European Association of Urology

GUIDELINES ON INFERTILITY

G. M. Colpi, T. B. Hargreave, G. K. Papp,

J. M. Pomerol, W. Weidner.

TABLE OF CONTENTS PAGE

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.**
   WHO laboratory manual for the examination of human semen and sperm-cervical mucus interaction. 4th edition, Cambridge, Cambridge University Press, 1999.
2. **ESHRE Andrology Special Interest Group.**
   Consensus workshop on advanced diagnostic andrology techniques. Hum Reprod 1996; 11:1463–1479.
3. **World Health Organization.**
   WHO manual for the standardized investigation, diagnosis and management of the infertile male. Cambridge, Cambridge University Press, 2000.

2. GENETIC DISORDERS IN INFERTILITY[1]

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)

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

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

Authors	Y deletion son	Y deletion father	Phenotype
Kobayashi *et al*. [28]	AZFc	AZFc	?
Vogt *et al*. [23]	AZFc	AZFc	< $0.1x10^6$
Kent-First *et al*. [39]	Small near AZFc	Small near AZFc	ICSI
	Small near AZFc Large AZFc –AZFb	Not detected Not detected	Normal
Pryor *et al*. [22]	sY153-sY267 sY207-sY272	sY153-sY267	0.3×10^6
Stuppia *et al*. [40]	AZFc	AZFc (smaller)	$< 2 \times 10^6$
Mulhall *et al*. [41]	Ongoing twin pregnancy	AZFc	ICSI
Silber *et al*. [42]	Two ongoing pregnancies Two ongoing 1 twin AZFc	AZFc Azoospermic AZFc Oligospermic	TESE-ICSI ICSI
Kamischke *et al*. [43]	AZFc	AZFc	ICSI Normal

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

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

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.

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

1. **Johnson MD.**
   Genetic risks of intracytoplasmic sperm injection in the treatment of male infertility: recommendations for genetic counseling and screening. Fertil Steril 1998; 70: 397-411.
2. **van Assche EV, Bonduelle M, Tournaye H, Joris H, Verheyen G, Devroey P, Van Steirtgehem A, Liebaers I.**
   Cytogenetics of infertile men. Hum Reprod 1996; 11 (Suppl 4): 1-24.
3. **Chandley AC.**
   Chromosomes; in Hargreave TB (ed): Male Infertility. London, Springer, 1994; 149-164.
4. **Martin RH.**
   The risk of chromosomal abnormalities following ICSI. Hum Reprod 1996; 11: 924-925.

5. **Wang C, Baker HW, Burger HG, De Kretser DM, Hudson B.**
Hormonal studies in men with Klinefelters syndrome. Clin Endocrinol Oxf 1975; 4: 399-411.
6. **Tournaye H, Staessen C, Liebaers I, van Assche E, Devroey P, Bonduelle M, Van Steirteghem A.**
Testicular sperm recovery in nine 47,XXY Klinefelter patients. Hum Reprod 1996; 11: 1644-1649.
7. **Chevret E, Rousseaux S, Monteil M, Usson Y, Cozzi J, Pelletier R, Sèle B.**
Increased incidence of hyperhaploid 24 XY spermatozoa detected by three-colour FISH in a 46,XY/47,XXY male. Hum Genet 1996; 97: 171-175.
8. **Martini E, Geraedts JPM, Liebaers I, Land JA, Capitanio GL, Ramaekers FC, Hopman AH.**
Constitution of semen samples from XYY and XXY males as analysed by *in-situ* hybridization. Hum Reprod 1996; 11: 1638-1643.
9. **Cozzi J, Chevret E, Rousseaux S, Pelletier R, Benitz V, Jalbert H, Sèle B.**
Achievement of meiosis in XXY germ cells: study of 543 sperm karyotypes from an XY/XXY mosaic patient. Hum Genet 1994; 93: 32-34.
10. **Guttenbach M, Michelmann HW, Hinney B, Engel W, Schmid M.**
Segregation of sex chromosomes into sperm nuclei in a man with 47,XXY Klinefelter's karyotype: a FISH analysis. Hum Genet 1997; 99: 474-477.
11. **Estop AM, Munne S, Cieply KM, Vandermark KK, Lamb AN, Fisch H.**
Meiotic products of a Klinefelter 47,XXY male as determined by sperm fluorescence *in-situ* hybridization analysis. Hum Reprod 1998; 13: 124-127.
12. **Foresta C, Galeazzi C, Bettella A, Stella M, Scandellari C.**
High incidence of sperm sex chromosomes aneuploidies in two patients with Klinefelter's syndrome. J Clin Endocrinol Metab 1998; 83: 203-205.
13. **Hennebicq S, Pelletier R, Rousseaux S, Sèle B.**
Segregation of sex chromosomes in a Klinefelter patient [47,XXY).
Hum Reprod (Abstract Book 1) 1999; 14: 66.
14. **Franco B, Guioli S, Pragliola A. Incerti B, Bardoni B, Tonlorenzi R, Carrozzo R, Maestrini E, Pieretti M, Taillon-Miller P et al.**
A gene deleted in Kallmann's syndrome shares homology with neural cell adhesion and axonal path-finding molecules. Nature 1991; 353: 529-536.
15. **Santen RJ, Paulsen CA.**
Hypogonadotrophic Eunuchoidism. I. Clinical study of the Mode of Inheritance.
J Clin Endocrinol Metab 1973; 36: 47-54.
16. **Tincello DG, Saunders PT, Hargreave TB.**
Preliminary investigations on androgen receptor gene mutations in infertile men.
Mol Hum Reprod 1997; 3: 941-943.
17. **Gonìalves J, McElreavey K, Carreiro H, Vale F, Marques R, Simào L, Boieiro F, Fellous M, Lavinha J.**
An azoospermic man with a submicroscopic interstitial deletion on the Xp pseudoautosomal region. Hum Reprod (Abstract Book 1) 1996; 11:158-159.
18. **Gabriel-Robez O, Rumpler Y, Ratomponirina C, Petit C, Levilliers J, Croquette MF, Couturier J.**
Deletion of the pseudoautosomal region and lack of sex-chromosome pairing at pachytene in two infertile men carrying an X,Y translocation. Cytogenet Cell Genet 1990; 54: 38-42.
19. **Humphries P, Farrar GJ, Kenna P, McWilliam P.**
Retinitis pigmentosa: genetic mapping in X-linked and autosomal forms of the disease.
Clin Genet 1990; 38: 1-13.
20. **Dinauer MC, Orkin SH.**
Chronic granulomatous disease. Molecular genetics. Hematol Oncol Clin North Am 1988; 2: 225-240.
21. **Horn N, Tonnesen T, Tumer Z.**
Menkes disease: an X -linked neurological disorder of the copper metabolism.
Brain Pathol 1992; 2: 351-362.
22. **Pryor JL, Kent-First M, Muallem A, van Bergen AH, Nolten WE, Meisner L, Roberts KP.**
Microdeletions in the Y chromosome of infertile men. New Engl J Med 1997; 336: 534-539.
23. **Vogt P, Edelmann A, Kirsch S, Henegariu O, Hirschmann P, Kiesewetter F, Köhn FM, Schill WB, Farah S. Ramos C, Hartmann M, Hartschuh W, Meschede D, Behre HM, Castel A. Nieschlag E, Weidner W, Grone HJ, Jung A, Engel W, Haidl G.**
Human Y chromosome azoospermic factors AZF mapped to different regions in Ya11.
Hum Mol Genet 1996; 5: 933-943.
24. **Ma K, Sharkey A, Kirsch S, Vogt P, Keil R, Hargreave TB, McBeath S, Chandley AC.**
Towards the molecular localisation of the AZF locus: mapping of microdeletions in azoospermic men within 14 subintervals of interval 6 of the human Y chromosome. Hum Mol Genet 1992; 1: 29-33.
25. **Mallidis C, Loveland K, Najmabadi H, McLaughlin R, Baker G, Bhasin S, de Kretser DM.**

The incidence of the deleted in azoospermia gene in infertile men. Hum Reprod (Abstract Book 1) 1996; 11: 56-57.

26. **Kent-First M, Muallem A.**
Development of a large highly diagnostic panel of multiplexed sequence tagged sites (STS'S) which cover key regions on human Yq: its application in fertile and infertile (azoospermic and oligozoospermic) populations. Proceedings of the second international workshop on the Y chromosome. Organised by the National Institutes of Health USA and Human genome organisation, Medical Research Council, UK. Asilomar Conference Centre, Pacific Grove, California, Sept 17-20, 1995; 24-25.

27. **Küpker W, Ludwig M, Hahn K, Al-Hasani S, Montzka P, Felberbaum R, Sturm R, Yilmaz A, Diedrich K.**
Prevalence of microdeletions in the azoospermia factor region of the Y chromosome in cases of azoospermia and severe oligoasthenoteratozoospermia. Hum Reprod (Abstract Book 1) 1996; 11: 57.

28. **Kobayashi K, Mizuno K, Hida A, Komaki R, Tomita K, Matsushita I, Namiki M,, Iwamoto T, Tamura S, Minowada et al.**
PCR analysis of the Y chromosome long arm in azoospermic patients - evidence for a second locus required for spermatogenesis. Hum Mol Genet 1994; 3: 1965-1967.

29. **Najmabadi H, Huang V, Yen P, Subbarao MN, Bhasin D, Banaag L, Naseeruddin S, de Kretser DM, Baker HW, McLachlan RI et al.**
Substantial prevalence of microdeletions of the Y chromosome in infertile men with idiopathic azoospermia and oligozoospermia detected using a sequence-tagged site-based mapping strategy. J Clin Endocrinol Metab 1996; 81: 1347-1352.

30. **Reijo R, Alagappan RK, Patrizio P, Page DC.**
Severe oligozoospermia resulting from deletions of azoospermia factor gene on Y-chromosome. Lancet 1996; 347: 1290-1293.

31. **Qureshi SJ, Ross AR, Ma K, Cooke HJ, Intyre MA, Chandley AC, Hargreave TB.**
Polymerase chain reaction screening for Y chromosome microdeletions: a first step towards the diagnosis of genetically determined spermatogenic failure in men. Mol Hum Reprod 1996; 2: 775-779.

32. **Foresta C, Rossato M, Garolla A, Ferlin A.**
Male infertility and ICSI : are there any limits? Hum Reprod 1996; 11: 2347-2348.

33. **Stuppia L, Mastroprimiano G, Calabrese G, Peila R, Tenaglia R, Palka G.**
Microdeletions in interval 6 of the Y chromosome detected by STS-PCR in 6 of 33 patients with idiopathic oligo- or azoospermia. Cytogenet Cell Genet 1996; 72: 155-158.

34. **Foresta C, Ferlin A, Garolla A, Rossato M, Barbaux S, De Bortoli A.**
Y-chrosome deletions in idiopathic severe testiculopathies.
J Clin Endocrinol Metab 1997; 82: 1075 1080.

35. **Simoni M, Gromoll J, Dworniczak B, Rolf C, Abshagen K, Kamischke A, Carani C, Meschede D, Behre HM, Horst J, Nieschlag E.**
Screening for deletions of the Y chromosome involving the DAZ (Deleted in AZoospermia) gene in azoospermia and severe oligozoospermia. Fertil Steril 1997; 67: 542-547.

36. **Girardi SK, Mielnik A, Schlegel PN.**
Submicroscopic deletions in the Y chromosome of infertile men. Hum Reprod 1997; 12: 1635-1641.

37. **Stuppia L, Gatta V, Calabrese G, Franchi PG, Morizio E, Bombieri C, Mingarelli R, Sforza V, Frajese G, Tenaglia R, Palka G.**
A quarter of men with idiopathic oligo-azospermia display chromosomal abnormalities and microdeletions of different types in interval 6 of Yq11. Hum Genet 1998; 102: 566-570.

38. **Reijo R, Lee TY, Salo P, Alagappan R, Brown LG, Rosenberg M, Rozen S, Jaffe T, Straus D, Hovatta O et al.**
Diverse spermatogenic defects in humans caused by Y chromosome deletions encompassing a novel RNA-binding protein gene. Nat Genet 1995; 10: 383-393.

39. **Kent-First MG, Kol S, Muallem A, Blazer S, Itskovitz-Eldor J.**
Infertility in intracytoplasmic sperm injection-derived sons. Lancet 1996; 348: 332.

40. **Stuppia L, Gatta V, Mastroprimiano G.**
Clustering of Y-chromosome deletions in subinterval E of interval 6 supports the existence of an oligozoospermia critical region outside the DAZ gene. J Med Genet 1997; 34: 881-883.

41. **Mulhall JP, Reijo R, Alagappan R, Brown L, Page D, Carson R, Oates RD.**
Azoospermic men with deletion of the DAZ gene cluster are capable of completing spermatogenesis: fertilization, normal embryonic development and pregnancy occur when retrieved testicular spermatozoa are used for intracytoplasmic sperm injection. Hum Reprod 1997; 12: 503-508.

42. **Silber SJ, Alagappan R, Brown LG, Page DC.**
Y chromosome deletions in azoospermic and severely oligozoospermic men undergoing

intracytoplasmic sperm injection after testicular sperm extraction. Hum Reprod 1998; 13: 3332-3337.

43. **Kamischke A, Gromoll J, Simoni M, Behre HM, Nieschlag E.**
Transmisson of a Y chromosomal deletion involving the deleted in azoospermia (DAZ) and chromodomain (CDYI) genes from father to son through intracytoplasmic sperm injection: case report. Hum Reprod 1999; 14: 2320-2322.

44. **Henegariu O, Hirschmann P, Kilian K, Kirsch S, Lengauer C, Maiwald R, Mielke K, Vogt P.**
Rapid screening of the Y chromosome in idiopathic sterile men, diagnostic for deletions in AZF, a genetic Y factor expressed during spermatogenesis. Andrologia 1994; 26: 97-106.

45. **Simoni M, Nieschlag E.**
Molecular diagnostics of Y chromosomal microdeletions: the international quality control programme of the European Academy of Andrology. Hum Reprod (Abstract Book 1) 1999; 14: 92-93.

46. **Donat R, McNeill AS, Fitzpatrick DR, Hargreave TB.**
The incidence of cystic fibrosis gene mutations in patients with congenital bilateral absence of the vas deferens in Scotland. Br J Urol 1997; 79: 74-77.

47. **Dean M, Santis G.**
Heterogeneity in the severity of cystic fibrosis and the role of CFTR gene mutations. Hum Genet 1994; 93: 364-368.

48. **Tournaye H, Devroey P, Liu J, Nagy Z, Lissens W, Van Steirteghem A.**
Microsurgical epididymal sperm aspiration and intracytoplasmic sperm injection: a new effective approach to infertility as a result of congenital bilateral absence of the vas deferens. Fertil Steril 1994; 61: 1045-1051.

49. **Oates RD, Amos JA.**
The genetic basis of congenital bilateral absence of the vas deferens and cystic fibrosis. J Androl 1994; 15:1-8.

50. **Mercier B, Verlingue C, Lissens W, Silber SJ, Novelli G, Bonduelle M, Audrezet MP, Ferec C.**
Is congenital bilateral absence of vas deferens a primary form of cystic fibrosis? Analyses of the CFTR gene in 67 patients. Am J Hum Genet 1995; 56: 272 277.

51. **De Braekeleer M, Ferec C.**
Mutations in the cystic fibrosis gene in men with congenital bilateral absence of the vas deferens. Mol Hum Reprod 1996; 2: 669-677.

52. **Chillon M, Casals T, Mercier B, Bassas L, Lissens W, Silber S, Romey MC, Ruiz Romero J, Verlingue C, Claustres M et al.**
Mutations in cystic fibrosis gene in patients with congenital absence of the vas deferens. New Engl J Med 1995; 332: 1475-1480.

53. **Drake MJ, Quinn FM.**
Absent vas deferens and ipsilateral multicystic dysplastic kidney in a child. Br J Urol 1996; 77: 756-757.

54. **Augarten A, Yahav Y, Kerem BS, Halle D, Laufer J, Szeinberg A, Dor J, Mashiach S, Gazit E, Madgar I.**
Congenital bilateral absence of the vas deferens in the absence of cystic fibrosis. Lancet 1994; 344: 1473-1474.

3. PRIMARY SPERMATOGENIC 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.

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

3.3 Testicular morphology

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

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

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

Score	Histological criteria
10	Full spermatogenesis
9	Many late spermatids, disorganized epithelium
8	Few late spermatids
7	No late spermatids, many early spermatids
6	No late spermatids, few early spermatids
5	No spermatids, many spermatocytes
4	No spermatids, few spermatocytes
3	Spermatogonia only
2	No germinal cells, Sertoli cells only
1	No seminiferous epithelium

Table 6. Scoring system for testicular biopsies (Holstein score [7])

1.	No seminiferous epithelial cells, tubular sclerosis
2.	No germ cells, Sertoli cells only
3.	Spermatogonia only
4.	No spermatids, few spermatocytes, arrest at primary spermatocyte stage
5.	No spermatids, many spermatocytes
6.	Few early spermatids, disturbance of spermatid differentiation
7.	No late spermatids, many early spermatids
8.	Few late spermatids
9.	Many late spermatids, disorganized tubular epithelium
10.	Full spermatogenesis

Typical findings for the history and physical examination of a patient with non-ohstructive acoospermia 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
•	Gnodadotoxic medication
•	Radiation or chemical exposure
•	Groin surgeries
•	Testicular cancer

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

•	azoospermia
•	Absense of testes
•	Abnormal secondary sexual characteristics
•	Gynaecomastia
•	Cryptochordism
•	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

Author	**Year**	**No. Patients**	**Presence of sperm in testicular biopsy**
Tournaye *et al*. [23]	1995	38	36 (94%)
Devroey *et al*. [24]	1995	15	13 (86%)
Kahraman *et al*. [25]	1996	29	14 (48%)
Chen & Chen [26]	1996	41	21 (51.2%)
Tournaye *et al*. [27]	1996	54	44 (81%)
Fahmy *et al*. [28]	1997	30	23 (77%)
Mansour *et al*. [29]	1997	103	60 (56.6%)
Friedler *et al*. [30]	1997	37	16 (43%)
Mulhall *et al*. [15]	1997	30	21 (70%)
Kim *et al*. [31]	1997	57	17 (30%)
Silber *et al*. [21]	1997	45	26 (58%)
Schlegel [32]	1997	16	10 (62%)
Ezeh *et al*.[16]	1998	35	22 (63%)
Ghazzawi *et al*. [33]	1998	41	30 (73%)
Hauser *et al*. [34]	1998	29	18 (62%)
Jezek [17]	1998	64	49 (77%)
Gil-Salom [35]	1998	154	63 (41%)
Palermo *et al*. [36]	1999	83	53 (63.9%)
Schlegel [37]	1999	27	17 (63%)

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%).

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

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

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 testicle.

Although fine needle aspiration enables more areas of the testis to be reached, open testicular biopsy allows more tissue and sperm to be retrieved [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 tree rim of each testis and small pieces of extruding testicular tissue are removed. The fragments of testicular tissue are immediately placed in a Petri dish containing 2 mL of culture medium and transferred to the 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 punctions 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.

3.11 References

1. **Willott GM.**
   Frequency of azoospermia. Forensic Sci Int 1982; 20: 9-10.
2. **Stanwell-Smith RE, Hendry WF.**
   The prognosis of male subfertility: a survey of 1025 men referred to a fertility clinic.
   Br J Urol 1984; 56: 422-428.
3. **Jequier AM, Holmes SC.**
   Aetiological factors in the production of obstructive azoospermia. Br J Urol 1984; 56: 540-543.
4. **Palermo G, Joris H, Devroey P, Van Steirteghem AC.**
   Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. Lancet 1992; 340: 17-18.
5. **Jarow JP, Espeland MA, Lipshultz LI.**
   Evaluation of the azoospermic patient. J Urol 1989; 142: 62-65.
6. **Johnsen SG.**
   Testicular biopsy score count - a method for registration of spermatogenesis in human testes: normal values and results in 335 hypogonadal males. Hormones 1970; 1: 2-25.
7. **De Kretser DM, Holstein AF.**
   Testicular biopsy and abnormal germ cells; in Hafez ESE (ed): Human Semen and Fertility Regulation in Men. St. Louis, Mosby, 1976, pp 332-343.
8. **Ben-Yosef D, Yogev L, Hauser R, Yavetz H, Azem F, Yovel I, Lessing JB, Amit A.**
   Testicular sperm retrieval and cryopreservation prior to initiating ovarian stimulation as the first line approach in patients with non-obstructive azoospermia. Hum Reprod 1999; 14: 1794-1801.
9. **Hendin BN, Patel B, Levin HS, Thomas AJ Jr, Agarwal A.**
   Identification of spermatozoa and round spermatids in the ejaculates of men with spermatogenic failure. Urology 1998; 51: 816-819.

10. **Hauser R, Temple-Smith PD, Southwick GJ, de Kretser D.**
Fertility in cases of hypergonadotropic azoospermia. Fertil Steril 1995; 63: 631-636.
11. **Martin-du Pan RC, Bischof P.**
Increased follicle stimulating hormone in infertile men. Is increased plasma FSH always due to damaged germinal epithelium? Hum Reprod 1995; 10: 1940-1945.
12. **De Kretser DM, Burger HG, Hudson B.**
The relationship between germinal cells and serum FSH in males with infertility.
J Clin Endocrinol Metab 1974; 38: 787-793.
13. **Pierik FH, Vreeburg JT, Stijnen T, De Jong FH, Weber RF.**
Serum inhibin B as a marker of spermatogenesis. J Clin Endocrinol Metab 1998; 83: 3110-3114.
14. **Schulze W, Rehder U.**
Organization and morphogenesis of the human seminiferous epithelium. Cell Tissue Res 1984; 237: 395-407.
15. **Mulhall JP, Burgess CM, Cunningham D, Carson R, Harris D, Oates RD.**
Presence of mature sperm in testicular parenchyma of men with nonobstructive azoospermia: prevalence and predictive factors. Urology 1997; 49: 91-96.
16. **Ezeh UI, Moore HD, Cooke ID.**
Correlation of testicular sperm extraction with morphological, biophysical and endocrine profiles in men with azoospermia due to primary gonadal failure. Hum Reprod 1998; 13: 3066-3074.
17. **Jezek D, Knuth UA, Schulze W.**
Successful testicular sperm extraction (TESE) in spite of high serum follicle stimulating hormone and azoospermia: correlation between testicular morphology, TESE results, semen analysis and serum hormone values in 103 infertile men. Hum Reprod 1998; 13: 1230-1234.
18. **Bergmann M, Behre HM, Nieschlag E.**
Serum FSH and testicular morphology in male infertility. Clin Endocrinol Oxf 1994; 40: 133-136.
19. **Turek PJ, Kim M, Gilbaugh JH 3rd, Lipshultz LI.**
The clinical characteristics of 82 patients with Sertoli cell-only testis histology. Fertil Steril 1995; 64: 1197-1200.
20. **Skakkebaek NE, Hammen R, Philip J, Rebbe H.**
Quantification of human seminiferous epithelium. 3. Histological studies in 44 infertile men with normal chromosomal complements. Acta Path Microbiol Scand A 1973; 81: 97-111.
21. **Silber SJ, Nagy Z, Devroey P, Tournaye H, Van Steirteghem AC.**
Distribution of spermatogenesis in the testicles of azoospermic men: the presence or absence of spermatids in the testes of men with germinal failure. Hum Reprod 1997; 12: 2422 2428.
22. **Silber SJ, Patrizio P, Asch RH.**
Quantitative evaluation of spermatogenesis by testicular histology in men with congenital absence of the vas deferens undergoing epididymal sperm aspiration. Hum Reprod 1990; 5: 89-93.
23. **Tournaye H, Camus M, Goossens A, Liu J, Nagy P, Silber S, Van Steirteghem AC, Devroey P.**
Recent concepts in the management of infertility because of non-obstructive azoospermia.
Hum Reprod 1995; 10 (Suppl 1): 115-119.
24. **Devroey P, Liu J, Nagy Z, Goossens A, Tournaye H, Camus M, Van Steirteghem A, Silber S.**
Pregnancies after testicular sperm extraction and intracytoplasmic sperm injection in non-obstructive azoospermia. Hum Reprod 1995; 10: 1457-1460.
25. **Kahraman S, Özgur S, Alatas C, Aksoy S, Tasdemir M, Nuhoglu A, Tasdemir I, Balaban B, Biberoglu K, Schoysman R, Nijs M, Vanderzwalmen P.**
Fertility with sperm extraction and intracytoplasmic sperm injection in non-obstructive azoospermic men. Hum Reprod 1996; 11: 756-760.
26. **Chen SU, Ho HN, Chen HF.**
Fertilization and embryo cleavage after intracytoplasmic spermatid injection in an obstructive azoospermic patient with defective spermatogenesis. Fertil Steril 1996; 66: 157-160.
27. **Tournaye H, Liu J, Nagy PZ, Camus M, Goossens A, Silber S, Van Steirteghem AC, Devroey P.**
Correlation between testicular histology and outcome after intracytoplasmic sperm injection using testicular spermatozoa. Hum Reprod 1996; 11: 127-132.
28. **Fahmy I, Mansour R, Aboulghar M, Serour G, Kamal A, Tawab NA, Ramzy AM, Amin Y.**
Intracytoplasmic sperm injection using surgically retrieved epididymal and testicular spermatozoa in cases of obstructive and non-obstructive azoospermia. Int J Androl 1997; 20: 37-44.
29. **Mansour RT, Kamal A, Fahmy I, Tawab N, Serour GI, Aboulghar MA.**
Intracytoplasmic sperm injection in obstructive and non-obstructive azoospermia.
Hum Reprod 1997; 12: 1974-1979.
30. **Friedler S, Raziel A, Soffer Y, Strassburger D, Komarovsky D, Ron-El R.**
Intracytoplasmic injection of fresh and cryopreserved testicular spermatozoa in patients with nonobstructive azoospermia - a comparative study. Fertil Steril 1997; 68: 892-897.

31. **Kim ED, Gilbaugh JH 3rd , Patel VR, Turek PJ, Lipshultz LI.**
Testis biopsies frequently demonstrate sperm in men with azoospermia and significantly elevated follicle-stimulating hormone levels. J Urol 1997; 157: 144-146.
32. **Schlegel PN, Palermo GD, Goldstein M, Menendez S, Zaninovic N, Veeck LL, Rosenwaks Z.**
Testicular sperm extraction with intracytoplasmic sperm injection for nonobstructive azoospermia. Urology 1997; 49: 435-440.
33. **Ghazzawi IM, Sarraf MG, Taher MR, Khalifa FA.**
Comparison of the fertilizing capability of spermatozoa from ejaculates, epididymal aspirates and testicular biopsies using intracytoplasmic sperm injection. Hum Reprod 1998; 13: 348-352.
34. **Hauser R, Botchan A, Amit A, Ben-Yosef D, Gamzu R, Paz G, Lessing JB, Yogev L, Yavetz H.**
Multiple testicular sampling in non-obstructive azoospermia - is it necessary?.
Hum Reprod 1998; 13: 3081-3085.
35. **Gil-Salom M, Romero J, Mínguez Y, Molero MD, Remohí J, Pellicer A.**
Testicular sperm extraction and intracytoplasmic sperm injection: a chance of fertility in nonobstructive azoospermia. J Urol 1998; 160: 2063-2067.
36. **Palermo GD, Schlegel PN, Hariprashad JJ, Ergun B, Mielnik A, Zaninovic N, Veeck LL, Rosenwaks Z.**
Fertilization and pregnancy outcome with intracytoplasmic sperm injection for azoospermic men. Hum Reprod 1999; 14: 741-748.
37. **Schlegel PN.**
Testicular sperm extraction microdissection improves sperm yield with minimal tissue excision. Hum Reprod 1999; 14: 131-135.
38. **Gottschalk-Sabag S, Weiss DB, Folb-Zacharow N, Zukerman Z.**
Is one testicular specimen sufficient for quantitative evaluation of spermatogenesis?
Fertil Steril 1995; 64: 399-402.
39. **Turek PJ, Cha I, Ljung BM.**
Systematic fine-needle aspiration of the testis:correlation to biopsy and results of organ “mapping” for mature sperm in azoospermic men. Urology 1997; 49: 743-748.
40. **Steinberger E, Tjioe DY.**
A method for quantitative analysis of human seminiferous epithelium. Fertil Steril 1968; 19: 959-961.
41. **Chen CS, Chu SH, Lai YM, Wang ML, Chan PR.**
Reconsideration of testicular biopsy and follicle-stimulating hormone measurement in the era of intracytoplasmic sperm injection for non-obstructive azoospermia? Hum Reprod 1996; 11: 2176-2179.
42. **Kim ED, Greer JA, Abrams J, Lipshultz LI.**
Testicular touch preparation cytology. J Urol 1996; 156: 1412-1414.
43. **Cohen MS, Frye S, Warner RS, Leiter E.**
Testicular needle biopsy in diagnosis of infertility. Urology 1984; 24: 439-442.
44. **Cohen MS, Warner RS.**
Needle biopsy of testes: a safe outpatient procedure. Urology 1987; 29: 279-281.
45. **Harrington TG, Schauer D, Gilbert BR.**
Percutaneous testis biopsy: an alternative to open testicular biopsy in the evaluation of the subfertile man. J Urol 1996; 156: 1647 1651.
46. **Craft I, Tsirigotis M, Courtauld E, Farrer-Brown G.**
Testicular needle aspiration as an alternative to biopsy for the assessment of spermatogenesis.
Hum Reprod 1997; 12: 1483-1487.
47. **Kessaris DN, Wasserman P, Mellinger BC.**
Histopathological and cytopathological correlations of percutaneous testis biopsy and open testis biopsy in infertile men. J Urol 1995; 153: 1151-1155.
48. **Gottschalk-Sabag S, Glick T, Bar-On E, Weiss DB.**
Testicular fine needle aspiration as a diagnostic method. Fertil Steril 1993; 59: 1129-1131.
49. **Foresta C, Varotto A, Scandellari C.**
Assessment of testicular cytology by fine needle aspiration as a diagnostic parameter in the evaluation of the oligospermic subject. Fertil Steril 1992; 57: 858-865.
50. **Odabas Ö, Ugras S, Aydin S, Yilmaz Y, Atilla MK.**
Assessment of testicular cytology by fine-needle aspiration and the imprint technique: are they reliable diagnostic modalities?. Br J Urol 1997; 79: 445-448.
51. **Rosenlund B, Kvist U, Plöen L, Rozell BL, Sjoblom P, Hillensjo T.**
A comparison between open and percutaneous needle biopsies in men with azoospermia.
Hum Reprod 1998; 13: 1266-1271.
52. **Oates RD, Mulhall J, Burgess C, Cunningham D, Carson R.**
Fertilization and pregnancy using intentionally cryopreserved testicular tissue as the sperm source for intracyto-

plasmic sperm injection in 10 men with non-obstructive azoospermia. Hum Reprod 1997; 12: 734-739.

53. **Schoysman R, Vanderzwalmen P, Nijs M, Segal L, Segal-Bertin G, Geerts L, van Roosendaal E.**
Pregnancy after fertilization with human testicular sperm. Lancet 1993; 342: 1237.

54. **Devroey P, Liu J, Nagy Z, Tournaye H, Silber SJ, Van Steirteghem AC.**
Normal fertilization of human oocytes after testicular sperm extraction and intracytoplasmic sperm injection. Fertil Steril 1994; 62: 639-641.

55. **Silber SJ, Van Steirteghem AC, Liu J, Nagy Z, Tournaye H, Devroey P.**
High fertilization and pregnancy rate after intracytoplasmic sperm injection with spermatozoa obtained from testicle biopsy. Hum Reprod 1995; 10: 148-152.

56. **Devroey P, Nagy P, Tournaye H, Liu J, Silber S, Van Steirteghem A.**
Outcome of intracytoplasmic sperm injection with testicular spermatozoa in obstructive and non-obstructive azoospermia. Hum Reprod 1996; 11: 1015-1018.

57. **Ezeh UI, Moore HD, Cooke ID.**
A prospective study of multiple needle biopsies versus a single open biopsy for testicular sperm extraction in men with non-obstructive azoospermia. Hum Reprod 1998; 13: 3075-3080.

58. **Bourne H, Watkins W, Speirs A, Baker HW.**
Pregnancies after intracytoplasmic sperm injection of sperm collected by fine needle biopsy of the testis. Fertil Steril 1995; 64: 433-436.

59. **Ron-El R, Strauss S, Friedler S, Strassburger D, Komarovsky D, Raziel A.**
Serial sonography and colour flow Doppler imaging following testicular and epididymal sperm extraction. Hum Reprod 1998; 13: 3390-3393.

60. **Gil-Salom M, Romero J, Minguez Y, Rubio C, De los Santos MJ, Remohí J, Pellicer A.**
Pregnancies after intracytoplasmic sperm injection with cryopreserved testicular spermatozoa. Hum Reprod 1996; 11: 1309-1313.

61. **Romero J, Remohí J, Mínguez Y, Rubio C, Pellicer A, Gil-Salom M.**
Fertilization after intracytoplasmic sperm injection with cryopreserved testicular spermatozoa. Fertil Steril 1996; 65: 877-879.

62. **Perraguin-Jayot S, Audebert A, Emperaire JC, Parneix I.**
Ongoing pregnancies after intracytoplasmic injection using cryopreserved testicular spermatozoa. Hum Reprod 1997; 12:2706-2709.

63. **Allan JA, Cotman AS.**
A new method for freezing testicular biopsy sperm: three pregnancies with sperm extracted from cryopreserved sections of seminiferous tubule. Fertil Steril 1997; 68: 741-744.

64. **Liu J, Tsai YL, Katz E, Compton G, Garcia JE, Baramki TA.**
Outcome of in-vitro culture of fresh and frozen-thawed human testicular spermatozoa. Hum Reprod 1997; 12: 1667-1672.

65. **Ron-El R, Friedler S, Strassburger D, Komarovsky D, Schachter M, Raziel A.**
Birth of a healthy neonate following the intracytoplasmic injection of testicular spermatozoa from a patient with Klinefelter's syndrome. Hum Reprod 1999; 14: 368-370.

66. **Reubinoff BE, Abeliovich D, Werner M, Schenker JG, Safran A, Lewin A.**
A birth in non-mosaic Klinefelter's syndrome after testicular fine needle aspiration, intracytoplasmic sperm injection and preimplantation genetic diagnosis. Hum Reprod 1998; 13: 1887-1892.

67. **Bourne H, Stern K, Clarke G, Pertile M, Speirs A, Baker HW.**
Delivery of normal twins following the intracytoplasmic injection of spermatozoa from a patient with 47,XXY Klinefelter's syndrome. Hum Reprod 1997; 11: 2447-2450.

68. **Brugo Olmedo S, Nodar F, Acosta A, Urrutia F, Noblia F, De Vincentiis S, Rawe V.**
Triple pregnancy obtained using testicular sperm from a patient with Klinefelter syndrome, following intracytoplasmic sperm injection (ICSI) augmented with testicular sperm extraction (TESE). Fertil Steril 1998; 70 (Suppl 1): S201.

69. **Sofikitis N, Miyagawa I, Agapitos E, Pasyianos P, Toda T, Hellström WJ. Kawamura H.**
Reproductive capacity of the nucleus of the male gamete after completion of meiosis. J Assist Reprod Genet 1994; 11: 335-341.

70. **Sofikitis NV, Toda T, Miyagawa I, Zavos PM, Pasyianos P, Mastelou E.**
Beneficial effects of electrical stimulation before round spermatid nuclei injections into rabbit oocytes on fertilization and subsequent embryonic development. Fertil Steril 1996; 65: 176-185.

71. **Kimura Y, Yanagimachi R.**
Development of normal mice from oocytes injected with secondary spermatocyte nuclei. Biol Reprod 1995; 53: 855-862.

72. **Edwards RG, Tarin JJ, Dean N, Hirsch A, Tan SL.**
Are spermatid injections into human oocytes now mandatory? Hum Reprod 1994; 9: 2217-2219.

73. Tesarik J, Mendoza C, Testart J.
Viable embryos from injection of round spermatids into oocytes. New Engl J Med 1995; 333: 525.
74. Fishel S, Green S, Bishop M, Thornton S, Hunter A, Fleming S, Al-Hassan S.
Pregnancy after intracytoplasmic sperm injection of spermatid. Lancet 1995; 345: 1641-1642.
75. Yamanaka K, Sofikitis NV, Miyagawa I, Yamamoto Y, Toda T, Antypas S, Dimitriadis D, Takenaka M, Taniguchi K, Takahashi K, Tsukamoto S, Kawamura H, Neil M.
Ooplasmic round spermatid nuclear injections as an experimental treatment for non-obstructive azoospermia. J Assist Reprod Genet 1997; 14: 55-62.
76. Antinori S, Versaci C, Dani G, Antinori M, Pozza D, Slman HA.
Fertilization with human testicular spermatids: four successful pregnancies. Hum Reprod 1997; 12: 286-291.
77. Amer M, Soliman E, El-Sadek M, Mendoza C, Tesarik J.
Is complete spermiogenesis failure a good indication for spermatid conception? Lancet 1997; 350: 116.
78. Vanderzwalmen P, Zech H, Birkenfeld A, Yemini M, Bertin G, Lejeune B, Nijs M, Segal L, Stecher A, Vandamme B, van Roosendaal E, Schoysman R.
Intracytoplasmic injection of spermatids retrieved from testicular tissue: influence of testicular pathology, type of selected spermatids and oocyte activation. Hum Reprod 1997; 12: 1203-1213.

4. OBSTRUCTIVE AZOOSPERMIA

4.1 Definition

Obstructive azoospermia means the absence of both spermatozoa and spermatogenetic 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/atresia 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 urethroprostatitis [16].

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

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 herniorrhaphy or traumas, and chronic sinopulmonary infections.

Clinical examination
This follows the suggestions for investigation of infertile men. The following are particularly importent:
- 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) biplanar 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.

Testicular 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

1. **Pryor JP.**
Indications for vasovesiculography and testicular biopsy. An update; in Colpi GM, Pozza D (eds): Diagnosing Male Infertility: New Possibilities and Limits. Basel, Karger: Basel, 1992, pp 130-135.

2. **Hendry WF, Parslow JM, Stedronska J.**
Exploratory scrototomy in 168 azoospermic males. Br J Urol 1983; 55: 785-791.

3. **Jequier AM.**
Obstructive azoospermia: a study of 102 patients. Clin Reprod Fertil 1985; 3: 21-36.

4. **Jarow JP, Espeland MA, Lipshultz LI.**
Evaluation of the azoospermic patient. J Urol 1989; 142: 62-65.

5. **Oates RD, Amos JA.**
The genetic basis of congenital bilateral absence of the vas deferens and cystic fibrosis. J Androl 1994; 15: 1-8.

6. **Handelsman DJ, Conway AJ, Boylan LM, Turtle JR.**
Young's syndrome: Obstructive azoospermia and chronic sinopulmonary infections.
New Engl J Med 1984; 310: 3-9.

7. **Silber SJ.**
Evolution of microsurgery of the epididymis; in Bollack C, Clavert A (eds): Epididymis and Fertility: Biology and Pathology. Basel, Karger, 1981, vol 8, pp 114-122.

8. **Schoysman R.**
Vaso-epididymostomy - a survey of techniques and results with considerations of delay of appearance of spermatozoa after surgery. Acta Eur Fertil 1990; 21: 239-245.

9. **Thomas AJ Jr.**
Vasoepididymostomy. Urol Clin North Am 1987; 14: 527-538.

10. **Poore RE, Schneider A, DeFranzo AJ, Humphries ST, Woodruff RD, Jarow JP.**
Comparison of puncture versus vasotomy techniques for vasography in an animal model.
J Urol 1997; 158: 464-466.

11. **Schlegel PN, Shin D, Goldstein M.**
Urogenital anomalies in men with congenital absence of the vas deferens. J Urol 1996; 155:1644-1648.

12. **Borovikov A.**
Treatment of large vasal defects; in Goldstein M (ed).Surgery of Male Infertility. Philadelphia, Saunders, 1995, pp 77-95.

13. **Elder JS, Mostwin JL.**
Cyst of the ejaculatory duct/urogenital sinus. J Urol 1984; 132: 768-771.

14. **Schuhrke TD, Kaplan GW.**
Prostatic utricle cysts (Mullerian duct cysts). J Urol 1978; 119: 765-767.

15. **Surya BV, Washecka R, Glasser J, Johanson KE.**
Cysts of the seminal vesicles: diagnosis and management. Br J Urol 1988; 62: 491-493.

16. **Schroeder-Printzen I, Ludwig M, Köhn F, Weidner W.**
Surgical therapy in infertile men with ejaculatory duct obstruction: technique and outcome of a standardized surgical approach. Hum Reprod 2000; 15: 1364-1368.

17. **Kuligowska E, Baker CE, Oates RD.**
Male infertility: role of transrectal US in diagnosis and management. Radiology 1992; 185: 353-360.

18. **Colpi GM, Casella F, Zanollo A, Ballerini G, Balerna M, Campana A, Lange A.**
Functional voiding disturbances of the ampullo-vesicular seminal tract: a cause of male infertility.
Acta Eur Fertil 1987; 18: 165-179.

19. **Hendry WF, Rickards D, Pryor JP, Baker LR.**

Seminal megavesicles with adult polycystic kidney disease. Hum Reprod 1998; 13: 1567-1569.

20. **Colpi GM, Negri L, Nappi RE, Chinea B.**
Is transrectal ultrasonography a reliable diagnostic approach in ejaculatory duct sub-obstruction? Hum Reprod 1997; 12: 2186-2191.

21. **Meacham RB, Hellerstein DK, Lipshultz LI.**
Evaluation and treatment of ejaculatory duct obstruction in the infertile male. Fertil Steril 1993; 59: 393-397.

22. **Jarow JP:**
Seminal vesicle aspiration of fertile men. J Urol 1997; 156: 1005-1007.

23. **Colpi GM, Negri L, Scroppo FI, Grugnetti C, Patrizio P.**
Seminal tract washout: a new diagnostic tool in complicated cases of male infertility.
J Androl 1994; 15 (Suppl): 17S-22S.

24. **Goldstein M.**
Vasography; in Goldstein MG (ed).Surgery of Male Infertility. Philadelphia, Saunders, 1995, pp 26-31.

25. **Silber SJ, Balmaceda J, Borrero C, Ord T, Asch R.**
Pregnancy with sperm aspiration from the proximal head of the epididymis: a new treatment for congenital absence of the vas deferens. Fertil Steril 1988; 50: 525-528.

26. **Schroeder-Printzen I, Zumbé G, Bispink L, Palm S, Schneider U, Engelmann U, Weidner W and the MESA/TESE Group Giessen.**
Microsurgical epididymal sperm aspiration: aspirate analysis and straws available after cryopreservation in patients with non-reconstructable obstructive azoospermia. Hum Reprod 2000; 50: 2531-2535.

27. **Matthews GJ, Schlegel PN, Goldstein M.**
Patency following microsurgical vasoepididymostomy and vasovasostomy: temporal consideration.
J Urol 1995; 154: 2070-2073.

28. **Jarow JP, Oates RD, Buch JP, Shaban SF, Sigman M.**
Effect of level of anastomosis and quality of intraepididymal sperm on the outcome of end-to-side epididymovasostomy. Urology 1997; 49: 590-595.

29. **Kim ED, Winkel E, Orejuela F, Lipshultz LI.**
Pathological epididymal obstruction unrelated to vasectomy: results with microsurgical reconstruction.
J Urol 1998; 160:2078-2080.

30. **Jarow JP, Sigman M, Buch JP, Oates RD.**
Delayed appearance of sperm after end-to-side vasoepididymostomy. J Urol 1995; 153: 1156-1158.

31. **Jarvi K, Zini A, Buckspan MB, Asch M, Ginzburg B, Margolis M.**
Adverse effects on vasoepididymostomy outcomes for men with concomitant abnormalities in the prostate and seminal vesicle. J Urol 1998; 160: 1410-1412.

32. **Kolettis PN, Thomas AJ Jr.**
Vasoepididymostomy for vasectomy reversal: a critical assessment in the era of intracytoplasmic sperm injection. J Urol 1997; 158: 467-470.

33. **Ruiz-Romero J, Sarquella J, Pomerol JM.**
A new device for microsurgical sperm aspiration. Andrologia 1994; 26: 119-120.

34. **Hendry WF.**
Azoospermia and surgery for testicular obstruction; in Hargreave TB (ed): Male Infertility. London, Springer, 1997, pp 319-336.

35. **Gilbert BR.**
Transurethral resection for ejaculatory duct obstruction; in Goldstein MG (ed): Surgery of Male Infertility. Philadelphia, Saunders, 1995, pp 220-238.

36. **Colpi GM, Negri L, Patrizio P, Pardi G.**
Fertility restoration by seminal tract washout in ejaculatory duct obstruction. J Urol 1995; 153: 1948-1950.

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.

Lenght 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.

Epidiclymovasotomy

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 retrival 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.

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

1. **Schlegel PN, Goldstein M.**
   Vasectomy; in Goldstein M (ed): Surgery of Male Infertility. Philadelphia, Saunders, 1995, pp 35-45.
2. **Li S, Goldstein M, Zhu J, Huber D.**
   The no-scalpel vasectomy. J Urol 1991; 145: 341-344.
3. **Kendrick JS, Gonzales B, Huber DH, Grubb GS, Rubin GL.**
   Complications of vasectomies in the United States. J Fam Pract 1987; 25: 245-248.
4. **Linnet L.**
   Clinical immunology of vasectomy and vasovasostomy. Urology 1983; 22: 101-114.
5. **Verhulst APM, Hoekstra JW.**
   Paternity after bilateral vasectomy. Br J Urol 1999; 83: 280-282.
6. **Bedford JM, Zelikovsky G.**
   Viability of spermatozoa in the human ejaculate after vasectomy. Fertil Steril 1979; 32: 460-463.
7. **Matthews GJ, Schlegel PN, Goldstein M.**
   Patency following microsurgical vasoepididymostomy and vasovasostomy: temporal considerations. J Urol 1995; 154: 2070-2073.
8. **Belker AM, Thomas AJ Jr, Fuchs EF, Konnak JW, Sharlip ID.**
   Results of 1.469 microsurgical vasectomy reversals by the Vasovasostomy Study Group. J Urol 1991; 145: 505-511.
9. **Weidner W, Schroeder-Printzen I, Weiske WH, Haidl G and the BMFT Study Group for Microsurgery, Giessen.**

Microsurgical aspects of the treatment of azoospermia. Int J Androl 1995; 18 (Suppl 2): 63-66.

10. **Pavlovich CP, Schlegel PN.**
Fertility options after vasectomy: a cost effectiveness analysis. Fertil Steril 1997; 67: 133-141.

11. **Kolettis PN, Thomas AJ Jr.**
Vasoepididymostomy for vasectomy reversal: a critical assessment in the era of intracytoplasmic sperm injection. J Urol 1997; 158: 467-470.

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 10^6/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 laparascopic varicocelectomy is feasible, it needs to be justified in terms of cost effectiveness.

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

Treatment		**Recurrence/ Persistence Rates**	**Complications**
Antegrade		9% [22]	Complication rate 0.3-2.2%
Sclerotherapy			Testicular atrophy; scrotal haematoma; epididymitis; left-flank erythema
Retrograde Sclerotherapy		Recurrence and persistence rate 9.8% [23,25]	Adverse reaction to the contrast medium; flank pain; persistent thrombophlebitis; vascular perforation [24]
Retrograde Embolisation		3.8-10% [26,27]	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]
Open Operation	Scrotal approach		Testicular atrophy [5]; arterial damage with risk of devascularisation and gangrene of the testicle
	Inguinal approach High ligation Micro-surgical	13.3% [29] 29% [29] 0.8-4% [31,32]	Possibility of missing out a branch of testicular vein 5-10% incidence of hydrocele [30] Post-operative hydrocele arterial injury Scrotal haematoma
Laparoscopy		3-7% [33-35]	Injury to testicular artery and lymph vessels; intestinal, vascular and nerve damage; pulmonary embolism; peritonitis [35]; bleeding; postoperative pain in right shoulder (due to diaphragmatic stretching during pneumoperitonium) [34]; pneumoscrotum; wound infection [35]

6.1.6 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 RECOMMANDATIONS

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.

6.1.8 References

1. **Hudson RW, Perez Marrero RA, Crawford VA, McKay DE.**
   Hormonal parameters in incidental varicoceles and those causing infertility. Fertil Steril 1986; 45: 692-700
2. **World Health Organization.**
   WHO manual for the standardized investigation, diagnosis and management of the infertile male. Cambridge University Press, 2000.
3. **Dhabuwala CB, Hamid S, Moghissi KS.**
   Clinical versus subclinical varicocele: improvement in fertility after varicocelectomy. Fertil Steril 1992; 57: 854-857.
4. **Kursh ED.**
   What is the incidence of varicocele in a fertile population? Fertil Steril 1987; 48: 510-511.
5. **Hargreave TB.**
   Varicocele in Male Infertility. Springer Verlag: London, Berlin, 1994.
6. **Nieschlag E, Hertle L, Fischedick A, Behre HM.**
   Treatment of varicocele: counselling as effective as occlusion of the vena spermatica. Hum Reprod 1995; 10:347-353.
7. **Peterson AC, Lance RS, Ruiz HE.**
   Outcomes of varicocele ligation done for pain. J Urol 1998; 159: 1565-1567.
8. **World Health Organization.**
   The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. Fertil Steril 1992; 57: 1289-1293.
9. **Laven JS, Haans LC, Mali WP, te Velde ER, Wensing CJ, Eimers JM.**
   Effects of varicocele treatment in adolescents: a randomized study. Fertil Steril 1992; 58: 756-762.
10. **Paduch DA, Niedzielski J.**
    Repair versus observation in adolescent varicocele: a prospective study. J Urol 1997; 158: 1128-1132.

11. **Butler GE, Ratcliffe SG.**
Serono symposia reviews. Serono Symposia Reviews 1984 (Suppl 1): 244.
12. **Hudson RW.**
Free sex steroid and sex hormone-binding globulin levels in oligozoospermic men with varicoceles. Fertil Steril 1996; 66: 299-304.
13. **Kass EJ.**
Pediatric varicocele; in O'Donnell B, Koff SA (eds): Pediatric Urology. Oxford, Boston, Johannesburg, Butterworth Heinemann, 1996, pp 608-617.
14. **Nilsson S, Edvinson A, Nilsson B.**
Improvement of semen and pregnancy rate after ligation and division of the internal spermatic vein: fact or fiction? Br J Urol 1979; 51: 591-596.
15. **Breznik R, Vlaisavljevic V, Borko E.**
Treatment of varicocele and male fertility. Arch Androl 1993; 30: 157-160.
16. **Madgar I, Weissenberg R, Lunenfeld B, Karasik A, Goldwasser B.**
Controlled trial of high spermatic vein ligation for varicocele in infertile men. Fertil Steril 1995; 63: 120-124.
17. **Nieschlag E, Hertle L, Fischedick A, Abshagen K, Behre HM.**
Update on treatment of varicocele: counselling as effective as occlusion of the vena spermatica. Hum Reprod 1998; 13: 2147-2150.
18. **Hargreave TB.**
Varicocele: overview and commentary on the results of the WHO varicocele trial; in Waites GM, Frick J, Baker GW (eds): Current Advances in Andrology. Proceedings of the VIth International Congress of Andrology, Salzburg, Austria. Bologna, Monduzzi Editore, 1997, pp 31-44.
19. **Evers JL.**
Varicocele; in Templeton A, Cooke ID (eds): 35th RCOG Study Group. Evidence based fertility treatment. London, RCOG Press, 1998.
20. **Yamamoto M, Hibi H, Hirata Y, Miyake K, Ishigaki T.**
Effect of varicocelectomy on sperm parameters and pregnancy rates in patients with subclinical varicocele: a randomized prospective controlled study. J Urol 1996; 155: 1636-1638.
21. **World Health Organization.**
Towards more objectivity in diagnosis and management of male fertility. Results of a World Health Organization multicentre study. Int J Androl 1987; (Suppl 7)
22. **Tauber R, Johnsen N.**
Antegrade scrotal sclerotherapy for the treatment of varicocele: Technique and late results. J Urol 1994; 151: 386-390.
23. **Thon W F, Sigmund G, Bahren W, Steimann J.**
Perkutane Sklerotherapie bei Vena testikularis Insuffiziens. Akt Urol 1986; 17: 240-243.
24. **Seyferth W, Jecht E, Zeitler E.**
Percutaneous sclerotherapy of varicocele. Radiology 1981; 139: 335-340.
25. **Sigmund G, Bahren W, Gall H, Lenz M, Thon W.**
Idiopathic varicoceles: feasibility of percutaneous sclerotherapy. Radiology 1987; 164: 161-168.
26. **Lenk S, Fahlenkamp D, Gliech V, Lindeke A.**
Comparison of different methods of treating varicocele. J Androl 1994; 15 (Suppl): 34S-37S.
27. **Feneley MR, Pal MK, Nockler IB, Hendry WF.**
Retrograde embolisation and causes of failure in the primary treatment of varicocele. Br J Urol 1997; 80:642-646.
28. **Lenz M, Hof N, Kersting-Sommerhoff B, Bautz W.**
Anatomic variants of the spermatic vein: importance for percutaneous sclerotherapy of idiopathic varicocele. Radiology 1996; 198: 425-431.
29. **Bassi R, Radice F, Bergami G, De-Grazia F, Papa B.**
Surgical treatment of varicocele. Our experience in the last 10 years. Minerva Chir 1996; 51: 533-536.
30. **Wallijn E, Desmet R.**
Hydrocele: a frequently overlooked complication after high ligation of the spermatic vein for varicocele. Int J Androl 1978; 1: 411-415.
31. **Goldstein M, Kim FY, Mathews GJ.**
Mini-incision microsurgical subinguinal varicocelectomy with delivery of the testis. J Urol 1996; 155 (Suppl) abstract videotape: 305A.
32. **Goldstein M.**
Varicocelectomy: General considerations; in Goldstein M (ed): Surgery of Male Infertility. Philadelphia, Saunders, 1995, pp 169-172.

33. McDougall E.
Minimally invasive therapy. J Urol 1995; 153: 712-713.
34. Miersch WD, Schoeneich G, Winter P, Buszello H.
Laparoscopic varicocelectomy: indication, technique and surgical results. Br J Urol 1995; 76: 636-638.
35. Tan SM, Ng FC, Ravintharan T, Lim PH, Chng HC.
Laparoscopic varicocelectomy: technique and results. Br J Urol 1995; 75: 523-528.
36. Tulloch WS.
Varicocele in subfertility: results of treatment. Br Med J 1955; 2: 356-358.

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 11. Disorders with male hypogonadism. Modified from [2]

Hypothalamic - pituitary origin (hypogonadotrophic = secondary hypogonadism)
• Idiopathic hypogonadotrophic hypogonadism (including Kallmann's syndrome)
• Delay of puberty
• Hyperprolactinaemia
Hypergonadotrophic syndromes = primary hypogonadism (= testicular origin)
• Anorchia (+ acquired)
• Klinefelter's syndrome
• Leydig cell tumours
• General diseases, e.g. liver cirrhosis
Target organ resistance to androgens
• Testicular feminization
• Reifenstein syndrome

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.

Testosterone supplementation is only indicated in men with levels consistently lower than normal (< 12 nmol/l = 300 ng/dl).

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

6.2.4 Conclusion

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

6.2.5 References

1. **Nachtigall LB, Boepple PA, Pralong FP, Crowey WF Jr.**
   Adult-onset idiopathic hypogonadotropic hypogonadism - a treatable form of male infertility. New Engl J Med 1997; 336: 410-415.
2. **Nieschlag E, Behre HM.**
   Testosterone: Action, Deficiency, Substitution, 2nd edition. Springer: Berlin, 1998.
3. **World Health Organization.**
   WHO manual for the standardized investigation, diagnosis and management of the infertile male. Cambridge University Press, 2000.
4. **Burris AS, Rodbard HW, Winters SJ, Sherins RJ.**
   Gonadotropin therapy in men with isolated hypogonadotropic hypogonadism: the response to human chorionic gonadotropin is predicted by initial testicular size. J Clin Endocrinol Metab 1988; 66: 1144-1151.
5. **Schopohl J, Mehltretter G, von Zumbusch R, Eversmann T, von Werder K.**
   Comparison of gonadotropin-releasing hormone and gonatropin therapy in male patients with idiopathic hypothalamic hypogonadism. Fertil Steril 1991; 56: 1143-1150.
6. **Manning M, Jünemann KP, Alken P.**
   Decrease in testosterone blood concentrations after testicular sperm extraction for intracytoplasmic sperm injection in azoospermic men. Lancet 1998; 352: 37.
7. **Tournaye H, Staessen C, Liebaers I, van Assche E, Devroey P, Bonduelle M, Van Steirteghem A.**
   Testicular sperm recovery in nine 47,XXY Klinefelter patients. Hum Reprod 1996; 11: 1644-1649.
8. **Gray A, Jackson DN, McKinlay JB.**
   The relation between dominance, anger, and hormones in normally aging men: results from the Massachusetts Male Aging Study. Psychosom Med 1991; 53: 375-385.
9. **Daniell HW.**
   Osteoporosis after orchiectomy for prostate cancer. J Urol 1997; 157: 439-444.
10. **Finkelstein JS.**
    Androgens and bone metabolism; in Nieschlag E, Behre HM (eds): Testosterone: Action, Deficiency, Substitution, 2nd edition. Berlin, Springer, 1998, pp 187-207.
11. **World Health Organization - Nieschlag E, Wang C, Handelsman DJ, Swerdloff RS, Wu F, Einer-Jensen N, Waites G.**
    Guidelines for the use of androgens. WHO, Geneva, 1992.

6.3 CRYPTORCHIDISM[2]

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

[2] Also partly based on The recommendations of the 'Infertility Guideline Group' of the Royal College of Obstetricians and Gynaecologists, London 1998.

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 hypogonadotrophic 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

1. **Leissner J, Filipas D, Wolf HK, Fisch M.**
The undescended testis: considerations and impact on fertility. Br J Urol 1999; 83: 885-892.

2. **Rozanski TA, Bloom DA.**
The undescended testis. Theory and management. Urol Clin North Am 1995; 22: 107-118.

3. **Cortes D.**
Cryptorchidism - aspects of pathogenesis, histology and treatment. Scand J Urol Nephrol 1998; 32 (Suppl): 196.

4. **Rogers E, Teahan S, Gallagher H, Butler MR, Grainger R, McDermott TE, Thornhill JA.**
The role of orchiectomy in the management of postpubertal cryptorchidism. J Urol 1998; 159: 851-854.

7. IDIOPATHIC OLIGOASTHENOTERATOZOOSPERMIA[3]

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.

[3] Also partly based on The recommendations of the 'Infertility Guideline Group' of the Royal College of Obstetricians and Gynaecologists, London 1998.

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

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

GnRH = gonadotrophin-releasing hormone; hCG = human chorionic 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
One single-blind, placebo-controlled randomized study [15] evaluated mast cell blockers in the treatment of severe oligozoospermia and revealed a positive effect on pregnancy rates.

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.

Alpha blockers are not a recommended treatment for OAT.

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

1. **O'Donovan A, Vandekerckhove P, Lilford RJ, Hughes E.**
   Treatment of male infertility: is it effective? Review and meta-analyses of published randomized controlled trials. Hum Reprod 1993; 8: 1209-1222.
2. **Howard ST.**
   Treatment of male infertility. New Engl J Med 1995; 332: 312-317.
3. **Collins JA, Burrows EA, Wilan AR.**
   The prognosis for live birth among untreated infertile couples. Fertil Steril 1995; 64: 22-28.
4. **Snick HK, Snick TS, Evers JL, Collins JA.**
   The spontaneous pregnancy prognosis in untreated subfertile couples: the Walcheren primary care study. Hum Reprod 1997; 12: 1582-1588.
5. **Kamischke A, Nieschlag E.**
   Analysis of medical treatment of male infertility. Hum Reprod 1999; 14 (Suppl 1): 1-23.
6. **Vandekerckhove P, Lilford R, Hughes E.**
   The medical treatment of idiopathic oligo/asthenozoospermia: androgens (mesterolone or testosterone) versus placebo or no treatment; in Lilford R, Hughes E, Vandekerckhove P (eds): Cochrane Review: The Cochrane Library, Issue 2. Oxford, Update Software, 1998.
7. **Vandekerckhove P, Lilford R, Hughes E.**
   The medical treatment of idiopathic oligo- and/or asthenozoospermia: antioestrogens (clomiphene or tamoxifen) versus placebo or no treatment; in Lilford R, Hughes E, Vandekerckhove P (eds): Cochrane Review: The Cochrane Library, Issue 2. Oxford, Update Software, 1998.
8. **Vandekerckhove P, Lilford R, Hughes E.**
   Kinin enhancing drugs for idiopathic male infertility; in LilfordR, Hughes E, Vanderkerckhove P (eds): Cochrane Review: The Cochrane Library, Issue 2. Oxford, Update Software, 1998.
9. **Knuth UA, Hönigl W, Bals-Pratsch M, Nieschlag E.**
   Treatment of severe oligospermia with human chorionic gonadotropin/human menopausal gonadotropin. A placebo-controlled double blind trial. J Clin Endocrinol Metab 1987; 65: 1081-1087.
10. **Kamischke A, Behre HG, Bergmann M, Simoni M, Schäfer T, Nieschlag E.**
    Recombinant human follicle stimulating hormone for treatment of male idiopathic infertility: a randomized, double-blind, placebo-controlled, clinical trial. Hum Reprod 1998; 13: 596-603.
11. **Schill WB, Parsch EM, Miska W.**
    Inhibition of angiotensin-converting enzyme - a new concept of medical treatment for male infertility?

Fertil Steril 1994; 61: 1123-1128.
12. **Kessopoulou E, Powers HJ, Sharma KK, Pearson MJ, Russelll JM, Cooke ID, Barratt CL.**
A double-blind randomized placebo cross-over-controlled trial using the antioxidant vitamin E to treat reactive oxygen species associated male infertility. Fertil Steril 1995; 64: 825-831.
13. **Suleiman SA, Ali ME, Zaki ZM, El-Malik EM, Nasr MA.**
Lipid peroxidation and human sperm motility: protective role of vitamin E. J Androl 1996; 17: 530-537.
14. **Lenzi A, Culasso F, Gandini L, Lombardo F, Dondero F.**
Placebo-controlled, double-blind, cross-over trial of glutathione therapy in male infertility.
Hum Reprod 1993; 8: 1657-1662.
15. **Yamamoto M, Hibi H, Miyake K.**
New treatment of idiopathic severe oligozoospermia with mast cell blocker: results of a single-blind study. Fertil Steril 1995; 64: 1221-1223.
16. **Yamamoto M, Hibi H, Miyake K.**
Comparison of the effectiveness of placebo and alpha-blocker therapy for the treatment of idiopathic oligozoospermia. Fertil Steril 1995; 64: 396-400.
17. **Katz M, Newill R.**
Steroid treatment for infertility associated with antisperm antibodies. Lancet 1980; 1: 1306.
18. **Haas GG Jr, Manganiello P.**
A double-blind, placebo-controlled study of the use of methylprednisolone in infertile men with sperm-associated immunoglobulins. Fertil Steril 1987; 47: 295-301.
19. **Hendry WF, Hughes L, Scammell G, Pryor JP, Hargreave TB.**
Comparison of prednisolone and placebo in subfertile men with antibodies to spermatozoa.
Lancet 1990; 335: 85-88.
20. **Bals-Pratsch M, Doren M, Karbowski B, Schneider HP, Nieschlag E.**
Cyclic corticosteroid immunosuppression is unsuccessful in the treatment of sperm antibody-related male infertility: a controlled study. Hum Reprod 1992; 7: 99-104.

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 diseasae has been classified into four clinical entities:

- acute bacterial prostatitis (ABP) and prostatic abscess as sequela of ABP,
- chronic bacterial prostatitis (CBP),
- non- or abacterial prostatitis (NBP) 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]

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

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, $> 1 \times 10^6$ 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 IIIB).

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]

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

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 sub- or infertility. 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

1. **Weidner W, Krause W, Ludwig M.**
   Relevance of male accessory gland infection for subsequent fertility with special focus on prostatitis. Hum Reprod Update 1999; 5: 421-432.
2. **World Health Organization.**
   WHO manual for the standardized investigation, diagnosis and management of the infertile male. Cambridge University Press, 2000.
3. **Purvis K, Christiansen E.**
   Infection in the male reproductive tract. Impact, diagnosis and treatment in relation to male infertility. Int J Androl 1993; 16: 1-13.
4. **Schiefer HG.**
   Microbiology of male urethroadnexitis: diagnostic procedures and criteria for aetiological classification. Andrologia 1998; 30 (Suppl 1): 7-13.
5. **Chambers RM.**
   The mechanism of infection in the urethra, prostate and epididymis; in Keith LG, Berger GS, Edelmann DA (eds): Infections in Reproductive Health: Common infections. Lancaster, MTP Press, pp 283-296.
6. **Ness RB, Markovic N, Carlson CL, Coughlin MT.**
   Do men become infertile after having sexually transmitted urethritis? An epidemiologic examination. Fertil Steril 1997; 68: 205-213.
7. **Trum JW, Mol BW, Pannekoek Y, Spanjaard L, Wertheim P, Bleker OP, van der Veen F.**
   Value of detecting leukocytospermia in the diagnosis of genital tract infection in subfertile men. Fertil Steril 1998; 70: 315-319.
8. **Purvis K, Christiansen E.**
   The impact of infection on sperm quality. J Br Fertil Soc 1995; 1: 31-41.
9. **Krieger JN.**
   New sexually transmitted diseases treatment guidelines. J Urol 1995; 154: 209-213.
10. **Nickel JC: Prostatitis.**
    Myths and realities. Urology 1998; 51: 362-366.
11. **Naber KG, Weidner W.**
    Chronic prostatitis - an infectious disease. J Antimicrob Chemother 2000; 46: 157-161.
12. **Weidner W, Schiefer HG, Krauss H, Jantos C, Friedrich HJ, Altmannsberger M.**
    Chronic prostatitis: A thorough search for etiologically involved microorganisms in 1,461 patients. Infection 1991; 19 (Suppl 3): S119-S125.
13. **Bruce AW, Reid G.**
    Prostatitis associated with Chlammydia trachomatis in 6 patients. J Urol 1989; 142: 1006 1007.
14. **Taylor-Robinson D.**
    Evaluation and comparison of tests to diagnose Chlamydia trachomatis genital infections. Hum Reprod 1997; 12 (Suppl 2): 113-120.
15. **Taylor-Robinson D.**
    Infections due to species of mycoplasma and ureaplasma: an update. Clin Infect Dis 1996; 23: 671-684.
16. **Krieger JN, Riley DE, Roberts MC, Berger RE.**
    Prokaryotic DNA sequences in patients with chronic idiopathic prostatitis. J Clin Microbiol 1996; 34; 3120-3128.
17. **Litwin MS, McNaughton-Collins M, Fowler FJ Jr, Nickel JC, Calhourn EA, Pontari MA, Alexander RB, Farrar JT, O'Leary MP.**
    The National Institute of Health chronic prostatitis symptom index: development and validation of a new outcome measure. Chronic Prostatitis Collaboration Research Network. J Urol 1999; 162: 369-375.
18. **Ludwig M, Schroeder-Printzen I, Lüdecke G, Weidner W.**
    Comparison of expressed prostatic secretions with urine after prostatic massage - a means to diagnose chronic prostatitis/inflammatory chronic pelvic pain syndrome. Urology 2000; 55: 175-177.

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.
20. **Weidner W, Krause W, Schiefer HG, Brunner H, Friedrich HJ.**
Ureaplasmal infections of the male urogenital tract, in particular prostatitis, and semen quality. Urol Int 1985; 40:5-9.
21. **Aitken RJ, Baker HW.**
Seminal leukocytes: passengers, terrorists or good samaritans? Hum Reprod 1995; 10: 1736-1739.
22. **Tomlinson MJ, Barratt CLR, Cooke ID.**
Prospective study of leukocytes and leukocyte subpopulations in semen suggests they are not a cause of male infertility. Fertil Steril 1993; 60: 1069-1075.
23. **Krieger JN, Berger RE, Ross SO, Rothman I, Müller CH.**
Seminal fluid findings in men with nonbacterial prostatitis and prostatodynia. J Androl 1996; 17: 310-318.
24. **Weidner W, Jantos C, Schiefer HG, Haidl G, Friedrich HJ.**
Semen parameters in men with and without proven chronic prostatitis. Arch Androl 1991; 26: 173-183.
25. **Giamarellou H, Tympanidis K, Bitos NA, Leonidas E, Daikos GK.**
Infertility and chronic prostatitis. Andrologia 1984; 16: 417-422.
26. **Christiansen E, Tollefsrud A, Purvis K.**
Sperm quality in men with chronic abacterial prostatovesiculitis verified by rectal ultrasonography. Urology 1991; 38: 545-549.
27. **Leib Z, Bartoov B, Eltes F, Servadio C.**
Reduced semen quality caused by chronic abacterial prostatitis: an enigma or reality? Fertil Steril 1994; 61: 1109-1116.
28. **Wolff H, Bezold G, Zebhauser M, Meurer M.**
Impact of clinically silent inflammation on male genital tract organs as reflected by biochemical markers in semen. J Androl 1991; 12: 331-334.
29. **Wolff H.**
The biologic significance of white blood cells in semen. Fertil Steril 1995; 63; 1143-1157.
30. **Dousset B, Hussenet F, Daudin M, Bujan L, Foliguet B, Nabet P.**
Seminal cytokine concentrations (IL-1beta, IL-2, IL-6, sR IL-2, sR IL-6], semen parameters and blood hormonal status in male infertility. Hum Reprod 1997; 12: 1476-1479.
31. **Huleihel M, Lunenfeld E, Levy A, Potashnik G, Glezerman M.**
Distinct expression levels of cytokines and soluble cytokine receptors in seminal plasma of fertile and infertile men. Fertil Steril 1996; 66: 135-139.
32. **Shimonovitz S, Barak V, Zacut D, Ever-Hadani P, Ben-Chetrit A, Ron M.**
High concentration of soluble interleukin-2 receptors in ejaculate with low sperm motility. Hum Reprod 1994; 9: 653-635.
33. **Zalata A, Hafez T, van Hoecke MJ, Comhaire F.**
Evaluation of beta-endorphin and interleukin-6 in seminal plasma of patients with certain andrological diseases. Hum Reprod 1995; 10: 3161-3165.
34. **Alexander RB, Ponniah S, Hasday J, Hebel JR.**
Elevated levels of proinflammatory cytokines in the semen of patients with chronic prostatitis /chronic pelvic pain syndrome. Urology 1998; 52: 744-749.
35. **Comhaire F, Verschraegen G, Vermeulen L.**
Diagnosis of accessory gland infection and its possible role in male infertility. Int J Androl 1980; 3: 32-45.
36. **Jarow JP, Kirkland JA Jr, Assimos DG.**
Association of antisperm antibodies with chronic nonbacterial prostatitis. Urology 1990; 36: 154-156.
37. **Witkin SS, Zelikovsky G.**
Immunosuppression and sperm antibody formation in men with prostatitis. J Clin Lab Immunol 1986; 21: 7-10.
38. **Munoz MG, Witkin SS.**
Autoimmunity to spermatozoa, asymptomatic Chlamydia trachomatis genital tract infection and gamma delta T lymphocytes in seminal fluid from the male partners of couples with unexplained infertility. Hum Reprod 1995; 10: 1070-1074.
39. **Jarow JP, Sanzone JJ.**
Risk factors for male partner antisperm antibodies. J Urol 1992; 148: 1805-1807.
40. **Depuydt CE, Bosmans E, Zalata A, Schoonjans F, Comhaire FH.**
The relation between reactive oxygen species and cytokines in andrological patients with or without male accessory gland infection. J Androl 1996; 17: 699-707.
41. **Weidner W, Ludwig M, Miller J.**

Therapy in male accessory gland infection-what is fact, what is fiction?
Andrologia 1998; 30 (Suppl 1): 87-90.

42. Comhaire FH, Rowe PJ, Farley TM.
The effect of doxycycline in infertile couples with male accessory gland infection: a double blind prospective study. Int J Androl 1986; 9: 91-98.

8.2 ORCHITIS AND EPIDIDYMITIS

8.2.1 Orchitis

Orchitis is an inflammatory lesion of the testicle associated with a predominantly leukocytic exsudate 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 spermatogenetic arrest [2], which may be reversible. Following orchitis, testicle atrophy occurs [2].

Orchitis is classified according to aetiology (Table 15).

Table 15. Classification of epididymo-orchitis [3]

Non-specific	Specific	Viral
Acute bacterial epididymo-orchitis: *N. gonorrhoeae* *C. trachomatis* *E. coli* (and other Enterobacteriaceae) Non-specific chronic epididymo-orchitis Granulomatous (idiopathic) orchitis *Pneumococcus* *Salmonella* *Klebsiella* *Haemophilus influenzae*	Specific granulomatous orchitis Tuberculosis Lues Brucellosis	Mumps orchitis Coxsackie-B

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 antiphlogistic 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

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

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

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

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].

8.2.3 References

1. **Purvis K, Christiansen E.**
   Infection in the male reproductive tract. Impact, diagnosis and treatment in relation to male infertility. Int J Androl 1993; 16: 1-13.
2. **Diemer T, Desjardins C.**
   Disorders of Spermatogenesis; in Knobil E, Neill JD (eds): Encyclopedia of Reproduction. San Diego, Academic Press, 1999, vol 4, pp 546-556.
3. **Weidner W, Krause W: Orchitis; in Knobil E, Neill JD (eds).**
   Encyclopedia of Reproduction. San Diego, Academic Press, vol 3, 1999, pp 92-95.
4. **Association of Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases.**
   National guideline for the management of epididymo-orchitis. Sex Transm Inf 1999; 75 (Suppl 1): 51-53.
5. **Weidner W, Garbe C, Weißbach L, Harbrecht J, Kleinschmidt K, Schiefer HG, Friedrich HJ.**
   Initiale Therapie der akuten einseitigen Epididymitis mit Ofloxacin. Andrologische Befunde. Urologe A 1990; 29: 277-280.
6. **Vicari E, Mongioi A.**
   Effectiveness of long-acting gonadotrophin-releasing hormone agonist treatment in combination with conventional therapy on testicular outcome in human orchitis/epididymo-orchitis. Hum Reprod 1995; 10: 2072-2078.
7. **Ruther U, Stilz S, Röhl E, Nunnensiek C, Rassweiler J, Dörr U, Jipp P.**
   Successful interferon-alpha 2, a therapy for a patient with acute mumps orchitis. Eur Urol 1995; 27: 174-176.
8. **Berger RE, Alexander RE, Harnisch JP, Paulsen CA, Monda GD, Ansell J, Holmes KK.**
   Etiology, manifestations and therapy of acute epididymitis: prospective study of 50 cases. J Urol 1979; 121: 750-754.
9. **Berger RE. Epididymitis; in Holmes KK, Mardh PA, Sparling PF et al. (eds).**
   Sexually Transmitted Diseases. New York, McGraw-Hill Book Company, 1984, pp 650-662.
10. **Weidner W, Schiefer HG, Garbe C.**
    Acute nongonococcal epididymitis. Etiological and therapeutic aspects. Drugs 1987; 34 (Suppl 1): 111-117.
11. **Nilsson S, Obrant KO, Persson, PS.**
    Changes in the testis parenchyma caused by acute nonspecific epididymitis. Fertil Steril 1968; 19: 748-757.
12. **Osegbe DN.**
    Testicular function after unilateral bacterial epididymo-orchitis. Eur Urol 1991; 19: 204-208.
13. **Weidner W, Krause W, Ludwig M.**
    Relevance of male accessory gland infection for subsequent fertility with special focus on prostatitis. Hum Reprod Update 1999; 5: 421-432.
14. **Ludwig G, Haselberger J.**
    Epididymitis und Fertilität. Fortschr Med 1977; 95: 397-399.
15. **Haidl G.**
    Macrophages in semen are indicative of chronic epididymal infection. Arch Androl 1990; 25: 5-11.
16. **Cooper TG, Weidner W, Nieschlag E.**
    The influence of inflammation of the human genital tract on secretion of the seminal markers alpha-glucosidase, glycerophosphocholine, carnitine, fructose and citric acid. Int J Androl 1990; 13: 329-336.
17. **Robinson AJ, Grant JB, Spencer RC, Potter C, Kinghorn GR.**
    Acute epididymitis: why patient and consort must be investigated. Br J Urol 1990; 66: 642-645.

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

Neural	**Drug-related**
Spinal cord injury	Antihypertensives
Cauda equina lesions	Antipsychotics
Retroperitoneal lymphadenectomy	Antidepressants
Aortoiliac surgery	Alcohol
Colorectal surgery	
Multiple sclerosis	
Parkinson’s disease	
Autonomic neuropathy (juvenile diabetes)	

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

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

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

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

Neurogenic	Urethral obstruction
Spinal cord injury (L1]	Ectopic ureterocele
Cauda equina lesions	Urethral stricture
Multiple sclerosis	Urethral valves
Autonomic neuropathy (juvenile diabetes)	
Retroperitoneal lymphadenectomy	
Sympathectomy	
Colorectal and anal surgery	

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
Aetological 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 than 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 bulbocavernosus 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.

9.6 References

1. **Buvat J.**
   Glossaire. Les pertubations de l'ejaculation; in Buvat J, Jouannet P (eds): L'éjaculation et ses pertubations. Lyon-Villeurbanne, SIMEP, 1983, p 9.
2. **Wang R, Monga M, Hellstrom WJ.**
   Ejaculatory dysfunction; in Comhaire FH (ed): Male Infertility: Clinical Investigation. Cause Evaluation and Treatment. London, Chapman Hall, 1996, pp 205-221.
3. **Pryor JP.**
   Erectile and ejaculatory problems in infertility; in Hargreave TB (ed): Male Infertility. London, Springer, 1997, pp 319-336.
4. **Yachia D.**
   Our experience with penile deformations: incidence, operative techniques, and results.
   J Androl 1994; 15 (Suppl): 63S-68S.
5. **Chapelle PA.**
   Séquelles génito-sexuelles du paraplégique. 2-Neuro-physiologie. Tempo Medical 1982; 103: 67-70.
6. **Hermabessière J, Bouquet de la Jolinière J, Buvat J.**
   L'éjaculation douloureuse. Recherche de causes organiques; in Buvat J, Jouannet P (eds): L'éjaculation et ses pertubations. Lyon-Villeurbanne, SIMEP, 1984, pp 129-134.
7. **Gilja I, Parazajder J, Radej M, Cvitkovic P, Kovacic M.**
   Retrograde ejaculation and loss of emission: possibilities of conservative treatment.
   Eur Urol 1994; 25: 226-228.
8. **Jonas D, Linzbach P, Weber W.**
   The use of midodrin in the treatment of ejaculation disorders following retroperitoneal lymphadenectomy. Eur Urol 1979; 5: 184-187.
9. **Schill WB.**
   Pregnancy after brompheniramine treatment of a diabetic with incomplete emission failure.
   Arch Androl 1990; 25: 101-104.
10. **Brooks ME, Berezin M, Braf Z.**
    Treatment of retrograde ejaculation with imipramine. Urology 1980; 15: 353-355.
11. **Hendry WF.**
    Disorders of ejaculation: congenital, acquired and functional. Br J Urol 1998; 82: 331-341.
12. **Crich JP, Jequier AM.**
    Infertility in men with retrograde ejaculation: the action of urine on sperm motility, and a simple method for achieving antegrade ejaculation. Fertil Steril 1978; 30: 572-576.
13. **Schill WB.**
    Diagnosis and treatment of ejaculatory sterility; in Paulson JD, Nigro-Vilar A, Lucena E, Martini L (eds): Andrology: Male Fertility and Sterility. Orlando (USA), Academic Press, 1986, pp 599-617.
14. **Hotchkiss RS, Pinto AB, Kleegman S.**
    Artificial insemination with semen recovered from the bladder. Fertil Steril 1955; 6: 37-42.
15. **Brindley GS.**
    Reflex ejaculation under vibratory stimulation in paraplegic men. Paraplegia 1981; 19: 299-302.
16. **Elliott S, Rainsbury PA.**
    Treatment of anejaculation; in Colpi GM, Balerna M (eds): Treating Male Infertility: New Possibilities. Basel, Karger, 1994, pp 240-254.
17. **Hirsh AV, Mills C, Tan SL, Bekir J, Rainsbury P.**
    Pregnancy using spermatozoa aspirated from the vas deferens in a patient with ejaculatory failure due to spinal injury. Hum Reprod 1993; 8: 89-90.
18. **Colpi GM, Negri L, Stamm J, Balerna M.**
    Full-term pregnancy obtained with sperm recovered by seminal tract washout from an anejaculating, spinal cord injury man. J Urol 1992; 148: 1266-1267.
19. **Silber SJ, Van Steirteghem AC, Liu J, Nagy Z, Tournaye H, Devroey P.**
    High fertilization and pregnancy rate after intracytoplasmic sperm injection with spermatozoa obtained from testicle biopsy. Hum Reprod 1995; 10: 148-152.

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 Gynaecologists, London 1998.

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