GUIDELINES ON INFERTILITY

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10. ABBREVIATIONS USED IN THE TEXT
INTRODUCTION

The following guidelines are aimed at providing a consensus view on special topics in urological andrology, which seem to the EAU Infertility Group to be key points in the daily work of urologists dealing with infertility. These topics reflect our literature review and rating, debates of the pros and cons, and final recommendations of our expert group, with special focus on the different national views and clinical practice in European countries.

The group is aware of the fact that infertility in particular has to be discussed as an original interdisciplinary subject, with paternity in a sterile partnership being the primary goal of all clinical work. This understanding implies the cooperation with non-urologists in all aspects of infertility in daily work, and knowledge of other pertinent guidelines, issued by well-accepted authorities such as WHO, the ESHRE Andrology Special Interest Group and the European Academy of Andrology. Accepting these recommendations, our group is convinced that the following guidelines will help European urologists in their interdisciplinary situation to focus on their special skills and knowledge and to understand better the outcome for the patient and the couple.

W. Weidner
(Chairman)

1. ANDROLOGICAL INVESTIGATIONS AND SPERMATOLOGY

1.1 Ejaculate analysis

Ejaculate analysis has been standardized by the World Health Organization (WHO) and propagated by continuing work and publications in the Laboratory Manual for Human Semen and Sperm-Cervical Mucus Interaction, which is in its fourth edition [1]. The consensus is that modern spermatology has to follow these guidelines without exclusions.

1.2 Advanced diagnostic spermatological tests

Computer-assisted sperm analysis (CASA), acrosome reaction tests, zona-free hamster egg penetration tests and sperm-zona pellucida bindings tests are not covered in toto by these guidelines, but are discussed with regard to relevance and clinical importance [2]. A critical assessment of these specialized tests using standardized laboratory techniques is absolutely necessary for given diagnostic situations.

1.3 Andrological status

Andrological status assessment has to consider the suggestions for the standardized investigation, diagnosis and management of the infertile man made by the WHO [3], so implementing evidence-based medicine in this interdisciplinary field of reproductive medicine.

1.4 References

1. World Health Organization. 

2. ESHRE Andrology Special Interest Group. 

3. World Health Organization. 
2. GENETIC DISORDERS IN INFERTILITY

A knowledge of genetic abnormalities in infertility is mandatory for every urologist working in andrology.

2.1 Chromosomal abnormalities

In a survey of pooled data from 11 publications, including a total of 9,766 infertile men, the incidence of chromosomal abnormalities was found to be 5.8% [1]. Of these, sex chromosome abnormalities accounted for 4.2% and autosomal abnormalities for 1.5%. In comparison, the incidence of abnormalities in pooled data from three series totalling 94,465 newborn male infants was 0.38%, of which 131 (0.14%) were sex chromosome abnormalities and 232 (0.25%) were autosomal abnormalities [2]. The possibility of abnormalities increases with increasing severity of impaired spermatogenesis [1,3]. By means of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) it is now possible for men with very low sperm counts to be given a reasonable chance of paternity (see below Idiopathic oligoasthenoteratozoospermia).

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

1 With support by Ch. Gosk, Dept of Urology, Western General Hospital Edinburgh, UK.

2.2 Sperm chromosomal abnormalities

Multicolour fluorescent In Situ hybridization (FISH) analysis makes it possible to examine sperm populations for chromosomal normality. A study using FISH revealed an increased frequency of aneuploidy, particularly of the sex chromosomes [4].

FISH analysis of spermatozoa remains a research investigation but should be encouraged, particularly to assess populations of spermatozoa from men with defined andrological conditions.

2.3 Sex chromosome abnormalities

Klinefelter’s syndrome and variants (46,XY; 47,XXY; 47,XXY mosaicism)

Klinefelter’s syndrome is the most frequent sex chromosome abnormality. Pooled data from cytogenetic analysis of 9,766 newborn infants found it was present in 66 (0.07%) of phenotypical males [2]. Adult men with Klinefelter’s syndrome have small firm testicles that are devoid of germ cells. The phenotype can vary from a normally virilized man to one with stigmata of androgen deficiency, including female hair distribution, scanty body hair and long arms and legs because of late epiphyseal closure. Leydig cell function is commonly impaired in men with Klinefelter’s syndrome [5]. Testosterone levels may be normal or low, oestradiol levels normal or elevated and follicle-stimulating hormone (FSH) levels are increased. Surprisingly, libido is often normal despite low testosterone levels, but androgen replacement may be needed with ageing. Germ cell presence and sperm production are variable in men with Klinefelter’s mosaicism 46,XY , 47,XXY. Pre-implantation FISH analysis of cells from embryos can be used to confirm normality [6]. The production of 24,XY sperm has been reported in 0.9% and 2.1% of men with Klinefelter’s mosaicism [7,8] and in 1.36–25% of men with somatic karyotype 47,XXY (9–13). This would indicate that some 47,XXY cells are able to achieve meiosis and produce mature spermatozoa. Conversely, it is not known whether haploid sperm in patients with Klinefelter’s syndrome are always the result of a clone of normal cells in a mosaic population or whether, in certain circumstances, some 47,XXY male germ cells are viable and capable of producing haploid sperm.

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

Men with Klinefelter’s syndrome are at risk for androgen deficiency as they get older and hormone replacement therapy may be needed.

Long-term follow-up from an endocrine point of view will be needed for all men with Klinefelter’s syndrome who have undergone testicular biopsy procedures for sperm retrieval.

2.4 Autosomal abnormalities

From time to time, men may ask for fertility treatments including IVF/ICSI when they are already known to have an autosomal defect. In these cases, genetic counselling is also required.
Genetic counselling should be offered to all couples where the male partner is known or found to have autosomal karyotype abnormality. When there is conflict between the wishes of the couple and the interests of the future child, it may be ethically correct to withhold therapy. In general best management is to agree treatment with the couple, providing them with full information about the genetic risk.

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

Kallmann's syndrome
The commonest X-linked disorder in infertility practice is Kallmann's syndrome and the predominant form is X-linked recessive caused by a mutation in the KALIG-1 gene on Xp 22.3 [14]. Rarer forms of Kallmann's syndrome include an autosomal-dominant form [15]. Patients with Kallmann's syndrome have hypogonadotrophic hypogonadism and may have other clinical features, including anosmia, facial asymmetry, cleft palate, colour blindness, deafness, maldescended testes and renal abnormalities. It is important to note that some men with Kallmann's syndrome have an isolated gonadotrophin deficiency without any other phenotypic abnormalities. These patients may present de novo with infertility, which can be treated successfully by hormone replacement therapy.

Androgen insensitivity: Reifenstein's syndrome
The rare disorder of androgen insensitivity may first present with infertility. The condition has X-linked recessive inheritance due to a defect in the androgen receptor gene located on Xq 11-12. The phenotype varies widely, from complete testicular feminization to an apparently normal man with infertility, although the latter is rare. A structured genetic search for androgen deficiency was conducted amongst men with high testosterone and low sperm counts, but no cases were found using base pair mismatch analysis technology [16]. Several de novo mutations of the androgen receptor were noted, but in all cases, these were associated with obvious genital abnormalities such as hypospadias. It was concluded that androgen insensitivity in the infertile male in the absence of any genital abnormality is rare.

Other X-disorders
A case report exists of an azoospermic man with biopsy-proven spermatogenetic arrest, who was found to have a submicroscopic interstitial deletion on the Xp pseudoautosomal region in peripheral blood and skin fibroblast samples. Other genetic and chromosome examinations were entirely normal, including probing of the Yq region [17]. There is also a report about two men with azoospermia and X pseudoautosomal deletions [18].

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

- retinitis pigmentosa, a condition that affects 1 in 3,000 people, may be recessive or dominant and causes visual impairment [19]
- chronic granulomatous disease (CGD), a condition that predisposes to severe bacterial and fungal infections [20]
- Menkes’ syndrome, an X-linked recessive disturbance of copper metabolism associated with progressive neurological symptoms [21]

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

Y-genes and male infertility
A large number of case series of Y microdeletions have been published (Table 1) and it is clear that while microdeletions may occur in the fertile population [22], they are more prevalent in the infertile population. Microdeletions have been found in three non-overlapping regions of the Y chromosome, AZF a-b-c [23]. Several genes have been described, including RBM, DAZ, DFFRY, DBY and XXX. The most commonly reported abnormality is a microdeletion in the AZFc region which encompasses the DAZ gene. However, there is no exact correlation between DAZ deletion and the presence or absence of spermatogenesis.
Table 1: Men with microdeletions (Adapted from published case series data)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Observation</th>
<th>Nr. of men</th>
<th>Nr. with deletion</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ma et al. [24]</td>
<td>Various all Yq</td>
<td>Various</td>
<td>3 azoo-oligo</td>
<td></td>
</tr>
<tr>
<td>Mallidis et al. [25]</td>
<td>1 AZFc</td>
<td>16</td>
<td>5</td>
<td>3%</td>
</tr>
<tr>
<td>Kent-First and Muallem [26]</td>
<td>Multiplex STS all Yq</td>
<td>239</td>
<td>24</td>
<td>(18–22%)</td>
</tr>
<tr>
<td>Kupker et al. [27]</td>
<td>6 all Yq</td>
<td>80 oligo</td>
<td>40 azoo</td>
<td>7.5% azoo</td>
</tr>
<tr>
<td>Kobayashi et al. [28]</td>
<td>53</td>
<td>10</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Najmabadi et al. [29]</td>
<td>26 interval 6</td>
<td>16 fertile men</td>
<td>7 fertile women</td>
<td>20% azoo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 azoo</td>
<td>10 oligo</td>
<td>10% oligo</td>
</tr>
<tr>
<td>Reijo et al. [30]</td>
<td>83 all Yq</td>
<td>89 azoo</td>
<td>12</td>
<td>13%</td>
</tr>
<tr>
<td>Reijo et al. [30]</td>
<td>118 probes all Yq</td>
<td>35 severe oligozoo</td>
<td>2</td>
<td>5.7%</td>
</tr>
<tr>
<td>Qureshi et al. [31]</td>
<td>23 all Yq</td>
<td>51 azoo</td>
<td>38&lt;5.0 oligo</td>
<td>8% azoo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11&gt;5.0 oligo</td>
<td>80 fertile</td>
<td>11%&lt;5.0 oligo</td>
</tr>
<tr>
<td>Foresta et al. [32]</td>
<td></td>
<td>16 azoo</td>
<td>23&lt;5.0 oligo</td>
<td>31%</td>
</tr>
<tr>
<td>Stuppia et al. [33]</td>
<td>13 probes interval 6</td>
<td>33 azoo-oligo</td>
<td>10 normal</td>
<td>26%</td>
</tr>
<tr>
<td>Vogt et al. [23]</td>
<td>76 probes all Yq</td>
<td>370 azoo-oligo</td>
<td>200</td>
<td>3.2%</td>
</tr>
<tr>
<td>Pryor et al. [22]</td>
<td>85 probes all Yq</td>
<td>200 infertile</td>
<td>200 normal</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Foresta et al. [34]</td>
<td>15 probes all Yq</td>
<td>38 azoo-oligo</td>
<td>10 normal</td>
<td>37.5% azoo</td>
</tr>
<tr>
<td>Simoni et al. [35]</td>
<td>4 probes AZF,a,b,c</td>
<td>168 azoo-oligo</td>
<td>86 normal</td>
<td>22.7% oligo</td>
</tr>
<tr>
<td>Girardi et al. [36]</td>
<td>36 all Yq</td>
<td>160 infertile</td>
<td>6 fertile</td>
<td>0% normal</td>
</tr>
<tr>
<td>Stuppia et al. [37]</td>
<td>27 interval 6</td>
<td>50 azoo-oligo</td>
<td>10 normal</td>
<td>14%</td>
</tr>
</tbody>
</table>

Clinical implications of Y microdeletions

There are no reports that men with microdeletions have any phenotypic abnormalities other than abnormal spermatogenesis [23,31,38]. As there is only one Y chromosome, it may be predicted that Y microdeletions will be transmitted to male offspring, although this is likely to be rare in the normal population because, without ICSI treatment, men with very low sperm counts are less likely to father children. Nevertheless, eight such cases have been reported (Table 2). More information is needed from father/son pairs where the son has a very low sperm count, and also about the outcome of ICSI attempts where spermatozoa have been used from men with microdeletions. Long-term follow-up of any male children is also required.
Table 2: Transmission of Y chromosome deletion from father to son

<table>
<thead>
<tr>
<th>Authors</th>
<th>Y deletion son</th>
<th>Y deletion father</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kobayashi et al. [28]</td>
<td>AZFc</td>
<td>AZFc</td>
<td>?</td>
</tr>
<tr>
<td>Vogt et al. [23]</td>
<td>AZFc</td>
<td>AZFc</td>
<td>&lt; 0.1x10^6</td>
</tr>
<tr>
<td>Kent-First et al. [39]</td>
<td>Small near AZFc</td>
<td>Small near AZFc</td>
<td>ICSI</td>
</tr>
<tr>
<td></td>
<td>Large AZFc -AZFb</td>
<td>Not detected</td>
<td>Normal</td>
</tr>
<tr>
<td>Pryor et al. [22]</td>
<td>sY153-sY267</td>
<td>sY153-sY267</td>
<td>0.3 x 10^6</td>
</tr>
<tr>
<td>Stuppia et al. [40]</td>
<td>AZFc</td>
<td>AZFc (smaller)</td>
<td>&lt; 2 x 10^6</td>
</tr>
<tr>
<td>Mulhall et al. [41]</td>
<td>Ongoing twin pregnancy</td>
<td>AZFc</td>
<td>ICSI</td>
</tr>
<tr>
<td>Silber et al. [42]</td>
<td>Two ongoing pregnancies</td>
<td>AZFc Azoospermic</td>
<td>TESE-ICSI</td>
</tr>
<tr>
<td>Kamischke et al. [43]</td>
<td>AZFc</td>
<td>AZFc</td>
<td>ICSI Normal</td>
</tr>
</tbody>
</table>

Testing for Y microdeletions
Testing for microdeletions is now widespread, but the lack of a standardized methodology makes it difficult to directly compare the reported results (Table 1). Several centres have developed screening methodologies [23,26,31,44].
As there is no correlation between the histopathology and deletion of DAZ, it is premature to rely on detection using specific gene probes, as this will fail to find a significant proportion of men with microdeletions.
Comparing results from 28 different European laboratories, it was concluded that use of a high number of primers did not improve the accuracy of results. Recommendations are being produced for standardization [45].

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

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

Autosomal defects with severe phenotypic abnormalities as well as infertility
There are a number of inherited disorders with severe or considerable generalized abnormalities as well as infertility (Table 3). Such patients will be well known to doctors often from childhood and any fertility problem has to be managed in the context of the care of the man as a whole and with consideration of his and his partner's ability to care for a child, should infertility treatment be successful.
Table 3. Less common inherited disorders associated with infertility and other alterations to phenotype

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

2.6 Cystic fibrosis mutations and male infertility

Cystic fibrosis, a fatal autosomal-recessive disorder, is the most common genetic disease of Caucasians; 4% are carriers of gene mutations involving the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This gene is located on the short arm of chromosome 7 and encodes a membrane protein that functions as an ion channel and also influences the formation of the ejaculatory duct, seminal vesicle, vas deferens and distal two thirds of the epididymis. Congenital bilateral absence of the vas deferens (CBAVD) is associated with CFTR mutations and was found in approximately 2% of men with obstructive azoospermia attending a clinic in Edinburgh [46]. However, the incidence in men with obstructive azoospermia varies in different countries.

The clinical diagnosis of absent vasa is easy to miss and all azoospermic men should be carefully examined to exclude CBAVD, particularly those with a semen volume of ≤ 1.5 mL and pH less than 7.0.

In recent years, more than 400 mutations of the CFTR gene have been characterized [47]. There are at least 17 published series of men with CBAVD who were tested for varying numbers of mutations. In general, the more mutations tested for, the higher the percentage of men found to have them. Consequently, detection rates are higher (70–81%) in more recent publications [46,48–50] than in earlier reports (around 40%). In a review of published series of 449 men with CBAVD, the Delta F508 mutation was detected in 244 men, the R117H mutation in 54 men and the W1282X mutation in 37 men; 63 other mutations were found in between one and nine men, but not all mutations were tested for in all case series [51]. It seems likely that as more mutations are defined and tested for, almost 100% of men with CBAVD will be found to have mutations. At present, it is not practical to test for all known mutations as many have a very low prevalence in a particular population. Testing is usually restricted to the 20–30 mutations that occur most commonly in a particular community.

Mutations may be found in both copies of the CFTR gene, but in most men with CBAVD, they are found in only one copy. In some of these supposedly heterozygous cases, there may be an unknown second mutation, but there is also another interesting mechanism. In up to 63% of these, a DNA variant - the 5t allele - can be detected in a non-coding region of CFTR [52]. Further work is needed to understand fully the genetics of CBAVD. It is noteworthy that heterozygous men with CBAVD often have mild clinical stigmata of cystic fibrosis, e.g. history of chest infections. It is therefore important to follow-up children born after ICSI where the father has CBAVD and is either heterozygous or homozygous.

When a man has CBAVD, it is important to test him and his partner for cystic fibrosis mutations. If she is also found to be a carrier, the couple must very carefully consider whether to proceed with ICSI using the husband’s sperm, as the chance of a baby with cystic fibrosis will be 25% if he is heterozygous or 50% if he is homozygous. If the female partner is negative for known mutations, her chance of being a carrier of unknown mutations is about 0.4%. In these circumstances, the possibility of her heterozygous partner fathering a child with cystic fibrosis is approximately 1:410.
2.7 Unilateral or bilateral absence or abnormality of the vas and renal anomalies
Unilateral absence of the vas deferens is usually associated with ipsilateral absence of the kidney [53] and probably has a different genetic causation. Men with unilateral absence of the vas deferens are usually fertile, and the condition is most commonly encountered as an incidental finding in the vasectomy clinic. Nevertheless, in men with unilateral absence of the vas deferens, cystic fibrosis mutations may underlie the same genetic diseases as those with true CBAVD. In addition, it was found that men with bilateral absence of vas deferens and renal abnormalities have no CFTR abnormalities [54].

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

2.8 Unknown genetic disorders
ICSI is now 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 foetal abnormality, because by bypassing the selective processes of female genital tract and egg coverings, defective sperm, that would not otherwise do so, might be enabled to fertilize eggs. It is therefore very reassuring that the collected foetal abnormality statistics from ICSI centres do not indicate any increase in congenital malformations compared with the general population. However, the indications for ICSI are constantly being extended to include fertilization with immature sperm forms and it will be particularly important to continue to monitor foetal abnormality rates with detailed subgroup analysis according to the clinical and molecular diagnosis of the father.

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

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

2.10 Conclusions
New insights into the genetic basis of infertility and the advent of ICSI necessitate a good understanding of genetics by clinicians and the public at large. Advances in diagnosis will allow identify the genetic basis of more disorders and easier and cheaper diagnosis of known disorders, for some of which gene therapy may become practicable.

2.11 References


Increased incidence of hyperhaploid 24 XY spermatozoa detected by three-colour FISH in a

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3. PRIMARY SPERMATOCYTIC FAILURE

3.1 Definition
Primary spermatogenic failure is defined as any spermatogenic alteration originated by causes different from hypothalamic-pituitary diseases.

The severe forms of primary spermatogenic failure, caused by different aetiologies, have a clinical presentation as non-obstructive azoospermia.

The prevalence of azoospermia in the general population has been estimated at 2% [1]. The incidence at a male infertility clinic was found to be as high as 10-20% [2,3]. Testicular histology shows different degrees of spermatogenic alterations, ranging from tubular damage to hypospermatogenesis. Even in cases of Sertoli cell-only Syndrome (SCOS), it is possible to find seminiferous tubules with some degree of spermatogenesis. Depending on the severity of the process, FSH levels can be elevated and the testes can be reduced in size and/or consistency. Before the ICSI era, increased serum FSH was considered a sign of severe spermatogenic failure, and no other diagnostic procedures were indicated. It was demonstrated that ICSI [4] could also be used to treat some cases of non-obstructive (testicular) azoospermia. However, about 20% of these cases are associated with chromosomal abnormalities or genetic translations of the Yq chromosome (see above Genetic...
disorders in infertility).

### 3.2 Aetiology

**Table 4. Causes of non-obstructive azoospermia.**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anorchia</td>
</tr>
<tr>
<td>2</td>
<td>Congenital</td>
</tr>
<tr>
<td>3</td>
<td>Acquired (trauma, testicular torsion, tumour, surgery)</td>
</tr>
<tr>
<td>4</td>
<td>Maldescended testes</td>
</tr>
<tr>
<td>5</td>
<td>Klinefelter's syndrome (see above Genetic disorders in infertility)</td>
</tr>
<tr>
<td>6</td>
<td>Other chromosomic alterations (see above Genetic disorders in infertility)</td>
</tr>
<tr>
<td>7</td>
<td>Germ cell aplasia</td>
</tr>
<tr>
<td>8</td>
<td>Complete and focal germ cell aplasia (SCOS) (either congenital or acquired: maldescended testes, irradiation, cytostatic drugs, etc.)</td>
</tr>
<tr>
<td>9</td>
<td>Spermatogenic arrest</td>
</tr>
<tr>
<td>10</td>
<td>Post-inflammatory (orchitis)</td>
</tr>
<tr>
<td>11</td>
<td>Exogenous factors (medications, toxics, irradiation, heat, etc.)</td>
</tr>
<tr>
<td>12</td>
<td>Systemic diseases (liver cirrhosis, renal failure)</td>
</tr>
<tr>
<td>13</td>
<td>Testicular tumour</td>
</tr>
<tr>
<td>14</td>
<td>Varicocele</td>
</tr>
<tr>
<td>15</td>
<td>Surgeries that can damage vascularization of the testes</td>
</tr>
<tr>
<td>16</td>
<td>Idiopathic</td>
</tr>
</tbody>
</table>

### 3.3 Testicular morphology

The most severe alteration of spermatogenesis is characterized by complete sclerotization, where no cells are present in the seminiferous tubules. In terms of severity, this alteration is followed by complete aplasia of germ cells, SCOS or del Castillo’s syndrome, where the seminiferous tubules are usually reduced in diameter. Another severe alteration is complete spermatogenic maturation arrest at the spermatocyte level, characterized by a normal population of Leydig’s and Sertoli’s cells, spermatagonia and spermatocytes, but an absence of spermatids and spermatozoa. Infrequently, maturation arrest can be observed at the spermatogonia or round spermatid level. In the latter cases, mature or elongated spermatids are absent. Less severe forms of spermatogenic alteration include hypospermatogenesis (proportional decrease in all spermatogenic cells), partial maturation arrest, focal SCOS and mixed patterns.

The estimated prevalence of non-obstructive azoospermia, determined by testicular biopsy, ranges between 40% and 60% [5]. For standardization, the use of scoring systems [6,7] is strongly suggested (Tables 5, 6).

**Table 5. Scoring system for testicular biopsies - Johnsen score [6]**

<table>
<thead>
<tr>
<th>Score</th>
<th>Histological criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Full spermatogenesis</td>
</tr>
<tr>
<td>9</td>
<td>Many late spermatids, disorganized epithelium</td>
</tr>
<tr>
<td>8</td>
<td>Few late spermatids</td>
</tr>
<tr>
<td>7</td>
<td>No late spermatids, many early spermatids</td>
</tr>
<tr>
<td>6</td>
<td>No late spermatids, few early spermatids</td>
</tr>
<tr>
<td>5</td>
<td>No spermatids, many spermatocytes</td>
</tr>
<tr>
<td>4</td>
<td>No spermatids, few spermatocytes</td>
</tr>
<tr>
<td>3</td>
<td>Spermatogonia only</td>
</tr>
<tr>
<td>2</td>
<td>No germinal cells, Sertoli cells only</td>
</tr>
<tr>
<td>1</td>
<td>No seminiferous epithelium</td>
</tr>
</tbody>
</table>
Table 6. Scoring system for testicular biopsies (Holstein score [7])

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>No seminiferous epithelial cells, tubular sclerosis</td>
</tr>
<tr>
<td>2.</td>
<td>No germ cells, Sertoli cells only</td>
</tr>
<tr>
<td>3.</td>
<td>Spermatogonia only</td>
</tr>
<tr>
<td>4.</td>
<td>No spermatids, few spermatocytes, arrest at primary spermatocyte stage</td>
</tr>
<tr>
<td>5.</td>
<td>No spermatids, many spermatocytes</td>
</tr>
<tr>
<td>6.</td>
<td>Few early spermatids, disturbance of spermatid differentiation</td>
</tr>
<tr>
<td>7.</td>
<td>No late spermatids, many early spermatids</td>
</tr>
<tr>
<td>8.</td>
<td>Few late spermatids</td>
</tr>
<tr>
<td>9.</td>
<td>Many late spermatids, disorganized tubular epithelium</td>
</tr>
<tr>
<td>10.</td>
<td>Full spermatogenesis</td>
</tr>
</tbody>
</table>

Typical findings for the history and physical examination of a patient with non-obstructive azoospermia are listed in Tables A and B.

Table 7a. Typical findings for the history of a patient with non-obstructive azoospermia

- Cryptorchidism
- Testicular torsion
- Genitourinary infection
- Testicular trauma
- Environmental toxin exposure
- Gnadalotoxic medication
- Radiation or chemical exposure
- Groin surgeries
- Testicular cancer

Table 7b. Typical findings for the physical examination of a patient with non-obstructive azoospermia

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

Semen analysis

In non-obstructive azoospermia, semen analysis shows normal ejaculate volume and azoospermia after several centrifugations have been performed.

A recommended method is semen centrifugation at 600 g for 10 minutes and thorough microscopical examination of the pellet (X 600). The upper fluid is then recentrifuged (8,000 g) for an additional 10 minutes and examined. All samples can be stained and reexamined under the microscope [8,9].

Hormonal determinations

FSH values are mainly correlated with the number of spermatogonia. When these cells are absent or markedly diminished, FSH values are usually elevated. When the number of spermatogonia is normal and there is complete spermatocyte or spermatid blockage, FSH values are within normal range.

Individuality, however, the role of FSH as a predictor of the status of spermatogenesis is uncertain [10-12]. Preliminary data indicate a stronger correlation between low inhibin-B level and spermatogenic damage [13]. At present, routine determination of inhibin-B is not suggested.
Special situations

Combination obstructive/non-obstructive azoospermia:
Some azoospermic patients may present with a combination of obstructive and spermatogenic pathologies and increased serum FSH levels [10]. It is therefore advisable to perform testicular biopsy in azoospermic patients with elevated FSH levels, who are known or suspected of having seminal duct obstruction, or when the size and/or consistency of one testis has decreased.

FSH levels and results of testicular sperm extraction (TESE):

Several different studies do not provide any correlation between FSH concentrations and the possibility of finding sperm in testicles with non-obstructive azoospermia [14-17].

Sertoli Cell-Only Syndrome (SCOS):

SCOS can be found in patients with normal and elevated FSH [18,19].

Patients usually present with azoospermia and normal ejaculate volume, elevated FSH, normal testosterone, LH and prolactin, normal secondary sexual characteristics and bilaterally small testes. It is suggested that the levels of LH and testosterone should be investigated only in cases with clinical signs of hypogonadism.

Genetic studies (see above Genetic disorders in infertility)

Testicular biopsy

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

Testicular biopsy can also be indicated in patients with clinical evidence of non-obstructive azoospermia who decide to undergo ICSI. Spermatogenesis may be focal. In these cases, one or more seminiferous tubules are involved in spermatogenesis while others are not [20-22]. About 50-60% of men with non-obstructive azoospermia have some seminiferous tubules with spermatozoa that can be used for ICSI (Table 6).

Table 8. Presence of mature sperm in testicular biopsies of men with non-obstructive azoospermia

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. Patients</th>
<th>Presence of sperm in testicular biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tournaye et al. [23]</td>
<td>1995</td>
<td>38</td>
<td>36 (94%)</td>
</tr>
<tr>
<td>Devroey et al. [24]</td>
<td>1995</td>
<td>15</td>
<td>13 (86%)</td>
</tr>
<tr>
<td>Kahraman et al. [25]</td>
<td>1996</td>
<td>29</td>
<td>14 (48%)</td>
</tr>
<tr>
<td>Chen &amp; Chen [26]</td>
<td>1996</td>
<td>41</td>
<td>21 (51.2%)</td>
</tr>
<tr>
<td>Tournaye et al. [27]</td>
<td>1996</td>
<td>54</td>
<td>44 (81%)</td>
</tr>
<tr>
<td>Fahmy et al. [28]</td>
<td>1997</td>
<td>30</td>
<td>23 (77%)</td>
</tr>
<tr>
<td>Mansour et al. [29]</td>
<td>1997</td>
<td>103</td>
<td>60 (56.6%)</td>
</tr>
<tr>
<td>Friedler et al. [30]</td>
<td>1997</td>
<td>37</td>
<td>16 (43%)</td>
</tr>
<tr>
<td>Mulhall et al. [15]</td>
<td>1997</td>
<td>30</td>
<td>21 (70%)</td>
</tr>
<tr>
<td>Kim et al. [31]</td>
<td>1997</td>
<td>57</td>
<td>17 (30%)</td>
</tr>
<tr>
<td>Silber et al. [21]</td>
<td>1997</td>
<td>45</td>
<td>26 (58%)</td>
</tr>
<tr>
<td>Schlegel [32]</td>
<td>1997</td>
<td>16</td>
<td>10 (62%)</td>
</tr>
<tr>
<td>Ezeh et al. [16]</td>
<td>1998</td>
<td>35</td>
<td>22 (63%)</td>
</tr>
<tr>
<td>Ghazzawi et al. [33]</td>
<td>1998</td>
<td>41</td>
<td>30 (73%)</td>
</tr>
<tr>
<td>Hauser et al. [34]</td>
<td>1998</td>
<td>29</td>
<td>18 (62%)</td>
</tr>
<tr>
<td>J ezek [17]</td>
<td>1998</td>
<td>64</td>
<td>49 (77%)</td>
</tr>
<tr>
<td>Gil-Salom [35]</td>
<td>1998</td>
<td>154</td>
<td>63 (41%)</td>
</tr>
<tr>
<td>Palermo et al. [36]</td>
<td>1999</td>
<td>83</td>
<td>53 (63.9%)</td>
</tr>
<tr>
<td>Schlegel [37]</td>
<td>1999</td>
<td>27</td>
<td>17 (63%)</td>
</tr>
</tbody>
</table>
Most authors recommend taking several testicular samples given the possible regional differences [38,39]. Other authors support the hypothesis that a single sample is demonstrative of the total histological pattern [20,40]. Many authors find a good correlation between diagnostic biopsy histology and the likelihood of finding mature sperm cells during testicular sperm retrieval and ICSI [14,31,41].

### 3.4 Biopsy techniques

Testicular biopsy is a simple outpatient procedure under local anaesthesia.

There are different techniques for performing a testicular biopsy:

1) **Open biopsy.** An incision is made on either side of the midline raphe. The tunica albuginea is visualized. With a scalpel blade, an incision is made into the tunica albuginea. Gentle pressure on the testis will facilitate tissue removal by using a pair of small straight blade scissors. The specimen is transferred into Bouin's solution. Formaldehyde solution should never be used. At this stage of surgery, the epididymis is mobilized to assess its morphological characteristics and to exclude mechanical causes of azoospermia. To date it is unclear whether a microsurgical approach [37] leads to better results. The standard testicular biopsy can also be combined with testicular touch preparation cytology [42].

2) **Percutaneous testicular biopsy.** Some authors prefer percutaneous biopsies for diagnostic purposes arguing that this procedure is simpler than open testicular biopsy [43-46]. Apart from being associated with insufficient tissue collection for histological examination [47], this technique may result in specimen artefacting, refractory haematomas and unintentional damage to the epididymis.

3) **Testicular fine needle aspiration.** Some authors advocate testicular spermatozoa fine needle aspiration as a diagnostic method [48-50], while others [51] do not find this technique as effective as open testicular biopsy for histopathological diagnosis.

Any type of testicular biopsy should provide sufficient material to cryopreserve sperm for future ICSI cycles [52]. If these spermatozoa have some degree of motility, they have a good potency for fertilization and successful implantation.

### 3.5 Treatment

TESE and ICSI were introduced in 1993 for treatment of obstructive azoospermia [53-55]. It was soon discovered that this technique could also be used for azoospermic men who appeared to have absent spermatogenesis [56]. If spermatozoa are detected in the testicular biopsy, ICSI with either cryopreserved or fresh spermatozoa can be proposed to the couple. A karyotype (if not performed previously) and Yq deletions screening are indicated to analyse any therapeutic consequences for the newborn child. If genetic anomalies are detected, the couple has to be properly informed and counselled (see above Genetic disorders in infertility). Table 9 shows the sperm retrieval/ICSI results of the most important series conducted to date. Of 616 TESE procedures, 373 (60.5%) yielded sperm for ICSI. The mean fertilization rate was 52.5% (38.6-69%) and the mean pregnancy rate was 29.2% (11.3-31%).

---

18
Table 9. Non-obstructive azoospermia: results obtained using TESE and ICSI. (Adapted from review of published series)

<table>
<thead>
<tr>
<th>Author</th>
<th>No. TESE</th>
<th>No. ICSI (%)</th>
<th>Fertilization (%)</th>
<th>Pregnancy (%)</th>
<th>Ongoing pregnancies and deliveries (%) (x 10^6)</th>
<th>Mean (± SD) sperm concentration/ml</th>
<th>Mean sperm motility (%) ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tournaye et al. [23]</td>
<td>38</td>
<td>36 (94%)</td>
<td>56.8%</td>
<td>28.9%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Devroey et al. [24]</td>
<td>15</td>
<td>13 (86%)</td>
<td>47.8%</td>
<td>25%</td>
<td>18%</td>
<td>2.5 ± 1</td>
<td>4.1%</td>
</tr>
<tr>
<td>Kahraman et al. [25]</td>
<td>29</td>
<td>14 (48%)</td>
<td>38.6%</td>
<td>42.9%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Devroey et al. [56]</td>
<td>19</td>
<td>17 (89%)</td>
<td>58%</td>
<td>26%</td>
<td>26%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tournaye et al. [27]</td>
<td>54</td>
<td>44 (81%)</td>
<td>45%</td>
<td>45%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mansour et al. [29]</td>
<td>103</td>
<td>60 (56.6%)</td>
<td>39%</td>
<td>11.3%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Friedler et al. [30]</td>
<td>37</td>
<td>16 (43%)</td>
<td>49%</td>
<td>13%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Schlegel et al. [32]</td>
<td>16</td>
<td>10 (62%)</td>
<td>52%</td>
<td>31%</td>
<td>25%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gil-Salom et al. [35]</td>
<td>154</td>
<td>63 (41%)</td>
<td>55%</td>
<td>28%</td>
<td>22%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ghazzawi et al. [33]</td>
<td>41</td>
<td>30 (73%)</td>
<td>69%</td>
<td>21%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Palermo et al. [36]</td>
<td>83</td>
<td>53 (64%)</td>
<td>57%</td>
<td>49.1%</td>
<td>39.6%</td>
<td>0.4 ± 1</td>
<td>6.7 ± 13</td>
</tr>
<tr>
<td>Schlegel [37]</td>
<td>27</td>
<td>17 (63%)</td>
<td>63%</td>
<td>-</td>
<td>1.6 ± 2.7</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Predictive parameters for successful TESE:

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

3.6 TESE techniques

Open biopsy and fine needle aspiration are the two main techniques to retrieve sperm from the testis.

Although fine needle aspiration enables more areas of the testis to be reached, open testicular biopsy allows more tissue and sperm to be recovered [57]. TESE is performed as described in the diagnostic section. TESE is always performed in both testes. Two or three small incisions are made through the tunica albuginea in different regions at the base of each testis and small pieces of extruding testicular tissue are removed. The fragments of testicular tissue are immediately placed in a Petri dish containing 2 mL of culture medium and transferred to the IVF laboratory.

For needle aspiration, a 21-gauge butterfly needle attached to a 20 mL plastic syringe serves as an aspiration device. The butterfly needle is passed directly into the testicular tissue. While holding the testicle between the index finger and the thumb, different entries are made in each testicle, sampling various locations. Before retrieving the needle from the testis, small artery forceps are used to clamp the butterfly needle's microtubing. Following aspiration, the needle is flushed with culture medium into one well of a four-well plate. For each puncture, a new butterfly needle is used [58].

Physiological consequences of testicular sperm retrieval:

In cases of non-obstructive azoospermia, multiple TESE or testicular punctures have been associated with focal inflammation and haematoma, as well as impaired testicular blood flow [59]. In small testes, an intermittent decrease of serum testosterone levels is under debate. The long-term consequences of these findings are unclear.

3.7 ICSI with cryopreserved testicular spermatozoa

ICSI performed with cryopreserved testicular spermatozoa has been successful [8,30,33,52,60-64].

In the majority of series, results obtained with fresh and cryopreserved sperm were not significantly different. It also appears that sperm survival after cryopreservation is not influenced by infertility aetiology, serum FSH concentration, or patient's age.
3.8 TESE and ICSI in Klinefelter's syndrome

Palermo [36] obtained spermatozoa in four out of seven TESE procedures in six men with non-mosaic Klinefelter's syndrome. Fertilization was achieved in 68% of oocytes. Five healthy newborns, all karyotypically normal, were delivered. Other pregnancies have been reported [65-68].

3.9 Testicular spermatid injection in combination with ICSI

Previous studies have shown that fertilization and delivery of healthy offspring can occur after transferring round spermatid nuclei into rabbit or mouse oocytes via microsurgical methods [69-71]. Edwards [72] first suggested that ooplasmic injections of spermatids might serve as a novel mode of therapy for non-obstructive azoospermia. Acceptable fertilization rates and pregnancies after ooplasmic injection of round spermatid nuclei have been reported [73-77]. Complete absence of spermatozoa from the ejaculate or testicular biopsy has an adverse effect on the clinical outcome [77,78].

In cases with very severe spermatogenetic defect, pregnancies can be achieved with elongated spermatid cells. However, the efficacy of round spermatids in achieving fertilization and pregnancy is disappointing.

3.10 Conclusions

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

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4. OBSTRUCTIVE AZOOSPERMIA

4.1 Definition
Obstructive azoospermia means the absence of both spermatozoa and spermatogenerative cells in semen and post-ejaculate urine (see above Andrological investigations and spermatology) because of a complete obstruction of seminal ducts. Total obstruction of the seminal ducts is often accompanied by secretory dysfunction of the gonads. Permanent absence of spermatozoa in the semen causes male infertility.

4.2 Classification

Proximal obstruction

Intratesticular obstruction occurs in 15% of obstructive azoospermia [1].

Congenital forms (disjunction between rete testis and efferent ductules) are less frequent than those acquired (post-inflammatory or post traumatic obstructions). The latter are often associated with an obstruction of epididymis and vas deferens.

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

Congenital epididymal obstruction usually manifests as bilateral corpus and/or congenital bilateral agenesis of the vas deferens (CBAVD), which is associated with at least one mutation of the cystic fibrosis gene in 82% of cases [5]. This form is often accompanied by seminal vesicle agenesis (see above Genetic disorders in infertility). Other congenital forms of obstruction (dysjunction between efferent ductules and corpus epididymidis, agenesis/atrophy of a short part of the epididymis) are very rare. Inborn forms also include chronic sinopulmonary infections (Young’s syndrome) [6], where obstruction results from a mechanical blockage due to debris within the proximal epididymal lumen. Among the acquired forms, those secondary to acute (gonococcal) and subclinical (e.g. chlamydial) epididymitis are considered to be most frequent [7,8] (see below Urogenital infections and disturbed male fertility). Acute or chronic traumas may result in epididymal damage [9].

Azoospermia caused by surgery is rare (e.g. after epididymal cyst removal in monorchid subjects). Epididymal obstruction secondary to long-lasting distal obstruction must be taken into account when repairing seminal ducts.

Proximal vas deferens obstruction is the most frequent cause of acquired obstruction following vasectomy for sterilization. About 1% of these men ask for vasectomy reversal. Of those undergoing vasovasostomy, 5-10% develop epididymal blockage due to tubule rupture, making epididymovasostomy mandatory (see below Vasectomy and vasovasostomy).

Vasal obstruction may occur after herniotomy and, more rarely, may result from long-lasting compression onto
the vas caused by an inguinal hernia. A previously performed vasography, if made with accurate cannulation of the vas deferens, should not cause any local obstruction [10].

The most common congenital vasal obstruction is CBAVD, often accompanied by cystic fibrosis. Unilateral agenesis or partial defect is associated with contralateral seminal duct anomalies or renal agenesis in 80% and 26% of cases, respectively [11] (see above Genetic disorders in infertility).

Distal obstruction
Distal vas deferens obstruction includes CBAVD and involuntary vas excision during hernia surgery in early childhood [12].

Ejaculatory duct obstruction is found in about 1-3% of obstructive azoospermia [1].

These obstructions can be classified as cystic or post-inflammatory. Cystic obstructions are usually congenital (Müllerian duct cyst or urogenital sinus/ejaculatory duct cysts) and are medially located in the prostate between the ejaculatory ducts. In urogenital sinus anomalies, one or both ejaculatory ducts empty into the cyst [13], while in Müllerian duct anomalies, ejaculatory ducts are laterally displaced and compressed by the cyst [14]. Paramedian or lateral intraprostatic cysts are Wolffian in origin and rarely found in clinical practice [15]. Post-inflammatory obstructions of the ejaculatory duct are usually secondary to acute, non-acute or chronic urethroprostatis [16].

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

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

4.3 Diagnostic management

Semen analysis

Semen analysis: At least two examinations must be performed with an interval between their of 2-3 months, according to WHO (see above Andrological investigations and spermatology). Azoospermia means absence of spermatozoa after centrifugation at X 400.

Careful repeat observation of several smears after semen liquefaction is necessary. Finding no spermatozoa in wet preparation involves the centrifugation of aliquots or of the whole semen sample (600 rpm for 15 minutes). The pellet must be examined for spermatozoa.

A semen volume of less than 1.5 mL, acid pH and low fructose suggest ejaculatory duct obstruction or CBAVD. When semen volume is low, spermatozoa in urine after ejaculation must always be searched for, as their presence confirms an ejaculation disorder.

Absence of spermatozoa and immature germ cells in semen smears suggest complete proximal or distal seminal duct obstruction.

Clinical history

Clinical history taking should follow the suggestions for investigation of infertile men (see above Andrological investigations and spermatology), including questions about the presence of haematospermia, post-ejaculatory pain, previous or present urethritis, prostatitis, obstructive or irritative urinary symptoms, previous scrotal enlargement or pain or surgery, previous inguinal hemiorrhaphy or traumas, and chronic sinopulmonary infections.

Clinical examination

This follows the suggestions for investigation of infertile men. The following are particularly important:

• at least one testis > 15 ml volume (although a smaller testicular volume may be found in some patients
with obstructive azoospermia and concomitant partial testicular failure)

- enlarged and hardened cauda or caput epididymidis
- nodules
- absence or partial atresia of the vas
- present urethritis
- prostatic deformations

Hormone levels
Serum FSH levels may be normal but do not exclude a testicular cause of azoospermia (e.g. spermatogenic arrest). On the contrary, a serum FSH of less than twice the upper limit of normal may be present in patients with one normal testis, associated with contralateral seminal tract obstruction [4].

Transrectal ultrasonography
TRUS has to be performed on all patients in whom proximal or distal obstruction is suspected, if possible with high resolution and high frequency (7 MHz) bidual transducers and in standard sexual abstinence conditions (e.g. immediately after ejaculation, for better definition of the ejaculatory ducts). Seminal vesicle enlargement (anterior-posterior diameter ≥ 15 mm) [17] and seminal vesicle roundish anechoic areas [20] 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 [16] and ejaculatory duct calcifications [21]. TRUS may also be applied to aspirate seminal vesicle fluid [22].

Invasive diagnosis, including testicular biopsy, scrotal exploration and distal seminal duct evaluation, should be mandatory in all patients with azoospermia in whom a mechanical obstruction of the seminal ducts cannot be excluded. It is advisable to perform explorative and recanalization surgery at the same time.

Tissue biopsy
This is necessary when a concomitant secretory pathology is suspected. The same surgical procedure may also be used to extract testicular spermatozoa (TESE) for cryopreservation and subsequent ICSI, when surgical recanalization cannot be performed or has failed (for details see above Primary spermatogenetic failure).

Distal seminal tract evaluation
Distal seminal tract has to consider the anatomical perviousness of the seminal ducts downstream to the proximal vas deferens.

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

In an alternative method, the proximal vas deferens is microsurgically hemitransected (X 15 power magnification) and any fluid from the lumen is placed on a slide and mixed with a drop of saline solution. Absence of spermatozoa on microscopic examination indicates epididymal obstruction (if testicular biopsy is normal or only slightly altered). However if spermatozoa are found inside the proximal vas deferens of an azoospermic patient this suggests a distal seminal duct obstruction. In this case, antegrade cannulation of the vas deferens and injection of saline solution plus methylene blue are performed. If the solution passes easily, vasography is not necessary [24]. If injection is difficult or impossible, an anatomical ejaculatory duct obstruction or vas deferens obstruction, respectively, are suspected. In both cases, vasography is indicated to identify the nature and site of obstruction. At the end of the procedure a microsurgical suture of the vas deferens is required [24].

4.4 Treatment

Intratesticular obstruction:
Since seminal duct recanalization at this level is impossible, TESE or fine needle aspiration are recommended (see above Primary spermatogenetic failure). The spermatozoa retrieved may be immediately used for ICSI or may be cryopreserved.

Both TESE and fine needle aspiration allow sperm retrieval in nearly all obstructive azoospermic patients.

Epididymal obstruction:
Microsurgical Epididymal Sperm Aspiration (MESA) [25] is mandatory in CBAVD. Retrieved spermatozoa are
usually used for ICSI. In general, one MESA procedure provides sufficient material for several ICSI cycles [26].

In patients with azoospermia due to acquired epididymal obstruction, end-to-end or end-to-side microsurgical epididymovasostomy must be performed.

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

Patency rates range between 60% and 87% [27-29] and cumulative pregnancy rates between 10% and 43%. Recanalization failures occur in 10% [30] to 21% [27]. Recanalization success rates may be adversely affected by pre-operative and operative findings such as concomitant abnormal testicular histology, absence of sperm in the spermatic fluid on sectioning the epididymis, small epididymal tubules and wide fibrosis of the epididymis.

The finding of motile or immotile spermatozoa at the level of the anastomosis does not appear to be related to the patency rate. Conversely, moving from the corpus to the caput epididymidis involves a significant adverse effect upon patency and pregnancy outcome. The same adverse effect occurs with the concomitant presence of ultrasonographic abnormalities in the prostate and seminal vesicles [31]. In terms of delivery rate, vasoepididymostomy in patients with epididymal obstruction secondary to vasectomy has proved more successful and more cost-effective than MESE and ICSI [32] (see also below Vasectomy and vasectomy reversal).

Proximal vas obstruction
Proximal vas obstruction after vasectomy requires microsurgical vasectomy reversal (see below Vasectomy and vasectomy reversal). Vasovasostomy must also be performed in the rare cases of proximal vasal obstructions (iatrogenic, post-traumatic, post-inflammatory). When spermatozoa are absent in the intraoperative vas fluid bilaterally, a concomitant secondary epididymal obstruction is usually present, and microsurgical vasoepididymostomy is mandatory.

Distal vas deferens obstruction:
Large bilateral vas defects resulting from involuntary vas excision during hernia surgery in early childhood or previous orchidopexy are usually untreatable [12]. In these cases, one can resort to proximal vas deferens sperm aspiration [33] or TESE/MESA in cases of concomitant epididymal obstruction. In large monolateral vas defects associated with contralateral testicular atrophy, the vas of the atrophic testis can be used for a crossover vasovasostomy or vasoepididymostomy.

Sperm reservoirs fixed onto epididymis or proximal vas deferens have been used during the past decade with poor results [34]. This type of surgery is not recommended.

Ejaculatory duct obstruction
The treatment of ejaculatory duct obstruction depends on aetiology. In large post-inflammatory obstruction and when one or both ejaculatory ducts empty into an intraprostatic midline cyst, transurethral resection of the ejaculatory ducts (TURED) [16,35] is recommended. Resection may remove part of the verumontanum. In case of obstruction due to a midline intraprostatic cyst, incision or unroofing of the cyst is required [16]. Intraoperative TRUS makes this procedure safer and more effective. If distal seminal tract evaluation is carried out at the time of the procedure, installation of methylene blue into the vas may be helpful to document opening of the ducts. Intraoperative haemostasis is advisable to avoid postoperative bleeding, which could result in rescarring of the ducts. Complications following TURED include retrograde ejaculation due to bladder neck injury, reflux of urine into ducts, seminal vesicles and vasa (causing poor sperm motility, acid semen pH and epididymitis). Although rectal injury, urine incontinence secondary to sphincteric injury, urethral injury, bladder neck contracture and erectile dysfunction have never been described to date, patients should be informed preoperatively about possible complications associated with this type of surgery [35].

Alternatives to TURED are MESA, TESE, proximal vas deferens sperm aspiration, seminal vesicle aspiration and direct ultrasonically-guided cyst aspiration.

In cases of functional obstruction of the distal seminal ducts, TURED often fails to improve the sperm output. Spermatozoa may then be retrieved by antegrade seminal tract washout [36].
Spermatozoa retrieved by any of the aforementioned surgical techniques should always be cryopreserved for assisted reproductive procedures.

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

4.6 References
5. VASECTOMY AND VASECTOMY REVERSAL

Vasectomy is the most simple and effective method of permanent surgical sterilization.

A man undergoing vasectomy should be interested in permanent surgical contraception.

Although the possibility of vasectomy reversal should be discussed initially, the patient should be informed about the failure rate.

Surgical techniques
The surgeon can choose the technique that is most appropriate. One standard technique is cauterization and ligation of the vasal lumina. Fascial interposition between the vasal ends is recommended [1]. Another recommended technique is the no-scalpel vasectomy [2]. Both techniques can be safely performed as an outpatient procedure under local anaesthesia.

Complications
Local complications include haematoma, wound infection and epididymitis.

Haematoma is the most common early complication of vasectomy, which occurs in 1% of cases [3]. As a minor complication, chronic testicular pain may develop [1]. Vasectomy does not significantly alter spermatogenesis and Leydig cell function [1]. Epididymal tubular damage (blow-out) is common, with consequent development of sperm granuloma. Presence of antisperm antibodies after vasectomy is typical [4]. The volume of ejaculate remains unchanged.

Potential systemic effects of vasectomy, including atherosclerotic diseases and interactions with genitourinary cancer, have not been proven. From long-term studies there is no evidence of a significant increase in any systemic disease after vasectomy [1].

Vasectomy failure
The failure rate of vasectomy is less than 1%.

Paternity consequent on recanalization can occur at any time after vasectomy and does not depend on the surgical procedure [5]. No motile spermatozoa should be detected 6-8 weeks after vasectomy; their presence is a sign of early recanalization [6]. If azoospermia fails to occur within 3 months, the procedure should be repeated.
Every patient has to be informed preoperatively that long-term recanalization may occur very rarely [5].

In summary, counselling has to address the following items concerning vasectomy:
• It is not irreversible
• It has complications
• It has a failure rate
• It needs normal methods of contraception after operation until evidence of azoospermia.

5.1 Conclusion
All available data indicate that vasectomy is safe and not associated with any serious, long-term side-effects.

5.2 Vasectomy reversal
There are at present no standardized and uniform criteria in reporting the results of vasectomy reversal. A wide range of surgical success rates have been published, up to 90% [7,8], depending on time that has elapsed since vasectomy, type of vasectomy (e.g. open-ended or sealed), type of reversal (vasovasostomy or vasoepididymostomy), whether reversal was unilateral or bilateral. The reversal technique used (macrosurgical or microsurgical, one-layer or two-layer anastomosis), surgeon skill and experience, presence or absence of other pathology (e.g. varicocele) and presence or absence of sperm antibodies. When case series are reported over a long period of time, there may be an improvement of anatomical or functional success due to improved technical skill of the surgeon, magnification and smaller suture materials used. Personal experience with a particular technique is an important factor in success.
Although there are no randomized controlled trials that compare macrosurgery (loops) and microsurgery for vasovasostomy, reports from case series indicate better results after microsurgery. Therefore, microsurgical vasectomy reversal is strongly recommended as the standard method.

Reported vasovasostomy results have shown patency rates (up to 90%) superior to pregnancy rates. The length of time since vasectomy

Reported vasovasostomy results have shown patency rates (up to 90%) superior to pregnancy rates. The reason for this discrepancy remains unclear [9]. However, the longer the interval from vasectomy to reversal, the lower the pregnancy rates. In a multicentre study, Belker et al. [8] followed 1,469 men who had undergone microsurgical vasectomy reversal at five different institutions in a 9-year period. Patency and pregnancy rates, respectively, were 97% and 76% if the interval had been 3 years after vasectomy, 88% and 53% for 3-8 years, 79% and 44% for 9-14 years and 71% and 30% for 15 years or longer.

Epididymovasostomy

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

Microsurgical vasectomy reversal versus epididymal or testicular sperm retrieval and ICSI.

An effectiveness analysis [10] evaluated two different initial approaches for treatment of post-vasectomy infertility. Microsurgical vasectomy reversal was compared with epididymal or testicular sperm retrieval and ICSI. The delivery rate was 47% after vasectomy reversal and 33% after one cycle of sperm retrieval and ICSI. Similar findings were reported by other authors [11] who observed a patency rate of 85% after 6 months with a pregnancy rate of 44% after one year, which led to a live delivery rate of 36%. Compared with a calculated 29% delivery rate for MESA and ICSI, this provides strong evidence for the advantage of simple vasectomy reversal over sperm retrieval and ICSI.

Conclusions

The most cost-effective approach to treatment of post-vasectomy infertility is microsurgical reversal. This also has the highest chance of delivery of a child for a single intervention. Successful vasectomy reversal will also mean that further pregnancies may result and unlike ICSI, conception follows normal intercourse without intervention for the female partner with the associated risks of ovarian hyperstimulation and multiple pregnancies. MESA/TESE and ICSI should be reserved for failed surgery or cases not amenable to surgical reconstruction.

5.3 References

6. SPECIAL PROBLEMS IN THE TREATMENT OF MALE INFERTILITY

6.1 VARICOCELE

6.1.1 Introduction
Varicocele is a common abnormality (see above Andrological investigations and spermatology) with the following andrological implications:

• Failure of ipsilateral testicular growth and development
• Symptoms of pain and discomfort
• Infertility

6.1.2 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 (finding of reflux on 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 |

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

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

6.1.4 Basic considerations

1. Varicocele is a physical abnormality present in 2-22% of the adult male population [4,5]. It is more common in men of infertile marriages, affecting 25% of those with abnormal semen analysis [6].
2. The incidence of pain and discomfort associated with varicocele is 2-10% [7]. Treatment to relieve symptoms is often recommended, but there are few outcome studies; however, most urologists accept discomfort as a valid indication.
3. The exact association between reduced male fertility and varicocele is unknown, but analysis of the WHO data [8] clearly indicates that varicocele is related to semen abnormalities, decreased testicular volume and decline in Leydig cell function.
4. Two prospective randomized studies show increased ipsi- and contralateral testis growth in adolescents who received varicocele treatment compared with those who did not [9,10]. A cohort follow-up study involving serial measurement of testicular size in growing children indicated arrest of testicular development coincident with development of varicocele and catch-up to the growth percentile after treatment [11].
5. A series of studies suggested that altered endocrine profiles in men with varicocele (exaggerated response to releasing factor) might predict those who would benefit from treatment [12,13].
6. Five prospective randomized studies of varicocele treatment in adults gave conflicting results [6,14-18], the largest of them indicating benefit [16,18]. It involved 10 centres, was externally randomized and
included men of infertile couples who had moderate oligozoospermia (5-20 x 10⁶/mL) and grade II or III varicocele. Immediate therapy was shown to be significantly more effective than delaying treatment for 1 year with regard to pregnancy achievement and pregnancy rate per cycle (fecundability). However, meta-analysis of the five trials indicated no benefit (the common odds ratio was 0.85% (95% CI 0.49-1.45)[19].

7. There is one prospective randomized study of treatment of subclinical varicocele, which failed to indicate fertility benefit from therapy [20].

8. Analysis of the large WHO infertility study [21] indicates that there is an excess of couples where both partners have factors associated with reduced fertility compared with the expected rate of coincidence in the general population. This implies that a minor cause of impaired fertility, such as varicocele, will only be manifest in couples where the female partner also has reduced fertility.

Treatment of varicocele to achieve pregnancy in infertile partnerships remains controversial and all investigations to date have been subject to criticism. Further investigations are needed, particularly for younger couples.

6.1.5 Treatment
Several treatment modalities can be chosen (Table 10).

The type of intervention is mainly dependent on the therapist’s experience. The consensus is that although laparoscopic varicocelectomy is feasible, it needs to be justified in terms of cost effectiveness.

Table 10. Recurrence and complication rates of different treatment methods for varicocele

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Recurrence/ Persistence Rates</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antegrade</td>
<td>9% [22]</td>
<td>Complication rate 0.3-2.2%</td>
</tr>
<tr>
<td>Sclerotherapy</td>
<td></td>
<td>Testicular atrophy; scrotal haematoma; epididymitis; left-flank erythema</td>
</tr>
<tr>
<td>Retrograde Sclerotherapy</td>
<td>Recurrence and persistence rate 9.8% [23,25]</td>
<td>Adverse reaction to the contrast medium; flank pain; persistent thrombophlebitis; vascular perforation [24]</td>
</tr>
<tr>
<td>Retrograde Embolisation</td>
<td>3.8-10% [26,27]</td>
<td>Pain due to thrombophlebitis [27]; bleeding; haematoma; infection; venous perforation; hydrocele; radiological complication such as reaction to contrast media; misplacement or migration of the coils [28]; retroperitoneal haemorrhage fibrosis; ureteric obstruction [5]</td>
</tr>
<tr>
<td>Open Operation</td>
<td>Scrotal approach</td>
<td>Testicular atrophy [5]; arterial damage with risk of devascularisation and gangrene of the testicle</td>
</tr>
<tr>
<td>Inguinal High ligation</td>
<td>13.3% [29]</td>
<td>Possibility of missing out a branch of testicular vein 5-10% incidence of hydrocele [30]</td>
</tr>
<tr>
<td>Micro-surgical</td>
<td>29% [29]</td>
<td>Post-operative hydrocele arterial injury Scrotal haematoma</td>
</tr>
<tr>
<td>Laparoscopy</td>
<td>3-7% [33-35]</td>
<td>Injury to testicular artery and lymph vessels; intestinal, vascular and nerve damage; pulmonary embolism; peritonitis [35]; bleeding; postoperative pain in right shoulder (due to diaphragmatic stretching during pneumoperitonium) [34]; pneumoscutum; wound infection [35]</td>
</tr>
</tbody>
</table>
6.1.6 Conclusions

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

While treatment of varicocele in adolescents may be effective, there is a significant risk of overtreatment. Data from an ongoing study will provide more information in this respect [10]. By the time the couple are aged 30 or over it is probably too late to treat varicocele in the context of infertility because the damage may be far proceeded and thus irreversible. Randomized studies and meta-analysis of randomized studies indicate no fertility benefit from varicocele ligation.

6.1.7 RECOMMENDATIONS

1. Treatment is recommended for adolescents who have progressive failure of testicular development documented by serial clinical examination.
2. Treatment is probably recommendable for adolescents with ipsilateral testicular atrophy. Further clinical studies are needed with long-term follow-up.
3. Treatment may be indicated for adolescents who have varicocele associated with an exaggerated response to releasing factor. Clinical trials are needed.
4. There is no evidence indicating benefit from varicocele treatment in adolescents who have no ipsilateral testicular atrophy and no endocrine abnormalities. In this situation, varicocele treatment cannot be recommended except in the context of clinical trials.
5. Meta-analysis of randomized clinical trials indicates no fertility benefit after varicocele ligation in adults. However, restoration of spermatogenesis has been reported, e.g. in an azoospermic man, proven by pre- and postoperative semen analyses and testicular biopsy [36]. Varicocele ligation for infertility should not be done unless there has been full discussion with the man about the uncertainties of treatment benefit.
6. It may be worth selecting subgroups of men from infertile marriages according to endocrine measurements (e.g. inhibin) for further clinical studies.
7. There is observational evidence that older men with varicocele may have lower testosterone levels than those without, but clinical trials are lacking to address whether varicocele ligation helps in this respect.

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6.2 HYPOGONADISM

6.2.1 Introduction
Men with hypogonadism usually present with symptoms of androgen deficiency (see above Andrological investigations and spermatology).

In some cases, hypogonadotrophic hypogonadism may be a cause of infertility [1].

<table>
<thead>
<tr>
<th>Table 11. Disorders with male hypogonadism. Modified from [2]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypothalamic - pituitary origin (hypogonadotrophic = secondary hypogonadism)</strong></td>
</tr>
<tr>
<td>• Idiopathic hypogonadotrophic hypogonadism (including Kallmann's syndrome)</td>
</tr>
<tr>
<td>• Delay of puberty</td>
</tr>
<tr>
<td>• Hyperprolactinaemia</td>
</tr>
<tr>
<td><strong>Hypergonadotrophic syndromes = primary hypogonadism (= testicular origin)</strong></td>
</tr>
<tr>
<td>• Anorchia (+ acquired)</td>
</tr>
<tr>
<td>• Klinefelter's syndrome</td>
</tr>
<tr>
<td>• Leydig cell tumours</td>
</tr>
<tr>
<td>• General diseases, e.g. liver cirrhosis</td>
</tr>
<tr>
<td><strong>Target organ resistance to androgens</strong></td>
</tr>
<tr>
<td>• Testicular feminization</td>
</tr>
<tr>
<td>• Reifenstein syndrome</td>
</tr>
</tbody>
</table>

6.2.2 Hypogonadotrophic hypogonadism
Aetiology, diagnosis and therapeutic management
Hypogonadotrophic hypogonadism is caused either by hypothalamic or pituitary diseases.

The failure of hormonal regulation can easily be determined [3].
Endocrine deficiency leads to a lack of spermatogenesis and testosterone secretion due to decreased secretion patterns of LH and FSH. The therapy of choice is human chorionic gonadotrophin (hCG) treatment, with the later addition of human menopausal globulin (hMG), dependent on initial testicular volume [4]. If hypogonadotrophic hypogonadism is hypothalamic in origin, a 1-year therapy with pulsatile gonadotrophin releasing hormone (GnRH) is as effective as gonadotrophins in stimulating spermatogenesis [5]. Once pregnancy has been induced, patients will go back to testosterone substitution (see below).

Conclusion
Effective drug therapy is available to achieve fertility in men with hypogonadotrophic hypogonadism.

6.2.3 Hypergonadotrophic hypogonadism
Aetiology, diagnosis and therapeutic management
Common conditions associated with hypergonadotrophic hypogonadism in younger men include injury to and loss of the testicles (e.g. after bilateral testicular cancer) (Table 11). More recently it has been recognized that
hypogonadism may occur after extensive testicular biopsy to recover sperm for IVF/ICSI [6]. Men with Klinefelter’s syndrome are at risk for spontaneous hypogonadism with ageing. Those undergoing extensive testicular biopsy in the context of IVF/ICSI will almost certainly have an exacerbated risk [7]. Hypergonadotrophic hypogonadism may occur spontaneously in the elderly, in patients with erectile dysfunction [8], and after LHRH treatment or surgical castration for prostatic cancer [9]. All these conditions are not clinically significant for infertile men. Hypogonadism may be associated with osteoporosis [10]. The laboratory diagnosis of hypergonadotrophic hypogonadism is based on decreased serum testosterone and increased LH levels [2]. Additional prolactin measurement is suggested.

Injectable, oral and transdermal testosterone preparations are available for clinical use [2]. The best preparation is the one that maintains serum testosterone levels as close to physiological concentrations as possible [11].

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

6.2.5 References

6.3 CRYPTORCHIDISM
The association between testicular maldescent and infertility has been well known for a long time.

6.3.1 Impact on fertility
Of men with untreated unilateral cryptorchidism (and still cryptorchid on semen analysis), 50-70% are

azoospermic or oligozoospermic [1]. In contrast, almost all men with untreated bilateral cryptorchidism are infertile [1]. Although the mechanisms for impaired fertility in these cases are not completely understood, the following alterations have been discussed aetiologically [1-3]:

- Decreased number of tubules containing spermatogonia
- Decreased number of spermatogonia per tubulus
- Mild concomitant hypogonadotropic hypogonadal situation
- Damaging effects on the contralateral testis
- Induction of sperm antibodies
- Epididymal malformations

Although no real consensus exists, it seems logical to suggest orchiectomy as treatment of choice for the majority of infertile men presenting with unilateral cryptorchidism. This is in accordance with accepted thinking that the malignant potential of abnormally located testis increases with age [4].

In the era of ICSI, TESE may be considered during operation for sperm retrieval in azoospermic men. In patients with bilateral cryptorchidism, it is very difficult to decide between conservative orchiectomy (plus testosterone substitution) and orchidopexy (after biopsy excluded carcinoma in situ). There is no consensus, neither in the literature nor in the infertility group.

6.3.2 References

7. IDIOPATHIC OLIGOASTHENOTERATOZOOSPERMIA

7.1 Introduction
Idiopathic oligoasthenoteratozoospermia (OAT) is one issue of empiric drug therapy in unexplained infertility. The effectiveness in terms of evidence-based medicine is low.

7.2 Diagnosis
Diagnosis is made according to WHO criteria (see above Andrological investigations and spermatology). However, even if semen analysis shows azoospermia or extreme oligospermia, it seems obvious that circumstances such as duration of the couple’s infertility, previous pregnancy history and the female partner’s age are more predictive than sperm quality findings.

Idiopathic male infertility

The majority of men presenting with infertility have OAT of unknown cause [1,2].

7.3 Treatment
The effect of any infertility treatment has to be considered with respect to the likelihood of spontaneous conception. Prediction scores for live births in untreated infertile couples have been 62% [3] and 76% [4]. Criteria for the analysis of all therapeutic trials have been re-evaluated [1,5-8], including study design, statistical analysis and goal of therapy.
There is consensus that only randomized controlled trials with the outcome parameter “pregnancy” can be accepted for efficacy analysis.

The following empiric therapies are under discussion (Table 12):

Table 12. Empiric therapy of idiopathic oligoasthenoteratozoospermia syndrome

<table>
<thead>
<tr>
<th>Hormonal</th>
<th>Non-hormonal</th>
<th>Assisted reproductive techniques (in cooperation with the gynaecologist, not covered by the urologist)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GnRH</td>
<td>Kinin-enhancing drugs</td>
<td>Intrauterine insemination IVF/ICSI</td>
</tr>
<tr>
<td>hCG/hMG</td>
<td>Bromocriptine</td>
<td></td>
</tr>
<tr>
<td>Recombinant FSH</td>
<td>Antioxidants</td>
<td></td>
</tr>
<tr>
<td>Androgens</td>
<td>Mast cell blockers</td>
<td></td>
</tr>
<tr>
<td>Anti-oestrogens</td>
<td>α-blockers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Systemic corticoids</td>
<td></td>
</tr>
</tbody>
</table>

GnRH = gonadotrophin-releasing hormone; hCG = human chorioc gonadotrophin; hMG = human menopausal gonadotrophin; FSH = follicle-stimulating hormone; IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection.

Gonadotrophin releasing hormone (GnRH)
GnRH is effective in hypogonadism. Its application in idiopathic male infertility has been tried with contradictory results [5]. Controlled studies are not available.

GnRH therapy is not recommended in OAT.

Human chorionic gonadotrophin (hCG) / Human menopausal gonadotrophin (hMG)
The only available randomized controlled study in normogonadotrophic OAT [9] failed to demonstrate any benefit of hCG/hMH therapy.

hCG/hMG-therapy is not recommended in OAT.

Recombinant follicle-stimulating hormone (FSH)
To date, controlled studies have not detected a significant increase in pregnancy rates due to FSH treatment [5], although one study showed a benefit for reduced testicular volumes [7]. Further controlled trials are necessary to define the value of this therapeutic approach [10].

Recombinant FSH therapy is not recommended in OAT.

Androgens
Administration of supplementary exogenous testosterone has been proposed as a therapy for infertile men with hypogonadism (see above Hypogonadism). The proposed mechanism by which androgens can be used for infertility treatment are the “stimulatory” or “rebound” therapies. A review of the literature [6] determined whether androgen treatment of the male increased pregnancy rates among couples with conception failure attributed to idiopathic oligo- and/or asthenozoospermia. Evaluation of randomized controlled trials using mesterolone or testosterone undecanoate as stimulatory therapy and testosterone-enanthate or testosterone-undecanoate as rebound therapy provided no evidence of effectiveness.

Androgens are not suggested for therapy in OAT.

Anti-oestrogens
Anti-oestrogens have been commonly used for hormonal treatment for idiopathic oligo- and/or asthenozoospermia. Clomiphene citrate and tamoxifen are the drugs applied in clinical practice. A systematic review of the literature [7] determined whether anti-oestrogen treatment of the male increased pregnancy rates.
among couples with conception failure attributed to idiopathic oligo- and/or asthenozoospermia. The meta-analysis of 19 trials suggested modest improvement in sperm concentration and motility in the treated group, but the increase in pregnancy rates did not reach significance. Meta-analysis of the five truly randomized trials revealed no significant benefit. Only one trial showed a statistically significant result.

A strong treatment effect of anti-oestrogens for oligozoospermia seems to be excluded. A smaller worthwhile effect is possible, which has to be counterbalanced by potential side-effects.

Kinin-enhancing drugs
All four components of the kinin system found in semen have been implicated in the reproductive system. A clear mechanism of action is missing, although multiple suggestions have been made on how increased kinin levels in the genital tract influence spermatogenesis at the testicular level [11].

Uncontrolled studies indicated that kallikrein may be beneficial to men with idiopathic infertility. A systematic review of the literature [8] determined whether treatment of the male with kinin-enhancing drugs increased pregnancy rates among couples with conception failure attributed to idiopathic oligo- and/or asthenozoospermia. Sixteen reports of randomized controlled trials on the therapeutic use of kallikrein or algiotensin-converting enzyme (ACE) inhibitors in subfertile men were analysed, which did not provide proof of effectiveness on pregnancy rates. A modest effect on sperm motility is possible.

Until effectiveness is proven, it is recommended that kallikrein should not be used to treat OAT except in the context of clinical trails.

Bromocriptine
Bromocriptine seems to reduce prolactin levels in normogonadotrophic subfertile males, but does not result in an improvement in sperm parameters. Uncontrolled series claiming a beneficial effect are not supported by controlled trials.

Bromocriptine therapy is not recommended in OAT.

Antioxidants
Reactive oxygen species (ROS) or free radicals may cause male infertility via peroxidation of phospholipids in the sperm plasma membrane. Antioxidants such as vitamin E or glutathionine interrupt such reactions and scavenge free radicals.

One double-blind randomized, placebo-controlled trial [12] was performed to assess the effect of the antioxidant vitamin E. Although the number of pregnancies did not differ significantly, the performance of spermatozoa in the zona binding test was significantly improved after vitamin E administration. In another double-blind randomized trial [13], asthenozoospermic men treated with vitamin E 100 mg/day showed significantly improved sperm motility compared with those who had received placebo, and pregnancy was achieved in 21% of the treatment group. Re-analysis of these two trials revealed a significant effect on pregnancy, particularly in the second study [5]. Glutathione therapy in a placebo-controlled, double-blind trial demonstrated a significant positive effect on sperm motility [14].

Although antioxidants may be of benefit in carefully selected groups with OAT syndrome, there is insufficient evidence to recommend their use outside the context of randomized controlled trials.

Mast cell blockers

Treatment with mast cell blockers may be worth further evaluation in OAT.

Alpha blockers
One double-blind, placebo-controlled randomized study [16] demonstrated that alpha blocker therapy resulted in significantly improved sperm concentration and motile sperm count, but the cumulative pregnancy rates were not significantly different.
Systemic corticoids
Antisperm antibodies have been associated with infertility in some couples, although the exact pathophysiology of their action remains unclear. They may be found in serum, seminal plasma or bound to spermatozoa, such as IgG and IgA antibodies.

Different tests for antisperm antibodies have been published and there are different levels of antibodies at which tests are considered positive. The baseline characteristics of included patients are also different, particularly with regard to duration of infertility, previous genital tract pathology and evaluation of the partner’s fertility. All these variables make comparisons among studies difficult.

Due to their immunosuppressive effect, glucocorticoids have been used in an attempt to reduce antisperm antibody levels. Three randomized controlled trials and one pseudo-randomized study assessed pregnancy rates after steroid administration to men with antisperm antibodies [17-20]. The situation is difficult due to conflicting evidence from methodologically flawed studies. In a recent meta-analysis of the literature including further trials, no significant influence on pregnancy rates in men presenting with immunological infertility was observed [5].

Due to lack of proven efficacy, there is consensus that patients with high concentrations of antisperm antibodies in the ejaculate should enter an ICSI protocol.

7.4 Conclusions
Drug therapy of idiopathic OAT syndrome is ineffective in many aspects. Controlled studies are necessary in some new fields, e.g. treatment of ROS and immunological infertility. Considering the baseline prognosis for pregnancy, an individual decision is necessary to submit the couple early enough to further reproductive techniques.

7.5 References
11. Schill WB, Parsch EM, Miska W. Inhibition of angiotensin-converting enzyme - a new concept of medical treatment for male infertility?


8. UROGENITAL INFECTIONS AND DISTURBED MALE FERTILITY

8.1 URETHRITIS AND PROSTATITIS

8.1.1 Introduction

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

8.1.2 Urethritis

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

Diagnosis and treatment

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

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

A negative influence of sexually transmitted microorganisms on sperm function is a matter of debate [1,6,7]. Urethral strictures and ejaculatory disturbances have been claimed to impair male fertility [2], as has the development of obstruction [8], either as normal urethral stricture or lesion in the posterior urethra in the area of the veromontanum, both of which can lead to ejaculatory disturbances [2].
Sexually transmitted disease treatment is standardized by the guidelines of the Centers of Disease Control and Prevention Atlanta, USA [9]. As the aetiology of acute urethritis is unknown in most cases at the time of diagnosis, empiric therapy is suggested, with one single dose of a fluoroquinolone, followed by a 2-week regimen of doxycycline. Treatment is effective both for gonococcal and (co-existing) chlamydial/ureaplasmal infections.

8.1.3 Prostatitis

Prostatitis represents the most common urological diagnosis in men under 50 years of age [10]. Traditionally, the disease has been classified into four clinical entities:

- acute bacterial prostatitis (ABP) and prostatic abscess as sequel of ABP,
- chronic bacterial prostatitis (CBP),
- non- or abacterial prostatitis (NBP) and
- prostatodynia (Pd).

To improve the definition and understanding of the prostatitis syndrome, a new classification system has been proposed by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Washington DC, USA [10] (Table 13).

### Table 13. New NIDDK classification of the prostatitis syndrome. Adapted from [10]

<table>
<thead>
<tr>
<th>Category (new)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Acute bacterial prostatitis</td>
</tr>
<tr>
<td></td>
<td>Acute infection of the prostate gland</td>
</tr>
<tr>
<td>II</td>
<td>Chronic bacterial prostatitis</td>
</tr>
<tr>
<td></td>
<td>Recurrent infection of the prostate</td>
</tr>
<tr>
<td>III</td>
<td>Chronic abacterial prostatitis/chronic pelvic pain syndrome (CPPS)</td>
</tr>
<tr>
<td></td>
<td>No demonstrable infection</td>
</tr>
<tr>
<td>III A</td>
<td>Inflammatory chronic pelvic pain syndrome</td>
</tr>
<tr>
<td></td>
<td>White cells in semen, expressed prostatic secretions or post-prostatic massage urine</td>
</tr>
<tr>
<td>III B</td>
<td>Non-inflammatory chronic pelvic pain syndrome</td>
</tr>
<tr>
<td></td>
<td>No white cells in semen, expressed prostatic secretions or post-prostatic massage urine</td>
</tr>
<tr>
<td>IV</td>
<td>Asymptomatic inflammatory prostatitis</td>
</tr>
<tr>
<td></td>
<td>No subjective symptoms. Inflammation detected either by prostate biopsy or the presence of white cells in expressed prostatic secretions or semen during evaluation for other disorders.</td>
</tr>
</tbody>
</table>

**Microbiology**

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

**Diagnosis**

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

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

An ejaculate analysis (see above Andrological investigations and spermatology) helps clarify whether the prostate is part of a generalized infection of the accessory sex glands (male accessory gland infection) and provides information about the sperm quality. Furthermore, leukocyte analysis allows differentiation between inflammatory and noninflammatory CPPS.

Microbiological findings

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

A concentration of \( \geq 10^3 \) cfu/mL of urinary tract pathogens in the ejaculate is regarded as significant bacteriospermia. Usually, various microorganisms are cultured from the genital tract of men seen in infertility clinics, with more than one strain of bacteria in most cases [1]. Furthermore, the time of sample taking influences the positive rate of microorganisms in semen and the frequency of isolation of different strains [19]. In patients with prostatitis symptoms without proven bacterial findings, cryptic infections, especially evidence of silent C. trachomatis or mycoplasma infections, remain a diagnostic challenge.

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

By analogy with mycoplasma, U. urealyticum seems only to be pathogenic in high concentrations (\( \geq 10^3 \) cfu/ml ejaculate). No more than about 10% of samples analysed for ureaplasmas exceed this number [20].

Normal colonization of the urethra hampers the necessary clarification of ‘mycoplasma-associated’ urogenital infections using samples such as the ejaculate [15].

White blood cells

The clinical significance of an increased concentration of white blood cells (WBC) in the ejaculate is highly controversial [21]. It seems to be generally accepted that only an increased number of leukocytes, particularly neutrophilic granulocytes, and their products secreted into the seminal fluid, e.g. leukocyte elastase, is an indicator of infection. The great majority of leukocytes are neutrophilic granulocytes, as suggested by the specific staining of the peroxidase reaction (WHO; see above Andrological investigations and spermatology).

Although most authors consider leukocytospermia a sign of inflammation, it is not necessarily associated with bacterial or viral infections [7]. This is in accordance with earlier findings that elevated leukocyte numbers are not a natural cause of male infertility [22].

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

Sperm quality

Deteriorative effects of chronic prostatitis on sperm density, motility and morphology are under debate [1]. All investigations to date have contradictory results and do not really confirm a decisive role of chronic prostatitis in alterations of these parameters (Table 14).
Table 14. Influence of chronic prostatitis on sperm density, motility and morphology.
Adapted from [1]

<table>
<thead>
<tr>
<th>Author</th>
<th>Negative influence on Density</th>
<th>Motility</th>
<th>Morphology</th>
<th>Prostatitis diagnosis based on leukocytes in EPS</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giamarellou et al. [25]</td>
<td>+</td>
<td>+</td>
<td>(+)</td>
<td>+</td>
<td>Correct diagnosis</td>
</tr>
<tr>
<td>Christiansen et al. [26]</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Diagnosis by ultrasonography is obsolete</td>
</tr>
<tr>
<td>Weidner et al. [24]</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Correct diagnosis</td>
</tr>
<tr>
<td>Leib et al. [27]</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Incorrect prostatitis diagnosis; only bacterial prostatitis excluded</td>
</tr>
<tr>
<td>Krieger et al. [23]</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Correct diagnosis</td>
</tr>
</tbody>
</table>

EPS = expressed prostatic secretions

Seminal plasma alterations

Seminal plasma elastase is accepted as a biochemical indicator of granulocyte activity in the ejaculate [1,28,29], with a suggested cutpoint of about 600 ng/mL [1]. Various cytokines are involved in inflammation and may influence sperm function. In this respect, several studies investigated the association between interleukin concentration, leukocytes and sperm function [30-32]. No differences were found among the subgroups defined on the basis of progressive motility, percentage of abnormal forms and diagnosis of prostatitis. The prostate seems to be the main site of origin of interleukin-6 (IL-6) in the seminal plasma. Although it is accepted that cytokines, especially IL-6, must play an important role in the male accessory gland inflammatory process [33], elevated cytokine levels do not depend on the number of leukocytes in EPS [34].

Glandular secretory dysfunction

Infections of the sex glands can impair their excretory function. Decreased quantities of citric acid, phosphatase, fructose, zinc and alpha-glutamyltransferase activity have been evaluated as disturbed prostatic secretory parameters [1] and reduced fructose concentration as an indicator of impaired vesicular function [20,35].

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 in cases of suspected chlamydial infections [38], only a history of vasectomy seems to be predictive of sperm antibody formation [39].

Reactive oxygen species

It is generally accepted that ROS may be increased in chronic urogenital infections associated with increased leukocyte numbers [40]. However, the biological significance in prostatitis remains unclear [1].

8.1.4 Therapy

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

- reduction or eradication of microorganisms in prostatic secretions and semen
- normalization of inflammatory parameters, such as leukocytes and secretory parameters
- possible improvement of sperm parameters to counteract fertility impairment [41]

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

Only antibiotic therapy of CBP has proved to be efficacious in providing symptomatic relief, eradication of microorganisms and a decrease in cellular and humoral inflammatory parameters in urogenital secretions.

None of the other treatment schedules mentioned above have been evaluated in the same manner.
Although antibiotic procedures may provide improvement in sperm quality [41], therapy does not always enhance the probability of conception [1,42].

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

8.1.6 References
19. Liversedge NH, Jenkins JM, Keay SD, LcLaughlin EA, Al-Sufyan H, Maile LA, Joels LA, Hull MG. Antibiotic treatment based on seminal cultures from asymptomatic male partners in in-vitro fertilization is unnecessary and may be detrimental. Hum Reprod 1996; 11; 1227-1231.


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Therapy in male accessory gland infection—what is fact, what is fiction?

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8.2 ORCHITIS AND EPIDIDYMITIS

8.2.1 Orchitis
Orchitis is an inflammatory lesion of the testicle associated with a predominantly leukocytic exudate inside and outside the seminiferous tubules resulting in tubular sclerosis. The inflammation causes pain and swelling. Chronic inflammatory changes in the seminiferous tubules disrupt the normal process of spermatogenesis and cause alterations both in sperm number and quality [1]. It is generally accepted that orchitis may also be an important cause of spermatogenic arrest [2], which may be reversible. Following orchitis, testicle atrophy occurs [2].

Orchitis is classified according to aetiology (Table 15).

<table>
<thead>
<tr>
<th>Non-specific</th>
<th>Specific</th>
<th>Viral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute bacterial epididymo-orchitis: N. gonorrhoeae C. trachomatis E. coli (and other Enterobacteriaceae)</td>
<td>Specific granulomatous orchitis Tuberculosis</td>
<td>Mumps orchitis Coxsackie-B</td>
</tr>
<tr>
<td>Non-specific chronic epididymo-orchitis Granulomatous (idiopathic) orchitis Pneumococcus Salmonella Klebsiella Haemophilus influenzae</td>
<td>Tuberculosis Luess Brucellosis</td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis
Patients with epididymo-orchitis usually present with unilateral scrotal pain [4]. The diagnosis is based on medical history and palpation. Ultrasonography demonstrates a swollen, enlarged testis. The sonographic feature of the tissue does not allow any differential diagnosis [5].

Ejaculate analysis
Ejaculate analysis, including leukocyte analysis, indicates persistent inflammatory activity (see above Andrological investigations and spermatology). In many cases, especially in acute epididymo-orchitis, transiently decreased sperm counts and reduced forward motility are observed [2]. Obstructive azoospermia due to complete obstruction is a rare complication. Mumps orchitis may result in bilateral testicular atrophy [3] and testicular azoospermia. When granulomatous orchitis is suspected, sperm-bound autoantibodies occur (see above Andrological investigations and spermatology).

Therapy
Only the therapy of acute bacterial epididymo-orchitis and of specific granulomatous orchitis is standardized [3] (Table 16).

Several regimens are thought to improve the inflammatory lesion. Therapies with corticoids and non-steroidal antiinflammatory substances, such as diclofenac, indometacin and acetylsalicylic acid, have unfortunately not been evaluated as to their andrological outcome [5]. A further therapeutic trial is based on the idea of preventing deleterious effects of inflammation on spermatogenesis by gonadotrophin-releasing hormone (GnRH) treatment [6].
In mumps orchitis, systemic interferon alpha-2b therapy has been reported to prevent testicular atrophy and azoospermia [7]. In idiopathic granulomatous orchitis, surgical removal of the testis is the therapy of choice.

### Table 16. Treatment of epididymo-orchitis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute bacterial epididymo-orchitis</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>N. gonorrhoeae</td>
<td></td>
</tr>
<tr>
<td>C. trachomatis</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>E. coli, Enterobacteriaceae</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Mumps orchitis</td>
<td>Interferon alpha-2b</td>
</tr>
<tr>
<td>Non-specific chronic epididymo-orchitis</td>
<td>Steroidal and nonsteroidal antiphlogistic substances (?)</td>
</tr>
<tr>
<td>Granulomatous (idiopathic) orchitis</td>
<td>Semicastration</td>
</tr>
<tr>
<td>Specific orchitis</td>
<td>According to therapy of underlying diseases</td>
</tr>
</tbody>
</table>

#### 8.2.2 Epididymitis

Inflammation of the epididymis causes pain and swelling, which is almost unilateral and relatively acute in onset. In many cases, the testicle is involved in the inflammatory process known as epididymo-orchitis. Among sexually active men younger than 35 years, epididymitis is most often caused by C. trachomatis or N. gonorrhoeae (Table 13) [8,9]. Sexually transmitted epididymitis is usually accompanied by urethritis. Non-sexually transmitted epididymitis is associated with UTI. This type occurs more frequently among men aged over 35 years, those who have recently undergone urinary tract instrumentation or surgery and those who have anatomical abnormalities [9].

**Diagnosis**

In acute epididymitis, inflammation and swelling usually begin in the tail of the epididymis, and may spread to involve the rest of the epididymis and testicular tissue [4]. Although men with epididymitis due to sexually transmitted microorganisms always have a history of sexual activity, exposure can have been months prior to onset. The microbial aetiology of epididymitis is usually easy to determine by gram-stained examination of both a urethral smear for urethritis and of a midstream urine specimen for gram-negative bacteriuria [8,9]. Intracellular gram-negative diplococci on the smear correlate with the presence of N. gonorrhoeae. Only white blood cells on urethral smear are indicative of non-gonorrhoeal urethritis; C. trachomatis will be isolated in approximately two thirds of these patients [10].

**Ejaculate analysis**

Ejaculate analysis according to WHO criteria, including leukocyte analysis, may indicate persistent inflammatory activity. In many cases, transiently decreased sperm counts and forward motility are observed [3,5,8]. Ipsilateral low-grade orchitis [11,12] has been discussed as the cause of this slight impairment in sperm quality (Table 17) [13].

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

### Table 17. Acute epididymitis and impact on sperm parameters

<table>
<thead>
<tr>
<th>Author</th>
<th>Negative Influence on</th>
<th>Density</th>
<th>Motility</th>
<th>Morphology</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ludwig &amp; Haselberger [14]</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Pyospermia in 19 of 22 cases</td>
<td></td>
</tr>
<tr>
<td>Berger et al. [8]</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weidner et al. [5]</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Azoospermia in 3 of 70 men</td>
<td></td>
</tr>
<tr>
<td>Haidl [15]</td>
<td></td>
<td>+</td>
<td></td>
<td>Chronic infections; macrophages elevated</td>
<td></td>
</tr>
<tr>
<td>Cooper et al. [16]</td>
<td></td>
<td></td>
<td></td>
<td>Decrease in epididymal markers: alpha-glucosidase, L-carnitine</td>
<td></td>
</tr>
</tbody>
</table>
Treatment

**Antibiotic therapy is indicated before culture results are available (Table 1).**

Treatment of epididymitis will result in:

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

Patients who have epididymitis known or suspected to be caused by *N. gonorrhoeae* or *C. trachomatis* should be instructed to refer sex partners for evaluation and treatment [17].

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9 DISORDERS OF EJACULATION

9.1 Definition
Ejaculation disorders are uncommon but important causes of infertility. Several heterogeneous dysfunctions belong to this group and may be of either psychogenic or organic origin.

9.2 Classification and aetiology

Anejaculation

Anejaculation is the complete absence of antegrade or retrograde ejaculation. It is caused by failure of emission of semen from the prostate and seminal ducts into the urethra [1]. True anejaculation is usually associated with a normal orgasmic sensation. Occasionally, for example in incomplete spinal cord injuries, this sensation may be altered or decreased. True anejaculation is always connected with central or peripheral nervous system dysfunctions or influence of drugs [2] (Table 18).

Table 18. Aetiology of anejaculation

<table>
<thead>
<tr>
<th>Neural</th>
<th>Drug-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord injury</td>
<td>Anthypertensives</td>
</tr>
<tr>
<td>Cauda equina lesions</td>
<td>Antipsychotics</td>
</tr>
<tr>
<td>Retroperitoneal lymphadenectomy</td>
<td>Antidepressants</td>
</tr>
<tr>
<td>Aortoiliac surgery</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Colorectal surgery</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td></td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td></td>
</tr>
<tr>
<td>Autonomic neuropathy (juvenile diabetes)</td>
<td></td>
</tr>
</tbody>
</table>

Anorgasmia

Anorgasmia is the inability to reach orgasm. This may give rise to anejaculation. Some patients report sporadic events of nocturnal emission or of ejaculation occurring during great emotional excitement unrelated to sexual activity [3]. The causes of anorgasmia are usually psychological.

Delayed ejaculation

Delayed ejaculation is the condition wherein abnormal stimulation of the erect penis is necessary to achieve orgasm with ejaculation [1]. Delayed ejaculation may be considered a moderate form of anorgasmia; both can be alternatively found in the same patient. The causes of delayed ejaculation may be psychological or organic, such as:

- Incomplete spinal cord lesion [3];
- Iatrogenic penile nerve damage [4];
- Pharmacological use of antidepressants, antihypertensives, antipsychotics [3].
Retrograde ejaculation is the total absence of antegrade ejaculation because semen passes backwards through the bladder neck into the bladder.

Patients experience a normal or decreased orgasmic sensation, except in paraplegia. It is usually complete and rarely partial. Partial antegrade ejaculation must not be confused with the secretion of bulbo-urethral glands. The causes of retrograde ejaculation are given in Table 19.

### Table 19. Aetiology of retrograde ejaculation

<table>
<thead>
<tr>
<th>Neurogenic</th>
<th>Pharmacological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord injury</td>
<td>Antihypertensives</td>
</tr>
<tr>
<td>Cauda equina lesions</td>
<td>Alpha1-adrenoceptor antagonist</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Antipsychotics</td>
</tr>
<tr>
<td>Autonomic neuropathy (juvenile diabetes)</td>
<td>Antidepressants</td>
</tr>
<tr>
<td>Retroperitoneal lymphadenectomy</td>
<td></td>
</tr>
<tr>
<td>Sympathectomy</td>
<td></td>
</tr>
<tr>
<td>Colorectal and anal surgery</td>
<td><strong>Bladder neck incompetence</strong></td>
</tr>
<tr>
<td></td>
<td>Congenital defects of hemitrigone</td>
</tr>
<tr>
<td><strong>Urethral obstruction</strong></td>
<td></td>
</tr>
<tr>
<td>Ectopic ureterocele</td>
<td>Bladder extrophy</td>
</tr>
<tr>
<td>Urethral stricture</td>
<td>Bladder neck resection</td>
</tr>
<tr>
<td>Urethral valves</td>
<td>Prostatectomy</td>
</tr>
</tbody>
</table>

Asthenic ejaculation

Asthenic ejaculation, also defined partial ejaculatory incompetence or ‘éjaculation baveuse’ [5], is characterized by an altered propulsive phase with a normal emission phase.

Orgasmic sensation is reduced and the typical rhythmic contractions associated with ejaculation are missing, while these are present in asthenic ejaculation due to urethral obstruction. The most frequent causes of asthenic ejaculation are shown in Table 20.
Table 20. Aetiology of asthenic ejaculation

<table>
<thead>
<tr>
<th>Neurogenic</th>
<th>Urethral obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord injury (L1)</td>
<td>Ectopic ureterocele</td>
</tr>
<tr>
<td>Cauda equina lesions</td>
<td>Urethral stricture</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Urethral valves</td>
</tr>
<tr>
<td>Autonomic neuropathy (juvenile diabetes)</td>
<td></td>
</tr>
<tr>
<td>Retroperitoneal lymphadenectomy</td>
<td></td>
</tr>
<tr>
<td>Sympathectomy</td>
<td></td>
</tr>
<tr>
<td>Colorectal and anal surgery</td>
<td></td>
</tr>
</tbody>
</table>

Asthenic ejaculation has no major consequences on male fertility.

Premature ejaculation

Premature ejaculation is the inability to control ejaculation for a ‘sufficient’ length of time before vaginal penetration.

Although a universally accepted meaning of ‘sufficient’ length of time does not exist, some patients are not able to delay ejaculation over a few coital thrusts, or even before vaginal penetration. Premature ejaculation may be organic or psychogenic, congenital or acquired, partner-related or unselective, whether or not associated with erectile dysfunction.

Premature ejaculation does not involve any impairment of fertility, when intravaginal ejaculation occurs.

Painful ejaculation

Painful ejaculation is usually an acquired condition, which may cause moderate sexual dysfunction.

The painful sensation, felt in the perineum or urethra and urethral meatus [6], can be caused by ejaculatory duct obstruction, prostatitis or urethritis, autonomic nerve dysfunction and psychological problems.

9.3 Diagnosis

Suggested diagnostic management includes the following procedures.

Clinical history
Diabetes, neuropathies, traumas, urogenital infections, previous surgery and drug assumption have to be checked carefully. Particular attention must be paid to micturition characteristics and ejaculation (nocturnal emission, ejaculatory ability in given circumstances, congenital or acquired disorder, evolution), as well as to the psychosexual sphere (education, features of affective relationship, pre-existent psychological traumas, previous psychological therapies).

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

• sensitivity of the scrotum, testes and perineum
• cremasteric and abdominal cutaneous reflex
• leg osteotendinous and plantar reflexes
Post-ejaculatory urinalysis
This will assess partial retrograde ejaculation.

Cultural examinations for urethritis and prostatitis (see above Urogenital infections and disturbed male fertility).

Further diagnostic work-up.
This includes:
• Neurophysiological tests (bulbocavernosus evoked response and dorsal nerve somatosensory evoked-potentials)
• Tests for autonomic neuropathies (e.g. appreciation of temperature regulation in the feet
• Psychosexual evaluation
• Videocystometry
• Cystoscopy
• Transrectal ultrasonography
• Uroflowmetry
• Penile vibratory stimulation

9.4 Treatment

Treatment of infertility due to ejaculation disorders is rarely aetiological, and generally consists of retrieving spermatozoa to be used in assisted reproduction techniques.

Decision-making depends on the following aspects:
• Age of patient and his partner
• Couple’s willingness and acceptance of the different fertility procedures
• Psychological problems in the patient and his partner
• Associated pathologies

When the ejaculatory disorder is psychogenic and the couple’s request is aimed at achieving pregnancy, the most important thing is that they should undergo a preliminary psychological evaluation to avoid any severe subsequent psychological reaction.

Aetiological treatment
Aetiological treatment can be summarized as follows:
• Interruption of pharmacological therapy interfering with ejaculation (if possible)
• Treatment of infectious forms (e.g. in case of painful ejaculation)
• Psychotherapy
• Surgical correction of a urethral pathology
• Correction of metabolic disorders (diabetes)

Symptomatic treatments
Retrograde ejaculation:

In the absence of spinal cord injury, anatomic urethral anomalies or pharmacological therapy, an attempt must be made to induce antegrade ejaculation by drug treatment (Table 21).

Table 21. Drug therapy for retrograde ejaculation

- Ephedrine sulphate, 10-15 mg four times daily [7]
- Midodrin, 5 mg three times daily [8]
- Brompheniramine maleate, 8 mg twice daily [9]
- Imipramine, 25-75 mg three times daily [10]
- Desipramine, 50 mg every second day [11]

Alternatively, the patient can be encouraged to ejaculate when his bladder is full, to increase bladder neck closure [12].
Sperm collection from post-ejaculatory urine for use in assisted reproductive techniques is suggested if:

- Drug treatment is ineffective or not tolerable due to side-effects
- The patient has a spinal cord injury
- Drug therapy inducing retrograde ejaculation cannot be interrupted

Sperm retrieval is timed with the partner's ovulation. Urine must be alkalinized by ingesting 1-3 g of sodium bicarbonate three to four times daily; pH must be in the range 7.2-7.8 immediately before ejaculation and must be checked at every micturition. Because osmolarity of urine deteriorates sperm motility, the patient is asked to drink about 500 mL of water 1 hour before ejaculation. The patient should then void his bladder. This procedure will help to control urine osmolarity. If the urine osmolarity is low, it will be rechecked after 15-20 minutes; if the urine osmolarity is high, the patient is again requested to drink about 200 mL of water. Once an optimal osmolarity has been reached (200-300 mOsm/kg), the patient is asked to have intercourse or to masturbate. Within 10 minutes after ejaculation, urine must be voided and centrifuged. The resulting pellet should be resuspended in 0.5 mL Tyrode’s or Ham’s F-10 medium and immediately inseminated [13]. Alternatively, a catheter may be applied to the bladder and 10-50 ml Tyrode’s or Ham’s F-10 medium instilled. The patient must ejaculate, and a second catheterism is performed immediately to retrieve spermatozoa. The latter treatment minimizes the contact of spermatozoa with urine [14]. In order to perform intrauterine insemination, sperm quality must be good. Otherwise, the couple undergo in vitro reproductive procedures (e.g. ICSI) with fresh or cryopreserved spermatozoa.

Anejaculation

Drug treatment for anejaculation due to lymphadenectomy and neuropathy is not very effective. The same applies to psychosexual therapy for anorgasmia. In all these cases and in spinal cord injured men, vibrostimulation is the first-line therapy.

In anejaculation, penile vibratory stimulation evokes the ejaculation reflex [15].

Vibrostimulation requires an intact lumbosacral spinal cord segment. The more complete the injury above Th10, the better the chance of response. Lack of pinprick or temperature sensation in the saddle area and glans penis, inability to feel testicular squeeze, and intact lower limb and bulbocavernous reflexes suggest a promising outcome. Negative prognostic factors are injuries below Th10 and flaccid paraplegia. Men with a history of autonomic dysreflexia are premedicated with 10-20 mg nifedipine sublingually. The bladder must be emptied before vibrostimulation. The vibrator is applied around the glans penis and frenulum, with a 1-3 mm peak-to-peak amplitude and a 80-100 Hz frequency. Ejaculation should be expected within 10 minutes and is followed by flushing, abdominal and leg spasm. Once the safety and efficacy of this procedure are assessed, patients can manage themselves at home. Intravaginal insemination via a 10-mL syringe during ovulation can be performed. If semen quality is poor, or ejaculation is retrograde, the couple may enter an in vitro fertilization programme.

If vibrostimulation fails, electroejaculation is the therapy of choice [16].

Electroejaculation is an electric stimulation of the periprostatic nerves via a probe inserted into the rectum, which seems not to be affected by reflex arc integrity. Electroejaculation requires good training because of the associated risks of autonomic hyperreflexia and rectal mucosa burning. Anaesthesia is required except in cases of complete high spinal cord injury. An automatic blood pressure cuff is applied to the patient for continuous readings; his bladder is emptied by a catheter and instilled with Ham’s F10 (or similar medium). Anoscopy is previously performed to check the integrity of the bowel wall. The probe is then placed directly onto the prostate, assuring continuous mucosal contact with the temperature sensor and metal plates. Most stimulations are performed for 5-7 minutes. In 90% of the patients electrostimulation induces ejaculation, which is retrograde in one third of them. Semen quality is often poor, although improving throughout repeated ejaculations, and most couples must resort to in vitro fertilization.

If electroejaculation fails or cannot be performed, sperm retrieval from the seminal ducts may be achieved by

- Sperm aspiration from vas deferens [17] (see above Obstructive azoospermia)
- Seminal tract washout [18] (see above Obstructive azoospermia)

Epididymal obstruction or testicular failure must be suspected in case of failed sperm retrieval. TESE is then performed [19] (see above Obstructive azoospermia).
9.5 Conclusions
Ejaculation disorders can be treated with a wide range of drugs and physical stimulation trials with a high percentage of efficacy.

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ACKNOWLEDGEMENTS
1 With support by Ch. Gosk, Dept. of Urology, Western General Hospital, Edinburgh, UK.
2 The EAU guidelines on Paediatric Urology.
3 The EAU guidelines on ‘Infertility Guideline Group’ of the Royal College of Obstetricians and

10. ABBREVIATIONS USED IN THE TEXT

ABP: acute bacterial prostatitis
CASA: computer-assisted sperm analysis
CBAVD: congenital bilateral absence of the vas deferens
CBP: chronic bacterial prostatitis
CFTR: cystic fibrosis transmembrane conductance regulator gene
CPPS: chronic pelvic pain syndrome
FSH: follicle-stimulating hormone
FISH: multicolour fluorescent in situ hybridization
GnRH: onadotrophin-releasing hormone
hCG: human chorionic gonadotrophin
hMG: human menopausal gonadotrophin
LH: luteinizing hormone
LHRH: luteinizing hormone releasing hormone
MESA: microsurgical epididymal sperm aspiration
NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases
NBP: non- or abacterial prostatitis
Pd: prostatodynia
TESE: testicular sperm extraction
TURED: transurethral resection of the ejaculatory ducts
UTI: urinary tract infection
WBC: white blood cells