



European Association of Urology

# GUIDELINES ON MALE INFERTILITY

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# 1 INTRODUCTION

The European Association of Urology (EAU) consensus group on male infertility consider that male infertility is an interdisciplinary subject in its own right, with paternity in a sterile partnership being the primary clinical objective. This understanding of male infertility implies co-operation with non-urologists in all aspects of infertility in daily work, and knowledge of other pertinent guidelines, issued by well-accepted authorities such as the World Health Organization (WHO), the ESHRE Andrology Special Interest Group [1] and the European Academy of Andrology. Accepting these recommendations, the EAU consensus group on male infertility is convinced that the following guidelines will help European urologists in their interdisciplinary situation to focus on their special skills and knowledge and to achieve a better understanding of the outcome for the male patient and the couple.

## 1.1 Definition

'Infertility is the inability of a sexually active, non-contracepting couple to achieve pregnancy in one year' [WHO]

## 1.2 Epidemiology and aetiology

About 25% of couples do not achieve pregnancy within 1 year, of whom 15% seek medical treatment for infertility and less than 5% remain unwillingly childless. Infertility affects both men and women. Male causes for infertility are found in 50% of involuntarily childless couples. If there is a single factor, the fertile partner may compensate for the less fertile partner. In many couples, however, a male and a female factor coincide. Infertility usually becomes manifest if both partners are sub-fertile or have reduced fertility.

Reduced male fertility can be the result of congenital and acquired urogenital abnormalities, infections of the genital tract, increased scrotal temperature (varicocele), endocrine disturbances, genetic abnormalities and immunological factors [2]. No causal factor is found in 60-75% of cases (idiopathic male infertility). These men present with no previous history associated with fertility problems and have normal findings on physical examination and endocrine laboratory testing. Semen analysis reveals a decreased number of spermatozoa (oligozoospermia), decreased motility (asthenozoospermia) and many abnormal forms on morphological examination (teratozoospermia). Usually, these abnormalities come together and are described as the oligo-astheno-teratozoospermia (OAT) syndrome. Table 1 summarizes the main aetiological causes of male subfertility.

**Table 1: Aetiology and distribution (%) of male infertility among 7,057 men [2]**

• Sexual factors	1.7
• Urogenital infection	6.6
• Congenital anomalies	2.1
• Acquired factors	2.6
• Varicocele	12.3
• Endocrine disturbances	0.6
• Immunological factors	3.1
• Other abnormalities	3.0
• Idiopathic abnormal semen (OAT syndrome) or no demonstrable cause	75.1

The unexplained forms of male infertility may be caused by several factors, such as chronic stress, endocrine disruption due to environmental pollution, reactive oxygen species and genetic abnormalities.

## 1.3 Prognostic factors

The main factors influencing the prognosis in infertility are:

- Duration of infertility
- Primary or secondary infertility
- Results of semen analysis
- Age and fertility status of the female partner.

When the duration of infertility exceeds four years of unprotected sexual intercourse, the conception rate per month is only 1.5%.

At present, in many Western countries, women postpone their first pregnancy until they have finished their education and have started a professional career. However, the fertility of a woman of 35 years of age is only 50% of the fertility potential of a woman aged 25 years. By the age of 38 years, this has reduced to only 25%, and over the age of 40 years it is less than 5%. Female age is the most important single variable influencing outcome in assisted reproduction [3].

#### 1.4 RECOMMENDATIONS

- To categorize infertility, both partners should be investigated simultaneously.
- In order to evaluate the infertile couple, it is important to obtain information about the duration of infertility, previous pregnancies and the age of the female partner.
- In the diagnosis and management of male infertility, it is essential to consider the fertility chances of the female partner, since this might determine the final outcome (Grade B) [3, 4].
- As a urogenital expert, the urologist/andrologist should examine any male with fertility problems for urogenital abnormalities. This applies to all males diagnosed with reduced sperm quality. A diagnosis is mandatory to initiate appropriate therapy (drugs, surgery, assisted reproduction) (Grade B).

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## 2 INVESTIGATIONS

### 2.1 Semen analysis

Andrological examination is indicated if semen analysis shows abnormalities (Table 2). Since semen analysis still forms the basis of important decisions concerning appropriate treatment, standardization of the complete laboratory work-up is highly desirable. Ejaculate analysis has been standardized by the WHO and propagated by continuing work and publications in the *WHO Laboratory Manual for Human Semen and Sperm-Cervical Mucus Interaction* (4th edition) [1]. The consensus is that modern spermatology has to follow these guidelines without exclusions.

**Table 2: Overview of standard values for semen analysis according to the 1999 WHO criteria**

• Volume	≥ 2.0 ml
• pH	7.0-8.0
• Sperm concentration	≥ 20 million/ml
• Total no. of spermatozoa	≥ 40 million/ejaculate
• Motility	≥ 50% with progressive motility or 25% with rapid motility within 60 min after ejaculation
• Morphology	≥ 14% of normal shape and form*
• Viability	> 50% of spermatozoa
• Leukocytes	< 1 million/ml
• Immunobead test (IBT)	< 50% spermatozoa with adherent particles
• MAR test**	< 50% spermatozoa with adherent particles

\* Assessment according to Kruger and Menkfeld criteria.

\*\* MAR = Mixed antiglobulin reaction.

#### 2.1.1 Frequency semen analyses

If values are normal according to WHO criteria, one test should be sufficient. Further andrological investigation is only indicated if the results are abnormal in at least two tests.

It is important to distinguish between oligozoospermia (< 20 million spermatozoa/ml), astenozoospermia (< 50% motile spermatozoa) and teratozoospermia (< 14% normal forms). Quite often, all three pathologies occur simultaneously as OAT syndrome. In extreme cases of OAT syndrome (< 1 million spermatozoa/ml), as in azoospermia, there is an increased incidence of obstruction of the male genital tract and genetic abnormalities.

## 2.2 Advanced diagnostic spermatological tests

These guidelines do not discuss computer-assisted sperm analysis (CASA), acrosome reaction tests, zona-free hamster egg penetration tests and sperm-zona pellucida bindings tests [2]. A critical assessment of these specialized tests using standardized laboratory techniques is absolutely necessary for given diagnostic situations.

## 2.3 RECOMMENDATIONS

- Andrological investigations are indicated if semen analysis is abnormal in at least two tests.
- Assessment of andrological status has to consider the suggestions for the standardized investigation, diagnosis and management of the infertile man made by the WHO [3] and by doing so, implementing evidence-based medicine in this interdisciplinary field of reproductive medicine (Grade B).
- Semen analysis has to follow the guidelines of the *WHO Laboratory Manual for Human Semen and Sperm-Cervical Mucus Interaction* (4th edition) [1] (Grade A).

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# 3 PRIMARY SPERMATOGENIC FAILURE

## 3.1 Definition

Primary spermatogenic failure is defined as any spermatogenic alteration caused by conditions different from hypothalamic-pituitary diseases. The severe forms of primary spermatogenic failure have different aetiologies but present clinically as non-obstructive azoospermia.

The prevalence of azoospermia in the general population has been estimated at 2% [1]. The incidence at a male infertility clinic was found to be as high as 10-20% [2,3]. Testicular histology shows different degrees of spermatogenic alterations, ranging from tubular damage to hypospermatogenesis. Even in cases of Sertoli cell-only syndrome (SCOS), it is possible to find seminiferous tubules with some degree of spermatogenesis.

Depending on the severity of the process, follicle-stimulating hormone (FSH) levels can be elevated and the testes can be reduced in size and/or consistency. Before the era of intracytoplasmic sperm injection (ICSI), increased serum FSH was considered a sign of severe spermatogenic failure and no other diagnostic procedures were indicated. It has been demonstrated that ICSI [4] could also be used to treat some cases of non-obstructive (testicular) azoospermia. However, about 20% of these cases are associated with chromosomal abnormalities or genetic translocations of the Yq chromosome (see Genetic disorders in infertility).

### 3.2 Aetiology

The causes of spermatogenic failure are summarized in Table 3.

**Table 3: Causes of spermatogenic failure**



### 3.3 Testicular morphology

The most severe alteration of spermatogenesis is characterized by complete sclerotization, where no cells are present in the seminiferous tubules. In terms of severity, this alteration is followed by complete aplasia of germ cells, SCOS or del Castillo's syndrome, where the seminiferous tubules are usually reduced in diameter.

Another severe alteration is complete spermatogenic maturation arrest at the spermatocyte level, characterized by a normal population of Leydig's and Sertoli's cells, spermatogonia and spermatocytes, but an absence of spermatids and spermatozoa. Infrequently, maturation arrest can be observed at the spermatogonia or round spermatid level. In the latter cases, mature or elongated spermatids are absent. Less severe forms of spermatogenic alteration include hypospermatogenesis (proportional decrease in all spermatogenic cells), partial maturation arrest, focal SCOS and mixed patterns.

The estimated prevalence of non-obstructive azoospermia, determined by testicular biopsy, ranges between 40% and 60% [5]. For standardization, the use of scoring systems [6] is strongly suggested (Table 4).

**Table 4: Scoring system for testicular biopsies (Johnsen score) [6]**

Score	Histological criteria
10	Full spermatogenesis
9	Slightly impaired spermatogenesis, many late spermatids, disorganized epithelium
8	Less than five spermatozoa per tubule, few late spermatids
7	No spermatozoa, no late spermatids, many early spermatids
6	No spermatozoa, no late spermatids, few early spermatids
5	No spermatozoa or spermatids, many spermatocytes
4	No spermatozoa or spermatids, few spermatocytes
3	Spermatogonia only
2	No germinal cells, Sertoli cells only
1	No seminiferous epithelium

### 3.4 History and physical examination

Typical findings from the history and physical examination of a patient with spermatogenic failure are:

- Cryptorchidism
- Testicular torsion
- Genito-urinary infection
- Testicular trauma
- Environmental toxin exposure
- Gonodadotoxic medication
- Radiation or chemical exposure
- Testicular cancer

- Absence of testes
- Abnormal secondary sexual characteristics
- Gynaecomastia
- Cryptorchidism
- Abnormal testicular volume and/or consistency
- Varicocele.

### 3.5 Investigations

Routine investigations include semen analysis and hormonal determinations. Other investigations are described according to the special situation.

#### 3.5.1 Semen analysis

In non-obstructive azoospermia, semen analysis shows normal ejaculate volume and azoospermia after several centrifugations have been performed. A recommended method is semen centrifugation at 600 g for 10 min and thorough microscopical examination of the pellet (x600). The upper fluid is then re-centrifuged (8000 g) for an additional 10 min and examined. All samples can be stained and re-examined under the microscope [7,8].

#### 3.5.2 Hormonal determinations

Generally, the levels of FSH are mainly correlated with the number of spermatogonia. When these cells are absent or markedly diminished, FSH values are usually elevated. When the number of spermatogonia is normal but there is complete spermatocyte or spermatid blockage, FSH values are within normal range. However, on an individual patient basis, FSH levels do not provide an accurate prediction of the status of spermatogenesis [9-11]. Preliminary data indicate a stronger correlation between low inhibin B level and spermatogenic damage [12]. At present, the routine determination of inhibin B is not suggested.

#### 3.5.3 Combination obstructive/non-obstructive azoospermia

Some azoospermic patients may present with a combination of obstructive and spermatogenic pathologies and increased serum FSH levels [9]. It is therefore advisable to perform testicular biopsy in azoospermic patients with elevated FSH levels, who are known or suspected of having seminal duct obstruction, or when the size and/or consistency of one testis has decreased.

#### 3.5.4 Sertoli cell-only syndrome (SCOS)

SCOS can be found in patients with normal and elevated FSH [13,14]. Patients usually present with azoospermia and normal volume of ejaculate, elevated FSH level, normal levels of testosterone, luteinizing hormone (LH) and prolactin, normal secondary sexual characteristics and bilaterally small testes. It is suggested that the levels of LH and testosterone should be investigated only in cases with clinical signs of hypogonadism.

#### 3.5.5 Testicular biopsy

Testicular biopsy is indicated in patients without evident factors (normal FSH and normal testicular volume) to differentiate between obstructive and non-obstructive azoospermia.

Testicular biopsy can also be performed as part of a therapeutic process in patients with clinical evidence of non-obstructive azoospermia who decide to undergo ICSI. Spermatogenesis may be focal. In these cases, one or more seminiferous tubules are involved in spermatogenesis while others are not [15-17]. About 50-60% of men with non-obstructive azoospermia have some seminiferous tubules with spermatozoa that can be used for ICSI.

Most authors recommend taking several testicular samples given the possible regional differences [18,19]. Other authors support the hypothesis that a single sample is demonstrative of the total histological pattern [15,20]. Many authors find a good correlation between diagnostic biopsy histology and the likelihood of finding mature sperm cells during testicular sperm retrieval and ICSI [21-23].

### 3.6 Biopsy techniques

Testicular biopsy is a simple out-patient procedure performed under local anaesthesia. There are several techniques for performing a testicular biopsy:

#### 3.6.1 Open biopsy

An incision is made on either side of the midline raphe. The tunica albuginea is visualized. With a scalpel blade, an incision is made into the tunica albuginea. Gentle pressure on the testis will facilitate tissue removal using a pair of small, straight-blade scissors. The specimen is transferred into Bouin's solution. Formaldehyde solution should never be used. At this stage of surgery, the epididymis is mobilized to assess its morphological

characteristics and to exclude mechanical causes of azoospermia. To date, it is unclear whether a microsurgical approach [24] leads to better results. The standard testicular biopsy can also be combined with testicular touch preparation cytology [25].

### 3.6.2 *Percutaneous testicular biopsy*

Some authors prefer percutaneous biopsies for diagnostic purposes because the procedure is simpler than open testicular biopsy [26-29]. However, this technique is likely to provide insufficient tissue for histological examination [30], and may result in specimen artefacts, refractory haematomas, and unintentional damage to the epididymis.

### 3.6.3 *Testicular fine-needle aspiration*

Some authors advocate testicular spermatozoa fine-needle aspiration as a diagnostic method [31-33], while others [34] do not find this technique as effective as open testicular biopsy for histopathological diagnosis.

Any type of testicular biopsy should provide sufficient material to cryopreserve sperm for future ICSI cycles [35]. If these spermatozoa have some degree of motility, they have a good potency for fertilization and successful implantation.

## 3.7 Treatment

Testicular sperm extraction (TESE) and ICSI were introduced in 1993 for treatment of obstructive azoospermia [36-38]. It was soon discovered that this technique could also be used for azoospermic men who appeared to have absent spermatogenesis [39]. If spermatozoa are detected in the testicular biopsy, ICSI with either cryopreserved or fresh spermatozoa can be proposed to the couple.

A karyotype (if not performed previously) and Yq deletions screening are indicated to analyze any therapeutic consequences for the newborn child. If genetic anomalies are detected, the couple has to be properly informed and counselled (see Genetic disorders in infertility).

Of 616 TESE procedures, 373 (60.5%) yielded sperm for ICSI. The mean fertilization rate was 52.5% (38.6-69%) and the mean pregnancy rate was 29.2% (11.3-31%).

### 3.7.1 *Predictive parameters for successful TESE*

In the majority of series, aetiological factors, patient's age, testicular volume, serum FSH and histopathological patterns showed that no potential predictive parameter precluded successful testicular sperm retrieval.

## 3.8 TESE techniques

Open biopsy and fine-needle aspiration are the two main techniques used to retrieve sperm from the testicle. Although fine-needle aspiration enables more areas of the testis to be reached, open testicular biopsy allows more tissue and sperm to be retrieved [40].

### 3.8.1 *Description*

TESE is always performed in both testes. Two or three small incisions are made through the tunica albuginea in different regions at the free rim of each testis and small pieces of extruding testicular tissue are removed. The fragments of testicular tissue are immediately placed in a Petri dish containing 2 ml of culture medium and transferred to the in-vitro fertilization (IVF) laboratory.

For needle aspiration, a 21-gauge butterfly needle attached to a 20 ml plastic syringe serves as an aspiration device. The butterfly needle is passed directly into the testicular tissue. While holding the testicle between the index finger and the thumb, different entries are made in each testicle to sample various locations. Before retrieving the needle from the testis, small artery forceps are used to clamp the butterfly needle's microtubing. Following aspiration, the needle is flushed with culture medium into one well of a four-well plate. For each puncture, a new butterfly needle is used [41].

### 3.8.2 *Physiological consequences of TESE*

In cases of non-obstructive azoospermia, multiple TESE or testicular punctures have been associated with focal inflammation and haematoma, as well as impaired testicular blood flow [42]. In small testes, an intermittent decrease of serum testosterone levels is under debate. The long-term consequences of these findings are unclear.

## 3.9 ICSI with cryopreserved testicular spermatozoa

ICSI has been successfully performed with cryopreserved testicular spermatozoa [7,35,43-49]. In the majority of series, results obtained with fresh and cryopreserved sperm were not significantly different. It also appears that sperm survival after cryopreservation was not influenced by infertility aetiology, serum FSH concentration, or the patient's age.

### 3.10 TESE and ICSI in Klinefelter's syndrome

Palermo [50] obtained spermatozoa in four out of seven TESE procedures in six men with non-mosaic Klinefelter's syndrome. Fertilization was achieved in 68% of oocytes. Five healthy newborns, all karyotypically normal, were delivered. Other pregnancies have been reported [51-54].

### 3.11 Testicular spermatid injection in combination with ICSI

Previous studies have shown that fertilization and delivery of healthy offspring can occur after transferring round spermatid nuclei into rabbit or mouse oocytes via microsurgical methods [55-57]. Edwards [58] first suggested that ooplasmic injections of spermatids might serve as a novel mode of therapy for non-obstructive azoospermia. Acceptable fertilization rates and pregnancies after ooplasmic injection of round spermatid nuclei have been reported [59-63]. Complete absence of spermatozoa from the ejaculate or testicular biopsy has an adverse effect on the clinical outcome [63,64].

### 3.12 CONCLUSIONS

1. Impaired spermatogenesis is frequently associated with elevated FSH concentration. Nevertheless, men with increased FSH levels may show normal spermatogenesis.
2. Testicular biopsy is the best procedure to define the histological diagnosis and the possibility of finding sperm. When spermatozoa are detected, these can be cryopreserved for use in future ICSI cycles.
3. Two or three samples of testicular tissue from different areas can better reveal an irregular distribution of spermatogenesis. Open testicular biopsy allows larger quantities of tissue to be retrieved. However, using fine-needle aspiration, it is possible to reach testicular areas more easily.
4. Spermatozoa are found in about 60% of patients with non-obstructive azoospermia. It is crucial that these men who are candidates for sperm retrieval are given appropriate genetic advice. Pre-implantation diagnosis is recommended in cases of mosaic or non-mosaic Klinefelter's syndrome in which pregnancy has been achieved.
5. For patients with non-obstructive azoospermia who have spermatozoa in their testicular biopsy, ICSI with fresh or cryopreserved spermatozoa is the only therapeutic option.
6. Fertilization and pregnancy are achieved in 30-50%. ICSI results with spermatids have been disappointing. This technique must still be considered to be experimental.

### 3.13 RECOMMENDATIONS

- A diagnostic testicular biopsy is indicated only in men with azoospermia, a normal testicular volume and normal FSH (Grade B).
- In couples with a non-obstructive azoospermia a TESE with cryopreservation of the spermatozoa to be used for ICSI can be offered (Grade B).

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## 4 GENETIC DISORDERS IN INFERTILITY

### 4.1 Chromosomal abnormalities

In a survey of pooled data from 11 publications, including a total of 9,766 infertile men, the incidence of chromosomal abnormalities was found to be 5.8% [1]. Of these, sex chromosome abnormalities accounted for 4.2% and autosomal abnormalities for 1.5%. In comparison, the incidence of abnormalities in pooled data from three series totalling 94,465 newborn male infants was 0.38%, of which 131 (0.14%) were sex chromosome abnormalities and 232 (0.25%) were autosomal abnormalities [2]. The possibility of abnormalities increases with increasing severity of impaired spermatogenesis [1,3]. By means of IVF and ICSI techniques, it is now possible for men with very low sperm counts to be given a reasonable chance of paternity. Standard karyotype analysis should be offered to all men with damaged spermatogenesis who are seeking fertility treatment by IVF/ICSI.

### 4.2 Sex chromosome abnormalities (Klinefelter's syndrome and variants [46,XY; 47,XXY; 47,XXY mosaicism])

Klinefelter's syndrome is the most frequent sex chromosome abnormality. Pooled data from cytogenetic analysis of 9,766 newborn infants found Klinefelter's syndrome was present in 66 (0.07%) of phenotypical males [2]. Adult men with Klinefelter's syndrome have small firm testicles that are devoid of germ cells. The phenotype can vary from a normally virilized man to one with stigmata of androgen deficiency, including female hair distribution, scanty body hair and long arms and legs because of late epiphyseal closure.

Leydig cell function is commonly impaired in men with Klinefelter's syndrome [4]. Testosterone levels may be normal or low, oestradiol levels normal or elevated and FSH levels are increased. Surprisingly, libido is often normal despite low testosterone levels, but androgen replacement may be needed with ageing.

Germ cell presence and sperm production are variable in men with Klinefelter's mosaicism 46,XY, 47,XXY. Pre-implantation fluorescent in-situ hybridization (FISH) analysis of cells from embryos can be used to confirm normality [5]. The production of 24,XY sperm has been reported in 0.9% and 2.1% of men with Klinefelter's mosaicism [6,7] and in 1.36-25% of men with somatic karyotype 47,XXY [8-12]. This would indicate that some 47,XXY cells are able to achieve meiosis and produce mature spermatozoa. Conversely, it is not known whether haploid sperm in patients with Klinefelter's syndrome are always the result of a clone of normal cells in a mosaic population or whether, in certain circumstances, some 47,XXY male germ cells are viable and capable of producing haploid sperm.

Patients with Klinefelter's syndrome have an increased chance of producing 47,XXY spermatozoa. When IVF/ICSI is performed, pre-implantation diagnosis should be used or, if not available, amniocentesis and karyotype analysis. Embryos with known Klinefelter's karyotype should not be implanted.

Men with Klinefelter's syndrome are at risk for androgen deficiency as they get older and hormone replacement therapy may be needed. Long-term follow-up from an endocrine point of view will be needed for all men with Klinefelter's syndrome who have undergone testicular biopsy procedures for sperm retrieval.

### 4.3 Autosomal abnormalities

From time to time, men may ask for fertility treatments including IVF/ICSI when they are already known to have an autosomal defect. In these cases, genetic counselling is also required.

Genetic counselling should be offered to all couples where the male partner is known or found to have an autosomal karyotype abnormality. When there is conflict between the wishes of the couple and the interests of the future child, it may be ethically correct to withhold therapy. In general, the best management is to agree treatment with the couple, providing them with full information about the genetic risk.

### 4.4 Genetic defects

#### 4.4.1 X-linked genetic disorders and male fertility

The man has only one X chromosome. This means that an X-linked recessive disorder will be manifest in males, and that the defect will be transmitted to his daughters but not to his sons.

#### 4.4.2 Kallmann's syndrome

Kallmann's syndrome is the commonest X-linked disorder in infertility practice. The predominant form is X-linked recessive caused by a mutation in the KALIG-1 gene on Xp 22.3 [13]. Rarer forms of Kallmann's syndrome include an autosomal-dominant form [14]. Patients with Kallmann's syndrome have hypogonadotrophic hypogonadism and may have other clinical features, including anosmia, facial asymmetry, cleft palate, colour blindness, deafness, maldescended testes and renal abnormalities.

It is important to note that some men with Kallmann's syndrome have an isolated gonadotrophin deficiency without any other phenotypic abnormalities. These patients may present de novo with infertility, which can be treated successfully by hormone replacement therapy.

#### 4.4.3 *Androgen insensitivity: Reifstein's syndrome*

The rare disorder of androgen insensitivity may first present with infertility. The condition has X-linked recessive inheritance due to a defect in the androgen receptor gene located on Xq 11-12. The phenotype varies widely, from complete testicular feminization to an apparently normal man with infertility, although the latter is rare.

A structured genetic search for androgen deficiency was conducted among men with high testosterone and low sperm counts. No cases were found using base-pair mismatch analysis technology [15]. Several de-novo mutations of the androgen receptor were noted; in all cases, these were associated with obvious genital abnormalities such as hypospadias. It was concluded that androgen insensitivity in the infertile male in the absence of any genital abnormality is rare.

#### 4.4.4 *Other X-disorders*

A case report exists of an azoospermic man with biopsy-proven spermatogenetic arrest, who was found to have a submicroscopic interstitial deletion on the Xp pseudoautosomal region in peripheral blood and skin fibroblast samples. Other genetic and chromosomal examinations were entirely normal, including probing of the Yq region [16]. There is also a report about two men with azoospermia and X pseudoautosomal deletions [17].

#### 4.4.5 *X-linked disorders not associated with male infertility*

A number of rare X-linked disorders are not associated with infertility. When recessive, these appear in male babies but skip several generations and therefore family history is important. Examples of such disorders include:

- retinitis pigmentosa, a condition that affects 1 in 3,000 people, may be recessive or dominant and causes visual impairment [18]
- chronic granulomatous disease, a condition that predisposes to severe bacterial and fungal infections [19]
- Menkes' syndrome, an X-linked recessive disturbance of copper metabolism associated with progressive neurological symptoms [20].

The couple should be given choices after appropriate genetic counselling, which should include consideration about the severity of any disorder that may result. It may be appropriate to offer pre-implantation sex determination and replacement of female embryos or amniocentesis and abortion.

#### 4.4.6 *Y-genes and male infertility*

A large number of case series of Y microdeletions have been published. It is clear that while microdeletions may occur in the fertile population [21], they are more prevalent in the infertile population. Microdeletions have been found in three non-overlapping regions of the Y chromosome, AZF a-b-c [22]. Several genes have been described, including RBM, DAZ, DFFRY, DBY and XXX. The most commonly reported abnormality is a microdeletion in the AZFc region which encompasses the DAZ gene. However, there is no exact correlation between DAZ deletion and the presence or absence of spermatogenesis.

#### 4.4.7 *Clinical implications of Y microdeletions*

There are no reports that men with microdeletions have any phenotypic abnormalities other than abnormal spermatogenesis [22-24]. As there is only one Y chromosome, it may be predicted that Y microdeletions will be transmitted to male offspring. However, this is likely to be rare in the normal population because, without ICSI treatment, men with very low sperm counts are less likely to father children. Nevertheless, eight such cases have been reported. More information is needed from father/son pairs where the son has a very low sperm count, and also about the outcome of ICSI attempts where spermatozoa have been used from men with microdeletions. Long-term follow-up of any male children is also required.

#### 4.4.8 *Testing for Y microdeletions*

Testing for microdeletions is now widespread, but the lack of a standardized methodology makes it difficult to compare directly the reported results. Several centres have developed screening methodologies [22,23,25,26]. As there is no correlation between the histopathology and deletion of DAZ, it is premature to rely on detection using specific gene probes, as this will fail to find a significant proportion of men with microdeletions. Comparing results from 28 different European laboratories, it was concluded that using a high number of primers did not improve the accuracy of results. Recommendations are being produced for standardization [27].

Testing for microdeletions is not necessary in men with obstructive azoospermia where ICSI is used, because spermatogenesis should be normal. For men with severely damaged spermatogenesis, testing for microdeletions before ICSI is desirable. However, as these men and their male children are unlikely to have any phenotypic abnormality other than impaired spermatogenesis, it is reasonable to take into account the cost and limitations of current testing methods and to discuss this with the couple. Wherever possible, testing should be encouraged and laboratories should join quality control schemes.

If a man with microdeletion and his partner wish to proceed with ICSI, they can be advised that microdeletions will be passed to sons, but not to daughters. They should also be advised that it is not known to what extent a son who inherits a microdeletion will in turn have a fertility problem, although there is some evidence that the microdeletion size in sons may be larger than in their fathers. Couples may be told that there is no evidence of any other health consequences of microdeletions.

#### 4.4.9 Autosomal defects with severe phenotypic abnormalities as well as infertility

There are a number of inherited disorders with severe or considerable generalized abnormalities as well as infertility (Table 5). Such patients will be well known to doctors often from childhood. Any fertility problem has to be managed in the context of the care of the man as a whole, as well as taking into consideration his and his partner's ability to care for a child that should result from fertility treatment.

**Table 5: Less common inherited disorders associated with infertility and other alterations to phenotype**

Disorder	Phenotype	Genetic basis
• Prader-Willi syndrome	Obesity, mental retardation	Deletion of 15q12 on paternally inherited chromosome
• Bardet-Biedle syndrome	Obesity, mental retardation retinitis pigmentosa, polydactyly	Autosomal recessive syndrome, q21
• Cerebellar ataxia and hypogonadotropic hypogonadism	Eunuchoidism, disturbances of gait and speech	Autosomal recessive
• Noonan's syndrome	Short stature, webbed neck, cardiac and pulmonary abnormality, cryptorchidism	Autosomal dominant
• Myotonic dystrophy	Muscle wasting, cataract testicular atrophy	Autosomal dominant, 19q13.3
• Dominant polycystic kidney disease	Renal cysts, obstruction from epididymal cysts	Autosomal dominant, 16p13.3 and 4q
• 5-alpha reductase deficiency	Perineal or scrotal hypospadias, vaginal pouch, immature female phenotype	Autosomal recessive

#### 4.5 Cystic fibrosis mutations and male infertility

Cystic fibrosis, a fatal autosomal-recessive disorder, is the most common genetic disease of Caucasians. Four per cent are carriers of gene mutations involving the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This gene is located on the short arm of chromosome 7. It encodes a membrane protein that functions as an ion channel and also influences the formation of the ejaculatory duct, seminal vesicle, vas deferens and distal two-thirds of the epididymis.

Congenital bilateral absence of the vas deferens (CBAVD) is associated with CFTR mutations and was found in approximately 2% of men with obstructive azoospermia attending a clinic in Edinburgh [28]. However, the incidence in men with obstructive azoospermia varies between different countries. The clinical diagnosis of absent vasa is easy to miss and all azoospermic men should be carefully examined to exclude CBAVD, particularly those with a semen volume of  $\leq 1.5$  ml and pH less than 7.0.

In recent years, more than 800 mutations of the CFTR gene have been characterized [29]. There are at least 17 published series of men with CBAVD who have been tested for varying numbers of mutations. In general, the more mutations tested for, the higher the percentage of men found to have them. Consequently, detection rates are higher (70-81%) in more recent publications [28,30-32] than in earlier reports (around 40%). In a review of published series of 449 men with CBAVD, the Delta F508 mutation was detected in 244 men, the R117H mutation in 54 men and the W1282X mutation in 37 men; 63 other mutations were found in between one and nine men, but not all mutations were tested for in all case series [33]. It seems likely that as more mutations are defined and tested for, almost 100% of men with CBAVD will be found to have mutations. At present, it is not practical to test for all known mutations as many have a very low prevalence in a particular population. Testing is usually restricted to the 20-30 mutations that occur most commonly in a particular community.

Mutations may be found in both copies of the CFTR gene. However, in most men with CBAVD, they are found in only one copy. In some of these supposedly heterozygous cases, there may be an unknown second mutation, but there is also another interesting mechanism. In up to 63% of supposedly heterozygous cases, a DNA variant known as the 5t allele can be detected in a non-coding region of CFTR [34].

Further work is needed to understand fully the genetics of CBAVD. It is noteworthy that heterozygous men with CBAVD often have mild clinical stigmata of cystic fibrosis, e.g. history of chest infections. It is therefore important to follow up children born after ICSI where the father has CBAVD and is either heterozygous or homozygous.

When a man has CBAVD, it is important to test him and his partner for cystic fibrosis mutations. If she is also found to be a carrier, the couple must very carefully consider whether to proceed with ICSI using the husband's sperm, as the chance of a baby with cystic fibrosis will be 25% if he is heterozygous or 50% if he is homozygous. If the female partner is negative for known mutations, her chance of being a carrier of unknown mutations is about 0.4%. In these circumstances, the possibility of her heterozygous partner fathering a child with cystic fibrosis is approximately 1:410.

#### **4.6 Unilateral or bilateral absence or abnormality of the vas and renal anomalies**

Unilateral absence of the vas deferens is usually associated with ipsilateral absence of the kidney [35] and probably has a different genetic causation. Men with unilateral absence of the vas deferens are usually fertile, and the condition is most commonly encountered as an incidental finding in the vasectomy clinic. Nevertheless, in men with unilateral absence of the vas deferens, cystic fibrosis mutations may underlie the same genetic diseases as those with true CBAVD. In addition, it was found that men with bilateral absence of vas deferens and renal abnormalities have no CFTR abnormalities [36].

Tests for cystic fibrosis mutations should be undertaken in men who are found to have unilateral absence of the vas deferens and/or seminal vesicles and normal kidneys or bilateral absence or bilateral abnormality. If the results are negative and renal anatomy has not been defined, it is worthwhile obtaining an abdominal ultrasound. Findings may range from unilateral absence of the vas with ipsilateral absence of the kidney to bilateral vasal abnormalities and renal abnormalities, such as pelvic kidney.

#### **4.7 Unknown genetic disorders**

ICSI is now used to enable men with severely damaged spermatogenesis to father children in situations formerly considered hopeless and in which very few spermatozoa can be obtained. This has led to worries that children may be born with a fetal abnormality that would otherwise not have occurred. This is because the selective processes of female genital tract and egg coverings are being bypassed to enable defective sperm, that would not otherwise have done so, to fertilize eggs. It is therefore very reassuring that the collected fetal abnormality statistics from ICSI centres do not indicate any increase in congenital malformations compared with the general population. However, the indications for ICSI are constantly being extended to include fertilization with immature sperm forms and it will be particularly important to continue to monitor fetal abnormality rates with detailed subgroup analysis according to the clinical and molecular diagnoses of the father.

#### **4.8 Genetic counselling and ICSI**

The best initial management is to give the couple full information about the risks to the child to help them decide whether or not to proceed with ICSI.

However, in the situation where both partners are known to carry defects (e.g. cystic fibrosis mutations), there can be up to a 50% chance of a child from the union developing clinical cystic fibrosis and dying early after a number of years of morbidity. Many clinicians and infertility clinic personnel may feel that their duty of care to the future child and the interests of society as a whole outweigh the wishes of the individual couple and that it is not ethical to proceed. When there is a conflict that cannot be resolved by agreement, the interests of a future child probably take precedence over the interests of a couple. Furthermore, the couple will need to give consideration to pre-implantation diagnosis and the replacement only of normal embryos.

#### **4.9 CONCLUSIONS**

New insights into the genetic basis of infertility and the advent of ICSI require a good understanding of genetics by clinicians and the general public. Diagnostic advances will allow the genetic basis of more disorders to be identified and will enable easier and cheaper diagnosis of known disorders, for some of which gene therapy may become practicable.

#### 4.10 RECOMMENDATIONS

- Standard karyotype analysis should be offered to all men with damaged spermatogenesis who are seeking fertility treatment by IVF/ICSI (Grade A).
- For men with severely damaged spermatogenesis, testing for Yq microdeletions before ICSI is desirable. However, as these men and their male children are unlikely to have any phenotypic abnormality other than impaired spermatogenesis, it is reasonable to take into account the cost and limitations of current testing methods and to discuss this with the couple (Grade B).
- Wherever possible, Yq microdeletion testing should be encouraged and laboratories should join quality control schemes (Grade B).
- When a man has structural abnormalities of the vas deferens (CBAVD, unilateral absence of the vas), it is important to test him and his partner for cystic fibrosis gene mutations (Grade A).
- Genetic counselling is mandatory in couples with a genetic abnormality found in clinical or genetic investigation and in patients who carry a (potential) inheritable disease (Grade A).

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## 5 OBSTRUCTIVE AZOOSPERMIA

### 5.1 Definition

Obstructive azoospermia means the absence of both spermatozoa and spermatogenic cells in semen and post-ejaculate urine due to bilateral obstruction of the seminal ducts.

### 5.2 Classification

#### 5.2.1 *Intratesticular obstruction*

Intratesticular obstruction occurs in 15% of obstructive azoospermia [1]. Congenital forms (dysjunction between rete testis and efferent ductules) are less common than acquired forms, i.e. post-inflammatory or posttraumatic obstructions. The latter are often associated with an obstruction of epididymis and vas deferens.

#### 5.2.2 *Epididymal obstruction*

Epididymal obstruction is the most common cause of obstructive azoospermia, affecting 30-67% of azoospermic men with a serum FSH less than twice the upper limit of normal [1-4].

Congenital epididymal obstruction usually manifests as congenital bilateral absence of the vas deferens (CBAVD), which is associated with at least one mutation of the cystic fibrosis gene in 82% of cases [5]. This form is often accompanied by absence of the distal part of the epididymis and seminal vesicle agenesis (see Genetic disorders in infertility). Other congenital forms of obstruction (dysjunction between efferent ductless and corpus epididymidis, agenesis/atresia of a short part of the epididymis) are rare.

Inborn forms also include chronic sinopulmonary infections (Young's syndrome) [6], where obstruction results from a mechanical blockage due to debris within the proximal epididymal lumen.

Among the acquired forms, those secondary to acute (gonococcal) and subclinical (e.g. chlamydial) epididymitis are considered to be most frequent [7,8] (see Male accessory gland infections). Acute or chronic traumas may result in epididymal damage [9].

Azoospermia caused by surgery may occur after epididymal cyst removal. Epididymal obstruction secondary to long-lasting distal obstruction must be taken into account when repairing seminal ducts.

#### 5.2.3 *Vas deferens obstruction*

Vas deferens obstruction is the most frequent cause of acquired obstruction following vasectomy for sterilization. About 2-6% of these men request vasectomy reversal. Of those undergoing vasovasostomy, 5-10% appear to have epididymal blockage due to tubule rupture, making epididymovasostomy mandatory (see Male contraception, vasectomy and vasectomy reversal). Vasal obstruction may also occur after herniotomy [10].

The most common congenital vasal obstruction is CBAVD, often accompanied by cystic fibrosis. Unilateral agenesis or a partial defect is associated with contralateral seminal duct anomalies or renal agenesis in 80% and 26% of cases, respectively [11] (see Genetic disorders in infertility). Distal vas deferens obstruction includes CBAVD and accidental injury to the vas deferens during hernia surgery [12].

#### 5.2.4 *Ejaculatory duct obstruction*

Ejaculatory duct obstruction is found in about 1-3% of obstructive azoospermia [1]. These obstructions can be classified as cystic or post-inflammatory.

Cystic obstructions are usually congenital (i.e. Müllerian duct cyst or urogenital sinus/ejaculatory duct cysts) and are medially located in the prostate between the ejaculatory ducts. In urogenital sinus anomalies, one or both ejaculatory ducts empty into the cyst [13], while in Müllerian duct anomalies, ejaculatory ducts are laterally displaced and compressed by the cyst [14].

Paramedian or lateral intraprostatic cysts are Wolffian in origin and rarely found in clinical practice [15]. Post-inflammatory obstructions of the ejaculatory duct are usually secondary to acute, non-acute or chronic urethroprostatitis [16].

Congenital or acquired complete obstructions of the ejaculatory ducts are commonly associated with low semen volume, decreased or absent seminal fructose and acid pH. The seminal vesicles are usually dilated (anterior-posterior diameter > 15 mm) [16,17].

#### 5.2.5 *Functional obstruction of the distal seminal ducts*

This might be attributed to local neuropathy [18]. Because of the vasographic patterns of ampullovesicular atony or of ejaculatory duct hypertony, this abnormality very often seems to be associated with urodynamic dysfunctions. Although it has been observed in patients suffering from juvenile diabetes and in polycystic kidney disease [19], no relevant pathology has been found in most cases described. Results of semen analysis vary between azoospermia, cryptozoospermia and severe oligo-astheno-zoospermia.

### 5.3 **Diagnostic management**

#### 5.3.1 *Semen analysis*

At least two examinations must be performed with an interval of 2-3 months, according to the WHO (see Investigations). Azoospermia means absence of spermatozoa after centrifugation at a magnification x400. Careful repeat observation of several smears after semen liquefaction is necessary. Finding no spermatozoa in wet preparation involves the centrifugation of aliquots or of the whole semen sample (600 rpm for 15 min). The pellet must be examined for spermatozoa.

A semen volume of less than 1.5 ml and with an acid pH and low fructose level suggests ejaculatory duct obstruction or CBAVD. When semen volume is low, spermatozoa in urine after ejaculation must always be searched for, as their presence confirms an ejaculatory disorder. Absence of spermatozoa and immature germ cells in semen smears suggest complete proximal or distal seminal duct obstruction.

#### 5.3.2 *Clinical history*

Clinical history taking should follow the suggestions for investigation of infertile men (see Investigations), including inquiring about the presence of:

- Haemospermia
- Post-ejaculatory pain
- Previous or present urethritis, prostatitis
- Obstructive or irritative urinary symptoms
- Previous scrotal enlargement or pain or surgery
- Previous inguinal herniorrhaphy or traumas
- Chronic sinopulmonary infections.

#### 5.3.3 *Clinical examination*

This follows the suggestions for investigation of the infertile man. The following findings are indicative for obstructive azoospermia:

- At least one testis > 15 ml volume (although a smaller testicular volume may be found in some patients with obstructive azoospermia and concomitant partial testicular failure)
- Enlarged and hardened epididymis
- Nodules in the epididymis or vas deferens
- Absence or partial atresia of the vas
- Signs of urethritis
- Prostatic abnormalities.

#### 5.3.4 *Hormone levels*

Serum FSH levels may be normal but do not exclude a testicular cause of azoospermia (e.g. spermatogenic arrest). In fact, FSH is normal in 40% of men with primary spermatogenic failure. Inhibin B appears to have a higher predictive value for the presence of normal spermatogenesis [4].

#### 5.3.5 *Ultrasonography*

Scrotal ultrasound can be helpful in finding signs of obstruction (e.g. dilatation of rete testis, enlarged epididymis with cystic lesions and absence of vas deferens) and to exclude signs of testicular dysgenesis, such as non-homogenous testicular architecture and microcalcifications.

Transurethral Ultrasound (TRUS) must be performed on patients with a low seminal volume and in whom distal obstruction is suspected. If possible, TRUS should be performed at high resolution and with high-frequency (7 MHz) biplane transducers. Seminal vesicle enlargement (anterior-posterior diameter  $\geq$  15 mm) [17]

and roundish, anechoic areas in the seminal vesicle [20] are TRUS anomalies more often associated with ejaculatory duct obstruction, especially when semen volume is  $\leq 1.5$  ml. Other known anomalies in cases of obstructive azoospermia are Müllerian duct cysts or urogenital sinus/ejaculatory duct cysts [16] and ejaculatory duct calcifications [21]. TRUS may also be applied to aspirate seminal vesicle fluid [22].

Invasive diagnosis, including testicular biopsy, scrotal exploration and distal seminal duct evaluation, are indicated in patients with obstructive azoospermia in whom an acquired obstruction of the seminal ducts is suspected. It is advisable to perform explorative and recanalization surgery at the same time.

#### 5.3.6 Testicular biopsy

This may be indicated to exclude spermatogenic failure in selective cases. The same surgical procedure may also be used to extract testicular spermatozoa (i.e. TESE) for cryopreservation and subsequent ICSI, when surgical recanalization cannot be performed or has failed (see Primary spermatogenetic failure).

#### 5.3.7 Distal seminal tract evaluation

Evaluation of the distal seminal tract must consider the anatomical patency of the seminal ducts downstream to the proximal vas deferens.

One technique involves cannulating each vas deferens and injecting a saline solution mixed with 0.5 ml of 10% methylene blue. If the saline solution passes through easily, radiographic contrast and X-ray evaluation (vasography) are not needed. The injected solution passed into the bladder is recovered through a Foley catheter, and spermatozoa are searched for and counted (seminal tract washout) [23].

In an alternative method, the proximal vas deferens is microsurgically hemitranssected (x15 power magnification) and any fluid from the lumen is placed on a slide and mixed with a drop of saline solution. Absence of spermatozoa on microscopic examination indicates epididymal obstruction (if testicular biopsy is normal or only slightly altered). However, if spermatozoa are found inside the proximal vas deferens of an azoospermic patient, this suggests a distal seminal duct obstruction. In this case, antegrade cannulation of the vas deferens and injection of saline solution plus methylene blue are performed. If the solution passes easily, vasography is not necessary [24]. If injection is difficult or impossible, an anatomical ejaculatory duct obstruction or vas deferens obstruction, respectively, are suspected. In both cases, vasography is indicated to identify the nature and site of obstruction. At the end of the procedure, a microsurgical suture of the vas deferens is required [24].

## 5.4 Treatment

### 5.4.1 Intratesticular obstruction

Since seminal duct recanalization at this level is impossible, TESE or fine-needle aspiration are recommended (see Primary spermatogenetic failure). The spermatozoa retrieved may be immediately used for ICSI or may be cryopreserved. Both TESE and fine-needle aspiration allow sperm retrieval in nearly all obstructive azoospermic patients.

### 5.4.2 Epididymal obstruction

Microsurgical epididymal sperm aspiration (MESA) [25] is indicated in men with CBAVD. Retrieved spermatozoa are usually used for ICSI. In general, one MESA procedure provides sufficient material for several ICSI cycles [26]. In patients with azoospermia due to acquired epididymal obstruction, end-to-end or end-to-side microsurgical epididymovasostomy is recommended.

Reconstruction may be done unilaterally or bilaterally; patency and pregnancy rates are usually higher with bilateral reconstruction. Before performing microsurgery, it is important to check that there is full patency downstream of the epididymis. Anatomical recanalization following surgery may require 3-18 months. Before performing microsurgery (and also in all cases where recanalization is impossible), epididymal spermatozoa should be aspirated and cryopreserved to be used for ICSI in case of surgical failure [26].

Patency rates range between 60% and 87% [27-29] and cumulative pregnancy rates between 10% and 43%. Recanalization success rates may be adversely affected by pre-operative and operative findings, such as concomitant abnormal testicular histology, absence of sperm in the spermatic fluid on sectioning the small epididymal tubules and wide fibrosis of the epididymis.

The finding of motile or immotile spermatozoa at the level of the anastomosis does not appear to be related to the patency rate, but moving from the corpus to the caput epididymidis has a significant adverse effect upon patency and pregnancy outcome. Spermatozoa need to pass through at least part of the epididymis to mature and be able to fertilize oocytes in a natural cycle. Concomitant presence of ultrasonographic abnormalities in the prostate and seminal vesicles is also associated with a less favourable outcome [30].

In terms of delivery rate, vasoepididymostomy in patients with epididymal obstruction secondary to vasectomy has proved more successful and more cost-effective than MESE and ICSI [31] (see Male contraception, vasectomy and vasectomy reversal).

#### 5.4.3 Proximal vas obstruction

Proximal vas obstruction after vasectomy requires microsurgical vasectomy reversal (see Vasectomy and vasectomy reversal). Vasovasostomy must also be performed in the rare cases of proximal vasal obstructions (iatrogenic, post-traumatic, post-inflammatory). When spermatozoa are absent in the intraoperative vas fluid, a secondary epididymal obstruction may be present, especially if the seminal fluid of the proximal vas has a thick 'toothpaste' appearance. Microsurgical vasoepididymostomy is indicated.

#### 5.4.4 Distal vas deferens obstruction

Large bilateral vas defects resulting from involuntary vas excision during hernia surgery in early childhood or previous orchidopexy are usually intractable [12]. In these cases, one can resort to proximal vas deferens sperm aspiration [32] or TESE/MESA to be used for ICSI. In large monolateral vas defects associated with contralateral testicular atrophy, the vas of the atrophic testis can be used for a crossover vasovasostomy or vasoepididymostomy.

Sperm reservoirs fixed onto epididymis or proximal vas deferens have been used during the past decade, but with poor outcome [33]. Therefore, this type of surgery is not recommended anymore.

#### 5.4.5 Ejaculatory duct obstruction

The treatment of ejaculatory duct obstruction depends on the aetiology. In large post-inflammatory obstruction and when one or both ejaculatory ducts empty into an intraprostatic midline cyst, transurethral resection of the ejaculatory ducts (TURED) [16,34] is recommended. Resection may remove part of the verumontanum. In cases of obstruction due to a midline intraprostatic cyst, incision or unroofing of the cyst is required [16]. Intraoperative TRUS makes this procedure safer and more effective. If distal seminal tract evaluation is carried out at the time of the procedure, installation of methylene blue dye into the vas may be helpful to document opening of the ducts.

Complications following TURED include retrograde ejaculation due to bladder neck injury, reflux of urine into ducts, seminal vesicles and vasa (causing poor sperm motility, acid semen pH and epididymitis). Alternatives to TURED are MESA, TESE, proximal vas deferens sperm aspiration, seminal vesicle aspiration and direct ultrasonically-guided cyst aspiration.

In cases of functional obstruction of the distal seminal ducts, TURED often fails to improve the sperm output. Spermatozoa may then be retrieved by antegrade seminal tract washout [35]. Spermatozoa retrieved by any of the aforementioned surgical techniques should always be cryopreserved for assisted reproductive procedures.

### 5.5 CONCLUSIONS

- Obstructive lesions of the seminal tract should be suspected in azoospermic or severely oligozoospermic patients with normal-sized testes and normal endocrine parameters.
- Results of reconstructive microsurgery depend on the cause and location of the obstruction and the expertise of the surgeon. Standardized procedures include vasovasostomy, epididymovasostomy and TURED.
- Sperm retrieval techniques such as MESA, TESE and testicular fine-needle aspiration can be applied additionally. The consensus is that these methods should only be performed with the facility for cryostorage of the material obtained.

### 5.6 RECOMMENDATIONS

- In cases of azoospermia due to epididymal obstruction a scrotal exploration with MESA and cryopreservation of the spermatozoa should be performed together with a microsurgical reconstruction (Grade B).
- Ejaculatory duct obstruction due to a midline prostatic cyst can be treated by TURED (Grade C).

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## 6 VARICOCELE

### 6.1 Introduction

Varicocele is a common abnormality (see Investigations) with the following andrological implications:

- Failure of ipsilateral testicular growth and development
- Symptoms of pain and discomfort
- Infertility.

### 6.2 Classification

The following classification of varicocele [1,2] is useful in clinical practice:

- Subclinical: Not palpable or visible at rest or during Valsalva manoeuvre, but demonstrable by special tests (reflux found upon Doppler examination) [3]
- Grade 1: Palpable during Valsalva manoeuvre but not otherwise
- Grade 2: Palpable at rest, but not visible
- Grade 3: Visible and palpable at rest.

### 6.3 Diagnosis

The diagnosis of varicocele has been defined by the WHO [2]. The consensus is that diagnostic procedures and classification of a varicocele, including analysis, have to follow these accepted criteria [2].

The diagnosis of varicocele is made by clinical examination and may be confirmed by colour Doppler analysis. In centres where treatment is performed by antegrade or retrograde sclerotherapy or embolization, the diagnosis is additionally confirmed by X-ray.

### 6.4 Basic considerations

- Varicocele is a physical abnormality present in 2-22% of the adult male population [4,5]. It is more common in men of infertile marriages, affecting 25% of those with abnormal semen analysis [6].
- The incidence of pain and discomfort associated with varicocele is 2-10% [7]. Treatment to relieve symptoms is often recommended, but there have been few outcome studies; however, most urologists accept discomfort as a valid indication.

- The exact association between reduced male fertility and varicocele is not known, but analysis of the WHO data [8] clearly indicates that varicocele is related to semen abnormalities, decreased testicular volume and decline in Leydig cell function.
- Two prospective randomized studies showed increased ipsi- and contralateral testis growth in adolescents who had received varicocele treatment compared with those who did not [9,10]. A cohort follow-up study involving serial measurement of testicular size in growing children indicated arrest of testicular development coincident with development of varicocele and catch-up to the growth percentile after treatment [11].
- A series of studies suggested that altered endocrine profiles in men with varicocele (exaggerated response to releasing factor) might predict those who would benefit from treatment [12,13].
- Five prospective randomized studies of varicocele treatment in adults gave conflicting results [6,14-18], with the largest of them indicating benefit [16,18]. The study involved 10 centres, was externally randomized and included men of infertile couples who had moderate oligozoospermia ( $5-20 \times 10^6/\text{ml}$ ) and grade II or III varicocele. Immediate therapy was shown to be significantly more effective than delaying treatment for 1 year with regard to pregnancy achievement and pregnancy rate per cycle (fecundability). However, meta-analysis of the five trials indicated no benefit (the common odds ratio was 0.85% (95% CI: 0.49-1.45) [19].
- There has been one prospective randomized study of treatment of subclinical varicocele, which failed to indicate fertility benefit from therapy [20].
- Analysis of the large WHO infertility study [21] indicated that there was an excess of couples where both partners had factors associated with reduced fertility compared with the expected rate of coincidence in the general population. This implied that a minor cause of impaired fertility, such as varicocele, will only manifest in couples in which the female partner also has reduced fertility.

## 6.5 Treatment

Several treatment modalities can be chosen (Table 6). The type of intervention is mainly dependent on the therapist's experience. Although laparoscopic varicocelectomy is feasible, it needs to be justified in terms of cost effectiveness.

**Table 6: Recurrence and complication rates of different treatment methods for varicocele**

Treatment	Recurrence/persistence rates	Complications
Antegrade sclerotherapy	9% [22]	Complication rate 0.3-2.2%; testicular atrophy; scrotal haematoma; epididymitis; left-flank erythema
Retrograde sclerotherapy	Recurrence and persistence rate 9.8% [23,24]	Adverse reaction to the contrast medium; flank pain; persistent thrombophlebitis; vascular perforation [25]
Retrograde embolization	3.8-10% [26,27]	Pain due to thrombophlebitis [27]; bleeding; haematoma; infection; venous perforation; hydrocele; radiological complication, e.g. reaction to contrast media; misplacement or migration of the coils [28]; retroperitoneal haemorrhage; fibrosis; ureteric obstruction [5]
<i>Open operation</i>		
• Scrotal approach		Testicular atrophy [5]; arterial damage with risk of devascularization and gangrene of the testicle
• Inguinal approach	13.3% [29]	Possibility of missing out a branch of testicular vein
• High ligation	29% [29]	5-10% incidence of hydrocele [30]
• Micro-surgical	0.8-4% [31,32]	Post-operative hydrocele arterial injury; scrotal haematoma
Laparoscopy	3-7% [33-35]	Injury to testicular artery and lymph vessels; intestinal, vascular and nerve damage; pulmonary embolism; peritonitis [35]; bleeding; postoperative pain in right shoulder (due to diaphragmatic stretching during pneumoperitonium) [34]; pneumoscrotum; wound infection [35]

## 6.6 CONCLUSIONS

Current information fits with the hypothesis that in some men the presence of varicocele is associated with progressive testicular damage from adolescence onwards and consequent reduction in fertility. However, in infertile couples this impaired fertility potential will only be manifest if female fertility is also reduced.

Although treatment of varicocele in adolescents may be effective, there is a significant risk of overtreatment. Data from an ongoing study will provide more information in this respect [10].

Randomized studies and meta-analysis of randomized studies indicate no fertility benefit from varicocele ligation.

## 6.7 RECOMMENDATIONS

- Treatment is recommended for adolescents who have progressive failure of testicular development documented by serial clinical examination (Grade B).
- There is no evidence indicating benefit from varicocele treatment in adolescents who have no ipsilateral testicular atrophy and no endocrine abnormalities. In this situation, varicocele treatment cannot be recommended except in the context of clinical trials (Grade B).
- Meta-analysis of randomized clinical trials indicates no fertility benefit after varicocele ligation in adults [19]. Varicocele ligation for infertility should not be done unless there has been full discussion with the man about the uncertainties of treatment benefit (Grade B).

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# 7 HYPOGONADISM

## 7.1 Introduction

Men with hypogonadism (Table 7) usually present with symptoms of androgen deficiency (see Investigations). In some cases, hypogonadotrophic hypogonadism, a treatable form of male infertility [1], is present.

**Table 7: Disorders with male hypogonadism. Modified from Nieschlag et al. [2]**

<b>Hypothalamic-pituitary origin (hypogonadotrophic state with secondary hypogonadism)</b>
• Idiopathic hypogonadotrophic hypogonadism (including Kallmann's syndrome)
• Delayed puberty
• Hyperprolactinaemia
• Drugs/anabolic steroids
<b>Hypergonadotrophic hypogonadism (= testicular insufficiency)</b>
• Anorchia
• Congenital factors (testicular dysgenesis)
• Acquired factors (trauma, testicular torsion, tumour, surgery)
• Maldescended testes
• Klinefelter's syndrome (see Genetic disorders in infertility)
• Other chromosomal alterations (see Genetic disorders in infertility)
• Germ cell aplasia
• Complete and focal germ cell aplasia (SCOS) (either congenital or acquired: maldescended testes, irradiation, cytostatic drugs)
• Spermatogenic arrest
• Post-inflammatory (orchitis)
• Exogenous factors (medications, toxins, irradiation, heat)
• Systemic diseases (liver cirrhosis, renal failure)
• Testicular tumour
• Varicocele
• Surgeries that can damage vascularization of the testes
• Idiopathic
<b>Target organ resistance to androgens</b>
• Testicular feminization
• Reifenstein's syndrome

## 7.2 Hypogonadotrophic hypogonadism

Primary hypogonadotrophic hypogonadism is caused either by hypothalamic or pituitary diseases. The failure of hormonal regulation can easily be determined [3]. Endocrine deficiency leads to a lack of spermatogenesis and testosterone secretion due to decreased secretion patterns of LH and FSH.

The therapy of choice is human chorionic gonadotrophin (hCG) treatment, with the later addition of human menopausal globulin (hMG), depending on the initial testicular volume [4].

If hypogonadotrophic hypogonadism is hypothalamic in origin, 1-year therapy with pulsatile gonadotrophin-releasing hormone (GnRH) is as effective as gonadotrophins in stimulating spermatogenesis [5]. Once pregnancy has been induced, patients can return to testosterone substitution.

Secondary hypogonadotrophic hypogonadism can be caused by some drugs, hormones and anabolic steroids.

## 7.3 Hypergonadotrophic hypogonadism

Common conditions associated with hypergonadotrophic hypogonadism in younger men include injury to and loss of the testicles (e.g. after bilateral testicular cancer) (Table 7). More recently, it has been recognized that hypogonadism may occur after extensive testicular biopsy to recover sperm for IVF/ICSI [6]. Men with Klinefelter's syndrome are at risk for spontaneous hypogonadism with ageing. Those undergoing extensive testicular biopsy in the context of IVF/ICSI will almost certainly have an increased risk [7].

Hypergonadotrophic hypogonadism may occur spontaneously in the elderly, in patients with erectile dysfunction [8], and after luteinizing hormone releasing hormone (LHRH) treatment or surgical castration for prostatic cancer [9]. All these conditions are not clinically significant for infertile men. Hypogonadism may be associated with osteoporosis [10].

The laboratory diagnosis of hypergonadotrophic hypogonadism is based on decreased serum testosterone and increased LH levels [2]. Additional prolactin measurement is suggested.

Testosterone supplementation is only indicated in men with levels consistently lower than normal (< 12 nmol/l = 300 ng/dl). Injectable, oral and transdermal testosterone preparations are available for clinical use [2]. The best preparation is the one that maintains serum testosterone levels as close to physiological concentrations as possible [11].

#### 7.4 CONCLUSION

There is general agreement that patients with primary or secondary hypogonadism should receive testosterone substitution therapy.

#### 7.5 RECOMMENDATION

Effective drug therapy is available to achieve fertility in men with hypogonadotropic hypogonadism (Grade A).

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# 8 CRYPTORCHIDISM

## 8.1 Introduction

Cryptorchidism is the most frequent congenital abnormality of the male genitalia with an incidence of 2-5% at birth. At the age of 3 months, the incidence is reduced spontaneously to 1-2%. Approximately 20% of undescended testes are non-palpable and may be located within the abdominal cavity.

The aetiology of cryptorchidism is multifactorial and both disrupted endocrine regulation and several gene defects may be involved. For a normal descent of the testes, a normal hypothalamo-pituitary-gonadal axis is needed. Although the majority of boys with maldescended testes show no endocrine abnormalities after birth, endocrine disruption in early pregnancy can potentially affect gonadal development and normal descent. It has been postulated that cryptorchidism can be the consequence of testicular dysgenesis, a developmental disorder of the gonads due to environmental and/or genetic influences early in pregnancy. The testicular dysgenesis syndrome (TDS) can result in maldescent, reduced fertility and an increased risk for malignant development [1].

## 8.2 Incidence of cryptorchidism

The Caucasian population has a three-fold higher incidence of cryptorchidism compared to African-Americans. Premature babies reveal a much higher incidence than full-term babies. One study examined more than 3,000 newborns in London, UK [2]. The incidence of cryptorchidism in boys weighing >2,500 g was 2.7% whereas in premature boys weighing <2,500 g the corresponding number was 21%. At the age of 3 months, spontaneous descent had occurred in the majority of cases and the incidence rate declined to 0.9 and 1.7%, respectively [2].

## 8.3 Testicular descent and maldescent

During the developmental phase of the "transabdominal descent", the development of the gubernaculum and genitoinguinal ligament play an important role. The anti-müllerian hormone additionally regulates the transabdominal descent of the testis. Induction of the gubernaculum is dependent on functional *Insl3* gene in mice [3]. This gene is expressed in Leydig cells, and its targeted deletion causes bilateral cryptorchidism with free-moving testes and genital ducts [4]. There are other gene families, e.g. the homeobox (HOX) genes and the GREAT gene, which are important for the development of genital organs and may be associated with testicular maldescent [5,6].

## 8.4 Hormonal control of testicular descent

Maldescent can be caused by two hormonal factors: hypogonadism and androgen insensitivity. In addition, the increasing incidence of reproductive abnormalities in human males may be explained by an increased oestrogen exposure during gestation [7]. Some pesticides and synthetic chemicals are known to act as hormonal modulators, often possessing oestrogenic activity (xeno-oestrogens) [8]. The oestrogenic and anti-androgenic properties of these chemicals may cause hypospadias, cryptorchidism, reduction of sperm density, and an increase of testicular tumours in animal models by receptor-mediated mechanisms or direct toxic effects [9].

## 8.5 Pathophysiological effects in maldescended testes

### 8.5.1 Degeneration of germ cells

It has been established that the degeneration of germ cells in maldescended testes becomes apparent after the first year. Depending on the different position of the testis, the degenerative changes are variable [10]. During the second year of life, the number of germ cells clearly starts to decline. In 10-45% of patients, a complete loss of germ cells can be detected. Thus, early treatment is recommended to conserve spermatogenesis, especially in bilateral cases. Surgical treatment is the most effective and reliable method to bring testes into the scrotum, but hormonal treatment with either hCG or GnRh analogs may be considered, particularly in cases where testes are located in the high scrotal position [4-7].

### 8.5.2 Relationship with fertility

Semen parameters in men with a history of cryptorchidism is often impaired: in 2-9% of infertile patients, a history of cryptorchidism is present [11]. It has been suggested that surgical treatment performed before the age of 3 years has a positive effect on semen quality [12]. However, paternity in men with a history of unilateral cryptorchidism is almost equal (89.7%) to paternity in men without cryptorchidism (93.7%). Also, in men with unilateral cryptorchidism, paternity seems independent of the age of orchidopexy, preoperative testicular location and testicular size [13]. In men with bilateral cryptorchidism, oligozoospermia can be found in 31% and azoospermia in 42%. In cases of bilateral cryptorchidism, paternity is only 35-53%.

### 8.5.3 Germ cell tumours

Cryptorchidism is a risk factor for testicular cancer development and is associated with testicular microcalcification and carcinoma *in situ* (CIS) of the testis. In about 5-10% of testicular cancers, a history of cryptorchidism can be found (14,15). The risk of a germ cell tumour is 3.6-7.4 times higher than in the general population: 2-6% of men with a history of cryptorchidism will develop a testicular tumour.

## 8.6 Treatment of undescended testes

### 8.6.1 Hormonal treatment

In randomized, controlled trials for the efficacy and side effects of hCG and GnRH treatment, a large variation in success rates has been reported. The corresponding figures in all randomized trials were 21%, 19% and 4% for GnRH, hCG and placebo, respectively [16]. A meta-analysis of 33 studies published between 1958 and 1990 by Pyorala et al. [17] showed that the success rate was best in prescrotal and high scrotal testes. Non-palpable testes rarely descend with hormonal treatment.

The current hormone protocol of high scrotal testes includes three hCG injections given once a week. The dose is 1500 IU per injection for children at ages 1-3 years, 3000 IU at ages 4-6 years, and 5000 IU at ages 6-15 years. The recommended age for this treatment is 12-18 months. In case of bilateral impalpable testes, an hCG stimulation test can be performed; a rise in testosterone levels confirms the presence of testes. Inhibin B is produced by the Sertoli cells of the testis and can be a good indicator for testicular function in children [18]. Hormonal treatment is considered safe and only a few side effects have been associated. Early harmful effects include penile growth, pain in the genital region, pain at the site of injection and psychological changes.

### 8.6.2 Surgical treatment

The success rates of surgical treatment is 70-90% in cases of undescended testes [19]. When the spermatic cord or vessels are too short to allow proper mobilization of the testis into the scrotum, a staged orchidopexy (Fowler-Stephenson procedure) can be performed. The applied techniques are open surgery, laparoscopy, or microsurgery.

Surgical operation may also reveal absence of a gonad, which has been reported in 16-59% of patients with an impalpable testis. Impalpable testes can also be dysgenetic. In unilateral cases, orchidectomy should be considered because of an increased risk for malignant development [20]. After orchidopexy, vascular damage is the most severe complication and may cause testicular atrophy in 1-2%. In non-palpable testes, the postoperative atrophy rate was found to be 12% in cases where the vascular pedicles were long enough to allow scrotal positioning. Postoperative atrophy was reported in up to 40% of cases of staged orchidopexia.

## 8.7 CONCLUSIONS

- Cryptorchidism is multifactorial in origin and may be caused by genetic factors and endocrine disruption early in pregnancy.
- Cryptorchidism is often associated with testicular dysgenesis and is a risk factor for infertility and germ cell tumours.
- Early surgical intervention may prevent germ cell loss.
- Paternity in men with unilateral cryptorchidism is almost equal to paternity in men without cryptorchidism.
- In bilateral cases of cryptorchidism paternity is significantly reduced.

## 8.8 RECOMMENDATIONS

- The success rate of hormonal treatment of cryptorchidism has only been shown for prescrotal and high scrotal testes. Non-palpable testes rarely descend with hormonal treatment (Grade B).
- Treatment of cryptorchidism before the age of 3 years is recommended to preserve fertility potential, especially in bilateral cases (Grade C).

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## 9 IDIOPATHIC MALE INFERTILITY

Many men presenting with infertility are found to have idiopathic oligo-astheno-teratozoospermia (OAT) syndrome. No demonstrable cause of male infertility, except for OAT, is found in 40-75% of infertile men. Drug treatments for idiopathic male infertility are discussed.

### 9.1 Empirical treatments

A wide variety of empirical drug approaches have been used (Table 8). However, there is little scientific evidence for an empirical approach [1]. Criteria for the analysis of all therapeutic trials have been re-evaluated. There is consensus that only randomized, controlled trials, with 'pregnancy' as the outcome parameter, can be accepted for efficacy analysis. Use of recombinant human FSH in patients with idiopathic oligozoospermia with normal FSH and inhibin B may be a debatable choice in the future to improve spermatogenesis. Further studies are necessary.

**Table 8: Empirical therapy of idiopathic oligo-astheno-teratozoospermia (OAT) syndrome†**

Therapeutic approaches	EAU recommendations
<i>Hormonal</i>	
GnRH	Contradictory results Not controlled trials Not recommended
HCG/hMG	Lack of efficacy Not recommended
FSH	Lack of efficacy Further trials needed [2]

Androgens	Lack of efficacy Not recommended
Anti-oestrogens (clomiphene citrate, tamoxifen-testosterone undecanoate)	Potentially effective [3] Use must be counterbalanced against possible side-effects
<i>Non-hormonal</i>	
Kinin-enhancing drugs	Unproven efficacy Clinical trials only
Bromocriptine	Lack of efficacy Not recommended
Antioxidants	May benefit selected patients Clinical trials only
Mast cell blockers	Some efficacy shown Further evaluation needed Clinical trials only
Alpha-blockers	Lack of efficacy Not recommended
Systemic corticosteroids	Lack of efficacy Patients with high levels of antisperm antibodies should enter an ART programme
Magnesium supplementation	Unproven efficacy [4] Not recommended

\* ART = assisted reproduction techniques; FSH = follicle-stimulating hormone; GnRH = gonadotrophin-releasing hormone; hCG = human chorionic gonadotrophin; hMG = human menopausal gonadotrophin.  
 ‡Also based in parts on the recommendations of the 'Infertility Guidelines Group' of the Royal College of Obstetricians and Gynaecologists, London 1998.

## 9.2 RECOMMENDATIONS

- Medical treatment of male infertility can only be advised in cases of hypogonadotropic hypogonadism (Grade A).
- Drugs are usually ineffective in the treatment of idiopathic male infertility (Grade B).
- The effect of any infertility treatment must be weighed against the likelihood of spontaneous conception.
- Tamoxifen and testosterone undecanoate appear to increase the natural conception rate in a selection of men with idiopathic oligozoospermie [3] (Grade B).

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# 10 MALE CONTRACEPTION

## 10.1 Introduction

It is more precise to discuss the male contribution to contraception rather than 'male contraception', because men do not conceive. According to the WHO (1992), there are 910,000 conceptions per day world-wide, of which 50% are unplanned and 25% are involuntary. There are an estimated 150,000 abortions daily with 500 women dying each day as a result of abortion.

Despite research efforts, three of the four methods of male contraception have been in use for 100s of years (i.e. condoms, periodic abstinence and withdrawal), while the fourth (vasectomy) is permanent. In order for men to take more responsibility for family planning, the contraceptive methods applied have to be effective, reversible, acceptable and cheap.

Biomedical research is now attempting to [1]:

- Prevent sperm production (through use of androgens, progestogen and GnRH in various combinations)
- Interfere with the maturation and fertilization ability of sperm (epididymal approach to create a hostile environment for sperms)
- Interrupt sperm transport device (better condoms, e.g. polyurethane)
- Inhibit sperm-egg interactions.

All these approaches remain experimental. To date, they have not been used in men. The development of new, effective methods of male contraception has been identified as a high priority by the WHO Task Force on methods of regulation of male fertility. With development of better and more physiological testosterone supplementation therapies, the endocrinological approach seems to be the most promising.

Hormonal male contraception is based on the suppression of gonadotrophins and testosterone substitution in order to maintain male sexual function and bone mineralization and to prevent muscle waste. For complete interruption of spermatogenesis, an adequate suppression of intratesticular testosterone production is needed. Various contraceptive regimens have been developed and tested, including testosterone monotherapy, androgen/progestin combinations, testosterone with GnRH analogs, and selective androgen and progestin receptor modulators. The combination of testosterone with progestogen is currently the most promising approach to hormonal male contraception [2].

## 10.2 Vasectomy

Vasectomy is the most simple and effective method of permanent surgical sterilization [3]. Men undergoing vasectomy must be interested in permanent contraception. Before the procedure is performed, accurate information must be given to the couple. The possibility of vasectomy reversal should be discussed, but the patient must be informed about the failure rate [4].

### 10.2.1 Surgical techniques

There are various techniques. The most popular and less invasive method seems to be the no-scalpel vasectomy technique [4]. The standard technique of cauterization and clipping, or ligation of, the vasal lumina may be less effective than the technique of cauterization and fascial interposition [5]. Most techniques can be safely performed as an out-patient procedure under local anaesthesia.

### 10.2.2 Complications

Acute local complications include haematoma, wound infection and epididymitis in up to 5% of all cases [6]. Long-term complications, such as chronic testicular pain [7] and development of antisperm antibodies [8] must be discussed with the patient. Epididymal tubal damage is common, with the consequent development of sperm granuloma. Vasectomy does not significantly alter spermatogenesis and Leydig cell function. The volume of ejaculate remains unchanged. Potential systemic effects of vasectomy, including atherosclerosis, have not been proven, and there is no evidence of a significant increase of any systemic disease after vasectomy. In a meta-analysis, Bernal-Delgado et al. could not detect an increased rate of prostate cancer in men who underwent vasectomy [9].

### 10.2.3 Vasectomy failure

The risk ratio for recanalization after vasectomy varies between different techniques but should be less than 2% [5]. Paternity due to re-canalization can occur at any time after vasectomy and does not seem to depend on the surgical procedure. No motile spermatozoa should be detected 3 months after vasectomy; their presence might be a sign of early re-canalization. If motile spermatozoa are present 3 months after vasectomy, the procedure should be repeated. A 'special clearance' can be given to men who continue to produce non-motile spermatozoa up to 1 year after vasectomy [10]. Every patient should be informed preoperatively that long-term re-canalization, although rare, may occur [11].

#### 10.2.4 Counselling

Counselling has to address the following items concerning vasectomy:

- It should be considered irreversible.
- It has a low complication rate.
- It has a low but existing failure rate.
- Couples need to continue their contraceptive measurements until azoospermia is achieved.
- All available data indicate that vasectomy is safe and not associated with any serious, long-term side-effects (Level A).

### 10.3 Vasectomy reversal

A wide range of surgical success rates have been published for vasectomy reversal (up to 90%), depending on the time that has elapsed after vasectomy, type of vasectomy (e.g. open-ended or sealed), type of reversal (vasovasostomy or vasoepididymostomy) and whether reversal was unilateral or bilateral. Although there have been no randomized, controlled trials that compare macrosurgery (loops) and microsurgery, there is consensus that microsurgical techniques with the help of magnification and smaller suture materials should be applied [12].

#### 10.3.1 Length of time since vasectomy

Vasovasostomy results have shown patency rates (up to 90%) superior to pregnancy rates. The longer the interval from vasectomy to reversal, the lower the pregnancy rates. Belker et al. [13] reported results in 1,469 men who had undergone microsurgical vasectomy reversal. Patency and pregnancy rates, respectively, were 97% and 76% for an interval up to 3 years after vasectomy, 88% and 53% for 3-8 years, 79% and 44 % for 9-14 years and 71% and 30% for 15 years or longer.

#### 10.3.2 Epididymovasostomy

The necessity of epididymovasostomy in some cases after vasectomy has been discussed before (see Obstructive azoospermia).

#### 10.3.3 Microsurgical vasectomy reversal versus epididymal or testicular sperm retrieval and ICSI

Calculations of cost per delivery for vasectomy reversal versus sperm retrieval-ICSI under a wide variety of initial assumptions clearly indicate that vasectomy reversal is associated with a considerably lower costs per delivery and higher delivery rates [14,15]. Recent calculations show that sperm retrieval and ICSI have to yield a 81% pregnancy rate per cycle to achieve equal costs to vasectomy reversal.

### 10.4 CONCLUSIONS

The most cost-effective approach to treatment of post-vasectomy infertility is microsurgical reversal. This also has the highest chance of delivery. Couples can have a family after successful vasectomy reversal and no hormonal treatment of the female partner with associated risks of ovarian hyperstimulation and multiple pregnancies is needed. MESA/TESE and ICSI should be reserved for failed surgery.

### 10.5 RECOMMENDATIONS

- Vasectomy is the only established and safe method for the male part of contraception (Grade B).
- Consultation has to include the information about the surgical method, side effects and complication rate.
- Other methods of male contraception are either unsafe or still experimental (hormonal approach).
- Microsurgical vasectomy reversal is a low-risk and (cost-) effective method of restoration of fertility (Grade B).
- Success of the procedure largely depends on the (micro)-surgical skills of the surgeon, the interval between vasectomy and vasectomy reversal and the age of the female partner (Grade B).
- Sperm aspiration together with ICSI is a second-line option for selective cases and in case of failed vaso-vasostomy.

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# 11 MALE ACCESSORY GLAND INFECTION

## 11.1 Introduction

It is generally accepted that infections of the male urogenital tract are potentially correctable causes of male infertility [1-3]. In this context, urethritis and prostatitis, orchitis and epididymitis have been described as male accessory gland infections by the WHO [2]. However, concrete data are lacking to confirm that these diseases have a negative influence on sperm quality.

## 11.2 Urethritis

Infectious, sexually acquired urethritis may be caused by a variety of pathogens, most commonly by *Chlamydia trachomatis*, *Ureaplasma urealyticum* and *Neisseria gonorrhoeae* [4]. Non-infectious causes of urethritis include irritations due to allergic reactions, trauma and manipulations. Urethral discharge and bladder voiding difficulties are the predominant symptoms of acute urethritis.

Diagnosis is based on the analysis of urethral smear and first-catch urine. Evidence of  $\geq 4$  granulocytes per microscopic field ( $\times 1000$ ) in urethral smear, or of 15 granulocytes per microscopic field ( $\times 400$ ) in the smear of the sediment of 3 ml VB 1, has been considered pathognomonic [4]. In urethritis, defined by inflammatory discharge, an examination to detect fertility disturbances is not credible as the anterior urethra is full of infectious and inflammatory material, which hampers any useful semen analysis [5].

Due to contamination of the ejaculate with inflammatory material from the urethra, the impact of urethritis on semen quality and fertility is not really proven.

It is debated whether or not sexually transmitted micro-organisms adversely affect sperm function [1,6,7]. Urethral strictures and ejaculatory disturbances have been claimed to impair male fertility [2], as has the development of obstruction [8], either as the usual urethral stricture or as a lesion in the posterior urethra in the area of the verumontanum. Both these lesions can lead to ejaculatory disturbances [2].

Sexually transmitted disease (STD) treatment is standardized by the guidelines of the Centers of Disease Control and Prevention Atlanta, USA [9]. As the aetiology of acute urethritis is unknown in most cases at the time of diagnosis, empirical therapy is suggested, with one single dose of a fluoroquinolone, followed by a 2-week regimen of doxycycline. Treatment is effective both for gonococcal and (co-existing) chlamydial/ureaplasma infections.

## 11.3 Prostatitis

Prostatitis represents the most common urological diagnosis in men under 50 years of age [10].

Traditionally, the disease has been classified into four clinical entities:

- Acute bacterial prostatitis (ABP) and prostatic abscess as sequela of ABP
- Chronic bacterial prostatitis (CBP)
- Non- or abacterial prostatitis (NBP)
- Prostatodynia (Pd).

### 11.3.1 Classification

To improve the definition and understanding of the prostatitis syndrome, a new classification system has been proposed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Washington DC, USA [10] (Table 9).

**Table 9: New NIDDK classification of the prostatitis syndrome. Adapted from [10].**

Category (new)	Description
I Acute bacterial prostatitis (ABP)	Acute infection of the prostate gland
II Chronic bacterial prostatitis (CBP)	Recurrent infection of the prostate
III Chronic abacterial prostatitis/chronic pelvic pain syndrome (CPPS)	No demonstrable infection
IIIA Inflammatory chronic pelvic	White cells in semen, expressed prostatic pain syndrome secretions or post-prostatic massage urine
IIIB Non-inflammatory chronic pelvic	No white cells in semen, expressed prostatic pain syndrome secretions or post-prostatic massage urine
IV Asymptomatic inflammatory prostatitis	No subjective symptoms Inflammation detected either by prostate biopsy or the presence of white cells in expressed prostatic secretions or semen during evaluation for other disorders

### 11.3.2 Microbiology

Acute and chronic bacterial prostatitis and, more significantly, prostatic abscesses are important, but uncommon, diseases. The most common aetiological causes of bacterial prostatitis are gram-negative pathogens, predominantly strains of *Escherichia coli* [11]. The role of gram-positive bacteria in bacterial prostatitis is controversial. Although enterococci may cause bacterial prostatitis and associated recurrent urinary tract infections, the significance of other gram-positive bacteria is doubtful [11], as is that of *C. trachomatis* and *C. mycoplasma*, particularly *U. urealyticum*, in chronic prostatitis [11-15]. Hidden bacterial infections may be aetiologically involved in patients with chronic idiopathic prostatitis after exclusion of typical bacterial infection [16].

### 11.3.3 Diagnosis

Symptoms must be evaluated by means of standardized scores, especially the new National Institutes of Health symptom score [17]. Further procedures include laboratory diagnosis of chronic bacterial prostatitis using the four-specimen test for bacterial localization [10,11]. Its principle is to perform sequential quantitative bacteriological cultures of the urethra, bladder urine and prostatic secretions both in expressed prostatic secretions (EPS) and urine after prostatic massage [12]. Simplified techniques compare bacterial and leukocyte counts in the urine before and after prostatic massage [18]. Screening of bladder voiding and imaging analysis of the prostate gland are clinical procedures that need to be integrated.

The key point for diagnosis is the demonstration of leukocytes in expressed prostatic secretions, urine after prostatic massage and/or ejaculate to differentiate between inflammatory and non-inflammatory CPPS.

**Ejaculate analysis:** An ejaculate analysis (see Investigations) helps to clarify whether the prostate is part of a generalized infection of the accessory sex glands (male accessory gland infection) and provides information about the sperm quality. Furthermore, leukocyte analysis allows differentiation between inflammatory and non-inflammatory CPPS.

**Microbiological findings:** After exclusion of urethritis and bladder infection,  $\geq 10^6$  peroxidase-positive white blood cells per ml ejaculate are indicative of an inflammatory process. In these cases, a culture should be performed for common urinary tract pathogens, particularly gram-negative bacteria.

A concentration of  $\geq 10^3$  cfu/ml of urinary tract pathogens in the ejaculate is regarded as significant bacteriospermia. Usually, various micro-organisms are cultured from the genital tract of men seen in infertility clinics, with more than one strain of bacteria found in most cases [1]. Furthermore, the time of sample taking influences the positive rate of micro-organisms in semen and the frequency of isolation of different strains [19].

In patients with symptoms of prostatitis without proven bacterial findings, cryptic infections, especially evidence of silent *C. trachomatis* or *C. mycoplasma* infections, remain a diagnostic challenge.

Despite modern DNA detection techniques, the ideal diagnostic test for *C. trachomatis* in semen has not yet been established [14]. In contrast to the serological findings in women, antibody tests for *C. trachomatis* in seminal plasma are not indicative if no type-specific methods are used [14].

By analogy with *C. mycoplasma*, *U. urealyticum* seems only to be pathogenic in high concentrations ( $\geq 10^3$  cfu/ml ejaculate). No more than about 10% of samples analyzed for ureaplasmas exceed this number [20]. Normal colonization of the urethra hampers the necessary clarification of 'mycoplasma-associated' urogenital infections using samples such as the ejaculate [15].

**White blood cell count (WBC):** The clinical significance of an increased concentration of WBC in the ejaculate is highly controversial [21]. It is generally accepted that only an increased number of leukocytes (particularly neutrophilic granulocytes) and their products secreted into the seminal fluid (e.g. leukocyte elastase) are an indicator of infection. The great majority of leukocytes are neutrophilic granulocytes, as suggested by the specific staining of the peroxidase reaction (see Investigations). Although most authors consider leukocytospermia to be a sign of inflammation, it is not necessarily associated with bacterial or viral infections [7]. This is in accordance with earlier findings that elevated leukocyte numbers are not a natural cause of male infertility [22].

According to WHO classification,  $> 1 \times 10^6$  WBC per mL are defined as leukocytospermia. Only two studies have analyzed alterations of WBC in the ejaculate of patients with proven prostatitis [23,24]; both have demonstrated a higher number of leukocytes than in men without inflammation (CPPS, type IIIB).

**Sperm quality:** Deteriorative effects of chronic prostatitis on sperm density, motility and morphology are under debate [1]. All investigations to date show contradictory results and do not really confirm a decisive role of chronic prostatitis in alterations of these parameters.

**Seminal plasma alterations:** Seminal plasma elastase is accepted as a biochemical indicator of granulocyte activity in the ejaculate [1,25,26], with a suggested cut-off point of about 600 ng/ml [1]. Various cytokines are involved in inflammation and may influence sperm function. In this respect, several studies investigated the association between interleukin concentration, leukocytes and sperm function [27-29]. No differences were found among the subgroups defined, on the basis of progressive motility, percentage of abnormal forms and diagnosis of prostatitis. The prostate seems to be the main site of origin of interleukin-6 (IL-6) in the seminal plasma. Although it is accepted that cytokines, especially IL-6, must play an important role in the male accessory gland inflammatory process [30], elevated cytokine levels do not depend on the number of leukocytes in EPS [31].

**Glandular secretory dysfunction:** Infections of the sex glands can impair their excretory function. Decreased quantities of citric acid, phosphatase, fructose, zinc and alpha-glutamyltransferase activity have been evaluated as disturbed prostatic secretory parameters [1], and reduced fructose concentration as an indicator of impaired vesicular function [20,32].

**Sperm antibodies:** Serum antibodies to sperm antigens are not useful in the diagnosis of immune infertility. Early reports stated an association between increased levels of sperm antibodies in serum and NBP [33,34]. However, except in cases of suspected chlamydial infections [35], only a history of vasectomy seems to be predictive of sperm antibody formation [36].

**Reactive oxygen species:** It is generally accepted that reactive oxygen species may be increased in chronic urogenital infections associated with increased leukocyte numbers [37]. However, their biological significance in prostatitis remains unclear [1].

#### 11.3.4 Therapy

Treatment of chronic prostatitis is normally targeted at relieving symptoms [10]. Andrologically, therapy for altered semen composition in male adnexitis is aimed at:

- Reduction or eradication of micro-organisms in prostatic secretions and semen
- Normalization of inflammatory parameters, such as leukocytes and secretory parameters
- Possible improvement of sperm parameters to counteract fertility impairment [38].

Treatment includes antibiotics, anti-inflammatory drugs, surgical procedures, normalization of urine flow, physical therapy and changes in general and sexual behaviour.

Only antibiotic therapy of chronic bacterial prostatitis has been effective in providing symptomatic relief, eradication of micro-organisms and a decrease in cellular and humoral inflammatory parameters in urogenital secretions.

None of the other treatment schedules mentioned above have been evaluated in the same manner.

Although antibiotic procedures may improve sperm quality [38], therapy does not always enhance the probability of conception [1,39].

### 11.4 Orchitis

Orchitis is an inflammatory lesion of the testicle associated with a predominantly leukocytic exudate inside and outside the seminiferous tubules resulting in tubular sclerosis. The inflammation causes pain and swelling. Chronic inflammatory changes in the seminiferous tubules disrupt the normal process of spermatogenesis and cause alterations both in sperm number and quality [40].

It is generally accepted that orchitis may also be an important cause of spermatogenetic arrest [41], which may be reversible. Following orchitis, testicle atrophy occurs [41].

#### 11.4.1 Diagnosis

Patients with epididymo-orchitis usually present with unilateral scrotal pain [42]. The diagnosis is based on medical history and palpation. Ultrasonography demonstrates a swollen, enlarged testis. The sonographic feature of the tissue does not allow any differential diagnosis [43].

Ejaculate analysis, including leukocyte analysis, indicates persistent inflammatory activity (see Investigations). Transiently decreased sperm counts and reduced forward motility are observed in many cases, especially in acute epididymo-orchitis [40]. Obstructive azoospermia due to complete obstruction is a rare complication. Mumps orchitis may result in bilateral testicular atrophy [41] and testicular azoospermia. When granulomatous orchitis is suspected, sperm-bound autoantibodies occur (see Investigations).

#### 11.4.2 Therapy

There is standardized therapy only for acute bacterial epididymo-orchitis and specific granulomatous orchitis [41] (Table 10). Several regimens are thought to improve the inflammatory lesions. Unfortunately, therapies

using corticosteroids and non-steroidal antiphlogistic substances, such as diclofenac, indomethacin and acetylsalicylic acid, have not been evaluated with regard to their andrological outcome [43]. A further therapeutic trial is based on the idea of preventing deleterious effects of inflammation on spermatogenesis with GnRH treatment [44]. In mumps orchitis, systemic interferon alpha-2b therapy has been reported to prevent testicular atrophy and azoospermia [45]. In idiopathic granulomatous orchitis, surgical removal of the testis is the therapy of choice.

**Table 10: Treatment of epididymo-orchitis**

Condition	Therapy
<i>Acute bacterial epididymo-orchitis</i>	
• <i>N. gonorrhoeae</i>	<i>Tetracyclines</i>
• <i>C. trachomatis</i>	<i>Tetracyclines</i>
• <i>E. coli, Enterobacteriaceae</i>	<i>Fluoroquinolones</i>
Mumps orchitis	Interferon alpha-2b
Non-specific chronic epididymo-orchitis	Steroidal and non-steroidal antiphlogistic substances
Granulomatous (idiopathic) orchitis	Semicastration
Specific orchitis	According to therapy of underlying diseases

## 11.5 Epididymitis

Inflammation of the epididymis causes pain and swelling, which is almost unilateral and relatively acute in onset. In many cases, the testicle is involved in the inflammatory process known as epididymo-orchitis.

Among sexually active men younger than 35 years, epididymitis is most often caused by *C. trachomatis* or *N. gonorrhoeae* [46,47]. Sexually transmitted epididymitis is usually accompanied by urethritis. Non-sexually transmitted epididymitis is associated with UTI. This type occurs more frequently among men aged over 35 years, those who have recently undergone urinary tract instrumentation or surgery, and those who have anatomical abnormalities [47].

### 11.5.1 Diagnosis

In acute epididymitis, inflammation and swelling usually begin in the tail of the epididymis, and may spread to involve the rest of the epididymis and testicular tissue [42]. Although men with epididymitis due to sexually transmitted microorganisms always have a history of sexual activity, exposure can have been months prior to onset. The microbial aetiology of epididymitis is usually easy to determine by gram-stained examination of both a urethral smear for urethritis and of a mid-stream urine specimen for gram-negative bacteriuria [46,47]. Intracellular gram-negative diplococci on the smear correlate with the presence of *N. gonorrhoeae*. Only white blood cells on the urethral smear are indicative of non-gonorrhoeal urethritis; *C. trachomatis* will be isolated in approximately two-thirds of these patients [48].

**Ejaculate analysis:** Ejaculate analysis according to WHO criteria, including leukocyte analysis, may indicate persistent inflammatory activity. In many cases, transiently decreased sperm counts and forward motility are observed [42,46,49]. Ipsilateral low-grade orchitis [49,50] has been discussed as the cause of this slight impairment in sperm quality (Table 11) [51].

Development of stenosis in the epididymal duct, reduction of sperm count, and azoospermia are more important in the follow-up of bilateral epididymitis (see Obstructive azoospermia). The real figure of azoospermia after epididymitis remains unclear.

**Table 11: Acute epididymitis and impact on sperm parameters**

Author	Adverse effects			Comment
	Density	Motility	Morphology	
Ludwig & Haselberger [53]	+	+	+	Pyospermia in 19 of 22 cases
Berger et al. [46]		+		
Weidner et al. [43]	+	+	+	Azoospermia in 3 of 70 men
Haidl [54]		+		Chronic infections; macrophages elevated
Cooper et al. [55]				Decrease in epididymal markers: alpha-glucosidase, L-carnitine

### 11.5.2 Treatment

Antibiotic therapy is indicated before culture results are available. Treatment of epididymitis will result in:

- Microbiological cure of infection
- Improvement of signs and symptoms
- Prevention of transmission to others
- Decrease in potential complications, e.g. infertility or chronic pain.

Patients who have epididymitis that is known or suspected to be caused by *N. gonorrhoeae* or *C. trachomatis* should be instructed to refer sexual partners for evaluation and treatment [56].

## 11.6 CONCLUSIONS

Urethritis and prostatitis are not always associated with male sub- or infertility [57]. In many cases, basic ejaculate analysis does not reveal a link between accessory sex gland infection and impaired sperm characteristics. Furthermore, antibiotic treatment often only eradicates micro-organisms; it has no positive effect on inflammatory alterations and/or cannot reverse functional deficits and anatomical dysfunctions.

## 11.7 RECOMMENDATIONS

- As the aetiology of acute urethritis is unknown in most cases at the time of diagnosis, empirical therapy is suggested, with one single dose of a fluoroquinolone, followed by a 2-week regimen of doxycycline. Treatment is effective both for gonococcal and (co-existing) chlamydial/ureaplasma infections (Grade B).
- Only antibiotic therapy of (chronic) bacterial prostatitis has proved to be efficacious in providing symptomatic relief, eradication of micro-organisms and a decrease in cellular and humoral inflammatory parameters in urogenital secretions (Grade B) [58,59].
- Although antibiotic procedures for male accessory gland infection may provide an improvement in sperm quality, therapy does not always enhance the probability of conception (Grade B).
- Patients who have epididymitis known or suspected to be caused by *N. gonorrhoeae* or *C. trachomatis* should be instructed to refer sexual partners for evaluation and treatment (Grade A).

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Summary consensus statement: diagnosis and management of chronic prostatitis/chronic pelvic pain syndrome. Eur Urol 2003;(Suppl 2):1-4.

## 12 GERM CELL MALIGNANCIES AND TESTICULAR MICROCALCIFICATIONS

### 12.1 Germ cell malignancies and male infertility

The most convincing evidence for a general decline in male reproductive health in humans is the increase in testicular cancer noted over the recent past in several Western countries [1]. The incidence of testicular cancer has increased in almost all countries that have reliable cancer registers [2]. In addition, both cryptorchidism and hypospadias appear to be associated with an increased risk of testicular cancer because men with cryptorchidism and/or hypospadias are over-represented among patients with testicular cancer.

Dysgenic testes have an increased risk of developing testicular cancer in adulthood. These cancers seem to arise from pre-malignant gonocytes or CIS cells [3]. Testicular microlithiasis (TM) can be associated with both germ cell tumours and CIS of the testis.

### 12.2 Testicular microlithiasis (TM)

Microcalcifications can be found inside the testicular parenchyma in 0.6-9% of men referred for testicular ultrasound [4-7]. Although the true incidence in the general population is unknown, TM is probably a rare condition. However, the ultrasound findings are prevalent in men with germ cell tumours, cryptorchidism, testicular dysgenesis, male infertility, testicular torsion and atrophy, Klinefelter's syndrome, hypogonadism, male pseudohermaphroditism, varicocele, epididymal cysts, pulmonary microlithiasis and non-Hodgkin's lymphoma. The incidence seems to increase with the use of high-frequency ultrasound machines [8].

The relationship between TM and infertility is unclear, but probably relates to dysgenesis of the testis, with slough of degenerated cells inside an obstructed seminiferous tubule and failure of the Sertoli cells to phagocytize the debris. Secondly, calcification occurs.

Testicular microlithiasis is a condition found in testes at risk for malignant development: the reported incidence of TM in men with germ cell malignancy is 6-46% [9-11]. This has resulted in the hypothesis that TM should be considered a premalignant condition. It remains, however, to be established whether TM is present before development of the invasive testicular germ cell tumours (TGCTs), and is therefore a putative parameter for the pre-invasive stage of TGCTs, known as CIS. On testicular biopsies in men with TM, CIS is more prevalent, especially in men with bilateral microlithiasis [12]. On the other hand, TM is more often found in men with a benign testicular condition and the microcalcifications themselves are not malignant.

Testicular germ cell tumours are the most common malignancy in Caucasian males aged between 15 and 40 years, affecting about 1% of subfertile males. It is generally accepted that seminomas and non-seminomas are always preceded by CIS, and that CIS will eventually progress to an invasive cancer if not treated [13,14]. Exploration of the association between TM and CIS requires testicular biopsies in large series of men without signs of a TGCT.

### 12.3 RECOMMENDATIONS

- It is recommended to follow up patients with TM with physical examination and ultrasound at least annually, although more studies are needed to calculate the actual risk for developing a germ cell tumour.
- It is also important to encourage and educate patients about self-examination, since this may result in early detection of germ cell tumours.
- The routine use of biochemical tumour markers, abdominal and pelvic CT or testicular biopsy does not seem to be justified for patients with isolated TM.
- A surgical exploration with testicular biopsy or orchidectomy should be considered when there are suspicious findings on physical examination or ultrasound in patients with TM.
- Due to a high prevalence of testicular cancer in infertile men, we recommend either biopsy or follow-up scrotal ultrasound when bilateral TM is observed in the testes of infertile men [12].

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## 13 ENDOCRINE DISRUPTION

### 13.1 Introduction

In most animal species, the reproductive functions are controlled by the endocrine system. Chemicals in the environment that mimic or block endogenous hormones may disturb the fine balance of the endocrine system [1].

In recent years, there has been an increasing concern about the potential of substances in the environment to disrupt endocrine systems in humans and wildlife. The primary emphasis to date has been on substances which might mimic oestrogen activity and so interfere with the normal functioning of the endocrine system. In wildlife, it has been demonstrated that environmental pollutants, especially endocrine-disrupting compounds, have an adverse effect on reproduction.

It has been postulated that the recent increase in the incidence of disorders of the male reproductive tract, such as testicular cancer, cryptorchidism and hypospadias, are due to in-utero exposure to oestrogens [2]. Fetal exposure to oestrogens and oestrogen-like compounds may result in a dysgenetic testis, susceptible to cryptorchidism, male infertility and testicular malignancies. Controversy exists as to whether oestrogens in the environment would cause significant male reproductive disorders. Exposure to endocrine-disrupting compounds is almost entirely through the diet, particularly milk and other dairy products, fish and meat, fruit and vegetables [3]. The question is whether endocrine disrupters exist in the environment at sufficient high levels to exert adverse effects on the male genital system.

Recently, it has been proposed that poor semen quality, cryptorchidism, hypospadias, and testicular cancer are symptoms of an underlying entity known as the testicular dysgenesis syndrome (TDS) [4]. TDS may be caused by genetic or environmental factors or both. Even though, clinically, symptoms appear postnatally, the cause might be irreversible testicular dysgenesis during early fetal development. TDS may cause disturbed Sertoli-cell function, resulting in impaired germ-cell differentiation and eventually reduced semen quality, CIS and testicular cancer [5].

In 1992, Carlsen et al. published a meta-analysis of semen quality over the period 1938-1990 and found a significant decrease in sperm concentrations and semen volumes, together with an increase in cryptorchidism, hypospadias and testicular cancer [6]. This study prompted several investigators to evaluate their data on semen quality. The studies of Auger et al. [7] and Irvine et al. [8] provided evidence for a decline in sperm concentration and total number of motile sperm. However, other studies have argued against a decrease in semen quality over the past 20-50 years [9-11]. Several factors may influence the outcome of sperm analysis and this may explain the differences between the studies published (Table 12). Moreover, the reported decrease in sperm concentration appears difficult to reconcile in the absence of any detectable decrease in male fertility.

**Table 12: Summary of factors that may affect the results of semen analysis. From Weber et al. [12]**

Methodology of semen analysis	Lack of standardization of sperm collection Lack of standardization of laboratory procedures
Complicating factors	Season of sampling Lifestyle Profession Diseases Medication Stress Age

Trends	Higher prevalence of varicoceles associated with increased body height Changes in lifestyle Environmental changes Changes in occupational activities
Fluctuations over the year	Seasonal changes
Influence of geography	Ethnicity Fertility status
Influence of study population	Changes in composition of the population visiting fertility (related) clinics Region of living

The major routes of exposure to environmental chemicals are thought to be dietary, environmental from pollution of air and water, domestic and occupational. Nevertheless, any proof that exposure to oestrogenic compounds may lead to deterioration of reproductive function only comes from wild life research.

### 13.2 RECOMMENDATION

Future research should be focussed on the environmental substances causing endocrine disruption and TDS.

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## 14 DISORDERS OF EJACULATION

### 14.1 Definition

Disorders of ejaculation are uncommon but important causes of male infertility. Several heterogeneous dysfunctions belong to this group, and may be of either organic or functional origin.

### 14.2 Classification and aetiology

#### 14.2.1 Anejaculation

Anejaculation is the complete absence of an antegrade or retrograde ejaculation. It is caused by a failure of emission of semen from the seminal vesicles, the prostate and the ejaculatory ducts into the urethra [1]. True anejaculation is usually associated with a normal orgasmic sensation. Occasionally (e.g. in incomplete spinal cord injuries), this sensation may be altered or decreased. True anejaculation is always connected with central or peripheral nervous system dysfunctions or with drugs [2] (Table 13).

**Table 13: Aetiologies of anejaculation**

Neurogenic causes	Drug-related causes
Spinal cord injury	Antihypertensives
Cauda equina lesion	Antipsychotics
Retroperitoneal lymphadenectomy	Antidepressants
Aortoiliac or horseshoe-kidney surgery	Alcohol
Colorectal surgery	
Multiple sclerosis	
Parkinson's disease	
Autonomic neuropathy (diabetes mellitus)	

#### 14.2.2 Anorgasmia

Anorgasmia is the inability to reach orgasm and this may give rise to anejaculation. The cause is usually psychological. Anorgasmia is very often a primary condition. Some patients report sporadic events of nocturnal emission or of ejaculation occurring during great emotional excitement unrelated to sexual activity [3].

#### 14.2.3 Delayed ejaculation

Delayed ejaculation is the condition wherein an abnormal stimulation of the erected penis is necessary to obtain an orgasm with ejaculation [1]. It may be considered a slight form of anorgasmia: both can be alternatively found in the same patient. The causes of delayed ejaculation may be psychological or organic, such as incomplete spinal cord lesion [3], iatrogenic penile nerve damage [4], pharmacological (antidepressants, antihypertensives, antipsychotics).

#### 14.2.4 Retrograde ejaculation

Retrograde ejaculation is the total, or sometimes partial, absence of an antegrade ejaculation because semen passes backwards through the bladder neck into the bladder. Patients experience a normal or decreased

orgasmic sensation, except in paraplegia. Partial antegrade ejaculation must not be confused with the secretion of bulbo-urethral glands. The causes of retrograde ejaculation can be subdivided as shown in Table 14.

**Table 14: Aetiology of retrograde ejaculation**

<b>Neurogenic</b>	<b>Pharmacological</b>
Spinal cord injury	Antihypertensives
Cauda equina lesions	Alpha1-adrenoceptor antagonists
Multiple sclerosis	Antipsychotics
Autonomic neuropathy (juvenile diabetes)	Antidepressants
Retroperitoneal lymphadenectomy	
Sympathectomy	<b>Bladder neck incompetence</b>
Colorectal and anal surgery	Congenital defects of hemitrigone
<b>Urethral</b>	Congenital dysfunction of hemitrigone
Ectopic ureterocele	Bladder extrophy
Urethral stricture	Bladder neck resection
Urethral valves or verumontanum hyperplasia	Prostatectomy
Congenital dopamine beta-hydroxylase deficiency	

#### 14.2.5 Asthenic ejaculation

Asthenic ejaculation, also defined as partial ejaculatory incompetence or 'éjaculation baveuse' [5], is characterized by an altered propulsive phase with a normal emission phase. The orgasmic sensation is reduced and the typically rhythmical contractions associated with ejaculation are missing, while in asthenic ejaculation due to urethral obstruction, these contractions are present. Asthenic ejaculation is generally due to the neurogenic or urethral pathologies already listed in Table 14. Asthenic ejaculation usually does not alter semen quality.

#### 14.2.6 Premature ejaculation

Premature ejaculation is the inability to control ejaculation for a 'sufficient' length of time during vaginal penetration. Although a universally accepted meaning of 'sufficient' length of time does not exist, some patients are not able to delay ejaculation beyond a few coital thrusts, or even after vaginal penetration. Premature ejaculation may be strictly organic (e.g. prostatitis-related) or 'psychogenic' (i.e. neurobiologically based), primary or acquired, partner-related or non-selective, and can be associated with erectile dysfunction. Premature ejaculation does impair fertility, provided that intravaginal ejaculation occurs.

#### 14.2.7 Painful ejaculation

Painful ejaculation is usually an acquired condition, often related to lower urinary tract symptoms [6], and sometimes causes moderate sexual dysfunction. The painful sensation may be felt in the perineum, or urethra and urethral meatus [7]. It can be caused by ejaculatory duct obstruction, all types of chronic prostatitis/chronic pelvic pain syndrome, urethritis, urethrocele, antidepressant drugs and psychological problems.

### 14.3 Diagnosis

Diagnostic management includes the following recommended procedures.

#### 14.3.1 Clinical history

The patient must be carefully checked for diabetes, neuropathies, traumas, urogenital infections, previous surgery and medications. Particular attention must be paid to the characteristics of micturition and ejaculation (presence of nocturnal emission, ejaculating ability in given circumstances, primary or acquired disorder, evolution) as well as to the psychosexual sphere (education, features of affective relationship, pre-existent psychological traumas, previous psychological therapies).

#### 14.3.2 Physical examination

Genital apparatus and rectal examination with evaluation of the prostate, bulbocavernosus reflex and anal sphincter tone are conducted. Minimal neurological tests include:

- Sensitivity of scrotum, testes and perineum
- Cremasteric and abdominal cutaneous reflex
- Leg osteotendinous and plantar reflexes.

#### 14.3.3 Post-ejaculatory urinalysis

This will determine if there is total or partial retrograde ejaculation.

#### 14.3.4 Microbiological examinations

Initial, mid-stream urine, prostatic expressed secretions and/or urine after prostatic massage are cultured for evidence of prostatic infection. In cases of increased leukocytes in semen, semen culture is also suggested [8].

#### 14.3.5 Optional diagnostic work-up

This may include:

- Neurophysiological tests (bulbocavernosus evoked response and dorsal nerve somatosensory evoked-potentials)
- Tests for autonomic neuropathies (i.e. appreciation of temperature regulation in the feet)
- Psychosexual evaluation
- Videocystometry
- Cystoscopy
- Transrectal ultrasonography
- Uroflowmetry
- Vibratory stimulation of the penis.

### 14.4 Treatment

The treatment of infertility due to disorders of ejaculation is rarely aetiological, and generally consists of retrieving spermatozoa to be used in assisted reproduction techniques (ART). In decision-making, the following aspects must be considered:

- Age of patient and of his partner
- Psychological problems in the patient and his partner
- Couple's willingness and acceptance of the different fertility procedures
- Associated pathologies
- Psychosexual counselling.

### 14.5 Aetiological treatments

If possible, stop any pharmacological treatments that are interfering with the ejaculation. Tamsulosin can be administered during antidepressant treatment [9]. Treatment should be given for urogenital infections (i.e. in cases of painful ejaculation) [8]. Selective serotonin re-uptake inhibitors (SSRIs) should be given for premature ejaculation, which appears to be related to serotonin levels [10]. If possible, any underlying urethral pathology or metabolic disorder (e.g. diabetes) should be corrected. Psychotherapy is usually not very effective.

### 14.6 Symptomatic treatments

#### 14.6.1 Premature ejaculation

This can be treated with topical anaesthetics to increase intravaginal ejaculation latency time or with SSRIs (e.g. paroxetine, fluoxetine).

#### 14.6.2 Retrograde ejaculation

In the absence of spinal cord injury, anatomical anomalies of the urethra, or pharmacological agents, an attempt to induce antegrade ejaculation must be made by drug treatment (Table 15).

Alternatively, the patient can be encouraged to ejaculate when his bladder is full, to increase bladder neck closure [11].

**Table 15: Drug therapy for retrograde ejaculation**

• Ephedrine sulfate, 10-15 mg 4 times a day [12]
• Midodrin, 5 mg 3 times a day [13]
• Brompheniramine maleate, 8 mg twice a day [14]
• Imipramine, 25-75 mg 3 times a day [15]
• Desipramine, 50 mg every second day [16]

Sperm collection from postorgasmic urine for use in ART is suggested if:

- Drug treatment is ineffective or intolerable due to side effects
- When the patient has a spinal cord injury
- Drug therapy inducing retrograde ejaculation cannot be interrupted.

Sperm retrieval is timed to coincide with the partner's ovulation. Urine must be alkalinized (pH 7.2-7.8) and osmolarity must be 200-300 mOsmol/kg. Then the patient is asked to have intercourse or to masturbate.

Within 10 minutes after ejaculation, urine must be voided and centrifuged, and the pellet resuspended in 0.5 ml Tyrode's or Ham's F-10 medium and immediately inseminated [17]. As an alternative, a catheter may be applied to the bladder and 10-50 ml Tyrode's or Ham's F-10 medium are instilled into the bladder. The patient must ejaculate, and a second catheterization is performed immediately to retrieve spermatozoa. The latter treatment minimizes the contact between spermatozoa and urine [18]. If the biological sperm preparation is not of sufficient quality for intrauterine insemination, the couple must undergo in-vitro reproductive procedures (i.e. ICSI) with fresh or cryopreserved spermatozoa.

#### 14.6.3 Anejaculation

Drug treatment for anejaculation due to lymphadenectomy and neuropathy is not very effective. The same statement applies to psychosexual therapy in anorgasmic subjects. In all these cases and in spinal cord injured men, vibrostimulation (i.e. the application of a vibrator to the penis) is first-line therapy.

In anejaculation, vibrostimulation evokes the ejaculation reflex [19]. It requires an intact lumbosacral spinal cord segment; complete injuries and injuries above T10 showing a better response better to vibrostimulation. Once the safety and efficacy of this procedure are assessed, patients can manage themselves in their own home. Intravaginal insemination via a 10 ml syringe during ovulation can be performed. If the quality of semen is poor, or ejaculation is retrograde, the couple may enter an IVF programme. In case of vibrostimulation failure, electroejaculation is the therapy of choice [20]. Electroejaculation is an electric stimulation of the periprostatic nerves via a probe inserted into the rectum, which seems not to be affected by reflex arc integrity. Anaesthesia is required except in cases of complete spinal cord injury. In 90% of patients, electrostimulation induces ejaculation, which is retrograde in one-third of them. Semen quality is often poor and most couples must resort to IVF programmes [21].

When electroejaculation fails or cannot be performed, sperm retrieval from the seminal ducts may be achieved by sperm aspiration from the vas deferens [22] (see Obstructive azoospermia) or seminal tract washout [23].

When there is a failure to retrieve sperm, epididymal obstruction or testicular failure must be suspected. TESE can then be performed [8,24]. Anejaculation following either surgery for testicular cancer or total mesorectal excision may be prevented by monolateral lymphadenectomy or autonomic nerve preservation [24], respectively.

## 14.7 CONCLUSIONS

Ejaculation disorders can be treated with a wide range of drugs and physical stimulation trials with a high percentage of efficacy.

## 14.8 RECOMMENDATIONS

- If present, aetiological treatments for ejaculatory disorders should be offered first, before sperm collection and ART is performed.
- Premature ejaculation can successfully be treated with either topical anaesthetic creams or SSRIs [22].
- Both vibrostimulation and electro-ejaculation are effective methods for sperm retrieval in men with spinal cord injury.

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## 15 SEMEN CRYOPRESERVATION

### 15.1 Definition

Cryopreservation is the branch of cryobiology dealing with cell or tissue suspension during a 'long-term' storage, obtained by an ultra-low temperature freezing process. It stops molecular movements and the biochemical processes of cell metabolism are interrupted.

### 15.2 Introduction

To be effective, cryopreservation requires that the biochemical system is subsequently able to return to a normal temperature without suffering structural or biochemical damage leading to cell death. Liquid nitrogen is presently used to reach the temperatures needed to stop all activities. The first pregnancy obtained with cryopreserved semen dates back to 1954 [1].

Before freezing is performed, cryoprotectants are mixed with the semen. Prior to use in clinical practice, the frozen matter must be thawed and processed.

The cryopreservation process includes three consequential stages:

- Freezing
- Storage
- Thawing.

### 15.3 Freezing and thawing

The following methods can be applied:

- Fast method, as suggested by Sherman [2]: sample exposure to nitrogen fumes for about 10 min, followed by its immersion into the liquid stage.
- Slow method, as suggested by Behrman and Sawada [3]: gradual exposure to fumes for about a total of 40 min.
- Slow computerized method: 1°C-10°C/min timed cooling which makes use of computerized biological freezers.

### 15.3.1 Cryopreservation technique

Seminal fluid is routinely cryopreserved in pailletes. In case of severely altered seminal fluids (rare spermatozoa in count chamber), the freezing technique in pellet form can be applied. This technique allows a quicker search for spermatozoa during thawing.

In case of surgical samples freezing, a suitable fragmentation of the biopsy sample is required since this is the best method to secure an optimal preservation of the sample [4]. In literature, some authors have reported the freezing process of small pieces of testicular tissue [5]; others have reported the freezing of individually isolated seminiferous tubuli [6].

Special cryogenic or cryobiological containers, strictly classified, are used for storage. The survival of sperm decreases as storage time goes by, particularly with repeated exposures to room temperature. The ideal storage time could be restricted to a period of time not exceeding 10 years [7].

### 15.3.2 Thawing technique

Three different methods are applied:

- At room temperature for 10 min followed by a further 10-min period inside a thermostat at 37°C.
- In a bain-marie at 37°C inside a thermostat for 10 min.
- At room temperature (22°C) for about 15 min.

### 15.3.3 Potential problems of cryopreservation

The potential problems associated with cryopreservation are:

- Damage by crystallization (irreversible cell damage, alteration of membrane integrity).
- Damage by dehydration (cell damage protected by the use of a cryoprotectant).
- Damage by contamination (micro-organisms and oxygen) [8].

## 15.4 Indications

The main indications for cryopreservation of sperm are malignant diseases and autoimmune diseases that require chemotherapy, radiotherapy, or surgical operations potentially causing anejaculation [9]; ejaculate samples from a patient should be cryopreserved before he has undergone any of these therapeutic procedures.

Other indications are:

- Progressive decrease of semen quality due to diseases with the risk of subsequent azoospermia (pituitary macroadenomas, craniopharyngiomas).
- Empty sella syndrome.
- Chronic nephropathies (unbalanced diabetes mellitus, multiple sclerosis).
- Psychogenic anejaculation in patients with repeated ejaculatory difficulties at the time of assisted reproduction.
- Obstructive azoospermia with surgically retrieved sperms from the testis (TESE), from the epididymis (MESA) or from the distal seminal tract.
- Non-obstructive azoospermia: spermatozoa or spermatids recovered from testes by microsurgery (microTESE) or conventional surgery (TESE).
- Donated sperm for artificial heterologous insemination.

## 15.5 Investigations

Before cryopreservation of human material is performed, the patients should be tested for viral infections (hepatitis, human immunodeficiency virus [HIV]) and STDs (*C. trachomatis*, *gonorrhoea*, *syphilis*) that may cross-contaminate the cryostorage unit.

## 15.6 Biological aspects

Cryopreservation induces deterioration of the seminal quality. After the sample has been thawed, motility [10] and morphology [11] appear worsened, including mitochondrial acrosomal and sperm tail damage [12]. Recent studies confirm some correlation between these parameters: sperm freezing decreases motility by 31%, morphology by 37%, and mitochondrial activity by 36% [13]. Motility seems to be the factor most strongly correlated with IVF capacity of the thawed sample. Recently, it has been advised that only the best part of the semen sample should be frozen rather than the whole sample.

## 15.7 CONCLUSIONS

- The purpose of sperm cryopreservation is to secure future pregnancies using ART.
- The procedure should always be explained to the patient and should be suggested in case of specific pathologies or before making a patient undergo surgery, chemotherapy or radiotherapy, which might damage his reproductive integrity.

## 15.8 RECOMMENDATIONS

- Cryopreservation of semen, epididymal fluid or testicular tissue should be offered to men who are candidates for chemotherapy, radiation or surgical interventions that might interfere with spermatogenesis or cause ejaculatory disorders.
- Before definitive cryopreservation, the patient should be investigated for viral infections (hepatitis, HIV and STDs) to prevent contamination of the cryostorage unit.

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### Grades of guideline recommendations (1)

#### Grade Nature of recommendations

- A Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial
  - B Based on well-conducted clinical studies, but without randomized clinical trials
  - C Made despite the absence of directly applicable clinical studies of good quality
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## 16 ABBREVIATIONS

ABP	acute bacterial prostatitis
ART	assisted reproduction techniques
CASA	computer-assisted sperm analysis
CBAVD	congenital bilateral absence of the vas deferens
CBP	chronic bacterial prostatitis
CFTR	cystic fibrosis transmembrane conductance regulator gene
CIS	carcinoma in situ
CPPS	chronic pelvic pain syndrome
EPS	expressed prostatic excretion
FISH	[multicolour] fluorescent in situ
HIV	human immunodeficiency virus
FSH	follicle-stimulating hormone
GnRH	gonadotrophin-releasing hormone
hCG	human chorionic gonadotrophin
hMG	human menopausal gonadotrophin
IBT	immunobead test
ICSI	intracytoplasmic sperm injection
IL-6	interleukin-6
IVF	in-vitro fertilization
LH	luteinizing hormone
LHRH	luteinizing hormone releasing hormone
MAR	mixed antiglobulin reaction
MESA	microsurgical epididymal sperm aspiration
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
OAT	oligo-astheno-teratozoospermia [syndrome]
Pd	prostatodynia
SCOS	Sertoli cell-only syndrome
SSRIs	selective serotonin reuptake inhibitors
STD	sexually transmitted disease
TDS	testicular dysgenesis syndrome
TESE	testicular sperm extraction
TM	testicular microlithiasis
TRUS	transurethral ultrasound
TURED	transurethral resection of the ejaculatory ducts
WBC	white blood cells