# Guidelines on Male Infertility

A. Jungwirth, T. Diemer, G.R. Dohle, A. Giwercman,
Z. Kopa, C. Krausz, H. Tournaye

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# 1. METHODOLOGY

## 1.1 Introduction

The European Association of Urology (EAU) Guideline Panel on Male Infertility has prepared these guidelines to assist urologists and healthcare professionals from related specialities in the treatment of male infertility.

Urologists are usually the specialists who are initially responsible for assessing the male partner when male infertility is suspected. However, infertility can be a multifactorial condition requiring multidisciplinary involvement. The Male Infertility Guidelines Panel consists of urologists and endocrinologists with special training in andrology and experience in the diagnosis and treatment of male infertility.

## 1.2 Data identification

The recommendations provided in the current guidelines are based on a systemic literature search performed by the panel members. MedLine, Embase, and Cochrane databases were searched to identify original and review articles. The controlled vocabulary of the Medical Subject Headings (MeSH) database was used alongside a 'free-text' protocol, combining 'male infertility' with the terms 'diagnosis', 'epidemiology', 'investigations', 'treatment', 'spermatogenic failure', 'genetic abnormalities', 'obstruction', 'hypogonadism', 'varicocele', 'cryptorchidism', 'testicular cancer', 'male accessory gland infection', 'idiopathic', 'contraception', 'ejaculatory dysfunction' and 'cryopreservation' .

All articles published between January 2010 (previous update) and November 2011 were considered for review. The expert panel reviewed these records and selected articles with the highest evidence.

## 1.3 Level of evidence and grade of recommendation

References in the text have been assessed according to their level of scientific evidence (Table 1), and guideline recommendations have been graded (Table 2) according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (1). Grading aims to provide transparency between the underlying evidence and the recommendation given.

**Table 1: Level of evidence (LE)***

| Level | Type of evidence |
|---|---|
| 1a | Evidence obtained from meta-analysis of randomised trials |
| 1b | Evidence obtained from at least one randomised trial |
| 2a | Evidence obtained from one well-designed controlled study without randomisation |
| 2b | Evidence obtained from at least one other type of well-designed quasi-experimental study |
| 3 | Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports |
| 4 | Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities |

**Modified from Sackett et al. (1).*

When recommendations are graded, the link between the level of evidence and grade of recommendation is not directly linear. Availability of RCTs may not translate into a grade A recommendation when there are methodological limitations or disparity in published results.

Absence of high-level evidence does not necessarily preclude a grade A recommendation, if there is overwhelming clinical experience and consensus. There may be exceptions where corroborating studies cannot be performed, perhaps for ethical or other reasons, and unequivocal recommendations are considered helpful. Whenever this occurs, it is indicated in the text as "upgraded based on panel consensus". The quality of the underlying scientific evidence must be balanced against benefits and burdens, values and preferences and cost when a grade is assigned (2-4).

The EAU Guidelines Office does not perform cost assessments, nor can it address local/national preferences systematically. The expert panels include this information whenever it is available.

**Table 2: Grade of recommendation (GR)***

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

**Modified from Sackett et al. (1).*

### 1.4 Publication history

The EAU Male infertility Guidelines were first published in 2001, followed by full text updates in 2004, 2007 and 2010. For this 2012 publication all sections have been revised and limited changes were implemented. Starting in 2012, the expert panel instigate start a new updating cycle. A quick reference guide presenting the main findings of the Male Infertility Guidelines is also available as well as a number of scientific publications in the EAU journal European Urology. All texts can be viewed and downloaded for personal use at the society website: http://www.uroweb.org/guidelines/online-guidelines/.

This document was peer-reviewed prior to publication.

### 1.5 Definition

'Infertility is the inability of a sexually active, non-contracepting couple to achieve spontaneous pregnancy in one year' World Health Organization (WHO) (5).

### 1.6 Epidemiology and aetiology

About 15% of couples do not achieve pregnancy within 1 year and seek medical treatment for infertility. Eventually, 5% remain unwillingly childless. Infertility affects both men and women. In 50% of involuntarily childless couples, a male infertility associated factor is found together with abnormal semen parameters. A fertile partner may compensate for the fertility problem of the man and thus infertility usually becomes manifest if both partners have reduced fertility (5). Male fertility can be reduced as a result of (5):

- congenital or acquired urogenital abnormalities;
- urogenital tract infections;
- increased scrotal temperature (e.g. as a consequence of varicocele);
- endocrine disturbances;
- genetic abnormalities;
- immunological factors.

In 30-40% of cases, no male infertility associated factor is found (idiopathic male infertility). These men present with no previous history of fertility problems and have normal findings on physical examination and endocrine laboratory testing. However, semen analysis reveals a decreased number of spermatozoa (oligozoospermia), decreased sperm motility (asthenozoospermia), and many abnormal forms of sperm (teratozoospermia). These sperm abnormalities usually occur together and are called oligo-astheno-teratozoospermia (OAT) syndrome. Table 3 summarises the main male infertility-associated factors. Idiopathic male infertility may be explained by several factors, including endocrine disruption as a result of environmental pollution, reactive oxygen species, or genetic abnormalities.

**Table 3: Male infertility associated factors and percentage of distribution in10,469 patients**

| Male infertility associated factor | Distribution % |
|---|---|
| Idiopathic male infertility | 31 |
| Maldescended testes | 7.8 |
| Urogenital infection | 8.0 |
| Disturbances of semen deposition and sexual factors | 5.9 |
| General and systemic disease | 3.1 |
| Varicocele | 15.6 |
| (Endocrine) Hypogonadism | 8.9 |
| Immunological factors | 4.5 |
| Obstructions | 1.7 |
| Other abnormalities | 5.5 |

## 1.7 Prognostic factors

Prognostic factors for male infertility are:

- duration of infertility;
- primary or secondary infertility;
- results of semen analysis;
- age and fertility status of female partner.

The cumulative pregnancy rate in infertile couples with 2 years of follow-up and oligozoospermia as the primary cause of infertility is 27% (7). Female age is the most important single variable influencing outcome in assisted reproduction (8). Compared to a woman aged 25 years, the fertility potential of a woman aged 35 years is reduced to 50%, to 25% at 38 years, and less than 5% at over 40 years. In many Western countries, women postpone their first pregnancy until after their education and starting a career.

## 1.8 Recommendations on epidemiology and aetiology

| Recommendations | GR |
|---|---|
| To categorise infertility, both partners should be investigated simultaneously. | C |
| In the diagnosis and management of male subfertility, the fertility status of the female partner must also be considered, as this might determine the final outcome (8). | B |
| 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 start appropriate therapy (drugs, surgery, assisted reproduction) (5). | C |

## 1.9 References


1. Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001). Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Produced by Updated by Jeremy Howick March 2009. http://www.cebm.net/index.aspx?o=1025 [Access date January 2012]
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# 2. INVESTIGATIONS

## 2.1 Semen analysis

A medical history and physical examination are standard assessments in all men, including semen analysis. A comprehensive andrological examination is indicated if semen analysis shows abnormalities compared with reference values (Table 4). As important treatment decisions are based on the results of semen analysis, it is essential that the complete laboratory work-up is standardised. Ejaculate analysis has been standardised by the WHO and disseminated by publication of the *WHO Laboratory Manual for the Examination and Processing of Human Semen* (5th edn.) (1). It is the consensus that modern spermatology must follow these guidelines.

**Table 4: Lower reference limits (5th centiles and their 95% confidence intervals) for semen characteristics**

| Parameter | Lower reference limit (range) |
|---|---|
| Semen volume (mL) | 1.5 (1.4-1.7) |
| Total sperm number ($10^6$ per ejaculate) | 39 (33-46) |
| Sperm concentration ($10^6$ per mL) | 15 (12-16) |
| Total motility (PR + NP) | 40 (38-42) |
| Progressive motility (PR, %) | 32 (31-34) |
| Vitality (live spermatozoa, %) | 58 (55-63) |
| Sperm morphology (normal forms, %) | 4 (3.0-4.0) |
| Other consensus threshold values | |
| pH | > 7.2 |
| Peroxidase-positive leukocytes ($10^6$ per mL) | < 1.0 |
| MAR test (motile spermatozoa with bound particles, %) | < 50 |
| Immunobead test (motile spermatozoa with bound beads, %) | < 50 |
| Seminal zinc (µmol/ejaculate) | ≥ 2.4 |
| Seminal fructose (µmol/ejaculate) | ≥ 13 |
| Seminal neutral glucosidase (mU/ejaculate) | ≥ 20 |

*PR = progressive; NP = non-progressive; MAR = Mixed antiglobulin reaction.*

### *2.1.1 **Frequency of semen analysis***

If the results of semen analysis are normal according to WHO criteria, one test should be sufficient. If the results are abnormal in at least two tests, further andrological investigation is indicated. It is important to differentiate between the following:

- oligozoospermia: < 15 million spermatozoa/mL
- asthenozoospermia: < 32% motile spermatozoa
- teratozoospermia: < 4% normal forms.

Quite often, all three anomalies occur simultaneously which is defined as OligoAsthenoTeratozoospermia (OAT). As in azoospermia, in extreme cases of oligozoospermia (< 1 million spermatozoa/mL), there is an increased incidence of obstruction of the male genital tract and genetic abnormalities.

### 2.2 Recommendations for investigations in male infertility

| Recommendations | GR |
|---|---|
| According to WHO criteria, andrological investigations are indicated if semen analysis is abnormal in at least two tests. | C |
| Assessment of andrological status must consider the suggestions made by WHO for the standardised investigation, diagnosis, and management of the infertile couple; this will result in implementation of evidence-based medicine in this interdisciplinary field of reproductive medicine (2). | C |
| Semen analysis must follow the guidelines of the *WHO Laboratory Manual for the Examination and Processing* (5th edn) (1). | B |

### 2.3 References


1. World Health Organization. WHO Laboratory Manual for the Examination and Processing of Human Semen. 5th edn. WHO, 2010. http://www.who.int/reproductivehealth/publications/infertility/9789241547789/en/index.html
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# 3. TESTICULAR DEFICIENCY (SPERMATOGENIC FAILURE)

### 3.1 Definition

Testicular deficiency as a consequence of spermatogenic failure is caused by conditions other than hypothalamic-pituitary disease and obstructions of the male genital tract. It is the commonest form of reduced male fertility. Testicular deficiency may have different aetiologies and present clinically as severe OAT or non-obstructive azoospermia (NOA) (1).

### 3.2 Aetiology

The causes of testicular deficiency are summarised in Table 5.

**Table 5: Causes of testicular deficiency**

| Factors | Causes |
|---|---|
| Congenital | Anorchia |
| | Testicular dysgenesis/cryptorchidism |
| | Genetic abnormalities (karyotype, Y chromosome deletions) |
| | Germ cell aplasia, resulting in Sertoli cell only syndrome |
| | Spermatogenic arrest (maturation arrest) |
| Acquired | Trauma |
| | Testicular torsion |
| | Post-inflammatory forms, particularly mumps orchitis |
| | Exogenous factors (medications, cytotoxic drugs, irradiation, heat) |
| | Systemic diseases (liver cirrhosis, renal failure) |
| | Testicular tumour |
| | Varicocele |
| | Surgery that may compromise vascularisation of the testes and subsequently testicular atrophy |
| Idiopathic | Unknown aetiology |
| | Unknown pathogenesis |

## 3.3 Medical history and physical examination

Typical findings from the history and physical examination of a patient with testicular deficiency are:

- cryptorchidism;
- testicular torsion;
- genitourinary infection;
- testicular trauma;
- exposure to environmental toxin(s);
- gonadotoxic medication;
- exposure to radiation or chemical(s);
- testicular cancer;
- absence of testes;
- abnormal secondary sexual characteristics;
- gynaecomastia;
- abnormal testicular volume and/or consistency;
- varicocele.

## 3.4 Investigations

Routine investigations include semen analysis and hormonal determinations. Other investigations may be required depending on the individual situation.

### *3.4.1* ***Semen analysis***

In NOA, semen analysis shows normal ejaculate volume and azoospermia after centrifugation. A recommended method is semen centrifugation at 3000 g for 15 minutes and a thorough microscopic examination by phase contrast optics at x200 magnification of the pellet. All samples can be stained and re-examined microscopically (2).

### *3.4.2* ***Hormonal determinations***

In men with testicular deficiency hypergonadotrophic hypogonadism is usually present, with high levels of follicle stimulating hormone [FSH] and luteinising hormone [LH], and sometimes low levels of testosterone. Generally, the levels of FSH correlate with the number of spermatogonia:

- When spermatogonia are absent or markedly diminished, FSH values are usually elevated.
- When the number of spermatogonia is normal, but spermatocyte or spermatid blockage is complete. FSH values are within normal range.

However, for an individual patient, FSH levels do not accurately predict the spermatogenesis status (3-5). Preliminary data indicate a stronger correlation between low inhibin B level and spermatogenic damage (6).

### *3.4.3* ***Testicular biopsy***

Testicular biopsy can be part of an intracytoplasmic sperm injection (ICSI) treatment in patients with clinical evidence of NOA. Testicular sperm extraction (TESE) is the technique of choice and shows excellent repeatability (7-9). Spermatogenesis may be focal, which means that in about 50-60% of men with NOA, spermatozoa can be found and used for ICSI. Most authors therefore recommend taking several testicular samples (10,11). There is a good correlation between the histology found upon diagnostic biopsy and the likelihood of finding mature sperm cells during testicular sperm retrieval and ICSI (12,13). However, no clear relationship has been found between FSH, inhibin B or testicular volume and successful sperm harvesting. When there are complete AZFa and AZFb microdeletions, the likelihood of sperm retrieval is virtually zero.

Microsurgical testicular sperm extraction may increase retrieval rates, even though comparative studies are not yet available (14-16). After opening the testis, tubules exhibiting larger diameter are excised using micro-scissors or forceps. Then, tubules are minced using mechanical or enzymatic digestion to facilitate sperm search (17). Positive retrievals are reported even in conditions, such as Sertoli cell only syndrome type II (14). Percutaneous Epididymal Sperm Aspiration (PESA) results in lower retrieval rates and does not allow histological examination to detect for instance carcinoma in situ (CIS) and testicular malignancies (18,19). PESA may also result in more tubular and vascular damage than TESE (20).

The results of ICSI are worse when using sperm retrieved from men with NOA compared to sperm from ejaculated semen and from men with obstructive azoospermia (OA) (21-24):

- Birth rates are lower in NOA versus OA (19% vs 28%) (25).
- Fertilisation and implantation rates are significantly lower (26).
- Miscarriage rates are higher in NOA versus OA (11.5% vs 2.5%) (27).

In OA, there were no significant differences in ICSI results between testicular and epididymal sperm (24). Also,

no significant differences have been reported in ICSI results between the use of fresh and frozen-thawed sperm (22,26-28).

### 3.5 Conclusions and recommendations for testicular deficiency

| Conclusions |
|---|
| Impaired spermatogenesis is often associated with elevated FSH concentration. |
| Testicular biopsy is the best procedure to define the histological diagnosis and the possibility of finding sperm. Spermatozoa should be cryopreserved for use in ICSI. |
| Spermatozoa are found in about 60% of patients with non-obstructive azoospermia (NOA). |
| Men who are candidates for sperm retrieval must receive appropriate genetic advice. |
| For patients with NOA, who have spermatozoa in their testicular biopsy, ICSI with fresh or cryopreserved spermatozoa is the only therapeutic option. |
| Pregnancies and live births are achieved in 30-50% of couples with NOA, when spermatozoa has been found in the testicular biopsy. |

| Recommendations | GR |
|---|---|
| Men with non-obstructive azoospermia (NOA) can be offered a testicular sperm extraction with cryopreservation of the spermatozoa to be used for intracytoplasmic sperm injection (28). | B |
| To increase the chances of positive sperm retrievals in men with NOA, testicular sperm extraction (single, multiple or microsurgical) should be used rather than PESA. | B |

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# 4. GENETIC DISORDERS IN INFERTILITY

## 4.1 Introduction

All urologists working in andrology must have an understanding of genetic abnormalities in infertility, so that they can provide correct advice to couples seeking fertility treatment. Men with very low sperm counts can be given a reasonable chance of paternity, using in vitro fertilisation (IVF), ICSI and sperm harvesting from the epididymis or the testis in case of azoospermia. However, the sperm of infertile men show an increase in aneuploidy, other genetic abnormalities and DNA damage and carry the risk of passing genetic abnormalities to the next generation. Although there are prospects for screening of sperm (1,2), current routine clinical practice is based on screening peripheral blood samples.

## 4.2 Chromosomal abnormalities

Chromosome abnormalities can be numerical (e.g. trisomy) or structural (e.g. inversions or translocations) (3,4). In a survey of pooled data from 11 publications, including 9,766 infertile men, the incidence of chromosomal abnormalities was 5.8% (3). Of these, sex chromosome abnormalities accounted for 4.2% and autosomal abnormalities for 1.5%. For comparison, the incidence of abnormalities was 0.38% in pooled data from three series, with a total of 94,465 newborn male infants, of which 131 (0.14%) were sex chromosome abnormalities and 232 (0.25%) autosomal abnormalities (4). The frequency of chromosomal abnormalities increases as the testicular deficiency becomes more severe. Patients with < 5 million spermatozoa/mL already show a 10-fold higher incidence (4%) of mainly autosomal structural abnormalities compared with the general population (5). At highest risk are secretory azoospermic men.

Based on the frequencies of chromosomal aberrations in patients with different sperm concentration, karyotype analysis is indicated in azoospermic men and in oligozoospermic men with < 5 million spermatozoa/mL (5). If there is a family history of recurrent abortions, malformations or mental retardation, karyotype analysis should be requested, regardless of the sperm concentration.

### *4.2.1 **Sperm chromosomal abnormalities***

Sperm can be examined for chromosomal normality using multicolour fluorescent *in situ* hybridisation (FISH). Aneuploidy in sperm, particularly sex chromosome aneuploidy, is associated with severe damage to spermatogenesis (3,6-10) and is also seen in men with translocations (11).

FISH analysis of spermatozoa is a research investigation. It should be used to assess spermatozoa from men with defined andrological conditions (6). Techniques are needed to separate populations of genetically abnormal sperm from normal sperm or to safely screen individual spermatozoa before IVF and ICSI.

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

Klinefelter's syndrome is the most common sex chromosome abnormality (3,12). Adult men with Klinefelter's syndrome have small firm testicles devoid of germ cells. The phenotype varies from a normally virilised man to a man with the stigmata of androgen deficiency, including female hair distribution, scant body hair, and long arms and legs due to late epiphyseal closure. Leydig cell function is commonly impaired in men with Klinefelter's syndrome (13). Testosterone levels may be normal or low, oestradiol levels normal or elevated, and FSH levels increased. Libido is often normal despite low testosterone levels, but androgen replacement may be needed as the patient ages.

Germ cell presence and sperm production are variable in men with Klinefelter's mosaicism, 46,XY/47,XXY. There is one case report of declining spermatogenesis in a man with Klinefelter's syndrome, with the recommendation that early sperm retrieval sperm should be considered (14). Based on sperm FISH studies showing an increased frequency of sex chromosomal abnormalities and increased incidence of autosomal aneuploidies (disomy for chromosomes 13, 18 and 21), concerns have been raised about the chromosomal normality of the embryos generated through ICSI (15).

The production of 24,XY sperm has been reported in 0.9% and 7.0% of men with Klinefelter's mosaicism (16-18) and in 1.36-25% of men with somatic karyotype 47,XXY (19-22). In azoospermic patients, TESE or (MicroTESE) can be proposed as a therapeutic option since spermatozoa can be recovered in about 30% of cases. To date, 49 healthy children have been born using ICSI without preimplantation genetic diagnosis (PDG) and the conception of one 47,XXY fetus has been reported (12). However, a study of ICSI combined with PDG in 113 embryos reported a significant fall in the rate of normal embryos for couples with Klinefelter's syndrome in respect to controls (54% vs 77.2%) (15). Due to the significant increase of sex chromosomal and autosomal abnormalities in the embryos of Klinefelter's patients, pre-implantation diagnosis or amniocentesis and karyotype analysis should be strongly advised.

Follow-up (possibly every year) of men with Klinefelter's syndrome is required and androgen replacement therapy should be started when testosterone level is in the range of hypoandrogenism. All men

with Klinefelter's syndrome who undergo testicular biopsy procedures for sperm retrieval need long-term endocrine follow-up.

#### *4.2.3 **Autosomal abnormalities***

Genetic counselling should be offered to all couples seeking fertility treatment (including IVF/ICSI) when the male partner is known or found to have an autosomal karyotype abnormality.

The most common autosomal karyotype abnormalities are Robertsonian translocations, reciprocal translocations, paracentric inversions and marker chromosomes. It is important to look for these structural chromosomal anomalies because there is an increased associated risk of aneuploidy or unbalanced chromosomal complements in the fetus. As with Klinefelter's syndrome, sperm FISH analysis provides a more accurate risk estimation of affected offspring.

When IVF/ICSI is carried out for men with translocations, preimplantation genetic diagnosis or amniocentesis and karyotype analysis should be used. Embryos with known unbalanced translocation should probably not be implanted.

### 4.3 Genetic defects

#### *4.3.1 **X-linked genetic disorders and male fertility***

Each man has only one X chromosome. An X-linked recessive disorder manifests in males. The defect will be transmitted to daughters, but not to sons.

#### *4.3.2 **Kallmann syndrome***

The most common X-linked disorder in infertility practice is Kallmann syndrome. The predominant form is an X-linked recessive disorder caused by a mutation in the KALIG-1 gene on Xp22.3 (23). A number of newly identified autosomal gene mutations can also cause Kallmann syndrome (24). Patients with Kallmann syndrome have hypogonadotrophic hypogonadism and anosmia, but may also have other clinical features, including facial asymmetry, cleft palate, colour blindness, deafness, maldescended testes, and renal abnormalities.

Since spermatogenesis can be relatively easily induced by hormonal treatment (25), genetic screening prior to therapy is strongly adviced. Treatment with gonadotrophins allows natural conception in most cases, even in men with a relatively low sperm count. Thus, identification of the involved gene (X-linked, autosomal dominant or recessive) can help to provide more accurate genetic counselling i.e. risk estimation for transmission to the offspring.

#### *4.3.3 **Mild androgen insensitivity syndrome***

The AR gene is located on the long arm of the X chromosome. Mutations in the AR gene may result in mild to complete androgen insensitivity (26).The phenotypic features of complete androgen insensitivity syndrome (CAIS) are female external genitalia and absence of pubic hair (Morris syndrome). In partial androgen insensitivity syndrome, several different phenotypes are evident, ranging from predominantly female phenotype through ambiguous genitalia, to predominantly male phenotype with micropenis, perineal hypospadias, and cryptorchidism. The later phenotype is also termed Reifenstein syndrome. In the above mentioned severe forms of androgen resistances there is no risk of transmission since affected men cannot generate their own biological children using the current technologies. Patients with mild AIS have male infertility as their primary or even sole symptom. Disorders of the androgen receptor causing infertility in the absence of any genital abnormality are rare, only a few mutations have been reported in infertile men (26-30).

#### *4.3.4 **Other X-disorders***

An unexpectedly high number of genes with a testis-specific or enriched expression pattern have been identified on the X chromosome and especially pre-meiotic genes are over-represented on the X chromosome compared with autosomal chromosomes (31,32). Nevertheless, up to now only two genes, USP26 and TAF7L, have been screened in relatively small study populations and neither of them appear relevant for male infertility (33,34).

### 4.4 Y chromosome and male infertility

#### *4.4.1 **Introduction***

The first association between azoospermia and microscopically detectable deletions of the long arm of the Y chromosome was demonstrated by Tiepolo and Zuffardi in 1976 (35). The first cases of Y microdeletions and male infertility were reported in 1992 (36), and many case series have subsequently been published. Microdeletions have been found in three non-overlapping regions, AZFa+b+c, of the Y chromosome (37). Several years after the discovery of the three AZF regions and with knowledge of the precise structure of the Y chromosome in Yq11, it was realised that the AZFb and AZFc regions overlap and that there was no AZFd region (38). Clinically relevant deletions remove partially, or in most cases completely, one or more of the AZF

regions, and are the most frequent molecular genetic cause of severe oligozoospermia and azoospermia (39). In each AFZ region, there are a number of candidate genes, but their function in spermatogenesis remains largely unknown (40).

Since deletions occur in block (i.e. removing more than one gene), it is not possible to determine the role of a single AZF gene from the AZF deletion phenotype and thus it is unclear if they are all participating in spermatogenesis. Gene-specific deletions, which remove a single gene, have been reported only in the AZFa region. These studies suggested that the USP9Y gene is not essential for spermatogenesis and is most likely to be a 'fine tuner' of sperm production (41).

A new type of Yq deletions, known as 'gr/gr deletion' has been described in the AZFc region (42). This deletion removes half of the AZFc region gene content and affects the dosage of multicopy genes mapping inside this region (e.g. DAZ, CDY1, BPY2).

#### *4.4.2 **Clinical implications of Y microdeletions***

The clinical significance of Yq deletions have been debated for a long time because of the large variability found in deletion frequencies and reports of Yq deletions in 'fertile' men. More than 10 years of clinical research has found the following about Y deletions:

- They are not found in normospermic men, proving there is clearly a cause-and-effect relationship between Y deletions and spermatogenic failure (43).
- The highest frequency of Y deletions is found in azoospermic men (8-12%), followed by oligozoospermic (3-7%) men.
- Deletions are extremely rare with a sperm concentration > 5 million of spermatozoa/mL (approximately 0.7%).
- AZFc deletions are most common (approximately 65-70%), followed by deletions of the AZFb and AZFb+c or AZFa+b+c regions (25-30%). AZFa region deletions are extremely rare (5%).
- Complete removal of the AZFa region is associated with severe testicular phenotype (Sertoli cell only syndrome), while complete removal of the AZFb region is associated with spermatogenic arrest. Complete removal of the AZFc region causes a variable phenotype ranging from azoospermia to oligozoospermia.
- Classical AZF deletions do not confer a risk for cryptorchidism or testicular cancer (39).

The specificity and genotype/phenotype correlation reported above means that Y deletion analysis has both a diagnostic and prognostic value for testicular sperm retrieval (39). In the case of gr/gr deletion, there is no such strict genotype/phenotype correlation. This type of partial AZFc deletion can also be found in normozoospermic men, although at a significantly lower frequency (0.5-1%) than in men with abnormal spermatogenesis (3-5%). In the largest Caucasian study population (> 1000 men), gr/gr deletion carriers were 7-fold more likely to develop oligozoospermia (44). The phenotypic expression may vary in different ethnic groups, depending on the Y chromosome background (45,46). An overall risk of 2.4-fold for reduced sperm production in gr/gr deletion carriers has recently been reported by a meta-analysis that included only studies free from methodological and selection bias (47). There has also been a report of gr/gr deletion as a potential risk factor for testicular germ cell tumours (48). However, this data needs further confirmation in an ethnically and geographically matched case-control study setting.

After conception, any Y deletions are transmitted automatically to a male offspring, and genetic counselling is therefore mandatory. In most cases, father and son have the same microdeletion (49-52), but occasionally the son has a larger microdeletion (53). It has been proposed that partial AZFc deletions (gr/gr and b2/b3) may predispose to complete AZFc deletion in the next generation (54). There is a substantial variation in the son's phenotype and the extent of spermatogenic failure (still in the range of azoo/oligozoospermia) cannot be predicted entirely, due to the different genetic background and the presence or absence of environmental factors with potential toxicity for reproductive function. A significant proportion of spermatozoa from men with complete AZFc deletion are nullisomic for sex chromosome (55,56), indicating a potential risk for any offspring to develop 45,X0 Turner's syndrome and other phenotypic anomalies associated with sex chromosome mosaicism, including ambiguous genitalia.

The screening for Y chromosome microdeletions in patients bearing a mosaic 46,XY/45,X0 karyotype with sexual ambiguity and/or Turner stigmata has shown a relatively high incidence of AZFc deletions (33%) (57). There is data to support the association of Yq microdeletions with an overall Y chromosomal instability, which leads to the formation of 45,X0 cell lines (58,59). Despite this theoretical risk, babies born from fathers affected by Yq microdeletions are phenotypically normal (39,60). This could be due to the reduced implantation rate and a likely higher risk of spontaneous abortions of embryos bearing a 45,X0 karyotype.

When ICSI is used in the presence of a Y microdeletion, long-term follow up of any male children is needed with respect to their fertility status and cryoconservation of spermatozoa at a young age can be considered. However, there has only been a single report (48) of an enhanced risk for testicular germ cell

tumours in carriers of gr/gr deletion. Thus, it is only necessary to consider introducing preventive measures (e.g. testis ultrasound) in the sons of gr/gr deletion carriers if confirmatory studies are published.

#### *4.4.2.1 Testing for Y microdeletions*

Indications for AZF deletions screening are based on sperm count and include azoospermia and severe oligozoospermia (< 5 million spermatozoa/mL). Thanks to the European Academy of Andrology (EAA) guidelines (60) and EAA/EMQN (European Molecular Genetics Quality Network) external quality control programme (http://www.emqn.org/emqn/), Yq testing has become more homogeneous and reliable in different routine genetic laboratories. The EAA guidelines provide a set of primers capable of detecting > 95% of clinically relevant deletions (60). The primers consist of two markers for each region and control markers from the Yp and X chromosome. The initial reports of large variability of deletion frequencies are more likely to have been caused by technical problems and unreliable markers rather than be an expression of true ethnic differences.

#### *4.4.2.2 Y chromosome: 'gr/gr' deletion*

A new type of Yq deletions, known as the gr/gr deletion, has been described in the AZFc region (42). This deletion removes half of the gene content of the AZFc region, affecting the dosage of multicopy genes mapping inside this region. There is an almost 8-fold higher risk of developing oligozoospermia (OR = 7.9, 95% CI: 1.8-33.8; $p < 0.001$) in gr/gr deletion carriers in the largest Caucasian study population published to date (43). The frequency of gr/gr deletion in oligozoospermic patients is about 4%. According to four meta-analyses, gr/gr deletion is a significant risk factor for impaired sperm production (61,62).

However, both the frequency of gr/gr deletion and its phenotypic expression vary between different ethnic groups, depending on the Y chromosome background. For example, in some Y haplogroups, the deletion is fixed and appears to have no negative effect on spermatogenesis). The routine screening for gr/gr deletion is a still a debated issue, especially in those laboratories serving diverse ethnic and geographic populations.

#### *4.4.2.3 Conclusions*

| |
|---|
| Testing for microdeletions is not necessary in men with obstructive azoospermia when ICSI is used because spermatogenesis should be normal. |
| Men with severely damaged spermatogenesis (with < 5 million spermatozoa/mL) should be advised to undergo Yq microdeletion testing for both diagnostic and prognostic purposes. Yq microdeletion also has important implications for genetic counselling (*see below*). |
| If complete AZFa or AZFb microdeletions are detected, microtesticular sperm extraction is not worth doing because it is extremely unlikely that any sperm will be found. |
| gr/gr deletion has been confirmed as a significant risk factor for impaired sperm production, whereas further evidence of the prognostic significance of gr/gr and development of TCGTs is needed. |
| If a man with microdeletion and his partner wish to proceed with ICSI, they should be advised that microdeletions will be passed to sons, but not to daughters. |
| A son who inherits a microdeletion will have abnormal spermatogenesis because complete AZF deletions are not reported in normozoospermic men. |

### *4.4.3* ***Autosomal defects with severe phenotypic abnormalities and infertility***

Several inherited disorders are associated with severe or considerable generalised abnormalities and infertility (Table 6). Patients with these defects will be well known to doctors, often from childhood. A fertility problem must be managed in the context of the care of the man as a whole and considering the couple's ability to care for a child.

**Table 6: 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 16q21 |
| Cerebellar ataxia and hyogonadotrophic hypogonadism | Eunuchoidism, disturbances of gait and speech | Autosomal recessive |
| Noonan's syndrome | Short stature, webbed neck, cardiac and pulmonary abnormalities, 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 is a fatal autosomal-recessive disorder. It is the most common genetic disease of Caucasians; 4% are carriers of gene mutations involving the CF 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 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 gene mutations and was found in approximately 2% of men with OA attending a clinic in Edinburgh (63). The incidence in men with OA varies between different countries. The clinical diagnosis of absent vasa is easy to miss and all men with azoospermia should be very carefully examined to exclude CBAVD, particularly those with a semen volume of < 1.5 mL and pH less than 7.0.

Approximately 1,500 mutations are listed on the CFTR database (http://www.genet.sickkids.on.ca/cftr/). Many series of men with CBAVD tested for varying numbers of mutations have been published. In general, the more mutations tested for, the higher the percentage of men found to have them. 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; 63 other mutations were found in 1 to 9 men, but not all mutations were tested for in all case series (64).

As more mutations are defined and tested for, almost all men with CBAVD will probably be found to have mutations. 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 most common mutations in a particular community.

Mutations may be found in both copies of the CFTR gene; however, in most men with CBAVD, mutation is found in only one copy. In some of these supposedly heterozygous cases, there may be an unknown second mutation, but there is also another mechanism. In two-thirds of men with CBAVD, a DNA variant (the fifth allele) can be detected in a non-coding region of CFTR (65). Consequently, since the 5T-tract variant is now considered a mild CFTR mutation rather than a polymorphism, it should be analysed in each CAVD patient.

Men with CBAVD often have mild clinical stigmata of CF (e.g. history of chest infections). Children born after ICSI, where the father has CBAVD and is either hetero- or homozygous, must be followed up.

When a man has CBAVD, it is important to test him and his partner for CF mutations. If the female partner is found to be a carrier of CFTR, the couple must consider very carefully whether to proceed with ICSI using the husband's sperm, as the risk of a having a baby with CF will be 25% if the man is heterozygous and 50% if the man is homozygous. If the female partner is negative for known mutations, the risk of being a carrier of unknown mutations is about 0.4%.

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

Unilateral absence of the vas deferens is usually associated with ipsilateral absence of the kidney (66) 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, men with unilateral absence of the vas deferens and CF mutations may have the same underlying genetic diseases as men with true CBAVD. Men with bilateral absence of vas deferens and renal abnormalities do not have CFTR gene abnormalities (67).

Men who have unilateral absence of the vas and normal kidneys or bilateral absence or bilateral abnormality, should be tested for CF mutations. If the results are negative and renal anatomy has not been defined, an abdominal ultrasound should be undertaken. Findings may range from unilateral absence of the vas with ipsilateral absence of the kidney, to bilateral vessel abnormalities and renal abnormalities, such as pelvic kidney.

### 4.7 Unknown genetic disorders

Considering the high predicted number of genes involved in male gametogenesis, it is likely that most 'idiopathic' forms of spermatogenic disturbances are caused by mutations or polymorphisms in spermatogenesis candidate genes (34). However, despite an intensive search for new genetic factors, no clinically relevant gene mutations or polymorphisms (except those related to the Y chromosome) have so far been identified (34, 68, 69, and references therein). The introduction of new analytical approaches is likely to provide major advancement in this field (70,71).

ICSI is used to enable men with severely damaged spermatogenesis to father children in situations formerly considered hopeless and where very few spermatozoa can be obtained. This has led to concern that children may be born with a fetal abnormality, because ICSI may enable defective sperm to bypass the selective processes of the female genital tract and egg covering. Alternatively, eggs may be fertilised that would otherwise not be fertilised. However, fetal abnormality statistics from ICSI centres do not indicate any increase in congenital malformations compared with the general population.

On the other hand, ICSI babies have a higher risk of *de novo* sex chromosomal aberrations (about a 3-fold increase compared with natural conceptions) and paternally inherited structural abnormalities (72-74).

Indications for ICSI are constantly being extended to include fertilisation with immature sperm forms, and it is therefore particularly important to continue to monitor fetal abnormality rates, using detailed subgroup analysis according to the father's clinical and molecular diagnosis.

### 4.8 DNA fragmentation in spermatozoa

There is increased DNA damage in spermatozoa from men with oligozoospermia. This increase is associated with reduced chances of natural conception and, to a lesser extent, conception after IVF/ICSI, and with an increase in early pregnancy loss (75,76). DNA damage may improve after varicocele ligation (77,78).

### 4.9 Genetic counselling and ICSI

The best management is to agree treatment with the couple and provide them with full information on the genetic risks. Initially, the couple should be given full information about the risks to the child to help them decide whether to proceed with ICSI. Where there is conflict between the wishes of the couple and the interests of the future child, it may be ethically correct to withhold therapy.

When both partners are known to carry defects (e.g. CF mutations), there is up to a 50% chance of the child developing a clinical condition and dying early after a number of years of morbidity. Many clinicians and infertility clinic personnel may consider it is unethical to proceed because their duty of care to the future child and the interests of society outweigh the wishes of the individual couple. If 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. The couple also need to give consideration to preimplantation diagnosis and replacement only of normal embryos.

### 4.10 Conclusions and recommendations for genetic disorders in male infertility

| **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 us to identify the genetic basis of more disorders and diagnose known disorders at a lower cost. For some of these disorders, gene therapy might be practical. |

| Recommendations | GR |
|---|---|
| Standard karyotype analysis should be offered to all men with damaged spermatogenesis (< 10 million spermatozoa/mL) who are seeking fertility treatment by in vitro fertilisation/intracytoplasmic sperm injection (ICSI) (2). | B |
| Men with Klinefelter's syndrome might require androgen replacement therapy as they get older. | B |
| All men with Klinefelter's syndrome who undergo testicular biopsy procedures for sperm retrieval need long-term endocrine follow-up. | B |
| For men with severely damaged spermatogenesis (< 5 million spermatozoa/mL), testing for Yq microdeletions is strongly advised (39,60). | B |
| When a man has structural abnormalities of the vas deferens (bilateral absence of vas deferens, unilateral absence of the vas), it is important to test him and his partner for CF gene mutations (64). | 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 (1). | A |

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# 5. OBSTRUCTIVE AZOOSPERMIA

## 5.1 Definition

Obstructive azoospermia (OA) is the inability to detect both spermatozoa and spermatogenetic cells in semen and post-ejaculate urine due to bilateral obstruction of the seminal ducts. OA is less common than NOA and occurs in 15-20% of men with azoospermia. Common causes of OA are summarised in Table 7.

Men with OA present with normal FSH, normal size testes and epididymal enlargement. Sometimes, the vas deferens is absent due to congenital factors or previous inguinal or scrotal surgery. Obstruction in primary infertile men is often present at the epididymal level; other sites of obstruction are the ejaculatory ducts and the vas deferens. In 25% of men with a suspected obstruction, no spermatozoa are found in the epididymis during scrotal exploration, indicating an intratesticular obstruction.

**Table 7: Classification of OA, on the basis of ductal obstruction due to congenital and acquired causes**

| Conditions | Congenital | Acquired |
|---|---|---|
| Epididymal obstruction | Idiopathic epididymal obstruction | Post-infective (epididymitis)<br>Post-surgical (epididymal cysts) |
| Vas deferens obstruction | Congenital absence of vas deferens | Post-vasectomy<br>Post-surgical (hernia, scrotal surgery) |
| Ejaculatory duct obstruction | Prostatic cysts (Müllerian cysts) | Post-surgical (bladder neck surgery)<br>Post-infective |

## 5.2 Classification

### *5.2.1 **Intratesticular obstruction***

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

### *5.2.2 **Epididymal obstruction***

Epididymal obstruction is the most common cause of OA, 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 CBAVD, which is associated with at least one mutation of the CF 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 above* Chapter 4: Genetic disorders in infertility). Other congenital forms of obstruction are rare, e.g. disjunction between efferent ductules and the corpus epididymis, agenesis/atresia of a short part of the epididymis.

Congenital forms of epididymal obstruction include chronic sinopulmonary infections (Young's syndrome) (6), in which obstruction results from a mechanical blockage due to debris within the proximal epididymal lumen.

Acquired forms secondary to acute (e.g. gonococcal) and subclinical (e.g. chlamydial) epididymitis are most common (7,8) (*see below* Chapter 11: Male accessory gland infections). Acute or chronic traumas can result in epididymal damage (9).

Azoospermia caused by surgery may occur after epididymal surgery, e.g. cyst removal. Epididymal obstruction secondary to long-lasting distal obstruction must be considered when repairing seminal ducts (10).

### *5.2.3 **Vas deferens obstruction***

Vas deferens obstruction is the most common cause of acquired obstruction following vasectomy for sterilisation, with possible subsequent germ cell impairment and fibrosis (11,12). Approximately 2-6% of these men request vasectomy reversal. Of those undergoing vaso-vasostomy, 5-10% have epididymal blockage as a result of tubule rupture, making epididymo-vasostomy mandatory (*see below* Chapter 10: Male contraception). Vasal obstruction may also occur after herniotomy (13). Polypropylene mesh herniorrhaphy appears to be able to induce a fibroblastic response able to entrap or obliterate the vas deferens (14).

The most common congenital vasal obstruction is CBAVD, often accompanied by CF. Unilateral agenesis or a partial defect is associated with contralateral seminal duct anomalies or renal agenesis in 80% and 26% of cases, respectively (15) (*see above* Chapter 4: Genetic disorders in infertility). Distal vas deferens obstruction includes CBAVD and accidental injury to the vas deferens during hernia surgery (16).

### *5.2.4 **Ejaculatory duct obstruction***

Ejaculatory duct obstruction is found in about 1-3% of OA (1) and is classified as either 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 abnormalities, one or both ejaculatory ducts empty into the cyst (17), while in Müllerian duct anomalies, ejaculatory ducts are laterally displaced and compressed by the cyst (18).

Paramedian or lateral intraprostatic cysts are Wolffian in origin and rare in clinical practice (19). Post-inflammatory obstructions of the ejaculatory duct are usually secondary to acute, non-acute, or chronic urethro-prostatitis (20).

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) (20,21).

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

Functional obstruction of the distal seminal ducts might be attributed to local neuropathy (22). This abnormality is often associated with urodynamic dysfunction because of the vasographic patterns of ampullo-vesicular atony or of ejaculatory duct hypertony. Functional obstruction of the distal seminal ducts has been reported in juvenile diabetes and polycystic kidney disease (23); however, no relevant pathology has been found in most cases. Results of semen analysis vary between azoospermia, cryptozoospermia and severe OAT syndrome.

## 5.3 Diagnosis

### *5.3.1 **Clinical history***

Clinical history taking should follow the suggestions for investigation of infertile men (*see* Chapter 2: Investigations).

Patients should be asked about:

- haematospermia;
- post-ejaculatory pain;
- previous or present urethritis or prostatitis;
- obstructive or irritative urinary symptoms;
- previous scrotal enlargement or pain or surgery;
- previous inguinal herniorrhaphy or traumas;
- chronic sinopulmonary infections.

### *5.3.2* ***Clinical examination***

Clinical examination should follow suggestions for investigation of the infertile man. The following findings indicate OA:

- at least one testis with a volume > 15 ml, although a smaller testicular volume may be found in some patients with OA 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.

### *5.3.3* ***Semen analysis***

At least two examinations must be carried out at an interval of 2-3 months, according to the WHO (*see above* Chapter 2: Investigations). Azoospermia means the inability to detect spermatozoa after centrifugation at x400 magnification. Careful repeat observation of several smears after semen liquefaction is needed. If no spermatozoa are found in a wet preparation, then aliquots or the whole semen sample should be centrifuged at 3000 G for 15 minutes. The pellet must be examined for spermatozoa.

Ejaculatory duct obstruction or CBAVD is suggested by a semen volume of less than 1.5 mL, acid pH and a low fructose level. When semen volume is low, a search must be made for spermatozoa in urine after ejaculation, 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.

### *5.3.4* ***Hormone levels***

Serum FSH levels may be normal, but do not exclude a testicular cause of azoospermia (e.g. spermatogenic arrest). Follicle-stimulating hormone is normal in 40% of men with primary spermatogenic failure. Inhibin B seems to have a higher predictive value for normal spermatogenesis (4).

### *5.3.5* ***Ultrasonography***

Scrotal ultrasound is helpful in finding signs of obstruction (e.g. dilatation of rete testis, enlarged epididymis with cystic lesions, absent vas deferens) and may demonstrate signs of testicular dysgenesis (e.g. non-homogenous testicular architecture and microcalcifications) and associated carcinoma *in situ* of the testis. For patients with a low seminal volume and in whom distal obstruction is suspected, transrectal ultrasound (TRUS) is essential. If possible, TRUS should be performed at high resolution and with high frequency (> 7 MHz) biplane transducers. Seminal vesicle enlargement (anterior-posterior diameter 15 mm) (21) and roundish, anechoic areas in the seminal vesicle (24) are TRUS anomalies more often associated with ejaculatory duct obstruction, especially when semen volume is < 1.5 mL. Müllerian duct cysts or urogenital sinus/ejaculatory duct cysts (20) and ejaculatory duct calcifications (25) are other known anomalies in obstructive azoospermia. Transrectal ultrasound may also be used to aspirate seminal vesicle fluid (26).

Invasive diagnosis, including testicular biopsy, scrotal exploration, and distal seminal duct evaluation, are indicated in patients with OA in whom an acquired obstruction of the seminal ducts is suspected. Explorative and recanalisation surgery should be carried out at the same time.

### *5.3.6* ***Testicular biopsy***

In selected cases, testicular biopsy may be indicated to exclude spermatogenic failure. Testicular biopsy should be combined with extraction of testicular spermatozoa (i.e. TESE) for cryopreservation and subsequent ICSI, when surgical recanalisation cannot be carried out or has failed. A scoring system for testicular biopsies is given in Table 8 (27).

**Table 8: Scoring system for testicular biopsies (Johnsen score)***

| Score | Histological criteria |
|---|---|
| 10 | Full spermatogenesis |
| 9 | Slightly impaired spermatogenesis, many late spermatids, disorganised epithelium |
| 8 | < 5 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 |

** From Johnsen, 1970 (27).*

## 5.4 Treatment

### *5.4.1 **Intratesticular obstruction***

At this level seminal duct recanalisation is impossible. Both Testicular Sperm Extraction (TESE) or Microsurgical Epididymal Sperm Aspiration (MESA) allow sperm retrieval in nearly all OA patients. TESE and MESA are therefore recommended. The spermatozoa retrieved may be used immediately for ICSI, or may be cryopreserved.

### *5.4.2 **Epididymal obstruction***

Microsurgical epididymal sperm aspiration (MESA) (28) is indicated in men with CBAVD. TESA and PESA are also viable options for retrieving epididymal sperm from men with OA (29). Retrieved spermatozoa are used for ICSI. Usually, one MESA procedure provides sufficient material for several ICSI cycles (30) and it produces high pregnancy and fertilisation rates (31). In patients with azoospermia due to acquired epididymal obstruction, end-to-end or end-to-side microsurgical epididymo-vasostomy is recommended, with the preferred technique being microsurgical intussusception epididymo-vasostomy (32).

Reconstruction may be carried out unilaterally or bilaterally; patency and pregnancy rates are usually higher with bilateral reconstruction. Before microsurgery, it is important to check for full patency downstream of the epididymis. Anatomical recanalisation following surgery may require 3-18 months. Before microsurgery (and in all cases where recanalisation is impossible), epididymal spermatozoa should be aspirated and cryopreserved for use in ICSI in case of surgical failure (30).

Patency rates range between 60% and 87% (33-35) and cumulative pregnancy rates between 10% and 43%. Recanalisation success rates may be adversely affected by pre-operative and operative findings (e.g. concomitant abnormal testicular histology, absence of sperm in the spermatic fluid on sectioning the small epididymal tubules, wide fibrosis of the epididymis).

### *5.4.3 **Proximal vas obstruction***

Proximal vas obstruction after vasectomy requires microsurgical vasectomy reversal (*see* Chapter 10: Male contraception). Vaso-vasostomy is also required in rare cases of proximal vasal obstructions (iatrogenic, post-traumatic, post-inflammatory). The absence of spermatozoa in the intraoperative vas deferens fluid may suggest the presence of a secondary epididymal obstruction, especially if the seminal fluid of the proximal vas has a thick 'toothpaste' appearance. Microsurgical vaso-epididymostomy is then indicated.

### *5.4.4 **Distal vas deferens obstruction***

It is usually impossible to correct large bilateral vas deferens defects, resulting from involuntary excision of the vas deferences during hernia surgery in early childhood or previous orchidopexy (16). In these cases, proximal vas deferens sperm aspiration (37) or TESE/MESA can be used for cryopreservation for future ICSI. In large unilateral vas deferens defects associated with contralateral testicular atrophy, the vas deferens of the atrophic testis can be used for a cross-over vaso-vasostomy or vaso-epididymostomy.

### *5.4.5 **Ejaculatory duct obstruction***

The treatment of ejaculatory duct obstruction depends on its aetiology. Transurethral resection of the ejaculatory ducts (TURED) (20,38) can be used in large post-inflammatory obstruction and when one, or both,

ejaculatory ducts empty into an intraprostatic midline cyst. 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 (20). Intra-operative TRUS makes this procedure safer. If distal seminal tract evaluation is carried out at the time of the procedure, installation of methylene blue dye into the vas deferens can help to document opening of the ducts. The limited success rate of surgical treatment of ejaculatory duct obstruction in terms of spontaneous pregnancies should be weighed against sperm aspiration and ICSI.

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

In cases of functional obstruction of the distal seminal ducts, TURED often fails to improve sperm output. Spermatozoa can then be retrieved by antegrade seminal tract washout (38). Spermatozoa retrieved by any of the aforementioned surgical techniques should always be cryopreserved for assisted reproductive procedures.

## 5.5 Conclusions and recommendation for obstructive azoospermia

| 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 surgeon's expertise. Standardised procedures include vaso-vasostomy and epididymo-vasostomy. |
| Sperm retrieval techniques, such as MESA, TESE, and PESA can be used additionally. These methods should be used only when cryostorage of the material obtained is available. |

| Recommendation | GR |
|---|---|
| In azoospermia caused by epididymal obstruction, a scrotal exploration with microsurgical epididymal sperm aspiration and cryopreservation of the spermatozoa should be carried out, together with a microsurgical reconstruction (35). | B |

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# 6. VARICOCELE

## 6.1 Introduction

Varicocele is a common abnormality (*see* Chapter 2: 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 can be shown by special tests (Doppler ultrasound studies) (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 is made by clinical examination and can be confirmed by colour Doppler analysis (2). In centres where treatment is carried out by antegrade or retrograde sclerotherapy or embolisation, diagnosis is additionally confirmed by X-ray.

## 6.4 Basic considerations

### *6.4.1 **Varicocele and fertility***

Varicocele is a physical abnormality present in 11.7% of adult men and in 25.4% of men with abnormal semen analysis (4). The exact association between reduced male fertility and varicocele is unknown, but a recent meta-analysis showed that semen improvement is usually observed after surgical correction (5). 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. Varicocele is associated

with increased sperm DNA damage, and this sperm pathology may be secondary to varicocele-mediated oxidative stress.Varicocelectomy can reverse this sperm DNA damage, as shown in several studies (6).

### *6.4.2 **Varicocelectomy***

Varicocele repair has been a subject of debate for decades: controversy exists as to whether varicocele repair results in more spontaneous pregnancies as compared to observation. The 2009 Cochrane Database review concluded that there is no evidence that treatment of the varicocele improves a couples' chance of conception (7). This meta-analysis was criticised for including several heterogenous studies, men with normal semen analysis and men with a subclinical varicocele (8). In 3 randomised controlled studies varicocele repair in men with a subclinical varicocele was found to be ineffective (9-11). Also, studies of men with a varicocele and normal semen analysis showed no clear benefit of treatment over observation (12,13).

The duration of the infertility also seems of importance: in a recent study it was shown that couples with an infertility duration of more than 2 years had a significant higher pregnancy rate compared to couples with an uncorrected varicocele. In couples with a shorter duration of infertility, such a difference was not observed (14).

In a recent meta-analysis of 4 RCTs on varicocelectomy in men with a clinical varicocele, oligospermia and otherwise unexplained infertility a trend in favour of surgical correction was observed (15). The combined odds ratio was 2.23 (95% confidence interval [CI], 0.86-5.78; p=0.091), indicating that varicocelectomy is moderately superior to observation, but the effect was not statistically significant.

There is a need for a large, properly conducted RCT of varicocele treatment in men with abnormal semen from couples with otherwise unexplained subfertility (16). While treatment of varicocele in infertile men may be effective, in adolescents there is a significant risk of overtreatment: most adolescents with a varicocele will have no problem achieving pregnancy later in life (17).

## 6.5 Treatment

Several treatments are available for varicocele (Table 9). The type of intervention chosen depends mainly on the experience of the therapist. Although laparoscopic varicocelectomy is feasible, it must be justified in terms of cost effectiveness.

**Table 9: Recurrence and complication rates associated with treatments for varicocele**

| Treatment | Ref. | Recurrence/ persistence % | Complication rates |
|---|---|---|---|
| Antegrade sclerotherapy | 18 | 9 | Complication rate 0.3-2.2%: testicular atrophy, scrotal haematoma, epididymitis, left-flank erythema |
| Retrograde sclerotherapy | 19 | 9.8 | Adverse reaction to contrast medium, flank pain, persistent thrombophlebitis, vascular perforation |
| Retrograde embolisation | 20,21 | 3.8-10 | Pain due to thrombophlebitis, bleeding haematoma, infection, venous perforation, hydrocele, radiological complication (e.g. reaction to contrast media), misplacement or migration of coils, retroperitoneal haemorrhage, fibrosis, ureteric obstruction |
| *Open operation* | | | |
| Scrotal operation | | - | Testicular atrophy, arterial damage with risk of devascularisation and gangrene of testicle, scrotal haematoma, post-operative hydrocele |
| Inguinal approach | 22 | 13.3 | Possibility of missing out a branch of testicular vein |
| High ligation | 23 | 29 | 5-10% incidence of hydrocele ( < 1%) |
| Microsurgical inguinal or subinguinal | 24,25 | 0.8-4 | Post-operative hydrocele arterial injury, scrotal haematoma |
| Laparoscopy | 26,27 | 3-7 | Injury to testicular artery and lymph vessels, intestinal, vascular and nerve damage, pulmonary embolism, peritonitis, bleeding, post-operative pain in right shoulder (due to diaphragmatic stretching during pneumoperitoneum), pneumoscrotum, wound infection |

## 6.6 Conclusions and recommendations for varicocele

| Conclusions |
|---|
| Current information supports the hypothesis that the presence of varicocele in some men is associated with progressive testicular damage from adolescence onwards and a consequent reduction in fertility. |
| Although the treatment of varicocele in adolescents may be effective, there is a significant risk of over-treatment. |
| Varicocele repair may be effective in men with subnormal semen analysis, a clinical varicocele and otherwise unexplained infertility. Further RCTs are needed to confirm that this subgroup of infertile couples will benefit from treatment. |

| Recommendations | GR |
|---|---|
| Varicocele treatment is recommended for adolescents with progressive failure of testicular development documented by serial clinical examination (9,10). | B |
| No evidence indicates benefit from varicocele treatment in infertile men who have normal semen analysis or in men with subclinical varicocele. In this situation, varicocele treatment cannot be recommended (15-17). | A |
| Varicocele repair should be considered in case of a clinical varicocele, oligospermia, duration of infertility of at least 2 years and otherwise unexplained infertility in the couple. | B |

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# 7. HYPOGONADISM

## 7.1 Introduction

Hypogonadism is characterised by impaired testicular function, which may affect spermatogenesis and/or testosterone synthesis. The symptoms of hypogonadism depend on the degree of androgen deficiency and if the condition develops before or after pubertal development of the secondary sex characteristics. The symptoms and signs of hypoandrogenism presenting before and after completion of puberty are given in Table 10.

**Table 10: Symptoms and signs of hypogonadism debuting before and after completion of puberty***

| Affected organ/function | Before completed puberty | After completed puberty |
|---|---|---|
| Larynx | No voice mutation | No voice mutation |
| Hair | Horizontal pubic hairline<br>Straight frontal hairline<br>Diminished beard growth | Diminished secondary body hair |
| Skin | Absent sebum production<br>Lack of acne<br>Pallor<br>Skin wrinkling | Decreased sebum production<br>Lack of acne<br>Pallor<br>Skin wrinkling |
| Bones | Eunuchoid tall stature<br>Osteoporosis | Osteoporosis |
| Bone marrow | Mild anaemia | Mild anaemia |
| Muscles | Underdeveloped | Hypotrophy |
| Prostate | Underdeveloped | Hypotrophy |
| Penis | Infantile | No change of size |
| Testes | Possibly maldescended testes<br>Small volume | Decrease of testicular volume |
| Spermatogenesis | Not initiated | Involuted |
| Libido and potency | Not developed | Loss |

**Modified from Nieschlag et al. (1998) (1).*

The aetiological and pathogenetic mechanisms of male hypogonadism can be divided into three main categories:

1. Primary (hypergonadotrophic) hypogonadism due to testicular failure.
2. Secondary (hypogonadotrophic) hypogonadism caused by insufficient gonadotrophin-releasing hormone (GnRH) and/or gonadotrophin (FSH, LH) secretion.
3. Androgen insensitivity (end-organ resistance).

The most common conditions within these three categories are given in Table 11 (*see also* Chapter 4: Genetic disorders in infertility).

**Table 11: Disorders with male hypogonadism***

| **Primary (hypergonadotropic) hypogonadism (testicular failure)*** |
|---|
| Anorchia |
| Maldescended testes |
| Klinefelter's syndrome |
| Y chromosome microdeletions |
| Numerical and structural chromosomal anomalies |
| Trauma, testicular torsion, orchitis |
| Iatrogenic (surgery, medications, irradiation, cytostatic drugs) |
| Exogenous factors (toxins, heat, occupational hazards) |
| Systemic diseases (liver cirrhosis, renal failure) |
| Testicular tumour |
| Varicocele |
| Idiopathic |
| **Secondary (hypogonadotropic) hypogonadism (secondary testicular failure)** |
| Congenital<br>o Idiopathic hypogonadotrophic hypogonadism<br>o Normosmic<br>o Iposmic/anosmic (Kallmann syndrome) |

| |
|---|
| Acquired (tumours in the following regions)<br>o Dyencephalon (craniopharyngiomas, meningiomas)<br>o Hypothalamus or pituitary |
| Empty sella |
| Granulomatous illnesses |
| Fractures of the skull base |
| Ischaemic or haemorrhagic lesions in hypothalamic area |
| Hyperprolactinaemia |
| Drugs/anabolic steroids, radiotherapy |
| **Target organ resistance to androgens** |
| Testicular feminisation |
| Reifenstein's syndrome |

### 7.2 Hypogonadotrophic hypogonadism: aetiology, diagnosis and therapeutic management

Idiopathic hypogonadotrophic hypogonadism (IHH) is characterised by low levels of gonadotrophins and sex steroid in the absence of anatomical or functional abnormalities of the hypothalamic-pituitary-gonadal axis (2). Idiopathic HH may be an isolated condition or may be associated with anosmia/hyposmia (Kallmann syndrome). Genetic factors causing a deficit of gonadotrophins may act at the hypothalamic or pituitary level. Mutations in candidate genes (X-linked or autosomal) can be found in about 30% of congenital cases (2) and should be screened prior to assisted reproduction (3).

Acquired hypogonadotrophic hypogonadism can be caused by some drugs, hormones, anabolic steroids, and by tumours. A suspected tumour requires imaging (CT or MR) of the sella region and a complete endocrine work-up.

The failure of hormonal regulation can easily be determined (4). Endocrine deficiency leads to a lack of spermatogenesis and testosterone secretion as a result of decreased secretion of FSH and LH. After having excluded secondary forms (drug, hormones, tumours), the therapy of choice depends on whether the goal is to achieve normal androgen levels or to achieve fertility.

Normal androgen levels and subsequent development of secondary sex characteristics (in cases of onset of hypogonadism before puberty) and eugonadal state can be achieved by androgen replacement alone. However, the stimulation of sperm production requires treatment with human chorionic gonadotrophin (hCG) combined with recombinant FSH or urinary FSH or human menopausal gonadotropins (HMG). In the rare cases of 'fertile eunuchs', who have sufficient production of FSH but not LH, treatment with hCG alone may be sufficient to stimulate sperm production and to achieve normal testosterone levels (5).

If hypogonadotrophic hypogonadism is hypothalamic in origin, an alternative to hCG treatment is therapy with pulsatile GnRH (6). In patients who have developed hypogonadism before puberty and have not been treated with gonadotropins or GnRH, 1-2 years of therapy may be needed to achieve sperm production. Once pregnancy has been established, patients can return to testosterone substitution.

### 7.3 Hypergonadotrophic hypogonadism: aetiology, diagnosis and therapeutic management

Many conditions are associated in men with hypogonadotrophic hypogonadism (Table 11, *see also* Chapter 4: Genetic disorders in infertility). Most conditions listed in Table 11 only affect the reproductive function of the testis so that only the FSH level is elevated. However, it has been reported that men with infertility problems are at higher risk for developing impaired Leydig cell function (7), while men with Klinefelter's syndrome often show high LH values and develop hypoandrogenism with ageing (8). A decrease in testosterone blood concentrations after extensive testicular biopsy in the context of TESE/ICSI has been observed, raising questions about the need for long-term endocrine follow-up of these patients (9).

Hypogonadism affecting both reproductive and endocrine functions of the testis occurs after treatment with GnRH analogues or surgical castration for prostatic cancer (10).

The laboratory diagnosis of hypergonadotrophic hypogonadism is based on a high level of FSH, decreased serum testosterone and increased LH levels (3). Testosterone levels should be evaluated in view of the concentration of the serum concentration of sex hormone binding globulin (SHBG). Based on levels of total testosterone and SHBG, free and bioavailable testosterone can be calculated (http://www.issam.ch/freetesto.htm).

Due to diurnal variation, blood samples for testosterone assessment should be taken before 10.00 am. The existing guidelines for androgen replacement are based on mainly total testosterone levels. There is general agreement that a total testosterone level > 12 nmol / L (350 ng / dL) does not require substitution. Similarly,

based on the data of younger men, there is consensus that patients with serum total testosterone levels < 8 nmol / L (230 ng / dL) will usually benefit from testosterone treatment. If the serum total testosterone level is between 8 and 12 nmol / L, testosterone supplementation is based on the presence of symptoms.

In obese men, decision-making may be helped by measuring total testosterone with SHBG to calculate free testosterone or measurement of free testosterone by equilibrium dialysis (11). Injectable, oral and transdermal testosterone preparations are available for clinical use (3). The best preparation to use is one that maintains serum testosterone levels as near as possible to physiological concentrations (11-13).

## 7.4 Conclusion and recommendation for hypogonadism

| Conclusion |
|---|
| It is generally agreed that patients with primary or secondary hypogonadism associated with hypoandrogenism should receive testosterone substitution therapy. |

| Recommendation | GR |
|---|---|
| Effective drug therapy is available to achieve fertility in men with hypogonadotrophic hypogonadism (4). | A |

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# 8. CRYPTORCHIDISM

## 8.1 Introduction

Cryptorchidism is the most common congenital abnormality of the male genitalia and is found in 2-5% of newborn boys, depending on gestational age (cryptorchidism occurs more often in premature boys) and age after birth. At the age of 3 months, the incidence of cryptorchidism falls 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, involving disrupted endocrine regulation and several gene defects. The normal descent of the testes requires a normal hypothalamo-pituitary-gonadal axis. Endocrine disruption in early pregnancy can potentially affect gonadal development and normal descent of the testes; however, most boys with maldescended testes show no endocrine abnormalities after birth. It has been postulated that cryptorchidism may be a part of the so-called testicular dysgenesis syndrome (TDS), which is a developmental disorder of the gonads caused by environmental and/or genetic influences early in pregnancy. Besides cryptorchidism, TDS includes hypospadias, reduced fertility, increased risk of malignancy, and Leydig cell dysfunction (1).

## 8.2 Incidence of cryptorchidism

The Caucasian population has a three-fold higher incidence of cryptorchidism compared to African-Americans. Even between Caucasians, there are significant differences in the risk of cryptorchidism, e.g. it is significantly more common among Danish than Finnish newborns (2). Premature babies have a much higher incidence of cryptorchidism than full-term babies. In a British study, the incidence of cryptorchidism was 2.7% in more than 3,000 boys weighing > 2500 g and 21% in premature boys weighing < 2500 g. At the age of 3 months, spontaneous descent occurred in most boys, and the incidence of cryptorchidism fell to 0.9% and 1.7%, in the > 2500 g and < 2500 g group, respectively (3).

## 8.3 Testicular descent and maldescent

The process of testicular descent has two distinct phases: transabdominal and inguinal. During transabdominal descent, development of the gubernaculum and genitoinguinal ligament plays an important role. The anti-Müllerian hormone regulates the transabdominal descent of the testes. Induction of the gubernaculum depends on a functional Insl3 gene in mice (4). This gene is expressed in Leydig cells and its targeted deletion causes bilateral cryptorchidism with free-moving testes and genital ducts (5). Androgens play an important role in both phases of testicular descent, while other gene families, e.g. the homeobox (HOX) and GREAT/RXFP2 genes (G-protein-coupled receptor affecting testis descent), are important in the development of genital organs and may be associated with testicular maldescent (6,7).

## 8.4 Hormonal control of testicular descent

Maldescent can be caused by two hormonal factors: hypogonadism and androgen insensitivity. The increasing incidence of reproductive abnormalities in male humans can be explained by increased oestrogen exposure during gestation (8). Some pesticides and synthetic chemicals act as hormonal modulators, often possessing oestrogenic activity (xeno-oestrogens) (9). The oestrogenic and anti-androgenic properties of these chemicals may cause hypospadias, cryptorchidism, reduced sperm density, and an increased incidence of testicular tumours in animal models, via receptor-mediated mechanisms or direct toxic effects associated with Leydig cell dysfunction (10).

## 8.5 Pathophysiological effects in maldescended testes

### *8.5.1 **Degeneration of germ cells***

The degeneration of germ cells in maldescended testes is apparent after the first year of life. Degenerative changes vary, depending on the position of the testis (11). During the second year, the number of germ cells declines. In 10-45% of affected patients, the complete loss of germ cells can be detected. Early treatment is therefore recommended to conserve spermatogenesis, especially in bilateral cases. Surgical treatment is the most effective and reliable method of bringing testes into the scrotum. Hormone treatment with hCG has been used widely in the past, but it has now been abolished because of increased germ cell apoptosis after treatment (12).

### *8.5.2 **Relationship with fertility***

Semen parameters are often impaired in men with a history of cryptorchidism (13). Surgical treatment during the first or second year of life may have a positive effect on subsequent fertility (14). However, there is no definitive proof of the protective effect of early orchidopexy. In men with a history of unilateral cryptorchidism, paternity is almost equal (89.7%) to that in men without cryptorchidism (93.7%).

In men with unilateral cryptorchidism, paternity is independent of age at orchidopexy and pre-

operative testicular location and testicular size (15). However, a history of unilateral cryptorchidism may result in reduced fertility potential and therefore a longer time to achieve pregnancy.

In men with bilateral cryptorchidism, oligozoospermia can be found in 31% and azoospermia in 42%. In cases of bilateral cryptorchidism, the rate of paternity is only 35-53%. In cases of bilateral cryptorchidism and azoospermia, orchidopexy performed even in adult life might lead to the appearance of spermatozoa in the ejaculate (16).

#### *8.5.3* ***Germ cell tumours***

Cryptorchidism is a risk factor for testicular cancer and is associated with testicular microcalcification and intratubular germ cell neoplasia of unclassified type [ITGCNU] former "CIS" of the testis. In 5-10% of testicular cancers, there is a history of cryptorchidism (17). The risk of a germ cell tumour is 3.6-7.4 times higher than in the general population and 2-6% of men with a history of cryptorchidism will develop a testicular tumour (17). Orchidopexy preformed before the age of puberty has been reported to decrease the risk of testicular cancer (18). However, this and other similar reports are based on retrospective data and does not exclude the possibility that boys undergoing early and late orchidopexy represent different pathogenetic groups of testicular maldescent.

## 8.6 Treatment of undescended testes

#### *8.6.1* ***Hormonal treatment***

Human chorionic gonadotrophin or GnRH has been used widely in the past to treat cryptorchidism. However, although 15-20% of retained testes descend during hormonal treatment, one-fifth of these re-ascend later. Also, treatment with hCG may be harmful to future spermatogenesis by increasing the apoptosis of germ cells (12), which is why hormonal treatment is no longer recommended.

#### *8.6.2* ***Surgical treatment***

The success rate of surgical treatment for undescended testes is 70-90% (19). If the spermatic cords or the spermatic vessels are too short to allow proper mobilisation of the testis into the scrotum, a staged orchidopexy (Fowler-Stephenson procedure) can be performed, using open surgery, laparoscopy or microsurgery.

The optimal age for performing orchidopexy is still debated. Some retrospective studies have indicated early treatment (during the first 2 years of life) has a beneficial effect on preserving future fertility (20), while a recent randomised study showed that surgery at 9 months resulted in a partial catch-up of testicular growth until at least age 4 years versus surgery at 3 years. The results clearly indicate that early surgery has a beneficial effect on testicular growth. Because testicular volume is an approximate indirect measure of spermatogenic activity, it is possible that orchidopexy at an early age might improve future spermatogenesis.

A biopsy at the time of orchidopexy (*see section* 8.5.3) can reveal intratubular germ cell neoplasia of unclassified type [ITGCNU], which can be removed thereby preventing development of a malignant tumour. If not corrected by adulthood, an undescended testis should not be removed because it still produces testosterone. Furthermore, as indicated above, correction of bilateral cryptorchidism, even in adulthood, can lead to sperm production in previously azoospermic men (16).

Vascular damage is the most severe complication of orchidopexy and can cause testicular atrophy in 1-2% of cases. In males with non-palpable testes, the post-operative atrophy rate was 12% in those cases with long vascular pedicles that enabled scrotal positioning. Post-operative atrophy in staged ochidopexy has been reported in up to 40% of patients (19).

## 8.7 Conclusions and recommendations for cryptorchidism

| **Conclusions** |
|---|
| Cryptorchidism is multifactorial in origin and can 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. |
| Whether early surgical intervention can prevent germ cell loss is still debatable, but in a randomised study it improved testicular growth in boys treated at the age of 9 months compared to those aged 3 years at the time of orchidopexy. |
| Paternity in men with unilateral cryptorchidism in almost equal to that in men without cryptorchidism. |
| Bilateral cryptorchidism significantly reduces the likelihood of paternity. |

| Recommendations | GR |
|---|---|
| Hormonal treatment of cryptorchidism should be abolished because of the risk of germ cell apoptosis and subsequent reduction of sperm production. | B |
| Early orchidopexy (6-12 months of age) might be beneficial for testicular development in adulthood. | B |
| If undescended testes are corrected in adulthood, testicular biopsy for detection of intratubular germ cell neoplasia of unclassified type [ITGCNU; former “CIS] is recommended at the time of orchidopexy (17). | B |

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# 9. IDIOPATHIC MALE INFERTILITY

## 9.1 Introduction

No demonstrable cause of male infertility, other than idiopathic OAT syndrome, is found in at least 44% of infertile men (1).

## 9.2 Empirical treatments

A wide variety of empirical drug treatments of idiopathic male infertility have been used; however, there is little scientific evidence for an empirical approach (2). Androgens, hCG/human menopausal gonadotrophin, bromocriptine, alpha-blockers, systemic corticosteroids and magnesium supplementation are not effective in the treatment of OAT syndrome. Follicle-stimulating hormone (3) and anti-oestrogens in combination with testosterone (4) might be beneficial in a selection of patients (3,4). A Cochrane analysis showed that men taking oral antioxidants had an associated statistically significant increase in live birth rate (pooled odds ratio (OR) = 4.85; 95% CI: 1.92-12.24; p = 0.0008; I(2) = 0%) when compared with men taking the control. No studies reported harmful side effects from the antioxidant therapy used. The evidence suggests that antioxidant supplementation in subfertile males may improve the outcomes of live birth and pregnancy rate for subfertile couples undergoing ART cycles. Further head-to-head comparisons are necessary to identify the superiority of one antioxidant over another (5).

| Recommendation | GR |
|---|---|
| Medical treatment of male infertility is recommended only for cases of hypogonadotrophic hypogonadism (1). | A |

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# 10. MALE CONTRACEPTION

## 10.1 Introduction

'Male contribution to contraception' is a more accurate phrase than 'male contraception', as men do not conceive. Development of male contraceptive methods is important because up to 40% of women have an unmet need for family planning, with approximately 80 million women every year having unintended or unwanted pregnancies (1).

Three of the four methods of male contraception have been in use for hundreds of years (i.e. condoms, periodic abstinence and withdrawal). The typical first-year failure rates of traditional male methods are high (withdrawal 19%, periodic abstinence 20%, and condoms 3-14%) compared to the failure rates of 0.1-3% for modern reversible female methods (2). For men to take more responsibility for family planning, male contraceptive methods must be acceptable, cheap, reversible, and effective.

Research is attempting to (3):

- Prevent sperm production by using exogenic androgens, progestogen and GnRH formulations in various combinations).
- Interfere with the ability of sperm to mature and fertilise, by using an epididymal approach to create a hostile environment for sperm.
- Produce better barrier methods, e.g. polyurethane condoms can be used by those with latex allergy, although they have higher breakage rates (4).
- Produce an antisperm contraceptive vaccine (5).
- Inhibit sperm-egg interactions.

These approaches remain experimental. The method nearest to being generally available clinically is hormonal male contraception, which is based on the suppression of gonadotrophins and testosterone substitution to maintain male sexual function and bone mineralisation and to prevent muscle wasting (6). Various contraceptive regimens have been developed and tested, including testosterone monotherapy, androgen/progestin combinations, testosterone with GnRH analogues, and selective androgen- and progestin-receptor modulators. There are racial differences in the response to androgens alone. However, a combination of testosterone with progestin has resulted in complete suppression of spermatogenesis in all races, and provides contraceptive efficacy equivalent to female hormonal methods (7). Phase III clinical trials of depot preparations of androgen/progestin combinations are in progress.

## 10.2 Vasectomy

Vasectomy is an effective method of permanent male surgical sterilisation (8). Before vasectomy, the couple should be fully informed about the benefits and risks, especially as an Australian telephone survey found that 9.2% of respondents regretted having a vasectomy (9).

### *10.2.1* ***Surgical techniques***

Various techniques are available for vasectomy. The least invasive approach is the no-scalpel vasectomy (10), which is also associated with a low rate of complications (11). The most effective occlusion technique is cauterisation of the lumen of the vas deferens and fascial interposition (12-14). Most techniques can be carried out safely under local anaesthesia in an outpatient clinic.

### *10.2.2* ***Complications***

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 in any systemic disease after vasectomy. An increased rate of prostate cancer in men who underwent vasectomy has not been detected (17).

Acute local complications associated with vasectomy include haematoma, wound infection, and epididymitis in up to 5% of cases (15). The potential long-term complications (e.g. chronic testicular pain) (16) must be discussed with the patient before the procedure. Epididymal tubal damage is common, and is associated with consequent development of sperm granuloma and time-dependent secondary epididymal obstruction, which limits vasectomy reversal.

### *10.2.3* ***Vasectomy failure***

If an effective occlusion technique is used, the risk of recanalisation after vasectomy should be < 1% (12). However, patients should be informed pre-operatively that, although rare, long-term re-canalisation might occur (19). No motile spermatozoa should be detected 3 months after vasectomy. Persistent motility is a sign of vasectomy failure, and the procedure will need to be repeated. A 'special clearance' with non-motile spermatozoa < 10,000/mL is still under discussion (18).

### *10.2.4* ***Counselling***

Counselling with regard to vasectomy must address the following aspects:

- Vasectomy should be considered irreversible.
- Vasectomy is associated with a low complication rate; however, because it is an elective operation, even small risks must be explained, because men (and their partners) might wish to consider these before giving consent.
- Vasectomy can fail, although the failure rate is low.
- Couples should be advised to continue with other effective contraception until clearance is confirmed.
- All available data indicate that vasectomy is not associated with any serious, long-term, side effects (15).
- Vascetomy involving cauterisation and fascial interposition appears to be the most effective technique (12-14).

## 10.3 Vasectomy reversal

A wide range of surgical success rates has been published for vasectomy reversal (up to 90%), depending on the time between vasectomy and re-fertilisation, type of vasectomy (e.g. open-ended or sealed), type of reversal (vaso-vasostomy or vaso-epididymostomy), and whether reversal was unilateral or bilateral. However, there have been no randomised controlled trials comparing macrosurgery (loops) and microsurgery. Microsurgical techniques with the help of magnification and smaller suture materials should be used (20).

### *10.3.1* ***Length of time since vasectomy***

Vaso-vasostomy results have shown patency rates up to 90%. The longer the interval is from vasectomy to reversal, the lower is the pregnancy rate. In a study of 1,469 men who had undergone microsurgical vasectomy reversal, patency and pregnancy rates were 97% and 76%, respectively, for an interval up to 3 years after vasectomy, 88% and 53%, respectively, for 3-8 years, 79% and 44%, respectively, for 9-14 years, and 71% and 30%, respectively, for > 15 years (21).

### *10.3.2* ***Epididymo-vasostomy***

The chance of secondary epididymal obstruction after vasectomy increases with time. After an interval of 10 years, 25% of men appear to have epididymal blockage. If secondary epididymal obstruction occurs, epididymo-vasostomy is needed to reverse the vasectomy (*see above* Chapter 5: Obstructive azoospermia) (22).

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

According to the calculations of cost per delivery for vasectomy reversal versus sperm retrieval/ICSI, under a wide variety of initial assumptions, it is clear that vasectomy reversal is associated with a considerably lower cost per delivery and higher delivery rates (23,24). Sperm retrieval and ICSI must yield an 81% pregnancy rate per cycle to achieve equal costs to vasectomy reversal.

## 10.4 Conclusions and recommendations for male contraception

| **Conclusions** |
|---|
| The most cost-effective approach to treatment of post-vasectomy infertility is microsurgical reversal. This procedure is also associated with the highest chance of pregnancy. |
| Pregnancy is still achievable after successful vasectomy reversal. |
| MESA/TESE/PESA (25) and ICSI should be reserved for failed vasectomy reversal surgery. |
| All available data indicate vasectomy is not associated with any serious, long-term, side effects (15). |
| Fascial interposition and cauterisation appears to be the most effective vasectomy technique (12-14). |

| **Recommendations** | **GR** |
|---|---|
| Patients seeking consultation about vasectomy must be informed about the surgical method, risk of failure, irreversibility, the need for post-procedure contraception until clearance, and the risk of complications. | C |
| Methods of male contraception other than vasectomy are associated with high failure rates or are still experimental (e.g. hormonal approach). | B |
| Microsurgical vasectomy reversal is a low-risk and (cost-) effective method of restoring fertility. | B |

| | |
|---|---|
| For couples wanting to achieve pregnancy, sperm aspiration together with ICSI is a second-line option for selected cases and in those with failed vaso-vasostomy. | B |

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# 11. MALE ACCESSORY GLAND INFECTIONS

## 11.1 Introduction

Infections of the male urogenital tract are potentially curable causes of male infertility (1-3). The WHO considers urethritis, prostatitis, orchitis and epididymitis to be male accessory gland infections (MAGIs) (2). However, specific data are not available to confirm that these diseases have a negative influence on sperm quality and male fertility in general.

## 11.2 Urethritis

Infectious, sexually acquired urethritis is caused by various pathogens, most often *Chlamydia trachomatis*, *Ureaplasma urealyticum*, and *Neisseria gonorrhoea* (4). Non-infectious causes of urethritis include irritations as a result of allergic reactions, trauma and manipulations. Urethral discharge and bladder voiding problems are the predominant symptoms of acute urethritis.

### *11.2.1* ***Diagnosis and treatment***

Diagnosis is based on the analysis of urethral smear and first-voided urine (VB1). Pathognomonic evidence is > 4 granulocytes per microscopic high-power field (×1000) in an urethral smear, or 15 granulocytes per microscopic field (×400) in the smear of the sediment of 3 mL VB1, is pathognomonic (4). In urethritis, defined by inflammatory discharge, semen analysis for disorders of male fertility is not possible because the anterior urethra is full of infectious and inflammatory material that hampers any useful analysis (5).

The impact of urethritis on semen quality and fertility has not been proven because the ejaculate is contaminated with inflammatory material from the urethra.

It is still debated whether infection with sexually transmitted micro-organisms has a negative effect on sperm function (1,6,7). Male fertility can be impaired by urethral strictures, ejaculatory disturbances (2), or the development of obstruction (8). Obstruction can develop as either a normal urethral stricture or a lesion in the posterior urethra in the area of the verumontanum, both of which can lead to ejaculatory disturbances and central obstruction of the seminal pathway (2).

The Centers for Disease Control and Prevention in Atlanta, GA, USA have published guidelines to standardise the treatment of sexually transmitted diseases (9). Because the aetiology of acute urethritis is usually unknown at the time of diagnosis, empirical therapy is used against potential pathogens. A single dose of a fluoroquinolone is given, followed by a 2-week regimen of doxycycline. Treatment is effective both for gonococcal and (co-existing) chlamydial/ureaplasmal infections.

## 11.3 Prostatitis

Prostatitis is the most common urological diagnosis in men < 50 years of age (10). Traditionally, prostatitis has been classified into four clinical entities:

- acute bacterial prostatitis (abp) and prostatic abscess as a sequela/complication of abp;
- chronic bacterial prostatitis (cbp);
- non- or abacterial prostatitis (nbp);
- prostatodynia.

To improve the definition and understanding of prostatitis, a classification system has been proposed by the National Institutes of Health (NIH) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (10) (Table 12).

**Table 12: NIH/NIDDK classification of prostatitis syndrome***

| New NIH category | Clinical entity | Description |
|---|---|---|
| I | ABP | Acute infection of the prostate gland |
| II | CBP | Recurrent infection of the prostate |
| III | Chronic abacterial prostatitis/CPPS | No demonstrable infection |
| IIIA | Inflammatory CPPS | White cells in semen, expressed prostatic secretions or post-prostatic massage urine |
| IIIB | Non-inflammatory CPPS | No white cells in semen, expressed prostatic secretions or post-prostatic massage urine |
| IV | Asymptomatic inflammatory prostatitis | No subjective symptoms. Inflammation detected either by prostate biopsy or by the presence of white cells in expressed prostatic secretions or semen during evaluation for other disorders |

** Adapted from Wagenlehner et al. (10).*
*ABP = acute bacterial prostatitis; CBP = chronic bacterial prostatitis; CPPS = chronic pelvic pain syndrome.*

### *11.3.1* ***Microbiology***

ABP (NIH I), CBP (NIH II) and, more significantly, prostatic abscesses are clinically relevant but uncommon diseases. The most common causes of bacterial prostatitis are Gram-negative bacteria, mainly strains of *Escherichia coli* (11). The role of Gram-positive bacteria in bacterial prostatitis is controversial. Although enterococci can cause bacterial prostatitis and associated recurrent urinary tract infection (UTI), the importance of other Gram-positive bacteria in chronic prostatitis is doubtful (11), as is that of *C. trachomatis* and *Mycoplasma*, particularly *U. urealyticum* (11-15). Hidden bacteria may be aetiologically involved in patients with chronic idiopathic prostatitis after exclusion of typical bacterial infection (16). Detection of bacteria by molecular techniques has not been evaluated definitively.

### *11.3.2* ***Diagnosis***

Symptoms must be evaluated using standardised scores, especially the NIH symptom score (17). Other investigative procedures include laboratory diagnosis of CBP using the four-specimen test for bacterial localisation (10,11), which measures sequential quantitative bacteriological cultures of the urethra, bladder urine and prostatic secretions, both in expressed prostatic excretion (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 must be integrated.

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

### *11.3.3* ***Ejaculate analysis***

An ejaculate analysis (*see* Chapter 2: Investigations) clarifies whether the prostate is involved as part of a generalised MAGI and provides information about sperm quality. In addition, leukocyte analysis allows differentiation between inflammatory and non-inflammatory CPPS (NIH IIa vs NIH IIIb).

### *11.3.4* ***Microbiological findings***

After exclusion of urethritis and bladder infection, > $10^6$ peroxidase-positive white blood cells (WBCs) per millilitre of ejaculate indicate an inflammatory process. In this case, a culture should be made for common urinary tract pathogens, particularly Gram-negative bacteria.

A concentration of > $10^3$ cfu/mL urinary tract pathogens in the ejaculate is indicative of significant bacteriospermia. Various micro-organisms are found in the genital tract of men seen in infertility clinics, usually with more than one strain of bacteria present (1). The sampling time can influence the positive rate of micro-organisms in semen and the frequency of isolation of different strains (19). The ideal diagnostic test for *C. trachomatis* in semen has not yet been established (14). In contrast to serological findings in women, antibody tests for *C. trachomatis* in seminal plasma are not indicative if no type-specific methods are used (14).

*Ureaplasma urealyticum* is pathogenic only in high concentrations (> $10^3$ cfu/mL ejaculate). No more than about 10% of samples analysed for ureaplasma exceed this concentration (20). Normal colonisation of the urethra hampers the clarification of mycoplasma-associated urogenital infections, using samples such as the ejaculate (15).

### *11.3.5* ***White blood cells***

The clinical significance of an increased concentration of leukocytes in the ejaculate is controversial (21). Infection is indicated only by an increased level of leukocytes (particularly polymorphonuclear leukocytes) and their products (e.g. leukocyte elastase) secreted into the seminal fluid. Most leukocytes are neutrophilic granulocytes, as suggested by the specific staining of the peroxidase reaction (2). Although leukocytospermia is a sign of inflammation, it is not necessarily associated with bacterial or viral infections (7). Earlier findings have shown that elevated leukocyte numbers are not a natural cause of male infertility (22).
According to WHO classification, leukocytospermia is defined as > $10^6$ WBCs/mL. Only two studies have analysed alterations of WBCs in the ejaculate of patients with proven prostatitis (23,24). Both studies found more leukocytes in men with prostatitis compared to those without inflammation (CPPS, type NIH IIIb).

### *11.3.6* ***Sperm quality***

The deleterious effects of chronic prostatitis on sperm density, motility and morphology are under debate (1). All investigations have given contradictory results, and have not confirmed that chronic prostatitis has a decisive role in altering conventional semen parameters (25-27).

### *11.3.7* ***Seminal plasma alterations***

Seminal plasma elastase is a biochemical indicator of polymorphonuclear lymphocyte activity in the ejaculate (1,28,29), with a suggested cut-off level of approximately 600 ng/mL (1). Various cytokines are involved in inflammation and can influence sperm function. Several studies have investigated the association between interleukin (IL) concentration, leukocytes and sperm function (30-32), but no correlations have been found. The prostate is the main site of origin of IL-6 in the seminal plasma. Cytokines, especially IL-6, play an important role in the male accessory gland inflammatory process (33). However, elevated cytokine levels do not depend on the number of leukocytes in EPS (34).

### *11.3.8* ***Glandular secretory dysfunction***

Infections of the sex glands can impair their excretory function. Decreased quantities of citric acid, phosphatase, fructose, zinc, and $\alpha$-glutamyl-transferase activity are indicators of disturbed prostatic secretory parameters (1). Reduced fructose concentration indicates impaired vesicular function (20,35).

### *11.3.9* ***Sperm antibodies***

Serum antibodies to sperm antigens are not useful in the diagnosis of immune infertility. Early studies found an association between increased levels of sperm antibodies in serum and NBP (36,37). However, except for suspected chlamydial infections (38), only a history of vasectomy is predictive of sperm antibody formation (39).

### *11.3.10* ***Reactive oxygen species***

Reactive oxygen species might be increased in chronic urogenital infections associated with increased leukocyte numbers (40). However, their biological significance in prostatitis remains unclear (1).

### *11.3.11* ***Therapy***

Treatment of chronic prostatitis is usually targeted at relieving symptoms (10,41). Andrologically, the aims of therapy for altered semen composition in male adnexitis (acute and chronic infections of the male urogenital tract) are:

- reduction or eradication of micro-organisms in prostatic secretions and semen;
- normalisation of inflammatory (e.g. leukocytes) and secretory parameters;
- improvement of sperm parameters to counteract fertility impairment (42).

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

Only antibiotic therapy of CBP (NIH II) has provided symptomatic relief, eradication of microorganisms and a decrease in cellular and humoral inflammatory parameters in urogenital secretions. The use of alpha-blockers for symptom relief is controversial. Although antibiotics might improve sperm quality (42), there is no evidence that treatment of chronic prostatitis increases the probability of conception (1,43).

## 11.4 Orchitis and epididymo-orchitis

### *11.4.1* ***Introduction***

Orchitis is an inflammatory lesion of the testis associated with a predominantly WBC exudate inside and outside the seminiferous tubules, which potentially results in tubular sclerosis. The inflammation causes pain and swelling. Chronic inflammatory alterations in the seminiferous tubules disrupt the normal process

of spermatogenesis and alter sperm number and quality (44). Orchitis might also be an important cause of spermatogenetic arrest (45), which might be reversible in most cases. Testicular atrophy can develop as a result of tubular sclerosis (45).

#### *11.4.2* ***Diagnosis***

Epididymo-orchitis usually presents with unilateral scrotal pain (46). Diagnosis is based on past medical history and palpation. Ultrasonography usually indicates a swollen, enlarged testis. The sonographic features of the tissue do not allow any differential diagnosis (47).

#### *11.4.3* ***Ejaculate analysis***

Ejaculate analysis, including leukocyte analysis, indicates persistent inflammatory activity. In many cases, especially in acute epididymo-orchitis, transiently decreased sperm counts and reduced forward motility occur (44,46). Obstructive azoospermia caused by complete obstruction is a rare complication. Mumps orchitis can result in bilateral testicular atrophy (45) and non-obstructive azoospermia. When granulomatous orchitis is suspected, sperm-bound autoantibodies occur.

#### *11.4.4* ***Therapy***

Only therapy of acute bacterial epididymo-orchitis and of specific granulomatous orchitis is standardised (45) (Table 13). Several regimens improve the inflammatory lesion. Unfortunately, corticosteroids and non-steroidal anti-inflammatory agents (e.g. diclofenac, indomethacin, acetylsalicylic acid) have not been evaluated for their andrological outcome (47). In mumps orchitis, systemic therapy with interferon $\alpha$-2b prevents testicular atrophy and azoospermia (50). In idiopathic granulomatous orchitis, surgical removal of the testis is the therapy of choice.

**Table 13: Treatment of epididymo-orchitis**

| **Condition and pathogen** | **Treatment** |
|---|---|
| Acute bacterial epididymo-orchitis | |
| *N. gonorrhoeae* | Tetracyclines |
| *C. trachomatis* | Tetracyclines |
| *E. coli, Enterobacteriaceae* | Fluoroquinolones |
| Mumps orchitis | Interferon $\alpha$-2b |
| Non-specific chronic epididymo-orchitis | Steroidal and non-steroidal inflammatory agents |
| Granulomatous (idiopathic) orchitis | Semi-castration |
| Specific orchitis | According to therapy of underlying diseases |

### 11.5 Epididymitis

#### *11.5.1* ***Introduction***

Inflammation of the epididymis causes unilateral pain and swelling, usually with acute onset. Among sexually active men < 35 years of age, epididymitis is most often caused by *C. trachomatis* or *N. gonorrhoea* (51,52). Sexually transmitted epididymitis is usually accompanied by urethritis. Non-sexually transmitted epididymitis is associated with UTI and occurs more often in men aged > 35 years, those who have recently undergone urinary tract instrumentation or surgery, and those who have anatomical abnormalities (52).

#### *11.5.2* ***Diagnosis***

In acute epididymitis, inflammation and swelling usually start in the tail of the epididymis and can spread to involve the rest of the epididymis and testicular tissue (46). Although men with epididymitis caused by sexually transmitted micro-organisms always have a history of sexual activity, exposure could have occurred several months before 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 (51,52). Intracellular Gram-negative diplococci on the smear indicate the presence of *N. gonorrhoea*. Only WBCs on urethral smear indicate non-gonorrhoeal urethritis; *C. trachomatis* will be isolated in about two-thirds of these patients (53).

#### *11.5.3* ***Ejaculate analysis***

Ejaculate analysis according to WHO criteria, including leukocyte analysis, might indicate persistent inflammatory activity. In many cases, transiently decreased sperm counts and forward motility are observed

(46,48,51). Ipsilateral low-grade orchitis (54,55) might be the cause of this slight impairment in sperm quality (Table 14) (56).

Development of stenosis in the epididymal duct, reduction of sperm count and azoospermia are more important in the follow-up of bilateral epididymitis *(see* Chapter 5: Obstructive azoospermia). The extent of azoospermia after epididymitis is unclear.

**Table 14: Acute epididymitis and impact on sperm parameters.**

| Authors | Negative influence | | | |
|---|---|---|---|---|
| | **Density** | **Motility** | **Morphology** | **Comment** |
| Ludwig & Haselberger (57) | + | + | + | Pyospermia in 19 of 22 cases |
| Berger *et al*. (51) | | + | | |
| Weidner *et al*. (47) | + | + | + | Azoospermia in 3 of 70 men |
| Haidl (58) | | + | | Chronic infections; macrophages elevated |
| Cooper *et al*. (59) | | | | Decrease in epididymal markers: $\alpha$-glucosidase, L-carnitine |

*11.5.4* ***Treatment***

Antibiotic therapy is indicated before culture results are available (Table 13). Treatment of epididymitis results in:

- microbiological cure of infection;
- improvement of clinical signs and symptoms;
- prevention of potential testicular damage;
- prevention of transmission;
- decrease of potential complications (e.g. infertility or chronic pain).

Patients with epididymitis known or suspected to be caused by *N. gonorrhoea* or *C. trachomatis* must be told to refer their sexual partners for evaluation and treatment (60).

## 11.6 Conclusions and recommendations for male accessory gland infections

| **Conclusions** |
|---|
| Urethritis and prostatitis are not associated clearly with male infertility. |
| Antibiotic treatment often only eradicates micro-organisms; it has no positive effect on inflammatory alterations, and cannot reverse functional deficits and anatomical dysfunction. |

| **Recommendations** | **GR** |
|---|---|
| In most cases, the aetiology of acute urethritis is unknown at the time of diagnosis; empirical therapy is therefore suggested using a single dose of a fluoroquinolone, followed by a 2-week regimen of doxycycline. Treatment is effective both for gonococcal and (co-existing) chlamydial/ureaplasmal infections (9). | B |
| Antibiotic therapy of (chronic) bacterial prostatitis has been shown to provide symptomatic relief, eradication of micro-organisms, and a decrease in cellular and humoral inflammatory parameters in urogenital secretions (61-64). | B |
| Although antibiotic procedures for MAGI might provide improvement in sperm quality, therapy does not necessarily enhance the probability of conception (1,43). | B |
| Patients with epididymitis that is known or suspected to be caused by *N.* gonorrhoea or *C. trachomatis* must be instructed to refer their sexual partners for evaluation and treatment (60). | B |

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# 12. GERM CELL MALIGNANCY AND TESTICULAR MICROCALCIFICATION

## 12.1 Germ cell malignancy and male infertility

Testicular germ cell tumour (TGCT) is the most common malignancy in Caucasian men aged 15-40 years and affects approximately 1% of subfertile men. The lifetime risk of TGCT varies between ethnic groups and countries. The highest annual incidence of TGCT occurs in Caucasians, and varies from 10/100,000 (e.g. in Denmark and Norway) to 2/100,000 (e.g. in Finland and the Baltic countries). Generally, seminomas and non-seminomas are always preceded by CIS, and untreated germ cell neoplasia of unclassified type ([ITGCNU] former CIS) will eventually progress to invasive cancer (1,2).

The most convincing evidence for a general decline in male reproductive health is the increase in testicular cancer seen in Western countries (3). In almost all countries with reliable cancer registers, the incidence of testicular cancer has increased (4). Cryptorchidism and hypospadias are associated with an increased risk of testicular cancer; men with cryptorchidism and/or hypospadias are over-represented among patients with testicular cancer.

Men with dysgenic testes have an increased risk of developing testicular cancer in adulthood. These cancers arise from premalignant gonocytes or CIS cells (5). Testicular microlithiasis, seen on ultrasound, can be associated with germ cell tumours and CIS of the testis.

## 12.2 Testicular germ cell cancer and reproductive function

Men with TGCT have decreased semen quality, even before cancer is diagnosed (6). Orchidectomy implies a risk of azoospermia in these men, with sperm found in the ejaculate before the tumour-bearing testis has been removed. Semen cryopreservation before orchidectomy should therefore be considered (*see* Chapter 14: Semen cryopreservation). Treatment of TGCT can result in additional impairment of semen quality (7).

In addition to spermatogenic failure, patients with TGCT have Leydig cell dysfunction, even in the contralateral testis (8). The risk of hypogonadism may therefore be increased in men treated for TGCT. The measurement of pretreatment levels of testosterone, SHBG, LH and oestradiol might help to anticipate post-treatment hypogonadism. Men who have had TGCT and have low normal androgen levels should receive long-term follow-up because they are at risk of developing hypogonadism as a result of an age-related decrease in testosterone production (9).

The risk of hypogonadism is most pronounced in TGCT patients treated with $\geq$ 3 cycles of chemotherapy and in patients who have received irradiation of retroperitoneal lymph nodes. However, this risk is greatest at 6-12 months post-treatment. This suggests there may be some improvement in Leydig cell function, and why it is reasonable to expect initiation of androgen replacement, until the patient shows continuous signs of testosterone deficiency, even at 2 years' follow-up (10). Even the risk of low libido and erectile dysfunction is increased in TGCT patients (11).

## 12.3 Testicular microlithiasis

Microcalcification inside the testicular parenchyma can be found in 0.6-9% of men referred for testicular ultrasound (12-14). Although the true incidence of microcalcification in the general population is unknown, it is probably rare. However, ultrasound findings of testicular microlithiasis (TM) are common in men with TGCT, cryptorchidism, testicular dysgenesis, infertility, testicular torsion and atrophy, Klinefelter's syndrome,

hypogonadism, male pseudohermaphroditism, varicocele, epididymal cysts, pulmonary microlithiasis and non-Hodgkin's lymphoma. The incidence reported seems to be higher with high-frequency ultrasound machines (16).

The relationship between TM and infertility is unclear, but probably relates to dysgenesis of the testes, with degenerate cells being sloughed inside an obstructed seminiferous tubule and failure of the Sertoli cells to phagocytose the debris. Subsequently, calcification occurs.

Testicular microlithiasis is found in testes at risk of malignant development. The reported incidence of TM in men with TGCT is 6-46% (17-19), and TM should therefore be considered premalignant. Testicular biopsies from men with TM have found a higher prevalence of CIS, especially in those with bilateral microlithiasis (20). However, TM is found most often in men with a benign testicular condition and the microcalcification itself is not malignant.

Further investigation of the association between TM and CIS will require testicular biopsies in large series of men without signs of a TGCT. However, available data indicate that men in whom TM is found by ultrasound, and who have an increased risk of TGCT, should be offered testicular biopsy for detection of CIS. The list of high-risk patients includes men with infertility and bilateral TM, atrophic testes, undescended testes and those with a history of TGCT, and contralateral TM (21).

## 12.4 Recommendations for germ cell malignancy and testicular microcalcification

| Recommendations | GR |
|---|---|
| It is important to encourage and educate patients with TM about self-examination, as this might result in early detection of TGCT. | B |
| Testicular biopsy should be offered to men with TM, who belong to one of the following high-risk groups: infertility and bilateral TM, atrophic testes, undescended testes, and men with a history of TGCT and contralateral TM (21). | B |
| If there are suspicious findings on physical examination or ultrasound in patients with TM and associated lesions, surgical exploration with testicular biopsy or orchidectomy should be considered. | B |
| Testicular biopsy, follow-up scrotal ultrasound, routine use of biochemical tumour markers, or abdominal or pelvic computed tomography is not justified for men with isolated TM without associated risk factors (e.g. infertility, cryptorchidism, testicular cancer, atrophic testis) (15). | B |
| Men with TGCT are at increased risk of developing hypogonadism and sexual dysfunction and should therefore be followed up (10,11). | B |

*TGCT = testicular germ cell tumour; TM = testicular microlithiasis*

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# 13. DISORDERS OF EJACULATION

## 13.1 Definition

Disorders of ejaculation are uncommon, but important, causes of male infertility. This group includes several heterogeneous dysfunctions, which can be either organic or functional.

## 13.2 Classification and aetiology

### *13.2.1 **Anejaculation***

Anejaculation involves complete absence of antegrade or retrograde ejaculation and is caused by 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 is altered or decreased. True anejaculation is always associated with central or

peripheral nervous system dysfunction or with drugs (2) (Table 15).

**Table 15: Aetiology of anejaculation**

| **Neurogenic** | **Drug-related** |
|---|---|
| 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) | |

### *13.2.2* ***Anorgasmia***

Anorgasmia is the inability to reach orgasm and can give rise to anejaculation. Anorgasmia is often a primary condition and its cause is usually psychological. Some patients report sporadic events of nocturnal emission or of ejaculation occurring during great emotional excitement unrelated to sexual activity (3).

### *13.2.3* ***Delayed ejaculation***

In delayed ejaculation, abnormal stimulation of the erect penis is needed to achieve orgasm with ejaculation (1). Delayed ejaculation can be considered a mild form of anorgasmia, and both conditions can be found alternately in the same patient. The causes of delayed ejaculation can be psychological or organic, e.g. incomplete spinal cord lesion (3), iatrogenic penile nerve damage (4), or pharmacological, e.g. antidepressants, antihypertensives, antipsychotics (5).

### *13.2.4* ***Retrograde ejaculation***

Retrograde ejaculation is the total, or sometimes partial, absence of antegrade ejaculation as a result of semen passing 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 divided into neurogenic, pharmacological, urethral, or bladder neck incompetence (Table 16).

**Table 16: Aetiology of retrograde ejaculation**

| **Neurogenic** | **Pharmacological** |
|---|---|
| Spinal cord injury | Antihypertensives |
| Cauda equina lesions | $\alpha$1-adrenoceptor antagonists |
| Multiple sclerosis | Antipsychotics |
| Autonomic neuropathy (juvenile diabetes) | Antidepressants |
| Retroperitoneal lymphadenectomy | **Bladder neck incompetence** |
| Sympathectomy | Congenital defects/dysfunction of hemitrigone |
| Colorectal and anal surgery | Bladder extrophy |
| **Urethral** | Bladder neck resection |
| Ectopic ureterocele | Prostatectomy |
| Urethral stricture | |
| Urethral valves or verumontaneum hyperplasia | |
| Congenital dopamine $\beta$-hydroxylase deficiency | |

### *13.2.5* ***Asthenic ejaculation***

Asthenic ejaculation, also defined as partial ejaculatory incompetence or 'ejaculation baveuse' (5), is characterised 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, whereas in asthenic

ejaculation caused by urethral obstruction, these contractions are present. Asthenic ejaculation generally is caused by the neurogenic or urethral pathologies already listed in Table 16. Asthenic ejaculation does not usually affect semen quality.

#### *13.2.6* ***Premature ejaculation***

Premature ejaculation is the inability to control ejaculation for a sufficient length of time during vaginal penetration. Although a universally accepted definition of sufficient length of time does not exist, some patients are unable 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, primary or acquired, partner-related or non-selective, and can be associated with erectile dysfunction. Premature ejaculation does not impair fertility, provided intravaginal ejaculation occurs. For more extensive discussion on this topic, the EAU Male Sexual Dysfunction guidelines should be consulted.

#### *13.2.7* ***Painful ejaculation***

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

### 13.3 Diagnosis

Diagnostic management includes the following recommended procedures.

#### *13.3.1* ***Clinical history***

The patient must be carefully checked for diabetes, neuropathy, trauma, urogenital infection, previous surgery, and medication. Particular attention must be paid to the characteristics of micturition and ejaculation (presence of nocturnal emission, ejaculatory ability in given circumstances, primary or acquired disorder), as well as to psychosexual aspects (education, features of affective relationship, pre-existent psychological trauma, previous psychological therapy).

#### *13.3.2* ***Physical examination***

Genital and rectal examinations are conducted, including evaluation of the prostate, bulbo-cavernosus reflex and anal sphincter tone. Minimal neurological tests include:

- sensitivity of scrotum, testes, and perineum
- cremasteric and abdominal cutaneous reflex
- leg osteotendinous and plantar reflexes.

#### *13.3.3* ***Post-ejaculatory urinalysis***

Post-ejaculatory urinalysis can be used to determine if there is total or partial retrograde ejaculation.

#### *13.3.4* ***Microbiological examination***

Initial, mid-stream urine, EPS 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).

13.3.5 Optional diagnostic work-up

This diagnostic workup can include:

- neurophysiological tests (bulbocavernosus evoked response and dorsal nerve somatosensory evoked potentials);
- tests for autonomic neuropathy;
- psychosexual evaluation;
- video-cystometry;
- cystoscopy;
- transrectal ultrasonography;
- uroflowmetry;
- vibratory stimulation of the penis.

### 13.4 Treatment

Infertility caused by disorders of ejaculation is seldom treated on the basis of aetiology. Treatment usually involves retrieving spermatozoa for use in assisted reproduction techniques (ARTs). The following aspects must be considered when selecting treatment:

- age of patient and his partner;

- psychological problems of the patient and his partner;
- couple's willingness and acceptance of different fertility procedures;
- associated pathology;
- psychosexual counselling.

## 13.5 Aetiological treatment

If possible, any pharmacological treatment that is interfering with ejaculation should be stopped. In painful ejaculations, tamsulosin can be administered during antidepressant treatment (9). Treatment should be given for urogenital infections (i.e. in cases of painful ejaculation) (8). Dapoxetin, a selective serotonin re-uptake inhibitor (SSRI) has been introduced for the therapy of premature ejaculation (PE) (10), since it appears that PE is related to serotonin levels. If possible, any underlying urethral pathology or metabolic disorder (e.g. diabetes) should be corrected. Psychotherapy is usually not very effective.

## 13.6 Symptomatic treatment

### *13.6.1* ***Premature ejaculation (PE)***

Premature ejaculation can be treated with the selective SSRI dapoxetine, topical anaesthetic agents to increase intravaginal ejaculation latency time, behavioural therapy and/or psychotherapy. Off-label use of SSRIs (e.g. paroxetine, fluoxetine) should be applied with caution.

### *13.6.2* ***Retrograde ejaculation***

In the absence of spinal cord injury, anatomical anomalies of the urethra, or pharmacological agents, drug treatment must be used to induce antegrade ejaculation (Table 17). Alternatively, the patient can be encouraged to ejaculate when his bladder is full to increase bladder neck closure (11).

**Table 17: Drug therapy for retrograde ejaculation**

| Drug | Dosage regimen | Ref. |
|---|---|---|
| Ephedrine sulphate | 10-15 mg four times daily | 12 |
| Midodrin | 5 mg three times daily | 13 |
| Brompheniramine maleate | 8 mg twice daily | 14 |
| Imipramine | 25-75 mg three times daily | 15 |
| Desipramine | 50 mg every second day | 16 |

Sperm collection from post-orgasmic urine for use in ART is recommended if:

- drug treatment is ineffective or intolerable as a result of side effects;
- 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 alkalinised (pH 7.2-7.8) and osmolarity must be 200-300 mOsmol/kg. 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). Alternatively, a catheter can be applied to the bladder and 10-50 mL Tyrode's or Ham's F-10 medium instilled into the bladder. The patient must ejaculate, and a second catheterisation is carried out immediately to retrieve spermatozoa. The latter treatment minimises 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 orcryopreserved spermatozoa.

### *13.6.3* ***Anejaculation***

Drug treatment for anejaculation caused by lymphadenectomy and neuropathy or psychosexual therapy in anorgasmic men is not very effective. In all these cases, and in men who have a spinal cord injury, vibrostimulation (i.e. the application of a vibrator to the penis) is first-line therapy.

In anejaculation, vibrostimulation evokes the ejaculation reflex (19), which requires an intact lumbosacral spinal cord segment. Complete spinal injuries and injuries above T10 show a better response to vibrostimulation. Once the safety and efficacy of this procedure has been assessed, patients can manage the process in their own home. Intravaginal insemination using a 10-mL syringe during ovulation can be carried out. If the quality of semen is poor, or ejaculation is retrograde, the couple may enter an IVF programme.

If vibrostimulation has failed, electro-ejaculation is the therapy of choice (20). Electro-ejaculation

involves electric stimulation of the periprostatic nerves via a probe inserted into the rectum, which seems unaffected 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 cases. Semen quality is often poor and most couples will need to enter an IVF programme (21).

When electro-ejaculation fails or cannot be carried out, sperm can be retrieved from the seminal ducts by aspiration from the vas deferens (22) (*see* Chapter 5 Obstructive azoospermia) or seminal tract washout (23).

When sperm cannot be retrieved, epididymal obstruction or testicular failure must be suspected. TESE can then be used (8,24). Anejaculation following either surgery for testicular cancer or total mesorectal excision can be prevented using monolateral lymphadenectomy or autosomic nerve preservation (24), respectively.

## 13.7 Conclusion and recommendations for disorders of ejaculation

| **Conclusion** |
|---|
| Ejaculation disorders can be treated using a wide range of drugs and physical stimulation, with a high level of efficacy. |

| **Recommendations** | **GR** |
|---|---|
| Aetiological treatments for ejaculatory disorders should be offered before sperm collection and ART is performed. | B |
| Premature ejaculation can be treated successfully with either topical anaesthetic creams or SSRIs (22). | A |
| In men with spinal cord injury, vibrostimulation and electro-ejaculation are effective methods of sperm retrieval. | B |

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# 14. SEMEN CRYOPRESERVATION

## 14.1 Definition

Cryopreservation is the storage of biological material at subzero temperatures [e.g. -80°C or -196°C (the boiling point of liquid nitrogen)], at which biochemical processes of cell metabolism are slowed or interrupted. At -196°C, the biochemical reactions that lead to cell death are stopped.

## 14.2 Introduction

Cryopreservation was first developed in the 1940s by veterinarians and adapted for human sperm in the 1950s. The first pregnancy that used cryopreservation took place in 1954 (1). In fertility practice, clinical indications for cryopreservation include storage of sperm, testicular and ovarian tissue and early embryos.

## 14.3 Indications for storage

Storage of sperm is available in many clinics for the following indications:

- Before potentially sterilising chemotherapy or radiotherapy for cancer (2) or for non-malignant diseases.
- Before surgery that might interfere with fertility (e.g. bladder neck surgery in a younger man or removal of a testical in a man with testicular malignancy, before vasectomy).
- For men with progressive decrease in semen quality as a result of diseases that have an associated

risk of subsequent azoospermia (i.e. pituitary macroadenoma, Craniopharyngioma, empty sella syndrome, chronic nephropathy, uncontrolled diabetes mellitus, multiple sclerosis).

- For men with paraplegia when sperm have been obtained by electro-ejaculation or obtained by using penile vibratory stimulation.
- For men with psychogenic anejaculation, after sperm have been obtained either by electro-ejaculation or a sperm retrieval procedure.
- After gonadotrophin treatment has induced spermatogenesis in men with hypogonadotrophic hypogonadism.
- For men with NOA, the chance of finding sperm using micro-TESE is approximately 60-70%. Cryopreservation can be used to separate sperm collection from ICSI, thus avoiding unnecessary hyperstimulation of the female partner. It can also be used to avoid repeated sperm retrieval procedures.
- In any situation where sperm have been obtained by a sperm retrieval procedure (e.g. after failed vasectomy reversal, or in some cases of epididymal obstruction not amenable to surgery).
- For storage of donor sperm, because cryopreservation and a quarantine period of 3-6 months reduces the risk of transmission of infection from sperm donors; in most countries, fresh sperm are no longer used.

## 14.4 Precautions and techniques

### *14.4.1* ***Freezing and thawing process***

The cryopreservation techniques currently used are not yet optimal as damage occurs to cells during cryopreservation and prolonged storage. Most damage occurs during freezing and thawing. Major causes of damage during freezing are ice crystal formation and cell dehydration that disrupt the cell wall and intracellular organelles. Sperm morphology, motility and vitality decrease significantly after thawing, and cryopreservation increases the damage done to sperm DNA (3-6). Further damage can be caused by contamination of samples with micro-organisms and high levels of superoxide radicals (7,8). To reduce ice crystal formation, a cryopreservation solution is added before freezing. Various cryopreservation solutions are available commercially, most of which contain varying proportions of glycerol and albumen. After freezing, the tissues are immersed in liquid nitrogen.

Several techniques have been developed to try to reduce damage caused by freezing and thawing, including:

- Rapid method (9,10): sample is held in the vapour phase for 10 minutes before being plunged into liquid nitrogen.
- Slow method (11): sample is gradually cooled in the vapour phase for approximately 40 minutes.
- Programmable automatic freezing machine, which is preset to cool at a rate of 1-10°C/min, is used.

The method available depends on the resources of the laboratory. Whichever freezing technique is used, it should be tested using donor sperm and post-thaw examination, and should regularly undergo a quality-control programme.

The likelihood of sperm survival decreases with increased storage time and repeated freezing and thawing. The maximum viable storage time for human sperm is not known. Many laboratory or regulatory authorities apply a storage time limit of up to 10 years (12). However, longer storage times are sometimes needed (e.g. for a 17-year-old man who has had sperm stored before undergoing chemotherapy for testicular cancer).

### *14.4.2* ***Cryopreservation of very small numbers of sperm***

Standard cryopreservation in straws is an efficient way of storing large number of sperm (e.g. for a donor insemination programme). However, in micro-TESE, very few sperm might be obtained, and the choice is either to freeze testicular tissue and find sperm after thawing the tissue, or to freeze very small numbers of sperm. If sperm are frozen in straws, it can be very difficult to find any sperm after thawing. Instead, the sperm should be frozen in a pellet (13) or in a container (14).

### *14.4.3* ***Testing for infections and preventing cross-contamination***

Sperm storage in straws is used extensively. Large numbers of straws are stored in canisters, with the straws being bathed in a pool of liquid nitrogen. Microbial contamination of the pool of liquid nitrogen results in contamination of the outside of all the straws. The most widely used safeguard is to accept samples for storage only from patients whose semen samples have been tested for infection and confirmed as safe. Donor samples should be tested for viral (hepatitis B and C, human immunodeficiency virus [HIV]) and sexually transmitted (*C. trachomatis*, gonorrhoea, syphilis) infections.

Until the test results are known, samples must be stored in an individual quarantine vessel (15)

(http://www.hfea.gov.uk/docs/8th_Code_of_Practice(2).pdf) [acces date December 2011]. Some laboratories use the additional safeguard of double-wrapping the straws before freezing, although this is more costly and can interfere with the freezing process, thus reducing sample quality upon thawing. Some centres carry out cytomegalovirus (CMV) testing and store CMV-negative and CMV-positive samples separately.

Considerable ethical issues surround the storage of samples before cancer chemotherapy for a man who is hepatitis-virus- or HIV-positive. Very few clinics have separate storage facilities for HIV-positive samples. However, the success of antiretroviral treatment is increasing the number of HIV-positive men who may wish to store sperm. There is also concern about HIV transmission to children conceived using HIV-positive sperm, as sperm-washing techniques fail in about 5%.

#### *14.4.4* ***Fail-safe precautions to prevent loss of stored materials***

Any laboratory that undertakes long-term storage of human biological materials should have procedures that guard against accidental loss of material caused by storage vessel failure. This is particularly important for sperm stored before potentially sterilising cancer chemotherapy because these patients may not be able to obtain further sperm. The level of precaution depends on the cost and resources available to the laboratory, but if possible the following safeguards should be in place:

- All in-use storage vessels should be fitted with an alarm system that is activated by rising temperature or liquid nitrogen leakage.
- The alarm system should alert a laboratory staff member, according to a 24-h, 365-day rota.
- Ideally, there should be a spare storage container, in which samples can be transferred following a vessel failure.

#### *14.4.5* ***Orphan samples***

In malignancy and some other situations, several years might pass before stored samples are required. Inevitably, during this time, the owners of some samples might disappear or die, leaving behind orphan samples for which the owner is no longer contactable. The duty of the laboratory and the legal ownership of these samples can create considerable problems.

It is best to obtain instructions from the owner of the sample at the time of, or very shortly after storage, about what to do with the sample in the event of death or untraceability. In some countries, owners are legally required to provide instructions/consent. Choices available for the owner of the sample depend on the laws of the country, might not be appropriate in all situations, and include:

- a request that the sample should be destroyed;
- use of the sample by their wife or partner;
- use of the sample in research;
- donation of the sample to help another infertile couple.

### 14.5 Biological aspects

Cryopreservation induces deterioration of the seminal quality. After the sample has been thawed, motility (16) and morphology (17,18) are worsened, including mitochondrial acrosomal and sperm tail damage (19). Sperm freezing decreases motility by 31% and mitochondrial activity by 36%, and causes morphological disruption in 37% of sperm (9). Motility is correlated best with IVF capacity of the thawed sample. Further improvement can be achieved by selecting the subpopulation of sperm with the best motility and DNA integrity and freezing these sperm in seminal plasma (13).

### 14.6 Conclusions and recommendations for semen cryopreservation

| **Conclusions** |
|---|
| The purpose of sperm cryopreservation is to enable future ART procedures. |
| Cryopreservation techniques are not optimal, and future efforts are needed to improve the outcome of sperm banking. |
| Cryopreservation should be offered and explained in patients with specific diseases, or before a patient undergoes surgery, chemotherapy or radiotherapy that might damage his reproductive integrity. |
| If testicular biopsies are indicated, sperm cryopreservation is strongly advised. |

| Recommendations | GR |
|---|---|
| Cryopreservation of semen should be offered to all men who are candidates for chemotherapy, radiation or surgical interventions that might interfere with spermatogenesis or cause ejaculatory disorders. | B |
| If cryopreservation is not available locally, patients should be advised about the possibility of visiting, or transferring to, the nearest cryopreservation unit before therapy starts. | C |
| Consent for cryopreservation should include a record of the man's wishes for his samples if he dies or is otherwise untraceable. | C |
| Precautions should be taken to prevent transmission of viral, sexually transmitted or any other infection by cryostored materials from donor to recipient, and to prevent contamination of stored samples. These precautions include testing of the patient and the use of rapid testing and quarantine of samples until test results are known. Samples from men who are positive for hepatitis virus or HIV should not be stored in the same container as samples from men who have been tested and are free from infection. | C |

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# 15. ABBREVIATIONS USED IN THE TEXT

*This list is not comprehensive for the most common abbreviations*

| | |
|---|---|
| ABP | acute bacterial prostatitis |
| ART | assisted reproduction techniques |
| CAIS | complete androgen insensitivity syndrome |
| CBAVD | congenital bilateral absence of the vas deferens |
| CBP | chronic bacterial prostatitis |
| CF | cystic fibrosis |
| CFTR | cystic fibrosis transmembrane conductance regulator |
| CIS | carcinoma *in situ* |
| CMV | cytomegalovirus |
| CPPS | chronic pelvic pain syndrome |
| EAA | European Academy of Andrology |
| EPS | espressed prostatic excretion |
| FISH | (multicolour) fluorescent *in situ* hybridisation |
| FSH | follicle-stimulating hormone |
| GnRH | gonadotrophin-releasing hormone |
| GR | grade of recommendation |
| GREAT | G-protein-coupled receptor affecting testis descent |
| hCG | human chorionic gonadotrophin |
| HIV | human immunodeficiency virus |
| ICSI | intracytoplasmic sperm injection |
| IHH | idiopathic hypogonadotrophic hypogonadism |
| IL-6 | interleukin-6 |
| ITGCNU | intratubular germ cell neoplasia of unclassified type |
| IVF | in vitro fertilisation |
| LE | level of evidence |
| LH | luteinising hormone |
| MAGI | male accessory gland infection |
| MAR | mixed antiglobulin reaction |
| MESA | microsurgical epididymal sperm aspiration |
| NBP | non- or abacterial prostatitis |
| NIDDK | National Institute of Diabetes and Digestive and Kidney Diseases |
| NIH | National Institutes of Health |
| NOA | non-obstructive azoospermia |
| OA | obstructive azoospermia |
| OAT | oligo-astheno-teratozoospermia [syndrome] |
| PE | premature ejaculation |
| PGD | preimplantation genetic diagnosis |
| SHBG | sex hormone binding globulin |
| SSRIs | selective serotonin reuptake inhibitors |
| TDS | testicular dysgenesis syndrome |
| TEFNA | testicular fine-needle aspiration |
| TESE | testicular sperm extraction |
| TGCT | testicular germ cell tumour |
| TM | testicular microlithiasis |
| TRUS | transurethral ultrasound |
| TURED | transurethral resection of the ejaculatory ducts |
| UTI | urinary tract infection |
| WBC | white blood cell |
| VB1 | first-voided urine |
| WHO | World Health Organization |

**Conflict of interest**

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