapies that may cause male infertility [1]. When the dispermia is due to medical or surgical causes, it is called iatrogenic infertility [2]. While reviews of iatrogenic causes of infertility in Western Europe reveal that these contribute to approximately 5 % of infertility both in men and women, in Africa this rate is higher [3].

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## 15.2 Chemotherapeutic Drugs

The use of chemotherapeutic drugs in the treatment of cancer and in the management of autoimmune disease can interfere with fertility.

The *alkylating chemotherapy* agent group does the most damage to fertility. These drugs include cyclophosphamide (Cytosan), chlorambucil (Leukeran), busulfan (Myleran), procarbazine (Natulan, Matulane), nitrosoureas (Carmustine, Lomustine), nitrogen mustard (Mustargen), and L-phenylalanine mustard (Alkeran). In high doses, platinum-based chemotherapy agents (cisplatin, oxaliplatin) or drugs like bleomycin (Blenoxane), often used to treat testicular cancer, can also damage fertility.

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### 15.2.1 Cyclophosphamide

Cyclophosphamide is one of the most frequently prescribed chemotherapeutic drugs. It is an anticancer and immunosuppressive agent commonly used in men of reproductive age and, when used in high dose or in combination regimens, can cause severe germ cell damage [4]. The damage done to spermatogenesis by cyclophosphamide appears to be dose dependent. A daily dose of 3.7 mg/kg body weight will produce oligospermia or even azoospermia, and this change is frequently permanent. Cyclophosphamide can also interfere with Leydig cell function, resulting in a reduced secretion of testosterone, thus increasing problems relating to infertility [5].

### 15.2.2 Chlorambucil

This is an aromatic nitrogen mustard that also acts as an alkylating agent. It is used in the treatments of lymphomas as well as in the management of leukemia. It can interfere with spermatogenesis, and its use frequently leads to azoospermia. Recovery in terms of fertility is very variable.

In the management of various types of cancer, it is common to use several different anticancer drugs in combination so that the effect upon the cancer is maximal. All these combinations will always give unpredictable and very uncertain recovery rate in terms of infertility [5] (Table 15.1).

It is very important to suggest patients to cryopreserve their semen before any chemotherapeutic treatment to save potential future fertility, as spermatogenesis will only return to normal in no more than 50 % of patients treated [6]. Certain cancers can cause men to have poor sperm quality, even prior to treatment [7, 8]. It is estimated that about 40 % of men with Hodgkin's disease and 50 % of those with testicular cancer will have low sperm counts at the time of diagnosis [9, 10]. This does not mean that these men should not consider sperm banking, as advances in reproductive techniques have made even poor-quality specimens useful for reproduction [11, 12].

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## 15.3 Common Drugs That Can Cause Male Infertility

There are numerous drugs and medications that have been shown to have adverse effects on male fertility, acting through diverse mechanisms [2].

The mechanisms of impaired fertility include direct effects on germ cells or their supporting cells, on the delicately balanced HPG axis, on erectile or ejaculatory function, and on libido.

In a thorough fertility evaluation of the male partner, the physician should determine what medication the patient is taking and his social habits involving alcohol consumption, tobacco, and recreational drug use. Simply discontinuing the offending agents can reverse most adverse effects from drugs and medications.

**Table 15.1** List of the drugs that can cause male infertility

Chemotherapy (dose to cause effect)	Known effect on sperm count
Chlorambucil (1.4 g/m <sup>2</sup> )	Prolonged or permanent azoospermia
Cyclophosphamide (19 g/m <sup>2</sup> )	
Procarbazine (4 g/m <sup>2</sup> )	
Melphalan (140 mg/m <sup>2</sup> )	
Cisplatin (500 mg/m <sup>2</sup> )	
BCNU (1 g/m <sup>2</sup> )	Azoospermia in adulthood if treated before puberty
CCNU (500 mg/m <sup>2</sup> )	
Busulfan (600 mg/m <sup>2</sup> )	Azoospermia likely, and they are often given with other highly sterilizing agents, adding to the effect
Ifosfamide (42 g/m <sup>2</sup> )	
BCNU (300 mg/m <sup>2</sup> )	
Nitrogen mustard	
Actinomycin D	
Doxorubicin (770 mg/m <sup>2</sup> )	When used alone, cause only temporary reductions in sperm count. In conjunction with above agents, may be additive in causing azoospermia
Thiotepa (400 mg/m <sup>2</sup> )	
Cytarabine (1 g/m <sup>2</sup> )	
Vinblastine (50 g/m <sup>2</sup> )	
Vincristine (8 g/m <sup>2</sup> )	
Amsacrine	When used in conventional regimens, cause only temporary reductions in sperm count. In conjunction with above agents, may be additive in causing azoospermia
Bleomycin	
Dacarbazine	
Daunorubicin	
Epirubicin	
Etoposide	
Fludarabine	
Fluorouracil	
6-mercaptopurine	
Methotrexate	
Mitoxantrone	
Thioguanine	

Adapted from Devita et al. [5]

### 15.3.1 Nitrofurantoin

Nitrofurantoin has been shown to reduce the sperm count in animals and humans. This suppression is short and never permanent after the cessation of treatment.

### 15.3.2 Cimetidine

Cimetidine is an H<sub>2</sub> inhibitor commonly used in the treatment of dyspepsia. It binds to the androgen receptors interfering with sperm production. Its action is short lived and reversible [2].



### 15.3.3 Sulfasalazine (Salazopyrin)

This drug is still widely used for the therapy of various different inflammatory bowel disorders, especially for ulcerative colitis. It causes a reduction of concentration and motility of the sperms and also alters the shape of sperm head. Upon cessation of therapy, the sperm count and motility will returns to normal [2].

### 15.3.4 Sex Steroids

Estrogens and testosterone will reduce gonadotropin secretion, and thus, therapy with testosterone will rapidly lead to azoospermia.

### 15.3.5 Gonadotropin-Releasing Hormone Analogs and Antiandrogens

These drugs, especially in the depot form, are frequently used in the treatment of hormone-dependent prostate cancer. These drugs quickly lead to azoospermia. Antiandrogens block the action of testosterone and can cause erectile failure. As prostate cancer is becoming more common and occurring in younger men, these aspects must be seriously considered [13–15].

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## 15.4 Radiation Therapy

After World War II, with the use of atomic energy and the following incidental irradiation of men, it became clear that sperm production could be reduced to zero due to the effects of irradiation. In 1964, McLeod reported that the accidental exposure of men to radiation after an accident at the Oakridge Nuclear Plant caused azoospermia in more than half of them [16]. Radiation has its most potent effect upon spermatogonia, the type B spermatogonia being the most sensitive.

Radiation therapy can slow down or stop sperm cell production if the testicle is in or near the target area for the radiation. A lead shield can help protect the testicles, but radiation “scatters” within the body, so it is impossible to shield the testicles completely.

The likelihood of infertility after radiation depends on the dose to the testes, shielding, and fractionation (single dose vs. multiple doses). Doses as small as 0.1 Gy can result in decreased sperm counts, and doses of 1.5–4 Gy can result in permanent sterility. As previously noted, the Leydig cells (responsible for testosterone production) are less sensitive to the effects of radiation, with damage occurring at 30 Gy in mature males (20 Gy in prepubescent males).

If the testicles are not the primary radiation targets, shielding can be used. This technique protects the testicle(s) from receiving radiation. Fractionation is the technique of dividing the total dose of radiation into multiple smaller doses. For most side effects, fractionation is used to lessen their severity, but in this case

fractionation (multiple smaller doses) causes more damage to sperm than a larger, single radiation dose.

Total body irradiation (TBI) is a technique used for preparation for stem cell and bone marrow transplants. As the name implies, it is irradiation of the entire body. It is estimated that 80 % of men who undergo TBI will have permanent azoospermia.

For those without permanent azoospermia, sperm counts are at their lowest 4–6 months after treatment. Counts typically return to their pretreatment levels 10–24 months after treatment but can take longer in those who received higher doses.

Radiation damage to the part of the brain that controls hormone production can sometimes interfere with the hormone messages that control sperm production [6].

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## 15.5 Surgery

If the cancer surgery requires the removal of both testes, fertility is affected because of the inability to produce sperm [17, 18].

Surgery on the prostate, bladder, urethra, or colon can result in a condition called retrograde ejaculation.

In normal ejaculation, the semen is propelled through the urethra and the opening to the bladder closes off, allowing the semen to exit the penis. In retrograde ejaculation, the opening to the bladder does not close, allowing the semen to enter the bladder instead of exiting the penis. While this condition is not medically harmful, it does impair fertility [19].

Men with testicular cancer or colon cancer sometimes have surgery that can damage nerves involved in orgasm. The result may be a “dry orgasm,” or the sensation of pleasure but without ejaculating any semen. Following a successful nerve-sparing radical prostatectomy, most men will have return of erections but will not be able to have children by natural means [20].

There should be no seminal fluid after the prostatectomy, so they will be “infertile” by natural means, but with in vitro fertilization techniques, it is still possible for a man to father a child after a radical prostatectomy. In this case intracytoplasmic sperm injection (ICSI) of single spermatozoon surgically recovered from the testis could lead to a pregnancy [21–23].

*Video: Sperm recovery after testicular sperm extraction (TESE)*<https://www.youtube.com/watch?v=45W5XkzHy7w>

Testicular cancer is associated with impaired spermatogenic function, even before orchiectomy, with a degree of dysfunction higher than that caused by local tumor effect [7].

Oligospermia is observed in more than 60 % of patients at the time of diagnosis of testicular cancer [8].

Storing sperm in a sperm bank before the operation is a recommended procedure for those men hoping to father children after the operation [24].

Last but not least, the vas deferens or the testicular blood supply may be injured or ligated at the time of inguinal surgery, hernia repair, hydrocelectomy, or varicocelectomy [25–27].

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Infertility is a major health problem affecting 15 % of couples in the reproductive age group. The male partner is contributory in up to 50 % cases and the cause of male infertility remains unknown in 25 % of men [1]. These men with idiopathic infertility are usually treated with a number of empirical therapies. The basis of the treatment is the fact that these products appear rational because of their mode of action or because of uncontrolled human studies [2]. Many over-the-counter (OTC) therapies have been historically used for male fertility, including herbs, vitamins, and nutritional supplements [3]. Many studies demonstrate the positive effects of OTC supplementation on semen parameters and pregnancy outcomes. Conversely, many studies also demonstrate a lack of improvement and potential complications with supplementation. Current and historical OTC medication studies suffer from a variety of drawbacks, including small short-duration studies, failure to perform randomized double-blinded placebo-controlled studies, and lack of standardization of dose and efficacy [4]. Definitive conclusions as to their true effects on male subfertility and dosing regimen could not be identified.

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## 16.1 Antioxidants

Oxidative stress has been a well-studied aetiology of abnormal semen parameters [5–7]. Because of this, many of the current OTC therapies rely on antioxidant properties. Seminal oxidative stress (OS) results from an imbalance between reactive oxygen species (ROS) production and ROS scavenging by seminal antioxidants. Seminal OS is believed to be one of the main factors in the pathogenesis of sperm

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dysfunction and sperm DNA damage in male infertility [8–11]. It is estimated that 25 % of infertile men possess high levels of seminal ROS, whereas fertile men do not have high levels of seminal ROS [12, 13]. Spermatozoa are particularly susceptible to oxidative injury due to the abundance of plasma membrane polyunsaturated fatty acids [14–16]. Seminal oxidative stress has been related to infection, industrial exposure, tobacco use, and elevated temperature [7]. The two main sources for antioxidants are physiologic and dietary. Physiologic antioxidants are present within seminal plasma and the spermatozoa themselves [5]. If the high seminal ROS levels are due to a decreased ROS scavenging capacity of semen, it would support the use of dietary antioxidant supplementation [17]. A higher intake of antioxidants can potentially improve semen quality as well as sperm DNA integrity [18]. In contrast, poor semen quality may be associated with a lower intake and resultant lower concentration of antioxidants within the body [19]. The practice of prescribing oral antioxidant is supported by the lack of serious side effects related to antioxidant therapy, although few studies have carefully evaluated the risk of overtreatment with antioxidants [20]. Despite a large body of literature, it is not possible to establish firm conclusions regarding the optimal antioxidant treatment for infertile men because the published studies report on different types and doses of antioxidants, the studies are small, the end points vary, and few of the studies are placebo controlled [8, 13]. The most commonly studied oral antioxidants (or antioxidant enzyme cofactors) include vitamin E, vitamin C, carnitines, lycopene, glutathione, selenium, omega-3 and omega-6 fatty acids, zinc, arginine, and coenzyme-Q10.

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## 16.2 Vitamin E

Vitamin E is a fat-soluble vitamin within the tocopherol family. It is a major lipophilic chain-breaking antioxidant known to inhibit free-radical-induced damage to cell membranes, protect tissue polyunsaturated fatty acids against peroxidation, and improve the activity of other antioxidants [21, 22]. Its antioxidant activity is similar to that of glutathione peroxidase. Therond et al. found that vitamin E is present in widely varying concentrations in human spermatozoa and semen plasma with the percent of motile spermatozoa significantly related to sperm  $\alpha$ -tocopherol content [23]. Infertile men may have lower vitamin E in serum and seminal plasma [24]. Vitamin E is also effective in decreasing seminal ROS in infertile males [25, 26]. Substantial literature supports improvements in sperm motility, seminal ROS, and DNA fragmentation rates with vitamin E supplementation. Six RCTs evaluated the effects of vitamin E alone or in combination with vitamin C or selenium. Two of these studies reported a significant improvement in sperm motility [27, 28] and one reported a significant improvement in sperm DNA integrity [29] in the treatment arm only. In a randomized study of 54 infertile men, 28 were supplemented daily with 400 mg of vitamin E and 225 mcg selenium for 3 months, while the remaining 26 received 4–5 gm vitamin B daily for the same duration [28]. In contrast, three RCTs reported no significant improvement in sperm parameters after vitamin E  $\pm$  C treatment [25, 30, 31]. Rolf et al. performed a placebo-controlled, double-blind

study of high-dose oral vitamins C and E for 56 days in 31 infertile men with asthenozoospermia and a normal or only moderately decreased sperm concentration. Of the patients 15 received 1,000 mg vitamin C and 800 mg vitamin E, while 16 received placebo capsules. No changes occurred in semen parameters and no pregnancies were initiated.

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### 16.3 Vitamin C

Vitamin C is a water-soluble vitamin that is an important cofactor for hydroxylation and amidation reactions. Vitamin C also functions as an important antioxidant and assists in recycling oxidized vitamin E [7]. It is highly concentrated within seminal plasma [32]. Vitamin C has been associated with various improvements in semen quality, although most studies have involved concurrent use of other vitamins and antioxidants. One RCT evaluated the effects of vitamin C alone and reported a significant improvement in sperm parameters in the treatment arm only [33]. Daily vitamin C supplementation with doses greater than 200 mg (up to 1,000 mg) was found to improve ( $P < .05$ ) sperm count, motility, and viability in heavy smokers. A direct correlation was found between serum and seminal vitamin C concentrations and improvements in sperm quality, with those receiving 1,000 mg daily having the most improvements. These included improvements ( $P < .05$ ) in count and viability of 34 %, motility of 5 %, and morphology of 33 % compared with baseline. Vitamin C plays an important role in protecting sperm and sperm DNA against oxidative damage by neutralizing ROS in a concentration-dependent manner [29]. Adequate vitamin C intake has also been shown to increase seminal vitamin C concentrations and reduce sperm DNA fragmentation [19, 34]. Greco demonstrated a reduction in DNA damage by 13 ( $P < .001$ ) after treatment, as measured by terminal deoxyribonucleotidyl transferase–mediated dUTP nick-end labelling (TUNEL) assay [29]. Vitamin C is available in many fruits and vegetables [35]. The RDA is 90 mg to maintain body stores [36]. Side effects, occurring above the daily upper limit of 2,000 mg, include dyspepsia, headache, and increased risk of nephrolithiasis [35].

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### 16.4 Carnitines

Carnitines are quaternary amines synthesized from the amino acids lysine and methionine. They are responsible for transporting long-chain fatty acids into the mitochondria for intracellular metabolism through  $\beta$ -oxidation. Carnitines assist sperm metabolism as an energy source for spermatozoa and affect motility and sperm maturation [37]. They have been proposed to have a role in sperm maturation during transit through the epididymis. They are also antioxidants protecting against ROS [38]. The two main forms of importance are *L*-carnitine (LC) and *L*-acetylcarnitine (LAC). Both are concentrated in the epididymis, spermatozoa, and seminal plasma [39]. Multiple randomized controlled studies supplementing

with carnitine therapy for idiopathic infertility demonstrate improvements in concentration, motility, and morphology. Four RCTs evaluated the effects of *L*-carnitine alone or in combination with *L*-acetylcarnitine and three of the four reported a significant improvement in sperm parameters in the treatment arm only [40–43]. Lenzi et al. demonstrated significant improvements of total motile sperm count in the carnitine treatment arm, with an increase of 19 million ( $P = .042$ ). The treatment group had a 13 % pregnancy rate compared with no pregnancies in the placebo group ( $P > .05$ ) [44]. Balercia also demonstrated significant improvements with a 20–41 % increase in motility and a 13 % increase in morphology with LC or LAC supplementation or both for 24 weeks compared with placebo ( $P < .05$ ) [40]. Nine pregnancies occurred in the treatment arms and three in the placebo arm ( $P > .05$ ). Cavallini studied the effects of a combination of carnitine and cinnocicam (nonsteroidal anti-inflammatory drug [NSAID]) therapy on sperm function [41]. Patients with no varicocele or small- or moderate-grade varicoceles treated with carnitine, alone or in combination with NSAID therapy, had significant improvements, with sperm concentration increases of 6–25 million/mL, motility increases of 2–22 %, and morphology increases of 8–23 % compared with placebo groups ( $P$  value not reported). Conversely, carnitine therapy has also been found to have non-significant effects on semen parameters by some investigators. Sigman et al. [43] performed a small randomized, double-blinded, placebo-controlled study on 21 patients. Patients were treated with carnitine therapy (2 g of LC and 1 g of LAC) or placebo daily for 24 weeks. At the end of the treatment period, there appeared to be a nonsignificant trend toward improvement in motility, with a 5.3 % increase in the treatment group compared with a 9.3 % increase in the placebo group ( $P > .05$ ).

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## 16.5 Lycopene

Lycopene is a powerful non-provitamin A carotenoid antioxidant that quenches singlet oxygen and scavenges peroxy radicals. Its multiple roles include protection of lipid peroxidation, gap junction communication, cell growth regulation, gene expression modulation, and immune responses [45]. Palan and Naz measured seminal lycopene by high-pressure liquid chromatography in 37 men and noted significantly lower lycopene in the seminal plasma of immuno-infertile men than in fertile men [46]. Increased dietary intake or supplementation has been demonstrated to have positive effects on semen parameters [19]. Gupta and Kumar treated 30 infertile men with 4 mg lycopene for 3 months and found a significant improvement in sperm counts and motility with no significant changes in morphology. A 20 % pregnancy rate was seen during the course of the study [47].

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## 16.6 Glutathione

Glutathione is the most abundant nonprotein thiol in mammalian cells. Glutathione reductases are selenoproteins. Glutathione is an endogenous antioxidant produced in the liver and is one of the most abundant antioxidants found in the body. It is a



molecule synthesized from cysteine, glutamic acid, and glycine that plays an important role in maintaining exogenous antioxidants (i.e., vitamins C and E) in their active (reduced) roles [48]. The selenoprotein phospholipid hydroperoxide glutathione peroxidase occurs in the active form in spermatids. It reduces phospholipid hydroperoxide and scavenges hydrogen peroxide in human spermatozoa. Decreased phospholipid hydroperoxide glutathione peroxidase expression has been found in the spermatozoa of infertile men. Raijmakers et al. evaluated 25 men and found that fertile men had significantly higher glutathione in seminal fluid than subfertile men [49]. Significant associations of glutathione with sperm motility and sperm morphology were also observed. Ochsendorf et al. found that glutathione in the spermatozoa of patients with oligozoospermia was significantly lower than in controls [50]. Lenzi et al. [51, 52] have demonstrated improved sperm motility in infertile men with glutathione supplementation in multiple studies. They also treated men with varicoceles with intramuscular glutathione, noting a 10 % increase over baseline in total sperm motility with therapy ( $P < .01$ ) [53]. Glutathione supplementation has been associated with improved sperm concentration and decreased sperm DNA fragmentation in a nonrandomized study using a combination of glutathione, vitamin C, and vitamin E [54]. Dietary sources of glutathione include fresh meat products, fruits, and vegetables [55].

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## 16.7 Selenium

In human beings, the nutritional functions of selenium are achieved by 25 selenoproteins that have selenocysteine at their active centre [56]. In men, selenoprotein GPx4 is found in the mitochondria that make up the midpiece sheath of the sperm tail. In the early phase of spermatogenesis, GPx4, as a peroxidase, protects spermatozoa by its antioxidant function, whereas in the later phase, it forms cross-links with midpiece proteins to become a structural component of the mitochondrial sheath surrounding the flagellum, which is essential for sperm motility [57]. The selenium intake required for optimal activity and concentration of GPx4 and selenoprotein P is around 75 mcg per day. Supplementation might not be necessary if adequate daily intake is obtained through a diverse diet [58]. Selenium has been associated with positive effects on male infertility, which appear synergistic when used with other OTC supplements. Optimal dosing appears to be between 100 and 210 µg on the basis of the studies. In a randomized trial, selenium supplementation (100 mcg per day) of subfertile men with low selenium intake significantly increased sperm motility and enabled 11 % of the men to achieve paternity, compared with none in the placebo group [56]. However, high selenium intake (about 300 mcg per day) was shown to decrease sperm motility [59]. Selenium in combination with other antioxidants has been noted to improve sperm count, motility, and morphology [60]. Selenium deficiency has been found to decrease sperm motility, affect spermatozoa midpiece stability, and result in abnormal sperm morphology [61]. Multiple studies have demonstrated selenium's synergistic effects with other OTC supplements on sperm motility. In one prospective randomized study, infertile men with OAT receiving a 3-month course of selenium (210 µg) and vitamin E (400 mg)

had a significant increase in sperm motility of 8 % ( $P < .05$ ) and a decrease in lipid peroxidation levels, measured by an 8 % decrease in the malondialdehyde (MDA) level ( $P < .05$ ) [28]. Three RCTs evaluated the effects of selenium alone or in combination with *N*-acetyl cysteine and two of the three studies reported a significant improvement in sperm parameters in the treatment arm only [60, 62, 63]. Contrary to the previous studies, one noncontrolled study treating 33 men with idiopathic infertility with 200 µg of selenium daily for 12 weeks noted no improvements in concentration, morphology, and motility despite increases in serum and seminal selenium levels [64].

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## 16.8 Omega-3 and Omega-6 Fatty Acids

The significant effects of dietary fatty acids (FAs) on male fertility have been well documented both in animal and human studies [65, 66]. Polyunsaturated fatty acids (PUFAs) are essential FAs, because they cannot be synthesized by the human body. Docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and  $\alpha$ -linolenic acid are the main omega-3 PUFAs. Linoleic acid,  $\gamma$ -linolenic acid, and arachidonic acid (AA) are the main omega-6 PUFAs. The first mechanism by which omega-3 and omega-6 PUFAs affect spermatogenesis is by the incorporation into the spermatozoa cell membrane [67]. Omega-3 and omega-6 PUFAs are structural components of cell membranes [68]. The lipid bilayer of cellular membranes is maintained by the presence of these PUFAs [69]. The successful fertilization of spermatozoa depends on the lipids of the spermatozoa membrane [70]. Increased omega-6/omega-3 ratio in spermatozoa has also been implicated in impaired semen quality in oligozoospermic and/or asthenozoospermic men [71]. Safarinejad et al. [72] investigated PUFA composition of the blood plasma and spermatozoa in men with idiopathic OAT. They found that fertile men had higher blood and spermatozoa levels of omega-3 PUFAs compared with the infertile counterparts. Attaman et al. [73] evaluated the relation between dietary fats and semen quality in 99 men. They concluded that higher intake of omega-3 PUFAs was positively correlated with sperm morphology.

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## 16.9 Zinc

Zinc has roles in testicular steroidogenesis, testicular development, spermatozoa oxygen consumption, nuclear chromatin condensation, the acrosome reaction, acrosin activity, sperm chromatin stabilization, and conversion of testosterone to 5 $\alpha$ -dihydrotestosterone [74]. The male genitourinary tract has a high concentration of zinc, especially in the prostate. Chronic mild zinc deficiency is associated with oligospermia, decreased serum testosterone levels, and compromised immune system function [75]. Five RCTs evaluated the effects of zinc alone or in combination with folic acid and all five reported a significant improvement in sperm parameters in the treatment arm only [60, 76–81]. Young studied the association of folate, zinc,

and antioxidant intake with sperm aneuploidy in 89 healthy nonsmoking men through a dietary and supplement questionnaire and sperm FISH studies [18]. In a controlled study 45 infertile men with asthenozoospermia were treated with three different regimens of zinc—200 mg orally twice daily with or without vitamin C, vitamin E for 3 months, and both regimens—compared with controls [78]. Zinc therapy with or without additional vitamins was associated with increases in sperm motility of at least 24 % ( $P < .001$ ).

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## 16.10 Arginine

Arginine is a biologic precursor of nitric oxide. In the male reproductive system, arginine is a biochemical precursor for synthesizing spermidine and spermine and is thought to be essential for sperm motility [82]. Multiple studies have evaluated arginine's effect on semen. Some studies have reported that supplementation up to 4 g/day improves sperm concentration and motility [83, 84], whereas others have failed to demonstrate improvement in semen parameters or pregnancy rates [85, 86].

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## 16.11 Coenzyme Q-10

Coenzyme Q-10 (CoQ10) plays a key role in transporting electrons in the mitochondrial respiratory chain [87]. It stabilizes and protects the cell membrane from oxidative stress [88]. CoQ10 levels are measurable within seminal fluid and can be directly correlated with sperm count and motility [89]. In a placebo-controlled, double-blinded, randomized controlled study, Balercia et al. [90] treated men with idiopathic subfertility with decreased motility (<50 %) with CoQ10. There was a 6 % absolute motility improvement in the treatment group after 6 months of treatment compared with the placebo group ( $P < .0001$ ) although no difference in pregnancy rates. In a placebo-controlled study, Safarinejad [91] demonstrated absolute increases in total sperm count of 9.8 %, motility of 4.5 %, and morphology of 1.8 % over baseline with CoQ10 therapy when compared with placebo ( $P = .01$ ).

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## 16.12 Phytotherapy

Herbal therapy is increasingly popular worldwide as a way to treat infertility. In the United States, 17 % constantly visited herbal therapies in the past 18 months out of the 29 % of infertile couples who use complementary and alternative medicine [92]. Ginseng is one of the most popular herbs used in the phytotherapy of male infertility. Both oligoasthenospermic patients and age-matched healthy counterpart showed an increase in spermatozoa density and motility after the use of *Panax ginseng* [93]. Asthenospermic patients treated with ginseng also showed a significant increase in progressive sperm motility [94]. In the last few years Maca, a perennial plant of the *Lepidium meyenii* species, has been extensively studied for

its pharmacological properties on human spermatogenesis. An open-label study conducted by administering daily 1,500–3,000 mg of Maca for 4 months resulted in increased seminal volume, sperm count, and sperm motility [95]. A strong natural lipophilic antioxidant, astaxanthin, has been studied in a prospective, double-blind, randomized trial, designed to evaluate the effect of 16 mg/day astaxanthin compared to placebo in 30 infertile men. At the end of the study, ROS and inhibin B decreased significantly and sperm linear velocity increased in the treated group. The total and per cycle pregnancy rates among the placebo cases (10.5 and 3.6 %) were lower compared with 54.5 and 23.1 %, respectively, in the astaxanthin group ( $P=0.028$ ;  $P=0.036$ ) [96].

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## 17.1 Introduction

A decline in sperm counts has emerged in recent years [1–3]. Consequently, it has been argued that male fertility is declining, and it is further proposed that environmental pollutants may play an active role [4–10]. By contrast, no apparent and clear decrease in population fertility has been noted in epidemiologic studies [11, 12]. Decline in sperm count of healthy men of reproductive age over the years has been higher in some regions (Denmark, Scotland, USA east coast) than in others (USA west coast, south of France, Baltic countries). Genetic and racial factors may also be involved [7–12].

It has been hypothesized that environmental chemicals with estrogenic properties, heavy metals, and solvents constitute detrimental factors for sperm count [13–18], even though the epidemiologic consequences are unclear. Nevertheless, some kind of toxicologic effect on spermatogenesis is hypothesized; clinical and laboratory research indicates that of all the changes in male reproductive health seem to be interrelated and may have a common origin in fetal life or childhood [19–23]. Furthermore, some epidemiologic studies confirm that exposure to endocrine disruptors, solvents, and heavy metals may play a role in male reproductive disorders [24].

Three categories of potential reproductive disruptor pollutants have been found: endocrine disruptors, heavy metals, and organic solvents.

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## 17.2 Endocrine Disruptors

Endocrine disruptors affect the male genital tract during fetal testis and germinal cell development (testicular dysgenesis syndrome), targeting pituitary gonadotropins [25] or the genetic regulation of steroidogenesis [26] at either the genomic [27] or proteomic [28, 29] levels. Gene pathways targeted include cholesterol transport and steroidogenesis, pathways involved in intracellular cholesterol/lipid homeostasis, insulin signaling, transcriptional regulation, oxidative stress [27],  $\alpha$ -inhibin (which is essential for physiologic Sertoli cell development), and genes involved with communication between Sertoli cells and gonocytes [27]. Environmental pollutants are thought to induce oxidative stress, peroxidation [30], and germ cell apoptosis in the human fetal testis [31].

There exists a critical period of exposure: diethylstilbestrol (an estrogenic compound) exposure during the perinatal period can influence behavior, accessory glands, and reproductive structures in humans and rodents [32] via hormonal or epigenetic mechanisms [33].

Given that animals represent an accepted experimental model for human male reproduction, it is noteworthy that pollutants are regarded as etiologic factors in the reproductive decline of wildlife [34, 35]. Perinatal exposure is critical for the development of testicular dysgenesis syndrome in animals [36–38]. A severe problem of pollutants is that some of these chemicals have long half-lives and have been detected in environmental samples 10–20 years after they were banned for use [39].

Pesticides, fungicides, heavy metals, defoliants, and other chemical weapons, in addition to oils and cleaning agents [40–44], are regarded as the main environmental pollutants capable of disrupting the human and wildlife endocrine system (endocrine disruptor chemicals or EDCs).

Endocrine disruption is a mechanism of toxicity that hinders the ability of cells, tissues, and organs to communicate hormonally [45], provoking reduced fertility and fecundity [17], spontaneous abortion, skewed sex ratios [46], male and female reproductive tract abnormalities [47–49], precocious puberty [50, 51], polycystic ovary syndrome [52], neurobehavioral disorders, impaired immune function, and a wide variety of cancers [53, 54]. Endocrine disruptors represent a wide range of chemical classes and include agonists of the estrogen receptor, androgen receptor antagonists, and aryl hydrocarbon receptor agonists [55]. Some chemicals have more than one mechanism of action [56]. A list of endocrine disruptors is shown in Table 17.1. Many of these chemicals persist in the environment. Some are lipophilic and, hence, sequestered in adipose tissue and secreted in milk, whereas others may only be present for short periods of time but at critical periods of development.

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## 17.3 Heavy Metals

All heavy metals are toxic and can affect the seminiferous epithelium [57–59]. Cadmium interacts with the zinc-dependent stability of the human sperm chromatin [60]. Salts of arsenic, cadmium, mercury, lead, and antimony are all toxic for

**Table 17.1** Environmental pollutants: their sources and health effects [66]

Pollutant	Origin	Health effects	
		During development	During adulthood
<sup>a</sup> Bisfenol A	Component of polycarbonate plastic and epoxy resins	Modified prostate development and puberty onset, hormonal changes, decreased semen quality, obesity	Decreased semen and oocyte quality, recurrent miscarriages
<sup>a</sup> Dioxin/furans	Manufacture or burning of products containing chlorine	Urologic malformations	Menstrual irregularities, epigenetic disorders
<sup>a</sup> Organochlorine pesticides	Largely banned in Western countries, still persist in the food chain (DDT)	Altered sex ratio, altered puberty onset, decreased semen quality	Altered puberty onset, decreased semen quality, endometriosis, fetal loss
<sup>a</sup> Pentachlorophenol	Wood preservative, railroad ties	Reduced fertility	Reduced fertility
<sup>a</sup> Ethylene oxide	Chemical sterilizer for dental practice	?	Decreased semen quality, miscarriage
<sup>a</sup> Glycol ethers	Paints, enamels, wood stains; printing inks, cosmetics	?	Reduced fertility, decreased semen quality, fetal loss, menstrual irregularities
<sup>a</sup> Nonylphenol, octylphenol	Detergents, pesticides, paints, plasticizers	Hormonal changes, altered puberty onset, decreased testicular size, decreased semen quality	?
<sup>a</sup> Perfluorinated compounds	Water-repellent treatments	Hormonal changes, fetal loss, reduced birth weight	?
<sup>a</sup> Phthalates	Cosmetics, toys, lubricants	Malformations of reproductive tract, hormonal changes, decreased semen quality	Earlier menarche, menstrual irregularities, endometriosis, ovulation alterations, decreased semen quality, fetal loss
<sup>a</sup> Polybrominated diphenyl esters	Flame retardants	?	Decreased semen quality
<sup>b</sup> Mercury	Thermometers, dental filling	Decreased semen quality	Decreased semen quality
<sup>b</sup> Cadmium	Batteries, pigments, some metal alloys	Sertoli cell and testicle damage	Toxic to Sertoli cells and spermatogenesis
<sup>b</sup> Lead	Batteries, ammunition, metal products, X-ray shields	Hormonal and pubertal onset alterations	Hormonal alterations, menstrual alterations, reduced fertility, fetal loss, altered puberty, reduced spermatogenesis

(continued)

**Table 17.1** (continued)

Pollutant	Origin	Health effects	
		During development	During adulthood
<sup>b</sup> Manganese	Dietary supplements, ceramics, pesticides, fertilizers	Hormonal changes, altered puberty onset	Hormonal changes, menstrual irregularities, fetal loss, altered puberty onset, damage to Sertoli cells and spermatogenesis
Organic solvents: benzene, toluene, 1-bromopropane, 2-bromopropane, perchloroethylene, trichloroethylene, etc	Plastic, resin, rubbers, synthetic fibers, lubricants, dyes, detergents, drugs, pesticides, fingernail polish, cleaning products, detergents, lacquers, fiberglass, food containers	Hormonal changes, pubertal onset alterations, reduced fertility, menstrual irregularities, miscarriage and fetal loss, decreased semen quality	Hormonal changes, reduced fertility, menstrual irregularities, miscarriage and fetal loss, decreased semen quality

<sup>a</sup>Chlorinated hydrocarbons (endocrine disruptors)

<sup>b</sup>Heavy metals

spermatogenesis in humans and animal models [61, 62]. Heavy metals are also present in some welding fluxes [63].

## 17.4 Solvents

Various organic solvents are also known to cause infertility, including glycol ethers [64], which are used in the printing industry and are also found in some paints (e.g., as used on naval vessels). Perchloroethylene, used in the dry cleaning industry, can also cause subfertility, but its effects on sperm morphology and kinematics are subtle, and their impact on fertility remains unclear [65].

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## 18.1 Background

Article 1 of 40/2004 of the Italian law [1] states that assisted reproduction techniques (ARTs) should be started only when any other therapy for infertility has failed. In some cases any attempt to improve spermatogenesis is useless; in others its improvement increases the probabilities of an ART take-home baby.

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## 18.2 Specific Indications for ART

Any medical or surgical therapy for male infertility is useless in the following cases; thus, ART should be immediately started.

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## 18.3 Globozoospermia

Globozoospermia, the so-called roundheaded syndrome, is a sperm defect of low frequency (incidence <0.1 % of infertile patients) but is associated with a severe teratozoospermia causing male sterility [2]. Globozoospermia is characterized by the absence of acrosome in roundheaded spermatozoa, leading to a complete inability

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to fertilize the oocyte; thus the affected males suffer from infertility. A genetic basis was suggested by the familial distribution of the syndrome [3], and different modes of inheritance have been described [4, 5].

### 18.3.1 Female Ageing

The size of the initial oocyte stock, the proportion that undergoes atresia, and the rate of initiation of growth of follicles are genetically determined variables. The number of oocytes in the ovaries declines naturally and progressively through the process of atresia, and fecundity declines gradually beginning at the age of 32 and even more rapidly after 37 years [6].

Anti-Müllerian hormone (AMH) correlates with the number of antral follicles and has been recently identified as an early reliable predictor of ovarian reserve [7, 8]. This data means that improvement of sperm count is useless when female partner is >40 years [9] and that correction of mild dyspermias is ineffective for natural conception when female partner is >35 [10] or in any case in which AMH and AFC (antral follicle count) are strongly reduced independently of the female age. Anyway andrological clinic evaluation and scrotal ultrasounds are necessary to verify the presence or the absence of a testicular cancer.

### 18.3.2 Micropolycystic Ovary

Polycystic ovary syndrome is a heterogeneous endocrine disorder found in 5 % of women of reproductive age and accounts for about 90–95 % of patients with anovulatory infertility. This syndrome presents defects in primary cellular control mechanisms that result in the expression of chronic anovulation, hyperandrogenism, and polycystic ovaries. Some studies employing DNA microarrays have identified over one thousand genes whose expression was altered in PCOS patients. These provide evidence that the genetic abnormality in PCOS affects key mechanisms of follicular development and steroidogenesis, resulting in increased ovarian androgen secretion and anovulatory infertility due to arrested folliculogenesis. These data means that gametes of women affected by polycystic ovary syndrome are too severely compromised to have their ART performance increased with a spermatogenesis improvement [11].

### 18.3.3 Presence of Y Microdeletions and/or High Follicle-Stimulating Hormone (FSH) >12 mIU/ml)

Short arm Y chromosome microdeletion and high FSH are laboratory signs of a spermatogenesis that is too compromised to be improved by any medical or surgical approach [12–14].

### 18.3.4 Unexplained Male Infertility

See Chap. 10.

### 18.3.5 Congenital Absence of the Vas Deferens

See Chap. 5.

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## 18.4 Specific Indications to Improve Spermatogenesis Before ART

An attempt to improve spermatogenesis should be performed in all other cases.

In fact complementary treatment with antioxidant-containing food supplements quadruples the spontaneous pregnancy rate and reduces the cost per pregnancy by 60 % [15]. Any andrological treatment lowers the number of couples who need ART for pregnancy [16].

In nonobstructive azoospermic (NOA) patients, the probabilities to conceive are directly linked to the monitors of spermatogenesis: sperm motility, testicular histology, follicle-stimulating hormone (FSH) level, previous testicular pathology, and number of sperm retrieved [17–20].

Gonadotropin supplementation of hypogonadal oligoasthenoteratospermic (OAT) patients improves sperm count and intracellular sperm injection (ICSI) offsprings [21, 22]. Patients who had their sperm count improved after a varicocele ligation seldom achieved a spontaneous pregnancy; however, they had greater probabilities of a take-home baby after ICSI than the patients who had no sperm ejaculated after varicocelectomy and who were submitted to (micro-)testicular sperm extraction [23]. The numbers of ICSI pregnancies and live births in severe idiopathic OAT patients improved with a course of L-carnitine, acetyl-L-carnitine, and cinnocicam. The improvement occurred in the patients who had their sperm aneuploidy reduced and their sperm morphology increased [24]. Further varicocele correction presents a possible method to optimize a couples' reproductive potential increasing ICSI offspring or decreasing the need for complex assisted reproductive technology [25].

Approximately 5 % of children born through ICSI are at an increased risk of chromosomal anomalies because of the de novo aberrations (aneuploidies) that arise during gametogenesis of their parents. This percentage is much higher than the expected value of 0.5 % in the general population [26, 27]. Thus a correction of spermatogenesis might lower the percentages of chromosome anomalies of spermatozoa and of children born after ICSI.

Actually intracytoplasmic morphologically selected sperm injection (IMSI) [28] or injection of spermatozoa which have undergone to acrosome [29] reaction is a valuable option for patients with severe male factors to improve ICSI offsprings; however, a correct andrological approach to OAT decreases the need of complex reproductive technology [25, 30].

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## 19.1 Epidemiology

It is estimated that male factor infertility is the main or a contributing cause of infertility in half of involuntarily childless couples [1].

Infertility is an emotional crisis and a physical challenge because it interferes with one of the most fundamental human activities. From a list of 87 items of stressful life events, infertility has been ranked as one of the most stressful situations similar to the death of a spouse or of a close relative [2].

This stressful condition frequently causes diminished sexual desire as a side effect of feelings of sexual unattractiveness, guilt, shame, depression and anger or can be the consequence of the stress and demands infertility places on the marriage, social relationships, work life and financial resources. Infertility frequently triggers feelings of failure, sexual inadequacy, diminished masculinity and altered sense of self, and all are contributory factors in male sexual dysfunction. Many men develop performance anxiety; sexual avoidance especially if sex is for “procreation purpose only” and the female partners have become sexually irresponsive and passive.

Sexual dysfunction is more openly discussed than in the past, but still only a fraction of the men with these problems seek medical care [3].

After sexual desire disorder the most common sexual problem is erectile failure in 5–10 % of the general male population, 4–10 % inhibited male orgasm in 35 % premature ejaculation [4].

The relationship between sexual dysfunctions and infertility can be mutual. Sexual dysfunction may cause difficulty conceiving but also attempts to conceive may cause sexual dysfunctions.

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## 19.2 Sexual Dysfunction Causing Infertility

For a small percentage of infertile couples, male sexual problems are the main cause of infertility [5]. For others it could be a relative cause: If a couple cannot or does not have sex near ovulation time, the woman is less likely to get pregnant. If they have sex once in a while because of low sexual desire or pain during sex, they may miss that important time for pregnancy.

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## 19.3 Erectile Dysfunction

It is traditionally referred to as impotence, and the NIH consensus conference has defined erectile dysfunction (ED) as the inability to achieve or maintain an erection adequate for sexual intercourse. Primary erectile failure is never having had the ability to achieve and/or maintain an erection sufficient for vaginal penetration or successful coitus. This condition is very rare but, when it does occur, is a direct cause of infertility. Treatment success rates for primary erectile dysfunction are the lowest among all sexual disorders in men and women.

Secondary erectile dysfunction is partial or weak erections, total absence of an erection or the inability to sustain erections long enough for vaginal penetration or sexual intercourse. Most men experience some form of episodic, transient erectile dysfunction at some point of their lifetime, especially when they age, although it affects men of all ages [6]. Years ago it was believed that the main cause of erectile dysfunctions was due to psychological factors, but nowadays it is believed that at least 50 % of erectile dysfunction problems are due to organic aetiology [7].

The pathophysiology of erectile dysfunction may be vascular, neurogenic, hormonal, anatomical, drug induced or psychogenic [6].

Erectile dysfunction is the most important cause of male factor infertility due to sexual dysfunction, although men rarely disclose this problem to caregivers [8]. In one study, 10 % of men were observed to experience sexual dysfunction of a psychogenic nature in response to the diagnosis of infertility [9].

The introduction of new oral therapies has completely changed the diagnostic and therapeutic approach to ED, and the current availability of effective and safe drugs for ED has resulted in an increasing number of men seeking help for ED. These patients may benefit from a prescription of a PDE-5 inhibitor. Neither sildenafil nor tadalafil has an adverse effect on sperm function or ejaculate quality [10, 11].

Patients who complain of difficulty with ejaculation and climax may be taking psychotherapeutic agents that block dopamine production and consequently blunt the hypothalamic-pituitary axis and possibly decrease libido. Other psychotherapeutic drugs can decrease vasodilation and worsen the quality of erections.

When ED is determined to be organic and not reversible (in case of injury or disease), treatment could involve intracavernous injection or surgical interventions such as penile prostheses [12]. Psychological treatments include decreasing performance anxiety, increasing awareness of erotic sensations and disputing irrational belief and myths.

## 19.4 Premature Ejaculation

Premature ejaculation (PE) is an extremely common condition. Kinsey, in his landmark report, had stated that it affects as many as 70 % of all men. PE is characterized by a lack of voluntary control over ejaculation. Many men occasionally ejaculate sooner than they or their partner would like during sexual activities. PE is a frustrating problem that can reduce the enjoyment of sex, harm relationships and affect quality of life. When it comes to conception, there are two things that must happen – intercourse with vaginal penetration and ejaculation. When the latter happens first, it will impact fertility, but only in those rare cases in which ejaculation happens before the introduction of the penis in the vagina. PE is usually not situational; it occurs with all partners because the men have not learned to voluntarily control his ejaculatory reflexes [13]. Although the exact cause of premature ejaculation (PE) is not known, new studies suggest that serotonin, a natural substance produced by nerves, is important [14].

A breakdown of the actions of serotonin in the brain may be a cause. Studies have found that high amounts of serotonin in the brain slow the time to ejaculation, while low amounts of serotonin can produce a condition like PE.

Psychological factors also commonly contribute to PE. Temporary depression, stress, unrealistic expectations about performance, a history of sexual repression or an overall lack of confidence can cause PE. Interpersonal dynamics may contribute to sexual function. PE can be caused by a lack of communication between partners, hurt feelings or unresolved conflicts that interfere with the ability to achieve emotional intimacy. These psychological factors may be related to infertility with its emphasis on sex for procreation.

There are several treatment choices for premature ejaculation: psychological therapy, behavioural therapy and medications [15].

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## 19.5 Inhibited or Delayed Ejaculation

Inhibited or delayed ejaculation (also called retarded ejaculation) is the persistent and recurrent inhibition of orgasm, manifested by delay or absence of ejaculation following adequate sexual stimulation; the most frequent physical situation which interferes with ejaculation is spinal cord injury; researchers report that ejaculation occurs in up to 70 % of men with incomplete lower-level injuries and in as many as 17 % of men with complete lower-level injuries. Ejaculation occurs in about 30 % of men with incomplete upper-level injuries and almost never in men with complete upper-level injuries [16].

These conditions prevent men from ejaculating during sexual intercourse even though they can often ejaculate normally through masturbation. The causes could be psychological and physical; psychological anejaculation is usually anorgasmic and it could be situational or total. Situational means that men can ejaculate in some conditions or situation but not in others. It also can occur in stressful situations, as when a man is asked to collect a sperm sample in an infertility

laboratory. Recently, delayed ejaculation has been identified as a common side effect of some antidepressant medications [17].

Treatments depend on the cause and include psychosexual counselling and drugs as ephedrine and imipramine. When delayed ejaculation affects fertility, vibrator or electroejaculation (a procedure in which ejaculation is stimulated by low electrical current) or surgical retrieval of sperm directly from the testis can be used to obtain sperm for insemination or used in IVF [18].

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## 19.6 Infertility as a Cause of Sexual Dysfunction

Infertility can negatively influence both the pleasure of sex and sexual function. In many couples, sexuality has already been compromised before infertility treatment because of the failure to conceive and the subsequent medical interventions [19]. The invasion of the couple's physical and emotional privacy during fertility treatments can further reduce sexual desire in both partners and damage the relationship [20].

Men are sensitive of the stress of infertility techniques as intrauterine insemination (IUI) and in vitro fertilization (IVF); this can be due to a diminished sense of male self-esteem. It has also been shown that the emotional stress of the men enrolled in the IVF programmes can negatively affect the quality of semen [21]. Moreover, the "super stress" of the moment, "this is the night" syndrome and the necessity to perform can deteriorate sexual performance and cause erectile failure. Some procedures such as the post-coital test are particularly involved in the impairment of sexual functioning [22].

When infertility results in relationship disturbances and sexual problems, the intervention of a caregiver is paramount. All too often the sexual problems of infertile couples are ignored and minimized in a belief that they will dissipate on their own or will have a few long-term consequences. Unfortunately these beliefs are not true: although some sexual problems may disappear when the pressures of infertility treatment end, sexual difficulties typically linger or become more problematic after treatment ends or parenthood is achieved [23]. Professional attention and care regarding sexual disturbances during infertility can lower the impact, and education can prevent many of the sexual difficulties infertile couples encounter. The European Society of Human Reproduction and Embryology (ESHRE) has set up specific guidelines in order to provide a framework for counselling in infertility being aware that sexual counselling is dependent upon the legal, ethical and cultural background of every country [24].

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