Guidelines on
Male Infertility

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TABLE OF CONTENTS   PAGE

1. INTRODUCTION

1.1 Definition

'Infertility is the inability of a sexually active, non-contracepting couple to achieve pregnancy in one year' (WHO) (1).

1.2 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 men and thus infertility usually becomes manifest if both partners have reduced fertility (1).

Male fertility can be reduced as a result of:
- congenital or acquired urogenital abnormalities (including obstructions and testicular dysgenesis
- urogenital tract infections
- increased scrotal temperature (e.g as a consequence of varicocele)
- endocrine disturbances
- genetic abnormalities
- immunological factors (1).

In at least 44% 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. Semen analysis, however, 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 1 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 1: Aetiology and distribution of male infertility among 7,057 men

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

* From WHO (2000) (1).
* OAT = Oligo-astheno-teratozoospermia.

1.3 Prognostic factors

The prognostic factors for male infertility are:
- duration of infertility
- primary or secondary infertility
- results of semen analysis
- age and fertility status of female partner.

If the duration of infertility is > 4 years of unprotected sexual intercourse, the conception rate per month is only 1.5%. In many Western countries, women postpone their first pregnancy until they have finished their education and have started a career. Female age is the most important single variable influencing outcome in assisted reproduction (2). Compared to a woman at 25 years old, the fertility potential is reduced to 50% at age 35, to 25% by 38 years and < 5% at over 40 years.

1.4 RECOMMENDATIONS (3)

Recommendations	GR
• To categorise infertility, both partners should be investigated simultaneously.	C
• In the diagnosis and management of male infertility, the fertility status of the female partner must be considered, as this might determine the final outcome (2).	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 initiate appropriate therapy (drugs, surgery, assisted reproduction) (1).	C

GR = grade of reccomendation

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2.   INVESTIGATIONS

2.1   Semen analysis

Andrological examination is indicated if semen analysis shows abnormalities compared with standard values (Table 2). Important treatment decisions are based on the results of semen analysis and standardisation of the complete laboratory work-up is essential. Ejaculate analysis has been standardised by the WHO and disseminated by continuing work and publications in the *WHO Laboratory Manual for Human Semen and Sperm-Cervical Mucus Interaction* (4th edition) (1). It is the consensus that modern spermatology must follow these guidelines, without exception.

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

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

* *From WHO (2000) (1).*
** *Assessment according to Kruger and Menkfeld criteria.*
† *IBT = Immunobead test*
‡ *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 distinguish between the following:
• oligozoospermia: < 20 million spermatozoa/mL
• asthenozoospermia: < 50% motile spermatozoa

- teratozoospermia: < 14% normal forms.

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

2.2 RECOMMENDATIONS

Recommendations	GR
• Andrological investigations are indicated if semen analysis is abnormal, according to WHO criteria, in at least two tests.	C
• Assessment of andrological status must consider the suggestions made by the WHO for the standardised investigation, diagnosis and management of infertile men; 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 Human Semen and Sperm-Cervical Mucus Interaction (4th edition) (1).	C

GR = grade of recommendation; WHO = World Health Organization

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3. PRIMARY SPERMATOGENIC FAILURE

3.1 Definition

Primary spermatogenic (testicular) failure is any spermatogenic alteration caused by conditions other than hypothalamic-pituitary disease. Severe forms of primary spermatogenic failure have different aetiologies but present clinically as non-obstructive azoospermia (NOA). The prevalence of azoospermia in the general population is approximately 2%; the incidence at a male infertility clinic 10-20% (1).

3.2 Aetiology

The causes of spermatogenic failure are summarized in Table 3.

Table 3: Causes of spermatogenic failure

• Anorchia
• Congenital factors (testicular dysgenesis)
• Acquired factors (trauma, testicular torsion, tumour, surgery)
• Maldescended testes
• Klinefelter's syndrome*
• Other chromosomal alterations*
• Germ cell aplasia
• Complete and focal germ cell aplasia (Sertoli cell-only syndrome), either congenital or acquired: maldescended testes, irradiation, cytostatic drugs
• Spermatogenic arrest
• Post-inflammatory (orchitis)
• Exogenous factors (medications, toxins, irradiation, heat)
• Systemic diseases (liver cirrhosis, renal failure)
• Testicular tumour
• Varicocele
• Surgeries that can damage vascularization of the testes
• Idiopathic

* See section 4 Genetic disorders in infertility.

3.3 History and physical examination

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

- cryptorchidism
- testicular torsion
- genito-urinary infection
- testicular trauma
- exposure to environmental toxin(s)
- gonadotoxic medication
- exposure to radiation or chemical(s)
- testicular cancer
- absence of testes
- abnormal secondary sexual characteristics
- gynaecomastia
- cryptorchidism
- 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 several centrifugations. A recommended method is semen centrifugation at 600 g for 10 min and thorough microscopic examination of the pellet (x 600). The upper fluid is then re-centrifuged (8000 g) for an additional 10 minutes and then examined. All samples can be stained and re-examined microscopically (2).

3.4.2 Hormonal determinations
Generally, the levels of follicle-stimulating hormone (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 is usually part of an ICSI treatment in patients with clinical evidence of NOA: part of the specimen is used for pathological examination and part is cryopreserved for future ICSI cycles if spermatozoa are present (7, 8). Spermatogenesis may be focal: in about 50-60% of men with NOA, only some seminiferous tubules have spermatozoa that can be used for ICSI.
    Most authors therefore recommend taking several testicular samples (9, 10). A good correlation is seen between diagnostic biopsy histology and the likelihood of finding mature sperm cells during testicular sperm retrieval and ICSI (11, 12).

No clear relationship has been found between successful sperm harvesting and FSH, Inhibin B or testicular volume. In case of AZFa and AZFb microdeletions, no spermatozoa can be retrieved (18, 19). Testicular sperm extraction and Microsurgical testicular sperm extraction (MicroTESE) are the techniques of choice and show excellent repeatability (20); TESE results in sperm retrievals in 50-60% of cases (21, 22). Microsurgical testicular sperm extraction may increase retrieval rates (21, 23, 24). After opening the testis, fluid from large calibre tubules is aspirated with the aid of the operating microscope: complications appear to be lower with MicroTESE than with classical TESE (25). Positive retrievals are reported even in conditions such as Sertoli cell only syndrome (21).

Testicular fine-needle aspiration (TEFNA) results in lower retrieval rates and does not allow histological examination to detect carcinoma *in situ* (CIS) and testicular malignancies (26, 27). TEFNA may also result in more tubular and vascular damage than TESE (28).

The results of ICSI are worse when sperm retrieved from men with NOA are used compared to sperm from men with obstructive azoospermia (OA) (29-31):

- fertilisation, implantation and birth rates are lower in NOA vs OA (19% vs 28%) (32,33)
- miscarriage rates are higher in NOA vs OA (11.5% vs 2.5%) (34).

In OA, no significant difference in ICSI results was found between testicular or epididymal sperm (35). Also, no significant differences have been reported in ICSI results between the use of fresh and frozen-thawed sperm (32, 35-39).

3.5 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 future ICSI.
- Spermatozoa are found in about 60% of patients with 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 life births are achieved in 30-50% of couples with NOA, when spermatozoa are found in the testicular biopsy.

3.6 RECOMMENDATIONS

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 (40-42). Part of the specimen can be used for pathological examination.	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 testicular fine-needle extraction.	B

GR = grade of recommendation; NOA = non-obstructive azoospermia

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4. GENETIC DISORDERS IN INFERTILITY

4.1   Introduction

All urologists working in andrology must have a knowledge 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 TESE. However, the sperm of infertile men show an increase in aneuploidy, other genetic abnormalities and DNA damage and therefore the possibility of passing genetic abnormalities to the next generation. Although there are prospects for screening of sperm (1), 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) (2, 3). In a survey of pooled data from 11 publications including 9,766 infertile men, the incidence of chromosomal abnormalities was 5.8% (2). Of these, sex chromosome abnormalities accounted for 4.2% and autosomal abnormalities for 1.5%. For comparison, the incidence of abnormalities in pooled data from three series totalling 94,465 newborn male infants was 0.38%, of which 131 (0.14%) were sex chromosome abnormalities and 232 (0.25%) autosomal abnormalities (3).

Standard karyotype analysis should be offered to all men with damaged spermatogenesis who are seeking fertility treatment by IVF/ICSI.

4.2.1   Sperm chromosomal abnormalities

Using multicolour fluorescent *in situ* hybridisation (FISH) analysis sperm can be examined for chromosomal normality. Aneuploidy in sperm, in particular sex chromosome aneuploidy, is associated with severe damage to spermatogenesis (2, 4, 5, 7-11) and is also seen in men with translocations (6).

FISH analysis of spermatozoa is a research investigation but should be used, particularly to assess spermatozoa from men with defined andrological conditions. Techniques are needed to separate populations of genetically abnormal sperm from normal sperm or to safely safe 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 frequent sex chromosome abnormality (3). Adult men with Klinefelter's syndrome have small firm testicles. The phenotype can vary from a normally virilised man to one with stigmata of androgen deficiency, including female hair distribution, scanty body hair and long arms and legs because of late epiphyseal closure.

Leydig cell function is commonly impaired in men with Klinefelter's syndrome (12). 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. Pre-implantation genetic diagnosis using FISH analysis of cells from embryos can be used to confirm normality (13). The production of 24,XY sperm has been reported in 0.9% and 7.0% of men with Klinefelter's mosaicism (14-16) and in 1.36-25% of men with somatic karyotype 47,XXY (17-21). 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 (22). Haploid sperm in men with Klinefelter's syndrome may be the result of a clone of normal cells in a mosaic population, and in certain circumstances some 47,XXY male germ cells may be viable and capable of producing haploid sperm (23). Klinefelter's syndrome patients have an increased chance of producing 47,XXY spermatozoa. When IVF/ICSI carried out, pre-implantation diagnosis or amniocentesis and karyotype analysis should undertake. Embryos with known Klinefelter's karyotype should probably not be implanted.

Men with Klinefelter's syndrome might require androgen replacement therapy as they get older. 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) where the male partner is known, or found to have, autosomal karyotype abnormality.

4.2.4   Translocations

Reciprocal balanced translocations occur in 1 in 500 people. An individual with a balanced translocation has a complete set of genetic information and a normal phenotype. However, when this individual has children,

the child receives unbalanced genetic information (either too much or too little genetic material). A parental balanced translocation involving chromosome 21 is one cause of Down's syndrome.

When IVF/ICSI is carried out for men with translocations, pre-implantation 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, and the defect will be transmitted to daughters but not to sons.

4.3.2 Kallmann's syndrome
The most common X-linked disorder in infertility practice is Kallmann's syndrome. The predominant form is an X-linked recessive disorder caused by a mutation in the KALIG-1 gene on Xp22.3 (24). Rarer forms of Kallmann's syndrome include an autosomal-dominant form (25). Patients with Kallmann's syndrome have hypogonadotropic hypogonadism and might have other clinical features, including anosmia, facial asymmetry, cleft palate, colour blindness, deafness, maldescended testes and renal abnormalities. Some men with Kallmann's syndrome have an isolated gonadotrophin deficiency without any other phenotypic abnormalities and might present de novo with infertility. It is often possible to stimulate spermatogenesis with replacement therapy (26).

4.3.3 Androgen insensitivity: Reifenstein's syndrome
Androgen insensitivity is a rare disorder and might first present with infertility. The condition has X-linked recessive inheritance as a result of a defect in the androgen receptor gene located on Xq 11-12. The phenotype varies widely, from complete testicular feminisation to an apparently normal man with infertility, although the latter is rare. Disorders of the androgen receptor causing infertility in the absence of any genital abnormality are rare (27), although some cases have been identified (28).

4.3.4 Other X-disorders
A case has been reported of an azoospermic man with biopsy-proven spermatogenetic arrest, who was found to have a submicroscopic interstitial deletion on the Xp pseudo-autosomal region in peripheral blood and skin fibroblast samples. Other genetic and chromosome examinations were entirely normal, including probing of the Yq region (29). There is also a report about two men with azoospermia and X pseudo-autosomal deletions (30).

4.4 Y genes and male infertility

4.4.1 Introduction
The first cases of Y microdeletions and male infertility were reported in 1992 (31) and many case series have subsequently been published. Microdeletions may occur in fertile men, but they are more prevalent in infertile men (32). Microdeletions have been found in three non-overlapping regions of the Y chromosome, AZF a-b-c (33). A fourth region AZFd overlaps with AZFc and is considered by some to be a separate area (34, 35).

The most common microdeletion is in the AZFc region, encompassing the DAZ gene. However, there is a poor correlation between AZFc microdeletions or DAZ gene deletion and spermatogenesis; men with apparently similar microdeletions can have different degrees of damage to their spermatogenesis (32, 36). TESE can be used for men with AZFc Y microdeletions (37). AZFa and AZFb microdeletions are much rarer. If the AZFa microdeletion is large enough to remove both the USP9Y (DFFRY) and the DDX3Y (DBY) genes, azoospermia occurs (38-40). There is no recorded case of sperm recovery by micro-TESE (37). Azoospermia also occurs in men with larger AZFb Y microdeletions (37). Microdeletions are a subset of rearrangments of the long arm of the Y chromosome, others include duplications and inversions. The biological significance of these haplotypes has yet to be determined (41), but some of them might be associated with reduced fertility (42).

4.4.2 Clinical implications of Y microdeletions
Men with Y microdeletions are unlikely to have phenotypic abnormalities other than abnormalities of the male reproductive system. Y microdeletions are associated with varying degrees of derangement of spermatogenesis (33, 35, 36, 39, 43). The AZFc microdeletion 51gr/51gr, which is associated with male infertility, (44) is a rare low penetrance allele that confers susceptibility to testicular germ cell tumour (TGCT) (45). This finding has implications when ICSI is used for a man with a gr/gr microdeletion. More information is needed about Y genes and Y microdeletions and diseases of the male reproductive system. There is also one report of a higher frequency of AZFc microdeletions in the husbands of women with recurrent pregnancy loss (46).

Y microdeletions can be transmitted to male offspring, although this is rare in the normal population

because, without ICSI treatment, men with very low sperm counts are unlikely to father children (32, 33, 47-53). In most cases, the microdeletion in the son is the same as in the father, but there have been reports that the size of the microdeletion is greater in the son (49, 53). 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, in the case of gr/gr microdeletions, their risk of developing germ cell tumours.

4.4.2.1   Testing for Y microdeletions
Testing for microdeletions is now widespread, and methodology is being standardised (33, 54, 55). The following genes are located in the AZF regions and specifically expressed in the testis, RBMY1A1, DAZ, VCY, XKRY, CDY1, DY2, HSFY, PRY, and BPY2. Other genes, including RPS4Y2, USP9Y, DDX3Y, UTY, JARIDID, and EIF1AY, are expressed in more than one tissue.

Studies are needed to correlate testis histopathology with different combinations of loss of one or more of these genes. (For complete listings of Y genes, see the NCBI web site http://www.ncbi.nlm.nih.gov). The best test is to use selected sequence tagged sites (STS) probes chosen to define the most likely microdeletions. In future, gene array analysis may replace testing for Y microdeletions. Direct testing for genes is a research procedure.

4.4.2.2 CONCLUSIONS
- For men with severely damaged spermatogenesis, testing for microdeletions before intracytoplasmic sperm injection (ICSI) is desirable. However, it is reasonable to consider the cost and availability of testing and to discuss this with the couple.
- If AZFa or AZFb Y microdeletions are detected, testicular sperm extraction is not worthwhile because the chance of finding sperm is extremely low.
- Microdeletions will be passed to sons, but not to daughters.
- A son who inherits a microdeletion will probably have a fertility problem.

4.4.3   Autosomal defects with severe phenotypic abnormalities as well as infertility
Several inherited disorders are associated with severe or considerable generalised abnormalities and infertility (Table 4). Patients with these defects will be well known to doctors, often from childhood, and any fertility problem must be managed in the context of the care of the man as a whole and with consideration of the couple's ability to care for a child.

Table 4: Less common inherited disorders associated with infertility and other alterations to phenotype

Disorder	Phenotype	Genetic basis
Prader–Willi	Obesity, mental retardation	Deletion of 15q12 on paternally inherited chromosome
Bardet–Biedle	Obesity, mental retardation, retinitis pigmentosa, polydactyly	Autosomal recessive 16q21
Cerebellar ataxia and hypogonadotropic 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 (CF), a fatal autosomal-recessive disorder, 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 also influences the formation of the ejaculatory duct, seminal vesicle, vas deferens and distal two-thirds of the epididymis.

Congenital bilateral absence of the vas deferens (CBAVD) is associated with CFTR mutations and was found in approximately 2% of men with OA attending a clinic in Edinburgh (56). 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 1500 mutations are listed on the CFTR database (http://www.genet.sickkids.on.ca/cftr/). Many series of men with CBAVD, who were 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 1-9 men, but not all mutations were tested for in all case series (57). 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 mutations that occur most commonly in a particular community.

Mutations may be found in both copies of the CFTR gene; however, in most men with CBAVD, 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 5th allele) can be detected in a non-coding region of CFTR (58). 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 chance 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, her chance of being a carrier of unknown mutations is about 0.4%. In these circumstances, the possibility of her heterozygous partner fathering a child with CF is approximately 1:410.

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 (59) 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 abnormalities (60).

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 Other single gene disorders

There is intense research into genes that control spermatogenesis, and in particular unique Y genes as their products may be targets for non-hormonal contraception. Many research publications discuss candidate genes for spermatogenesis, for example:
- ubiquitin protease 26 gene (61, 62)
- polymorphisms in the oestrogen receptor gene (63, 64)
- polymorphisms of the gonadotrophin-regulated testicular helicase gene (65)
- UTP14c (66)
- SPAG16L (67)
- BGR-like gene (68)
- SPO11, EIF5A2, ACT (69)
- N372H variant of the BRCA2 gene (70)
- heat shock transcription factor in AZFb (71).

Clinical application of these findings is limited; single gene mutations of these various genes probably account for only a small proportion of male infertility. The practicality of testing is limited by expense and availability of testing techniques; however, the advent of cheap gene array testing techniques, with the capacity to screen all or most of the known single gene defects with one test, might change the approach to testing.

4.8 Unknown genetic disorders

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 worries 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. Fetal abnormality statistics from ICSI centres do not, however, indicate any increase in congenital malformations compared with the general population. 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 clinical and molecular diagnosis of the father.

4.9 Genetic and DNA abnormalities in sperm

The DNA damage in spermatozoa from men with oligozoospermia is increased. This increase is associated with reduced chances of natural conception and, to a lesser extent, conception after IVF/ICSI (72) and with an increase in early pregnancy loss (73). DNA damage may improve after varicocele ligation (74).

4.10 Genetic counselling and ICSI

The best management is to agree treatment with the couple and provide them with complete details of the genetic risk. 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), the chance of the child developing a clinical condition and dying early after a number of years of morbidity can be up to 50%. Many clinicians and infertility clinic personnel may consider it is unethical to proceed on the basis that the 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 pre-implantation diagnosis and replacement only of normal embryos.

4.11 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.

4.12 RECOMMENDATIONS

Recommendations	GR
• Standard karyotype analysis should be offered to all men with damaged spermatogenesis who are seeking fertility treatment by in vitro fertilisation/intracytoplasmic sperm injection (ICSI) (2).	A
• For men with severely damaged spermatogenesis, testing for Yq microdeletions before ICSI is desirable.	B
• When a man has structural abnormalities of the vas deferens (congenital bilateral absence of the vas deferens [CBAVD]), it is important to test him and his partner for cystic fibrosis gene mutations (57).	
• 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

GR = grade of recommendation

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5.   OBSTRUCTIVE AZOOSPERMIA

5.1   Definition

OA is the absence of 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 5.

Table 5: Classification of OA on the basis of ductal obstruction due to congenital and acquired causes.

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

Men with OA present with normal size testes and normal FSH. On examination, enlargement of the epididymis can be found. Sometimes, the vas deferens is absent due to congenital factors or previous inguinal or scrotal surgery. Obstructions in primary infertile men are 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.

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 OB, 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 Section 4 Genetic disorders in infertility). Other congenital forms of obstruction (e.g. dysjunction between efferent ductules and corpus epididymis, agenesis/atresia of a short part of the epididymis) are rare.

Congenital forms of epididymal obstruction include chronic sino-pulmonary 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 frequent (7, 8) (see Section 11 Male accessory gland infections)Acute or chronic traumas can result in epididymal damage (9).

Azoospermia caused by surgery might occur after epididymal 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 Section 10 Male contraception). Vasal obstruction may also occur after herniotomy (13). Polypropylene mesh herniorrhaphy seems 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 Section 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). These obstructions can be classified as cystic or post-inflammatory.

Cystic obstructions are usually congenital (i.e. Müllerian duct cyst or urogenital sinus/ejaculatory duct cysts) and are medially located in the prostate between the ejaculatory ducts. In urogenital sinus abnormalitiesone 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 seldom found 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 dysfunctions because of the vasographic patterns of ampullo-vesicular atony or of ejaculatory duct hypertony. Functional obstruction of the distal seminal ducts has been seen 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 section 2 Investigations), ask 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 sino-pulmonary 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 > 15 mL volume (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 section 2 Investigations). Azoospermia means absence of spermatozoa after centrifugation at x400 magnification. Careful repeat observation of several smears after semen liquefaction is needed. If no spermatozoa are found in wet preparation, aliquots or the whole semen sample should be centrifuged (600 rpm for 15 min). The pellet must be examined for spermatozoa.

A semen volume <1.5 mL and with an acid pH and low fructose level suggests ejaculatory duct obstruction or CBAVD. 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). FSH is normal in 40% of men with primary spermatogenic failure. Inhibin B appears has a higher predictive value for normal spermatogenesis (4).

5.3.5 Ultrasonography

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

For patients with a low seminal volume and in whom distal obstruction is suspected, transurethral 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. Other known anomalies in cases of obstructive azoospermia are Müllerian duct cysts or urogenital sinus/ejaculatory duct cysts (20) and ejaculatory duct calcifications (25). 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 can also be used to extract 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 6 (27).

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

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

* From Johnsen, 1970 (27)

5.4 Treatment

5.4.1 Intratesticular obstruction

At this level seminal duct recanalisation is impossible; TESE or fine-needle aspiration is therefore recommended. The spermatozoa retrieved may be used immediately for ICSI or may be cryopreserved. Both TESE and fine-needle aspiration allow sperm retrieval in nearly all OA patients.

5.4.2 Epididymal obstruction

Microsurgical epididymal sperm aspiration (28) is indicated in men with CBAVD. Retrieved spermatozoa are usually used for ICSI. Usually, one MESA procedure provides sufficient material for several ICSI cycles (29). There is limited evidence that a micropuncture with nerve stimulation may be better for sperm recovery than a simple MESA technique, as it produces higher pregnancy and fertilisation rates (30). In patients with azoospermia due to acquired epididymal obstruction, end-to-end or end-to-side microsurgical epididymo-vasostomy is recommended, with microsurgical intussusception epididymo-vasostomy being the preferred technique (31).

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 (29).

Patency rates range between 60% and 87% (32-34) 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 section 10 Male contraception). Vaso-vasostomy is also required in the rare cases of proximal vasal obstructions (iatrogenic, post-traumatic, post-inflammatory). When spermatozoa are absent in the intraoperative vas fluid, a secondary epididymal obstruction may be present, especially if the seminal fluid of the proximal vas has a thick 'toothpaste' appearance. Microsurgical vaso-epididymostomy is indicated.

5.4.4 Distal vas deferens obstruction

It is usually impossible to correct, large bilateral vas defects resulting from involuntary vas excision during hernia surgery in early childhood or previous orchidopexy (16). In these cases, proximal vas deferens sperm aspiration (35) or TESE/MESA can be used for cryopreservation for future ICSI. In large mono-lateral vas defects associated with contralateral testicular atrophy, the vas of the atrophic testis can be used for a crossover vaso-vasostomy or vaso-epididymostomy.

5.4.5 Ejaculatory duct obstruction

Treatment of ejaculatory duct obstruction depends on the aetiology. In large post-inflammatory obstruction and when one or both ejaculatory ducts empty into an intraprostatic midline cyst, transurethral resection of the ejaculatory ducts (TURED) (20, 36) can be used. 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). Intraoperative 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 can help to document opening of the ducts.

Complications following TURED include retrograde ejaculation due to bladder neck injury, and reflux of urine into ducts, seminal vesicles and vasa (causing poor sperm motility, acid semen pH and epididymitis). Alternatives to TURED are MESA, TESE, proximal vas deferens sperm aspiration, seminal vesicle 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 (36). Spermatozoa retrieved by any of the aforementioned surgical techniques should always be cryopreserved for assisted reproductive procedures.

5.5 CONCLUSIONS

- Obstructive lesions of the seminal tract should be suspected in azoospermic or severely oligozoospermic patients with normal-sized testes and normal endocrine parameters.
- Results of reconstructive microsurgery depend on the cause and location of the obstruction and the expertise of the surgeon. Standardised procedures include vaso-vasostomy and epididymo-vasostomy.
- Sperm retrieval techniques such as MESA, TESE and testicular fine-needle aspiration can be used

additionally. These methods should be used only when cryostorage of the material obtained is available.

5.6 RECOMMENDATIONS

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 (37)	B

GR=grade of recommendation

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6.   VARICOCELE

6.1   Introduction
Varicocele is a common abnormality (see section 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 demonstrable by special tests (reflux found upon Doppler examination) (3)
*   Grade 1: Palpable during Valsalva manoeuvre but not otherwise
*   Grade 2: Palpable at rest, but not visible
*   Grade 3: Visible and palpable at rest.

6.3   Diagnosis
The diagnosis of varicocele has been defined by the WHO (2). Diagnostic procedure and classification of a varicocele, including analysis, must follow these accepted criteria (2).
        The diagnosis of varicocele is made by clinical examination and can be confirmed by colour Doppler analysis. 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
Various studies have been conducted on the epidemiology of varicocele, its association with male infertility and whether treatment is beneficial.
*   Varicocele is a physical abnormality present in 11% of adult males (4, 5) and in 25% of those with abnormal semen analysis (6).
*   The incidence of pain and discomfort associated with varicocele is 2-10% (7).
*   The exact association between reduced male fertility and varicocele is not known, but WHO data (8) clearly indicates that varicocele is related to semen abnormalities, decreased testicular volume and decline in Leydig cell function.
*   Two prospective randomised studies showed increased ipsi- and contra-lateral testis growth in adolescents who had received varicocele treatment compared with those who did not (9, 10). A cohort follow-up study, which took serial measurements of testicular size in children, showed that varicocele halted testicular development. However, following treatment for varicocele, catch-up growth occurred and reached the expected growth percentile (11).
*   A series of studies suggested that altered endocrine profiles in men with varicocele might predict who would benefit from treatment (12, 13).
*   Five prospective randomised studies of varicocele treatment in adults gave conflicting results (6, 14-18); the largest study indicated that treatment was beneficial (16, 18). The externally randomised study involved 10 centres and included men of infertile couples who had moderate oligozoospermia (5-20 x 106/mL) and grade II or III varicocele. Immediate therapy was significantly more effective than delaying treatment for 1 year with regard to achieving pregnancy and the pregnancy rate per

menstrual cycle (fecundability). However, a meta-analysis of the five trials indicated no benefit (common odds ratio 0.85%; 95% confidence interval: 0.49-1.45) (19).

The studies mentioned above were summarised in a recent review (20), criticising the Cochrane meta-analysis of randomised controlled trials on varicocele treatment and pregnancies (21). The authors concluded that the Cochrane meta-analysis conclusions should not support guidelines recommendation against varicocele treatment in subfertile patients.
In a randomised controlled study varicocele repair in men with a subclinical varicocele was found to be ineffective (22). A recent meta-analysis excluding men with subclinical varicoceles and studies that included embolisation for treatment showed a benefit in favour of surgical treatment with an odds ratio of 2.87 (95 % CI, 1.33-6.2) for inducing pregnancy (23).

6.5 Treatment
Several treatments are available for varicocele (Table 7). The type of intervention chosen depends mainly on the therapist's experience. Although laparoscopic varicocelectomy is feasible, it must be justified in terms of cost effectiveness.

Table 7: Recurrence and complication rates of different treatment methods for varicocele

Treatment	Recurrence/persistence rates	Complications
• Antegrade sclerotherapy	9%	Complication rate 0.3-2.2%; testicular atrophy; scrotal haematoma; epididymitis; left-flank erythema
• Retrograde sclerotherapy	Recurrence and persistence rate 9.8% (25)	Adverse reaction to the contrast medium; flank pain; persistent thrombophlebitis; vascular perforation (26)
• Retrograde embolisation	3.8-10% (27,28)	Pain due to thrombophlebitis (28); bleeding haematoma; infection; venous perforation; hydrocele; radiological complication, e.g. reaction to contrast media; misplacement or migration of coils (29); retroperitoneal haemorrhage; fibrosis; ureteric obstruction (5)
Open operation		
• Scrotal operation	–	Testicular atrophy (5); arterial damage with risk of devascularization and gangrene of testicle
• Inguinal approach	13.3% (30)	Possibility of missing out a branch of testicular vein
• High ligation	29% (30)	5-10% incidence of hydrocele (31)
• Microsurgical	0.8-4% (32,33)	Post-operative hydrocele arterial injury; scrotal haematoma
• Laparoscopy	3-7% (34-36)	Injury to testicular artery and lymph vessels; intestinal, vascular and nerve damage; pulmonary embolism; peritonitis (36); bleeding; post-operative pain in right shoulder (due to diaphragmatic stretching during pneumo-peritoneum) (35); pneumoscrotum; wound infection (36)

6.6 CONCLUSIONS
- Current information supports the hypothesis that in some men, the presence of varicocele is associated with progressive testicular damage from adolescence onwards and consequent reduction in fertility. However, in infertile couples this impaired fertility potential will only manifest if female fertility is also reduced.
- Although 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 a partner without obvious fertility problems. Further studies are needed to confirm that this subgroup of infertile couples will benefit from treatment.

6.7   RECOMMENDATIONS

Recommendations	GR
• Varicocele treatment is recommended for adolescents who have progressive failure of testicular development documented by serial clinical examination (9, 10).	B
• No evidence indicates benefit from varicocele treatment in adolescents who have normal semen analysis or in men with subclinical varicocele. In this situation, varicocele treatment cannot be recommended. (14,20)	B
• Although varicocele treatment may be effective in selected couples, reviews of randomised clinical trials have raised doubts about the benefit of varicocele treatment in infertile men. Varicocele treatment for infertility should not be undertaken, unless there has been full discussion with the infertile couple regarding the uncertainties of treatment benefit (19, 22, 23)	B

GR = grade of recommendation

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7. HYPOGONADISM

7.1 Introduction

Hypogonadism is deficient androgen secretion. The symptoms of hypogonadism depend on the degree of androgen deficiency and whether the condition develops before or after pubertal development of the secondary sex characteristics. The symptoms and signs of hypogonadism debuting before and after completion of puberty are given in Table 8.

Table 8: The 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 Straight frontal hairline Diminished beard growth	Diminished secondary body hair
• Skin	Absent sebum production Lack of acne Pallor Skin wrinkling	Decreased sebum production Lack of acne Pallor Skin wrinkling
• Bones	Eunuchoid tall stature Osteoporosis	Osteoporosis
• Bone marrow	Low-level anaemia	Low-level anaemia
• Muscles	Underdeveloped	Atrophy
• Prostate	Underdeveloped	Atrophy
• Penis	Infantile	No change of size
• Testes	Possibly maldescended testes Small volume	Decrease of testicular volume
• Spermatogenesis	Not initiated	Involuted
• Libido and potency	Not developed	Loss

The aetiological and pathogenetic mechanisms of male hypogonadism can be divided into three main categories:
1. Primary (hypergonadotropic) hypogonadism due to testicular failure
2. Secondary (hypogonadotropic) hypogonadism caused by insufficient gonadotrophin-releasing hormone (GnRH) and/or gonadotrophin secretion
3. Androgen insensitivity (end-organ resistance).

The most common conditions within these three categories are given in Table 9.

Table 9: Disorders with male hypogonadism*

Primary (hypergonadotropic) hypogonadism (= testicular insufficiency)
•   Anorchia
•   Congenital factors (testicular dysgenesis)
•   Acquired factors (trauma, testicular torsion, tumour, surgery)
•   Maldescended testes
•   Klinefelter's syndrome**
•   Other chromosomic abnormalities
•   Germ cell aplasia
•   Complete and focal germ cell aplasia (Sertoli cell-only syndrome), either congenital or acquired: maldescended testes, irradiation, cytostatic drugs
•   Spermatogenic arrest
•   Post-inflammatory (orchitis)
•   Exogenous factors (medications, toxins, irradiation, heat)
•   Systemic diseases (liver cirrhosis, renal failure)
•   Testicular tumour
•   Varicocele
•   Surgeries that can damage vascularisation of the testes
•   Idiopathic

Secondary (hypothalamic or pituitary origin) (hypogonadotropic state with secondary hypogonadism)

•	Idiopathic hypogonadotropic hypogonadism (including Kallmann's syndrome)
•	Delay of puberty
•	Hyperprolactinaemia
•	Drugs/anabolic steroids

Target organ resistance to androgens

•	Testicular feminization
•	Reifenstein's syndrome

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

** See Section 4 Genetic disorders in infertility.

7.2 Hypogonadotropic hypogonadism: aetiology, diagnosis and therapeutic management

Primary hypogonadotropic hypogonadism is caused by either hypothalamic or pituitary diseases. The failure of hormonal regulation can easily be determined (2). Endocrine deficiency leads to a lack of spermatogenesis and testosterone secretion as a result of decreased secretion of luteinising hormone (LH) and FSH. 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, stimulation of sperm production requires treatment with human chorionic gonadotrophin (hCG) combined with recombinant FSH. In the rare cases of 'fertile eunuchs' having sufficient production of FSH but not LH, treatment with hCG alone may be sufficient to stimulate sperm production and to achieve normal testosterone levels (3).

If hypogonadotropic hypogonadism is hypothalamic in origin, an alternative to hCG treatment is therapy with pulsatile GnRH (4). 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.

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

7.3 Hypergonadotropic hypogonadism: aetiology, diagnosis and therapeutic management

Common conditions associated in men with hypergonadotropic hypogonadisminclude injury to, and loss of, the testicles (e.g. after bilateral testicular cancer) (Table 9). Men with Klinefelter's syndrome are at risk of hypogonadism (5) with ageing. Men with infertility problems are at higher risk for developing hypogonadism (6). Men undergoing extensive testicular biopsy in the context of IVF/ICSI will almost certainly have an increased risk of developing hypogonadism (7).

Hypergonadotropic hypogonadism may occur spontaneously in the ageing men, in patients with erectile dysfunction (8), and after luteinising hormone-releasing hormone (LHRH) treatment or surgical castration for prostatic cancer (9). Hypogonadism may result in osteoporosis (10).

Laboratory diagnosis of hypergonadotropic hypogonadism is based on decreased serum testosterone and increased LH levels (2). 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, and testosterone supplementation is indicated only in men with levels consistently lower than normal (< 12 nmol/L [300 ng/dL]). Injectable, oral and transdermal testosterone preparations are available for clinical use (2). The best preparation to use is one that maintains serum testosterone levels as close as possible to physiological concentrations (11).

7.4 CONCLUSIONS

It is generally agreed that patients with primary or secondary hypogonadism should receive testosterone substitution therapy.

7.5 RECOMMENDATIONS

Recommendations	GR
• Effective drug therapy is available to achieve fertility in men with hypogonadotropic hypogonadism (4).	A

GR = grade of recommendation

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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 (frequency of cryptorchidism is higher 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 can be located within the abdominal cavity.

The aetiology of cryptorchidism is multi-factorial; both disrupted endocrine regulation and several gene defects may be involved. For a normal descent of the testes, a normal hypothalamo-pituitary-gonadal axis is needed. 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 the consequence of testicular dysgenesis, a developmental disorder of the gonads resulting from environmental and/or genetic influences early in pregnancy. Testicular dysgenesis syndrome can result in maldescence, hypospadias, reduced fertility and an increased risk of malignancy (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 this malformation; cryptorchidism is significantly more common among Danish than among Finish newborns (2). Premature babies have a much higher incidence of cryptorchidism than full-term babies. In a UK study, the incidence of cryptorchidism in more than 3000 boys weighing > 2500 g was 2.7%; in premature boys weighing < 2500 g the corresponding number was 21%. At the age of 3 months, spontaneous descence 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: a) transabdominal and b) inguinal.

During 'transabdominal descence', development of the gubernaculum and genito-inguinal ligament plays an important role. The antiMüllerian hormone regulates the transabdominal descence of the testis. Induction of the gubernaculum depends on 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). Other gene families (e.g. the homeobox (HOX) genes, GREAT gene), are important for the development of genital organs and may be associated with testicular maldescence (6, 7).

8.4   Hormonal control of testicular descent

Maldescence can be caused by two hormonal factors: hypogonadism and androgen insensitivity. The increasing incidence of reproductive abnormalities in human males might be explained by an 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 might cause hypospadia, cryptorchidism, reduction of sperm density, and an increase in the incidence of testicular tumours in animal models by receptor-mediated mechanisms or direct toxic effects (10).

8.5   Pathophysiological effects in maldescended testes

8.5.1   Degeneration of germ cells

Degeneration of germ cells in maldescended testes is apparent after the first year. The degenerative changes vary, depending on the position of the testis (11). During the second year of life, the number of germ cells declines. In 10-45% of affected patients, 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, but hormone treatment with either hCG or GnRH analogues can be considered, particularly in cases where testes are located in the high scrotal position (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 might 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 paternity in men without cryptorchidism (93.7%).

In men with unilateral cryptorchidism, paternity is independent of the age at orchidopexy, pre-operative testicular location and testicular size (15) However, a history of unilateral cryptorchidism may result in reduced fertility potential (i.e. causing a prolonged 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%.

8.5.3   Germ cell tumours

Cryptorchidism is a risk factor for testicular cancer and is associated with testicular microcalcification and CIS of the testis. In about 5-10% of testicular cancers, there is a history of cryptorchidism (16). 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 (16). There is no evidence for a protective effect of early orchidopexy (17).

8.6   Treatment of undescended testes

8.6.1   Hormonal treatment

In randomised, controlled trials investigating the efficacy and safety of hCG and GnRH treatment, a large variation in success rates has been reported. The corresponding figures in a multicenter randomised trial were 21%, 19% and 4% for GnRH, hCG and placebo, respectively (12) A meta-analysis of 33 studies showed that the success rate was highest in pre-scrotal and high scrotal testes (18). Non-palpable testes rarely descend as a result of hormonal treatment.

The current hormonal protocol used for high scrotal testes is three hCG injections given once per week. The dosage is 1500 IU per injection for children aged 1-3 years, 3000 IU at age 4-6 years, and 5000 IU at age 6-15 years. The recommended age for treatment using hCG is 12-18 months. In a patient with bilateral impalpable testes, an hCG stimulation test can be carried out; a rise in testosterone level confirms the presence of testes. Inhibin B is produced by the Sertoli cells of the testis and can be a good indicator of testicular function in children (19).

Hormonal treatment is generally considered safe, with few side-effects. However, some studies have

indicated an increased risk of interstitial fibrosis and germ cell apoptosis following hCG treatment (20). Early adverse effects include penile growth, pain in the genital region, pain at the site of injection and psychological changes as a result of androgen effects.

8.6.2   Surgical treatment
The success rate of surgical treatment for undescended testes is 70-90% (21). When the spermatic cord or vessels are too short to allow proper mobilisation of the testis into the scrotum, a staged orchidopexy (Fowler-Stephenson procedure) can be used. The applied techniques are open surgery, laparoscopy, or microsurgery.

A biopsy at the time of orchidopexy (see page 51, sections 12.1-12.2) can reveal a CIS, which can be removed, thus preventing development of a malignant tumour. If not corrected by adulthood, an undescended testis should not be removed.

Following orchidopexy, vascular damage is the most severe complication and can cause testicular atrophy in 1-2% of cases. In non-palpable testes, the post-operative atrophy rate was 12% in cases where the vascular pedicles were long enough to allow scrotal positioning. Up to 40% post-operative atrophy was reported in cases of staged orchidopexy.

8.7   CONCLUSIONS
- Cryptorchidism is multi-factorial in origin and may be caused by genetic factors and endocrine disruption early in pregnancy.
- Cryptorchidism can be associated with testicular dysgenesis and is a risk factor for infertility and germ cell tumours.
- Paternity in men with unilateral cryptorchidism in almost equal to paternity in men without cryptorchidism.
- Bilateral cryptorchidism, significantly reduces the likelihood of paternity.

8.8   RECOMMENDATIONS

Recommendations	GR
• Early surgical treatment of undescended testis may prevent germ cell loss.	C
• If undescended testes are corrected in adulthood, a testicular biopsy for detection of carcinoma *in situ* is recommended at the time of the orchidopexy (16).	B

GR = grade of recommendation

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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 approaches for the treatment of idiopathic male infertility have been used; however, there is little scientific evidence for an empirical approach (2).

Androgens, hCG/hMG, bromocriptine, alpha-blockers, systemic corticosteroids and magnesium supplementation are not effective in the treatment of OAT syndrome. FSH (3) and anti-oestrogens in combination with testosterone (4) might be beneficial in a selection of patients; however, further evaluation in multicenter studies of these agents is required (3, 4).

9.3   RECOMMENDATIONS

Recommendation	GR
• Medical treatment of male infertility is recommended only for cases of hypogonadotropic hypogonadism (1).	A

GR = grade of recommendation

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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; 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 between 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 androgens, progestogen and GnRH 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; 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 suppression of gonadotrophins and the use of 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 provided 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 the vasectomy, the couple should be given accurate information about the benefits and risks. An Australian telephone survey found that 9.2% of respondents said they 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); this is associated with a low rate of complications (11). The most effective occlusion technique is cauterisation of the lumen of the vas and fascial interposition (12-14). Most techniques can be carried out safely under local anaesthesia in the out-patient 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 of 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 may 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' can be given to men who continue to produce non-motile spermatozoa up to 1 year after vasectomy (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, as 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 fascial interposition and cauterisation 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 since vasectomy, type of vasectomy (e.g. open-ended or sealed), type of reversal (vaso-vasostomy or vaso-epididymostomy) and whether reversal was unilateral or bilateral. Although there have been no randomised, controlled trials that compare macro-surgery (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 from vasectomy to reversal, the lower 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% for 3-8 years, 79% and 44% for 9-14 years and 71% and 30% for ≥15 years (21).

10.3.2   Epididymovasostomy
The chance of secondary epididymal obstruction after vasectomy increases with time. If secondary epididymal obstruction occurs, epididymo-vasostomy is needed to reverse the vasectomy (see Section 5 Obstructive azoospermia).

10.3.3   Microsurgical vasectomy reversal versus epididymal or testicular sperm retrieval and ICSI
Calculations of cost per delivery for vasectomy reversal versus sperm retrieval-ICSI under a wide variety of initial assumptions clearly indicate that vasectomy reversal is associated with a considerably lower cost per delivery and higher delivery rates (live births) (22, 23). Sperm retrieval and ICSI must yield a 81% pregnancy rate per cycle to achieve equal costs to vasectomy reversal.

10.4   CONCLUSIONS
- All available data indicate vasectomy is not associated with any serious, long-term side-effects (15).
- 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 and ICSI should be reserved for failed vasectomy reversal surgery.

10.5   RECOMMENDATIONS

Recommendations	GR
• Fascial interposition and cauterisation appears to be the most effective technique (12-14).	B
• Patients seeking consultation regarding vasectomy must be given information about the surgical method, risk of failure, irreversibility, need for post-procedure contraception until clearance, and 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 intracyctoplasmic spermic injection is a second-line option for selected cases and in cases of failed vaso-vasostomy.	B

GR = grade of recommendation

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11. MALE ACCESSORY GLAND INFECTIONS (MAGIs)

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 can be caused by various of pathogens, most commonly *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 analysis of urethral smear and first-voided urine (VB1). Evidence of ≥ 4 granulocytes per microscopic high-power field (x1000) in an urethral smear, or of 15 granulocytes per microscopic field (x400) 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 as 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 as the ejaculate is contaminated with inflammatory material from the urethra.

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

The Centers of Disease Control and Prevention in Atlanta (GA, USA) have published guidelines standardising the treatment of sexually transmitted diseases (9). As the aetiology of acute urethritis is usually unknown at the time of diagnosis, empirical therapy directed against potential pathogens is suggested. 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 represents 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 the prostatitis, a classification system has been proposed by the National Institute of Health (NIH) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Washington DC, USA (10) (Table 10).

Table 11: New NIH/NIDDK classification of the prostatitis syndrome (10).

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 Wgenlehner et al (10).
ABP = acute bacterial prostatitis; CBP = chronic bacterial prostatitis; CPPS = chronic pelvic pain syndrome.

11.3.1 Microbiology

Acute bacterial prostatits (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,

predominantly strains of *Escherichia coli* (11). The role of Gram-positive bacteria in bacterial prostatitis is controversial. Although enterococci may cause bacterial prostatitis and associated recurrent urinary tract 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.

Key for diagnosis is demonstration of leukocytes in EPSs, urine after prostatic massage and/or ejaculate to differentiate between inflammatory and non-inflammatory CPPS.

11.3.3   Ejaculate analysis
An ejaculate analysis (see section 2 Investigations) helps to clarify whether the prostate is part of a generalised infection of the accessory sex glands (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, ≥ 106 peroxidase-positive white blood cells per mL ejaculate are indicative of an inflammatory process. In these cases, a culture should be made for common urinary tract pathogens, particularly Gram-negative bacteria.

A concentration of ≥ 103 cfu/mL urinary tract pathogens in the ejaculate is a significant bacteriospermia. Various micro-organisms are found in genital tract of men seen in infertility clinics, with more than one strain of bacteria in most cases (1). The time of sampling 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 (≥ 103 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 'mycoplasmal-associated' urogenital infections using samples such as the ejaculate (15).

11.3.5   White blood cells
The clinical significance of an increased concentration of white blood cells (WBC) or 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 showed that elevated leukocyte numbers are not a natural cause of male infertility (22).

According to WHO classification, > 1 x 106 WBC/mL have been defined as leukospermia. Only two studies have analysed alterations of WBC in the ejaculate of patients with proven prostatitis (23, 24); both studies found more leukocytes in men with prostatitis compared to men 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 may influence sperm function. Several studies have investigated the association between

interleukin concentration, leukocytes and sperm function (30-32): no correlations were found. The prostate is the main site of origin of interleukin-6 (IL-6) in the seminal plasma.

Cytokines, especially IL-6, must 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 reports stated an association between increased levels of sperm antibodies in serum and NBP (36, 37). However, except 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, the biological significance in prostatitis remains unclear (1).

11.3.11 Therapy
Treatment of chronic prostatitis is usually targeted at relieving symptoms (10, 41). Andrologically, therapy for altered semen composition in male adnexitis (acute and chronic infections of the male urogenital tract) is aimed at:
- 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 micro-organisms 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, potentially resulting 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 feature of the tissue does 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 due to complete obstruction is a rare complication.

Mumps orchitis may result in bilateral testicular atrophy (45) and testicular azoospermia. When granulomatous orchitis is suspected, sperm-bound auto-antibodies occur.

11.4.4 Therapy
Only therapy of acute bacterial epididymo-orchitis and of specific granulomatous orchitis is standardised (45) (Table 11). Several regimens improve the inflammatory lesion. Unfortunately, therapies using corticosteroids and non-steroidal antiphlogistic substances (e.g. diclofenac, indomethacin, and acetylsalicylic acid) have not

been evaluated for their andrological outcome (47). In mumps orchitis, systemic interferon alpha-2b therapy prevents testicular atrophy and azoospermia (48). In idiopathic granulomatous orchitis, surgical removal of the testis is the therapy of choice.

Table 12: 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 antiphlogistic 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* (Table 11) (49, 50). 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 (50).

11.5.2 Diagnosis
In acute epididymitis, inflammation and swelling usually begin 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 may 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 (49, 50). Intracellular Gram-negative diplococci on the smear indicate presence of *N. gonorrhoea.* Only WBCs on urethral smear indicate non-gonorrhoeal urethritis; *C. trachomatis* will be isolated in approximately two-thirds of these patients (51).

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, 49, 52). Ipsilateral low-grade orchitis (53, 54) might be the cause of this slight impairment in sperm quality (Table 12) (55).

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

Table 13: Acute epididymitis and impact on sperm parameters

Author	Negative influence on:			
	Density	**Motility**	**Morphology**	**Comment**
Ludwig & Haselberger (56)	+	+	+	Pyospermia in 19 of 22 cases
Berger et al. (49)		+		
Weidner et al. (47)	+	+	+	Azoospermia in 3 of 70 men
Haidl (57)		+		Chronic infections; macrophages elevated
Cooper et al. (58)				Decrease in epididymal markers: alpha-glucosidase, L-carnitine

11.5.4 Treatment
Antibiotic therapy is indicated before culture results are available (Table 11). Treatment of epididymitis will result 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 that is known or suspected to be caused by *N. gonorrhoea* or *C. trachomatis* must be told to refer their sexual partners for evaluation and treatment (59).

11.6 CONCLUSIONS
- Urethritis and prostatitis are not clearly associated with male infertility.
- Antibiotic treatment often only eradicates micro-organisms; it has no positive effect on inflammatory alterations and/or cannot reverse functional deficits and anatomical dysfunctions.

11.7 RECOMMENDATIONS

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
• 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 (59).	B

GR = grade of recommendation

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12. GERM CELL MALIGNANCIES AND TESTICULAR MICROCALCIFICATIONS

12.1 Germ cell malignancies and male infertility

Testicular germ cell tumour is the most common malignancy in Caucasian males aged 15-40 years and affects approximately 1% of subfertile men. The lifetime risk of TGCT varies between ethnic groups and from country to country. 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 CIS will eventually progress to an 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 that have reliable cancer registers, the incidence of testicular cancer has increased (4). Both 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.

Males with dysgenic testes have an increased risk of developing testicular cancer in adulthood. These cancers arise from pre-malignant gonocytes or CIS cells (5). Testicular microlithiasis can be associated with both 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 Section 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. Obtaining pre-treatment 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 be followed up long term because they are at risk of developing hypogonadism as a result of age-related decrease in testosterone production (9).

12.3   Testicular microlithiasis

Microcalcifications inside the testicular parenchyma can be found in 0.6-9% of men referred for testicular ultrasound (10-13). Although the true incidence of microcalcifications in the general population is unknown, it is probably rare. However, ultrasound findings of testicular microlithiasis are common in men with TGCT, cryptorchidism, testicular dysgenesis, male infertility, testicular torsion and atrophy, Klinefelter's syndrome, hypogonadism, male pseudo-hermaphroditism, varicocele, epididymal cysts, pulmonary microlithiasis and non-Hodgkin's lymphoma. The incidence reported seems to be higher with high-frequency ultrasound machines (14).

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

Testicular microcalcification is a condition found in testes at risk of malignant development. The reported incidence of TM in men with TGCT is 6-46% (15-17); TM should therefore be considered premalignant. However, it has not been established whether TM is present before development of invasive TGCT, or whether TM might be an indicator for the preinvasive stage of TGCTs (i.e. CIS). Testicular biopsies from men with TM have found a higher prevalence of CIS, especially in men with bilateral microlithiasis (18). However, TM is found most often in men with a benign testicular condition and the microcalcifications themselves are 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. Available data indicate high-risk patients (e.g. patients referred for infertility and/or cryptorchidism) in whom TM is found, should be followed-up by repeated ultrasound and/or testicular biopsy for detection of CIS.

12.4   RECOMMENDATIONS

Recommendations	GR
• In men with testicular microlithiasis (TM) and a history of male infertility, cryptorchidism or testicular cancer and in men with atrophic testis, a testicular biopsy or a follow-up scrotal ultrasound is recommended to rule out carcinoma *in situ* of the testis (17, 18).	B
• It is important to encourage and educate these patients about self-examination, as this may result in early detection of testicular germ cell tumour (TGCT).	
• If there are suspicious findings on physical examination or ultrasound in patients with TM and associated lesions, a surgical exploration with testicular biopsy or orchidectomy should be considered.	B
• Testicular biopsy, follow-up scrotal ultrasound or routine use of biochemical tumour markers, abdominal and pelvic computed tomography scanning is not justified for men with isolated TM without associated risk factors (e.g. male infertility, cryptorchidism, testicular cancer, atrophic testis) (11).	B
• Men with TGCT are at increased risk of developing hypogonadism and should therefore be followed up (9).	B

GR = grade of recommendation

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

Table 14: Aetiologies of anejaculation

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

13.2.2   Anorgasmia
Anorgasmia is the inability to reach orgasm and may 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; both conditions can be found alternately in the same patient. The causes of delayed ejaculation may be psychological or organic, e.g. incomplete spinal cord lesion (3), iatrogenic penile nerve damage (4) or pharmacological (antidepressants, antihypertensives, antipsychotics) (5).

13.2.4   Retrograde ejaculation
Retrograde ejaculation is the total, or sometimes partial, absence of an 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 14).

Table 15: Aetiology of retrograde ejaculation

Neurogenic causes	Pharmacological causes
• Spinal cord injury	• Antihypertensives
• Cauda equina lesions	• Alpha$_1$-adrenoceptor antagonists
• Multiple sclerosis	• Antipsychotics
• Autonomic neuropathy (juvenile diabetes)	• Antidepressants
• Retroperitoneal lymphadenectomy	
• Sympathectomy	
• Colorectal and anal surgery	

Urethral causes	Bladder neck incompetence
• Ectopic ureterocele	• Congenital defects/dysfunction of hemitrigone
• Urethral stricture	• Bladder extrophy
• Urethral valves or verumontaneum	• Bladder neck resection

	hyperplasia		
•	Congenital dopamine beta-hydroxylase deficiency	•	Prostatectomy

13.2.5   Asthenic ejaculation
Asthenic ejaculation, also defined as partial ejaculatory incompetence or 'ejaculation baveuse' (6), 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, while in asthenic ejaculation due to urethral obstruction, these contractions are present. Asthenic ejaculation is generally due to the neurogenic or urethral pathologies already listed in Table 14. Asthenic ejaculation does not usually alter 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' (i.e. neurobiologically based), 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 may be consulted (http://www.uroweb.org/nc/professional-resources/guidelines/online/).

13.2.7   Painful ejaculation
Painful ejaculation is usually an acquired condition, often related to lower urinary tract symptoms (7). It sometimes causes moderate sexual dysfunction. The painful sensation may be felt in the perineum, or urethra and urethral meatus (8). It can be caused by ejaculatory duct obstruction, all types of chronic prostatitis/chronic pelvic pain syndrome, 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, neuropathies, traumas, urogenital infections, previous surgery and medications. 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 traumas, previous psychological therapies).

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 will determine if there is total or partial retrograde ejaculation.

13.3.4   Microbiological examinations
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 (9).

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 neuropathies (i.e. appreciation of temperature regulation in the feet)
•   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 (ART). 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 pathologies
- psychosexual counselling.

13.5 Aetiological treatments

If possible, stop any pharmacological treatments that are interfering with ejaculation. Tamsulosin can be administered during antidepressant treatment (10). Treatment should be given for urogenital infections (i.e. in cases of painful ejaculation) (9). Selective serotonin re-uptake inhibitors (SSRIs) should be given for premature ejaculation, which appears to be related to serotonin levels (11). If possible, any underlying urethral pathology or metabolic disorder (e.g. diabetes) should be corrected. Psychotherapy is not usually very effective.

13.6 Symptomatic treatments

13.6.1 Premature ejaculation
This can be treated with topical anaesthetic agents to increase intravaginal ejaculation latency time or the off-label use of SSRIs (e.g. paroxetine, fluoxetine), behavioural therapy and/or psychotherapy.

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 15). Alternatively, the patient can be encouraged to ejaculate when his bladder is full to increase bladder neck closure (12).

Table 16: Drug therapy for retrograde ejaculation

•	Ephedrine sulphate, 10-15 mg four times daily (13)
•	Midodrin, 5 mg three times daily (14)
•	Brompheniramine maleate, 8 mg twice daily(15)
•	Imipramine, 25-75 mg three times daily (16)
•	Desipramine, 50 mg every second day (17)

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 (18). Alternatively, a catheter may 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 (19). If the biological sperm preparation is not of sufficient quality for intrauterine insemination, the couple must undergo *in vitro* reproductive procedures (i.e. ICSI) with fresh or cryopreserved spermatozoa.

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, vibro-stimulation (i.e. the application of a vibrator to the penis) is first-line therapy.

In anejaculation, vibro-stimulation evokes the ejaculation reflex (20), which requires an intact

lumbosacral spinal cord segment. Complete spinal injuries and injuries above T10 show a better response to vibro-stimulation.

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 vibro-stimulation has failed, electro-ejaculation is the therapy of choice (21). 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, electro-stimulation 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 (22).

When electro-ejaculation fails or cannot be carried out, sperm can be retrieved from the seminal ducts by aspiration from the vas deferens (23) (*see* Section 5 Obstructive azoospermia) or seminal tract washout (24).

When sperm cannot be retrieved, epididymal obstruction or testicular failure must be suspected. TESE can then be used (9, 25). Anejaculation following either surgery for testicular cancer or total meso-rectal excision can be prevented using monolateral lymphadenectomy or autosomic nerve preservation (25), respectively.

13.7 CONCLUSIONS
- Ejaculation disorders can be treated using a wide range of drugs and physical stimulation trials with a high level of efficacy.

13.8 RECOMMENDATIONS

Recommendations	GR
• Aetiological treatments for ejaculatory disorders should be offered before sperm collection and ART is performed.	
• Premature ejaculation can be treated successfully with either topical anaesthetic creams or SSRIs (23).	
• In men with spinal cord injury, vibro-stimulation and electro-ejaculation are effective methods of sperm retrieval.	

GR = grade of recommendation

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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 effectively 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 involved the use of cryopreservation techniques was in 1954 (1). In fertility practice, clinical indications for cyropreservation 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 disease (e.g. Behçet's disease)
- before surgery that might interfere with fertility (e.g. bladder neck surgery in a younger man or removal of the second testicle in a man with bilateral testicular malignancy)
- for men with progressive decrease in semen quality as a result of diseases carrying an associated risk of subsequent azoospermia (i.e. pituitary macro-adenomas, cranio-pharyngiomas, empty sella syndrome, chronic nephropathies, uncontrolled diabetes mellitus, multiple sclerosis).
- for men with paraplegia when sperm have been obtained by electro-ejaculation
- for men with psychogenic anejaculation, after sperm have been obtained either by electro-ejaculation or a sperm retrieving procedure
- after gonadotrophin treatment has induced spermatogenesis in men with hypogonadotropic 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 hyper-stimulation of the female partner. It may also be used to avoid repeated sperm retrieval procedures.
- in any situation where sperm have been obtained by a sperm retrieving procedure (e.g. after failed vasectomy reversal, or in some cases of epididymal obstruction not amenable to surgery)
- for storage of sperm before vasectomy; this service is offered by a few clinics as an insurance policy against change of mind or circumstances
- for storage of donor sperm; cryopreservation and a 3-6 months quarantine period reduce 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 in use are not yet optimal as damage occurs to cells during cyropreservation and during prolonged storage. Most damage occurs during freezing and thawing. Major causes of damage during freezing are ice crystal formation and cell dehydration causing disruption of the cell wall and intracellular organelle .Sperm morphology, motility and vitality decrease significantly after thawing, and cryopreservation increases the damage done to sperm DNA (3-5, 6). Further damage may 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.
- Rapid method (9, 10): sample is held in the vapour phase for 10 min before being plunged into liquid nitrogen.
- Slow method (11): sample is gradually cooled in the vapour phase for approximately 40 min.
- A programmable automatic freezing machine, which is pre-set to cool at a rate of 1-10°C/min, is used.

The method available depends on the laboratory's resources. Whichever freezing technique is employed, 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 male 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 the form of 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, and the straws are bathed in a pool of liquid nitrogen. Micro-organism 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, HIV) and sexually transmitted infections (*C. trachomatis*, gonorrhoea, syphilis).

Until the test results are known, samples must be stored in an individual quarantine vessel (15) (http://www.hfea.gov.uk/cps/rde/xchg/SID-3F57D79B-1F88B22E/hfea/hs.xsl/576.html). 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, 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- 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 undertaking 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 will depend 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 activated by a rising temperature or liquid nitrogen leakage
- The alarm system should alert a laboratory staff member, according to a 24-hour 365-day rota
- Ideally, there should be a spare storage container into which samples can be transferred following a vessel failure.

14.4.5   'Orphan' samples

In malignancy and some other situations, years may 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 or 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%, morphology by 37%, and mitochondrial activity by 36% (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
- The purpose of sperm cryopreservation is to secure future pregnancies using ART.
- Cryopreservation techniques are not optima, and future efforts are needed to improve the outcome of sperm banking.

14.7 RECOMMENDATIONS

Recommendations
• 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.
• 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.
• Precautions should be taken to prevent transmission of viral, sexually transmitted or any other infection by cryostored materials from donor to recipient and also to prevent contamination of stored samples.

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15. LEVELS OF EVIDENCE AND GRADES OF GUIDELINE RECOMMENDATIONS

Table 17: Levels of evidence.*

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 (e.g. comparative studies, correlation studies and case reports)
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

* Modified from Sacket et al. (1).

Table 18: Grades of guideline recommendations.*

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 Sacket et al. (1).

15.1 REFERENCES

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16. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

ABP	acute bacterial prostatitis
ART	assisted reproduction techniques
CBAVD	congenital bilateral absence of the vas deferens
CBP	chronic bacterial prostatitis
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator gene
CIS	carcinoma *in situ*
CMV	cytomegalovirus
CPPS	chronic pelvic pain syndrome
CFTR	cystic fibrosis transmembrane conductance regulator
EPS	espressed prostatic excretion
FISH	(multicolour) fluorescent in situ hybridisation
HIV	human immunodeficiency virus
FSH	follicle-stimulating hormone
GnRH	gonadotrophin-releasing hormone
hCG	human chorionic gonadotrophin
hMG	human menopausal gonadotrophin
IBT	immunobead test
ICSI	intracytoplasmic sperm injection
IL-6	interleukin-6
IVF	in vitro fertilisation
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 Institute of Health
NOA	non-obstructive azoospermia
OA	obstructive azoospermia
OAT	oligo-astheno-teratozoospermia [syndrome]
SHBG	sex hormone binding globulin
SSRIs	selective serotonin reuptake inhibitors
STS	sequence tagged sites
TESE	testicular sperm extraction
TEFNA	testicular fine-needle aspiration
TGCT	testicular germ cell tumour
TM	testicular microlithiasis
TRUS	transurethral ultrasound
TURED	transurethral resection of the ejaculatory ducts
WBC	white blood cells
VB1	first-voided urine

The male's fertility is directly linked to the quality and quantity of sperm count. If the sperm is of poor quality, then it causes infertility. Although reproduction is the most natural thing in this world, most couples are finding it difficult to conceive. Today, along with women men are also facing the issue of infertility. Infertility has become a widespread concern and almost 1 in every 5 couples have the problem of infertility. Not being able to conceive a baby can be frustrating and depressing. Male Infertility. A.Jungwirth (Chair), T. Diemer, G.R Dohle, A. Giwercman, Z. Kopa, C.Krausz, H. Tournaye. © European Association of Urology 2015. 3. THE GUIDELINE. 6. 3A MALE INFERTILITY. 6. 3A.1 Epidemiology and aetiology. Infertility — See also: Female infertility, Male infertility, and Sterility (physiology) Infertility Classification and external resources ICD 10 N46, N97.0 … Wikipedia. infertility — in·fer·til·i·ty (ĭn fər tĭlˈĭ tē) n. 1. Absent or diminished fertility. 2. The persistent inability to conceive a child. * * * Inability of a couple to conceive and reproduce. It is defined as failure to conceive after one year of regular… … Universalium. Infertility — The diminished ability or the inability to conceive and have offspring.