Guidelines on
Male Infertility

G.R. Dohle, A. Jungwirth, G. Colpi,
A. Giwercman, T. Diemer, T.B. Hargreave

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**European
Association
of Urology**

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1. INTRODUCTION

1.1   Definition

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

1.2   Epidemiology and aetiology

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

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

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

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

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

OAT = Oligo-astheno-teratozoospermia.

1.3   Prognostic factors

The main factors influencing the prognosis in infertility are:
* Duration of infertility
* Primary or secondary infertility
* Results of semen analysis
* Age and fertility status of the female partner.

When the duration of infertility exceeds 4 years of unprotected sexual intercourse, the conception rate per month is only 1.5%.

At present, in many Western countries, women postpone their first pregnancy until they have finished their education and have started a professional career. However, the fertility of a woman of 35 years of age is only 50% of the fertility potential of a woman aged 25 years. By the age of 38 years, this has reduced to only 25%, and over the age of 40 years it is less than 5%. Female age is the most important single variable influencing outcome in assisted reproduction (2).

1.5   REFERENCES

1.   World Health Organization. *WHO Manual for the Standardised Investigation and Diagnosis of the Infertile Couple*. Cambridge: Cambridge University Press, 2000.
2.   Rowe T. Fertility and a woman's age. J Reprod Med 2006:51(3);157-163.
       http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=16674009&query_hl=4&itool=pubmed_docsum
3.   Agency for Health Care Policy and Research. *Clinical Practice Guidelines Development, Methodological Perspectives.* Washington DC: US Department of Health and Human Services, Public Health Service, 1992, pp. 115-127.

2.   INVESTIGATIONS

2.1   Semen analysis

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

Table 2: Overview of standard values for semen analysis according to the 1999 WHO criteria (1)

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

* Assessment according to Kruger and Menkfeld criteria.
** MAR = Mixed antiglobulin reaction.

2.1.1   Frequency of semen analysis

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

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

2.3   REFERENCES
1.   World Health Organization. *WHO Laboratory Manual for the Examination of Human Semen and Sperm-cervical Mucus Interaction*. 4th edn. Cambridge: Cambridge University Press, 1999.
2.   World Health Organization. *WHO Manual for the Standardised Investigation, Diagnosis and Management of the Infertile Male*. Cambridge: Cambridge University Press, 2000.

3.   PRIMARY SPERMATOGENIC FAILURE

3.1   Definition
Primary spermatogenic failure is defined as any spermatogenic alteration caused by conditions other than hypothalamic-pituitary disease. The severe forms of primary spermatogenic failure have different aetiologies but present clinically as non-obstructive azoospermia (NOA). The prevalence of azoospermia in the general population has been estimated at 2%. The incidence at a male infertility clinic was found to be as high as 10-20% (1).

3.2   Aetiology
The causes of spermatogenic failure are summarized in Table 3.

Table 3: Causes of spermatogenic failure

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

* See section 4 Genetic disorders in infertility.

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

•	Cryptorchidism
•	Testicular torsion
•	Genito-urinary infection
•	Testicular trauma
•	Environmental toxin exposure
•	Gonodadotoxic medication

•	Radiation or chemical exposure
•	Testicular cancer
•	Absence of testes
•	Abnormal secondary sexual characteristics
•	Gynaecomastia
•	Cryptorchidism
•	Abnormal testicular volume and/or consistency
•	Varicocele

3.4 Investigations

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

3.4.1 Semen analysis

In NOA, semen analysis shows normal ejaculate volume and azoospermia after several centrifugations have been performed. A recommended method is semen centrifugation at 600 g for 10 min and thorough microscopic examination of the pellet (x600). The upper fluid is then re-centrifuged (8000 g) for an additional 10 min and examined. All samples can be stained and re-examined under the microscope (2).

3.4.2 Hormonal determinations

Generally, the levels of follicle-stimulating hormone (FSH) are mainly correlated with the number of spermatogonia. When these cells are absent or markedly diminished, FSH values are usually elevated. When the number of spermatogonia is normal, but there is complete spermatocyte or spermatid blockage, FSH values are within normal range. However, on an individual patient basis, FSH levels do not provide an accurate prediction of the status of spermatogenesis (3-5). Preliminary data indicate a stronger correlation between low inhibin B level and spermatogenic damage (6).

3.4.3 Testicular biopsy

A diagnostic testicular biopsy is indicated in patients without evident factors (normal FSH and normal testicular volume) to differentiate between obstructive and NOA.

Testicular biopsy can also be performed as part of a therapeutic process in patients with clinical evidence of NOA who decide to undergo intracytoplasmic sperm injection (ICSI). Spermatogenesis may be focal. In these cases, one or more seminiferous tubules are involved in spermatogenesis while others are not (7,8). About 50-60% of men with NOA have some seminiferous tubules with spermatozoa that can be used for ICSI.

Most authors recommend taking several testicular samples given the potential for regional differences (9,10). Many authors find a good correlation between diagnostic biopsy histology and the likelihood of finding mature sperm cells during testicular sperm retrieval and ICSI (11,12).

3.5 Treatment

Testicular sperm extraction (TESE) and ICSI were introduced in 1993 for treatment of obstructive azoospermia (13-15). It was soon discovered that this technique could also be used for azoospermic men who appeared to have disturbed spermatogenesis (16). If spermatozoa are detected in the testicular biopsy, ICSI with either cryopreserved or fresh spermatozoa can be proposed to the couple.

A karyotype (if not performed previously) and Yq deletions screening are indicated to analyze any therapeutic consequences for the newborn child. If genetic anomalies are detected, the couple has to be properly informed and counselled (see section 4 Genetic disorders in infertility).

In case of azoospermia or ejaculatory failure not responding to vibro- or electro-ejaculation, spermatozoa can be harvested surgically for ICSI. The surgical technique depends on the cause of the azoospermia:

- In NOA, TESE is needed to retrieve spermatozoa.
- In OA, microsurgical or percutaneous epididymal sperm aspiration (MESA/PESA) can be applied. If no spermatozoa are found in the epididymal fluid, TESE is recommended.
- In anejaculation unresponsive to vibration or electro-ejaculation, TESE or seminal tract washout can be applied.

In NOA, the only good predictor of successful retrieval is testicular histology (17). No clear relation was found with FSH, Inhibin B or testicular volume. In case of AZFa and AZFb microdeletions no spermatozoa can be retrieved (18,19). TESE is the technique of choice and shows excellent repeatability (20): TESE results in sperm

retrievals in 50-60% of cases (21,22). Microsurgical TESE may increase retrieval rates (21,23,24): after opening of the testis fluid from large calibre tubules is aspirated with the aid of the operating microscope: complications appears to be lower than with classical TESE (25). Positive retrievals are reported even in conditions, such as Sertoli Cell Only Syndrome (21). Testicular fine needle aspiration (TEFNA) results in lower retrieval rates and does not allow histological examination for the detecting carcinoma in situ and testicular malignancies (26,27). TEFNA may also result in more tubular and vascular damage than (micro)TESE (28).

In OA, surgical retrieval can be combined with reconstruction of the seminal tract. TESE is usually successful and allows retrieval of a large number of spermatozoa suitable for cryopreservation. However, when epididymal tubules are enlarged, MESA enables both quantitatively and qualitatively better recovery of motile spermatozoa, with excellent chances for successful cryopreservation.

The results of ICSI are worse when using sperm retrieved in men with non-obstructive azoospermia as compared to obstructive azoospermia (29-31): birth rates of 19% in NOA versus 28% in OA (32) with significantly lower fertilisation and implantation rates (33) and higher miscarriage rates (11.5% vs. 2.5%) (34). In OA, no significant difference in ICSI results was found between testicular or epididymal sperm (35). Also, no significant differences in ICSI results between the use of fresh and frozen-thawed sperm have been reported (32,35,36-39).

3.6 CONCLUSIONS

- Impaired spermatogenesis is often associated with elevated FSH concentration.
- Testicular biopsy is the best procedure to define the histological diagnosis and the possibility of finding sperm. When spermatozoa are detected, these can be cryopreserved for use in future ICSI cycles.
- Spermatozoa are found in about 60% of patients with NOA. It is crucial that these men who are candidates for sperm retrieval are given appropriate genetic advice.
- For patients with NOA who have spermatozoa in their testicular biopsy, ICSI with fresh or cryopreserved spermatozoa is the only therapeutic option.
- Fertilization and pregnancy are achieved in 30-50% of couples with NOA, when spermatozoa are found in the testicular biopsy.

3.7 RECOMMENDATIONS

- A diagnostic testicular biopsy is indicated only in men with azoospermia, a normal testicular volume and normal FSH (40) (grade B recommendation).
- In couples with a NOA, a TESE with cryopreservation of the spermatozoa to be used for ICSI can be offered (41-43) (grade B recommendation).
- In order to increase the chances of positive sperm retrievals in men with non-obstructive azoospermia testicular sperm extraction (TESE, either single, multiple or microsurgical) should be used rather than testicular fine needle aspiration (TEFNA).

3.8 REFERENCES

1. World Health Organization. *WHO Manual for the Standardised Investigation, Diagnosis and Management of the Infertile Male.* Cambridge: Cambridge University Press, 2000.
2. World Health Organization. *WHO Laboratory Manual for the Examination of Human Semen and Sperm-cervical Mucus Interaction*. 4th edn. Cambridge: Cambridge University Press, 1999.
3. Hauser R, Temple-Smith PD, Southwick GJ, de Kretser DM. Fertility in cases of hypergonadotropic azoospermia. Fertil Steril 1995;63(3):631-636.
   http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7851598&dopt=Abstract
4. 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(8):1940-1945.
   http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8567817&dopt=Abstract
5. 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(5):787-793.
   http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=4823921&dopt=Abstract

6.   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(9):3110-3114.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9745412&dopt=Abstract

7.   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(6):1197-1200.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7589676&dopt=Abstract

8.   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(11):2422-2428. *Erratum* in Hum Reprod 1998;13(3):780.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9436677&dopt=Abstract

9.   Gottschalk-Sabag S, Weiss DB, Folb-Zacharow N, Zukerman Z. Is one testicular specimen sufficient for quantitative evaluation of spermatogenesis? Fertil Steril 1995;64(2):399-402.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7615120&dopt=Abstract

10. 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(5):743-748.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9145981&dopt=Abstract

11. Schulze W, Rehder U. Organization and morphogenesis of the human seminiferous epithelium. Cell Tissue Res 1984;237(3):395-407.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=6488283&dopt=Abstract

12. 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(1):144-146.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8976237&dopt=Abstract

13. Schoysman R, Vanderzwalmen P, Nijs M, Segal L, Segal-Bertin G, Geerts L, van Roosendaal E, Schoysman D. Pregnancy after fertilization with human testicular spermatozoa. Lancet 1993;342(8881):1237.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7901551&dopt=Abstract

14. 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(2):639-641.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8062963&dopt=Abstract

15. 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(1):148-152.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7745045&dopt=Abstract

16. 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(5):1015-1018.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8671382&dopt=Abstract

17. Zheng J, Huang X, Li C. [Predictive factors for successful sperm recovery in azoospermia patients.] Zhonghua Wai Ke Za Zhi 2000;38(5):366-368. [Chinese]
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11832060&query_hl=13&itool=pubmed_docsum

18. Foresta C., Ferlin A, Rossi A, Salata E, Tessari A. [Alteration of spermatogenesis and Y chromosome microdeletions. Analysis of the DAZ gene family.] Minerva Endocrinol. 2002;27(3): 193-207. [Italian]
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12091794&query_hl=6&itool=pubmed_docsum

19. Hopps CV, Mielnik A, Goldstein M, Palermo GD, Rosenwaks Z, Schlegel PN. Detection of sperm in men with Y chromosome microdeletions of the AZFa, AZFb, and AZFc regions. Hum Reprod 2003;18(8):1660-1665.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12871878&query_hl=9&itool=pubmed_docsum

20. Amer M, Haggar SE, Moustafa T, Abd El-Naser, Zohdy W. Testicular sperm extraction: impact to testicular histology on outcome, number of biopsies to be performed and optional time for repetition. Hum Reprod 1999;14(12):3030-3034.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10601092&query_hl=11&itool=pubmed_docsum

21. Colpi GM, Piediferro G, Nerva F, Giacchetta D, Colpi EM, Piatti E. Sperm retrieval for intra-cytoplasmic sperm injection in non-obstructive azoospermia. Minerva Urol Nefrol 2005(2); 57:99-107.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15951734&query_hl=1&itool=pubmed_docsum

22. Vernaeve V, Verheyen G, Goossens A, Van Steirteghem A, Devroey P, Tournaye H. How successful is repeat testicular sperm extraction in patients with azoospermia? Hum Reprod 2006; 21(6):1551-1554.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16473930&query_hl=4&itool=pubmed_docsum

23. Schlegel PN. Testicular sperm extraction: microdissection improves sperm yield with minimal tissue excision. Hum Reprod 1999:14(1):131-135.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10374109&query_hl=15&itool=pubmed_DocSum

24. Okada H, Dobashi M, Yamazaki T, Hara I, Fujisawa M, Arakawa S, Kamidono S. Conventional versus microdissection testicular sperm extraction for non obstructive azoospermia. J Urol 2002;168(3):1063-1067.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12187223&query_hl=17&itool=pubmed_docsum

25. Dardashti K, Williams RH, Goldstein M. Microsurgical testis biopsy: a novel technique for retrieval of testicular tissue. J Urol 2000;163(4):1206-1207.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10737497&query_hl=20&itool=pubmed_docsum

26. Shulze W, Thoms F, Knuth UA. Testicular sperm extraction: comprehensive analysis with simultaneously performed histology in 1418 biopsies from 766 subfertile men. Hum Reprod 1999; 14 Suppl:82-96.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10573026&query_hl=35&itool=pubmed_docsum

27. Piediferro G, Contalbi GF, Nerva F, Colpi GM. Carcinoma *in situ* in azoospermia non-ostruttiva sfuggito alla TEFNA e diagnosticato con TESE: Case report. Arch Ital Urol Androl 2004;11:123.

28. Shufaro Y, Prus D, Laufer N, Simon A. Impact of repeated fine needle aspiration (TEFNA) and testicular sperm extraction (TESE) on the microscopic morphology of the testis: an animal model. Hum Reprod 2002;17(7):1795-1799.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12093842&query_hl=23&itool=pubmed_docsum

29. Monzo A, Kondylis F, Lynch D, Mayer J, Jones E, Nehchiri F, Morshedi M, Schuffner , Muasher S, Gibbons W, Oehninger S. Outcome of intracytoplasmic sperm injection in azoospermic patients: stressing the liaison between the urologist and reproductive medicine specialist. Urology 2001;58(1):69-75.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11445482&query_hl=43&itool=pubmed_docsum

30. Vernaeve V, Tournaye H, Osmanagaoglu K, Verheyen G, Van Steirteghem A, Devroey P. Intracytoplasmic sperm injection with testicular spermatozoa is less successful in men with nonobstructive azoospermia than in men with obstructive azoospermia. Fertil Steril 2003;79(3):529-533.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12620435&query_hl=46&itool=pubmed_docsum

31. Silber S, Munné S. Chromosomal abnormalities in embryos derived from testicular sperm extraction (tese) in men with non-obstructive azoospermia. Proceedings EAA International Symposium "Genetics of Male Infertility: from Research to Clinic", 2003, October 2-4, Florence, Italy.

32. Schwarzer J, Friedler K, Hertwig I, Krusmann G, Wurfel W, Schleyer M, Muhlen B, Pickl U, Lochner-Ernst D. Sperm retrieval procedures and intracytoplasmatic spermatozoa injection with epididymal and testicular sperms. Urol Int 2003;70(2):119-123.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12592040&query_hl=49&itool=pubmed_docsum

33. Ghanem M, Bakr NI, Elgayaar MA, El Mongy S, Fathy H, Ibrahim AH. Comparison of the outcome of intracytoplasmic sperm injection in obstructive and non- obstructive azoospermia in the first cycle: a report of case series and meta-analysis. Int J Androl. 2005;28(1):16-21.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15679616&query_hl=53&itool=pubmed_docsum

34. Borges E Jr, Rossi-Ferragut LM, Pasqualotto FF, dos Santos DR, Rocha CC, Iaconelli A Jr. Testicular sperm results in elevated miscarriage rates compared to epididymal sperm in azoospermic patients. Sao Paulo Med J 2002; 120(4):122-126.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12436160&query_hl=51&itool=pubmed_docsum

35. Gil Salom M. [Spermatic recovery techniques for intracytoplasmic spermatozoid injection (ICSI) in male infertility.]Arch Esp Urol 2004;57(9):1035-1046. [Spanish]
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15624403&query_hl=27&itool=pubmed_docsum

36. 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(7):1794-1801.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10402392&query_hl=56&itool=pubmed_docsum

37. Gil-Salom M, Romero J, Rubio C, Ruiz A, Remohi J, Pellicer A. Intracytoplasmic sperm injection with cryopreserved testicular spermatozoa. Mol Cell Endocrinol 2000;169(1-2):15-19.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11155947&query_hl=59&itool=pubmed_docsum

38. Sousa M, Cremades N, Silva J, Oliveira C, Ferraz L, Teixeira da Silva J, Viana P, Barros A. Predictive value of testicular histology in secretory azoospermic subgroups and clinical outcomes after microinjection of fresh and frozen-thawed sperm and spermatids.
Hum Reprod 2002;17(7):1800-1810.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12093843&query_hl=61&itool=pubmed_docsum

39. Hauser R, Yogev L, Amit A, Yavetz H, Botchan A, Azem F, Lessing JB, Ben-Yosef D. Severe hypospermatogenesis in cases of nonobstructive azoospermia: should we use fresh or frozen testicular spermatozoa? J Androl 2005;26(6):772-778.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16291973&query_hl=29&itool=pubmed_docsum

40. 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(12):3390-3393.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9886520&dopt=Abstract

41. 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(5):892-897.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9389822&dopt=Abstract

42. 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(2):348-352.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9557836&dopt=Abstract

43. 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(3):741-748.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10221707&dopt=Abstract

4.   GENETIC DISORDERS IN INFERTILITY

4.1   Introduction

A knowledge of genetic abnormalities in infertility is mandatory for every urologist working in andrology so that correct advice can be given to couples seeking fertility treatment because of male infertility. By means of in-vitro fertilization (IVF), ICSI and TESE men with very low sperm counts can be given a reasonable chance of paternity. However, this also increases the possibility of passing genetic abnormalities on to the next generation because the sperm of infertile men shows an increase in aneuploidy, other genetic abnormalities and DNA damage. Although there are prospects for screening of sperm (1), current routine clinical practice is based on the screening of peripheral blood samples.

4.2   Chromosomal abnormalities

Chromosome abnormalities can be numerical, such as trisomy, or structural, such as inversions or translocations. In a survey of pooled data from 11 publications including 9,766 infertile men, the incidence of chromosomal abnormalities was 5.8% (2). Of these, sex chromosome abnormalities accounted for 4.2% and autosomal abnormalities for 1.5%. For comparison, the incidence of abnormalities in pooled data from three series totalling 94,465 newborn male infants was 0.38%, of which 131 (0.14%) were sex chromosome abnormalities and 232 (0.25%) autosomal abnormalities (3).

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

4.2.1   Sperm chromosomal abnormalities

Multicolour fluorescent *in situ* hybridisation (FISH) analysis makes it possible to examine sperm populations for chromosomal normality. There is an increase in aneuploidy in sperm, and in particular sex chromosome aneuploidy in association with severe damage to spermatogenesis(2,4,5,7-11) and also in men with translocations (6).

FISH analysis of spermatozoa remains a research investigation but should be encouraged, particularly in assessing populations of spermatozoa from men with defined andrological conditions. There is a need to develop techniques to separate populations of genetically abnormal sperm from normal sperm or to identify safe techniques of screening individual spermatozoa prior to IVF and ICSI.

4.2.2   Sex chromosome abnormalities (Klinefelter's syndrome and variants (47,XXY; 46,XY; 47,XXY mosaicism)

Klinefelter's syndrome is the most frequent sex chromosome abnormality. Pooled data from cytogenetic analysis of 9,766 newborn infants showed its occurrence in 66 (0.07%) phenotypical males (3). Adult men with Klinefelter's syndrome have small firm testicles devoid of germ cells. The phenotype can vary from a normally virilised man to one with stigmata of androgen deficiency, including female hair distribution, scanty body hair and long arms and legs because of late epiphyseal closure.

Leydig cell function is commonly impaired in men with Klinefelter's syndrome (12). Testosterone levels may be normal or low, oestradiol levels normal or elevated and FSH levels increased. 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 genetic diagnosis using FISH analysis of cells from embryos can be used to confirm normality (13). The production of 24,XY sperm has been reported in 0.9% and 7.0% of men with Klinefelter's mosaicism (14-16) and in 1.36-25% of men with somatic karyotype 47,XXY (17-21). There is one case report of declining spermatogenesis in a man with Klinefelter's syndrome, with the recommendation that early sperm retrieval sperm should be considered (22). Haploid sperm in men with Klinefelter's syndrome may be the result of a clone of normal cells in a mosaic population, and in certain circumstances some 47,XXY male germ cells may be viable and capable of producing haploid sperm (23). Klinefelter's syndrome patients have an increased chance of producing 47,XXY spermatozoa. When IVF/ICSI is performed, pre-implantation diagnosis should be used or, if not available, amniocentesis and karyotype analysis. Embryos with known Klinefelter's karyotype should probably not be implanted.

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

4.2.3   Autosomal abnormalities

From time to time, men may ask for fertility treatments, including IVF/ICSI, when there is already a known 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.

4.2.4 Translocations

Recipricol balanced translocations occur in 1 in 500 people. A person with a balanced translocation has a complete set of genetic information and is normal. However, when he or she has children, the child receives unbalanced genetic information, getting either too much or too little genetic material. A parental balanced translocation involving chromosome 21 is one of the causes of Down's syndrome.

When IVF/ICSI is performed for men with translocations, pre-implantation genetic diagnosis should be used or, if not available, amniocentesis and karyotype analysis. Embryos with known unbalanced translocation should probably not be implanted.

4.3 Genetic defects

4.3.1 X-linked genetic disorders and male fertility

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

4.3.2 Kallmann's syndrome

The commonest X-linked disorder in infertility practice is Kallmann's syndrome. The predominant form is an X-linked recessive disorder caused by a mutation in the KALIG-1 gene on Xp22.3 (24). Rarer forms of Kallmann's syndrome include an autosomal-dominant form (25). Patients with Kallmann's syndrome have 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 and may present de novo with infertility. It is often possible to stimulate spermatogenesis with replacement therapy (26).

4.3.3 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. Disorders of the androgen receptor causing infertility in the absence of any genital abnormality seem to be rare (27), although some cases have been identified (28). Longer CAG (cytosine-adenine-guanosine) repeats in exon one have been implicated and there appear to be racial differences.

4.3.4 Other X-disorders

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

4.3.5 X-linked disorders not associated with male infertility

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

*   Retinitis pigmentosa, a condition that affects 1 in 3,000 people, which may be recessive or dominant and causes visual impairment (31).
*   Chronic granulomatous disease, a condition that predisposes to severe bacterial and fungal infections (32).
*   Menkes disease, an X-linked recessive disturbance of copper metabolism associated with progressive neurological symptoms (33).

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

4.4 Y genes and male infertility

4.4.1 Introduction

The first cases of Y microdeletions and male infertility were reported in 1992 (34) and since that time many case series have been published. Although microdeletions may occur in fertile men, they are more prevalent in infertile men (35). Microdeletions have been found in three non-overlapping regions of the Y chromosome, AZF a-b-c (36). A fourth region AZFd overlaps with AZFc and is considered by some to be a separate area (37,38).

The most commonly found microdeletion is in the AZFc region, encompassing the DAZ gene. However, there is a poor correlation between AZFc microdeletions or DAZ gene deletion and spermatogenesis; different men with apparently similar microdeletions can have different degrees of damage to their spermatogenesis (35,39). TESE can be used for men with AZFc Y microdeletions (40). AZFa and AZFb microdeletions are much rarer. If the AZFa microdeletion is large enough to remove both the USP9Y (DFFRY) and the DDX3Y (DBY) genes, azoospermia occurs (41-43). There is no recorded case of sperm recovery by micro-TESE (40). Azoospermia also occurs in men with larger AZFb Y microdeletions (40). Microdeletions are a subset of rearrangements of the long arm of the Y chromosome, others include duplications and inversions. The biological significance of these haplotypes has yet to be determined (44), but it is possible that some of them are associated with reduced fertility (45).

4.4.2 Clinical implications of Y microdeletions

Generally, genes on the Y chromosome do not affect vital processes but code for male characteristics (half of humanity does not have a Y chromosome!). Thus, men with Y microdeletions are unlikely to have phenotypic abnormalities other than abnormalities of the male reproductive system. Y microdeletions are associated with varying degrees of derangment of spermatogenesis (36,38,39,42,46). The AZFc microdeletion 51gr/51gr is associated with male infertility (47). It is a rare low penetrance allele that confers susceptibility to testicular germ cell tumour (TGCT) (48). This finding has implications when ICSI is used to achieve fertility for a man with a gr/gr microdeletion, and there is a need for more information about Y genes and Y microdeletions and diseases of the male reproductive organs. There is also one report of a higher frequency of AZFc microdeletions in the husbands of women with recurrent pregnancy loss (49).

Y microdeletions can be transmitted to male offspring. However, this is rare in the normal population because, without ICSI treatment, men with very low sperm counts are less likely to father children (35,36,50-56). In most cases, the microdeletion in the son is the same as in the father, but there have been reports that the size of the microdeletion can increase (52,56). More information is needed from father/son pairs about the fertility status of the son and whether the microdeletions remain the same size. When ICSI is used in the presence of a Y microdeletion, consideration needs to be given to long-term follow up of any male children with respect to their fertility status, and in the case of gr/gr microdeletions their risk of developing germ cell tumours.

4.4.2.1 Testing for Y microdeletions

Testing for microdeletions is now widespread, and methodology is becoming standardised (36,57,58). The following genes are located in the AZF regions and specifically expressed in the testis, including RBMY1A1, DAZ, VCY, XKRY, CDY1, DY2, HSFY, PRY, and BPY2. Other genes are expressed in more than one tissue, including RPS4Y2, USP9Y, DDX3Y, UTY, JARIDID, and EIF1AY, and there are probably others.

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

4.4.2.2 CONCLUSIONS
- 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 other risks (e.g. the risk of developing TGCT) are remote, it is reasonable to take into account the cost and availability of testing and to discuss this with the couple.
- If AZFa or AZFb Y microdeletions are detected, then it is doubtful whether micro-TESE is worthwhile because the chance of finding sperm is extremely low.
- There is a need for further evidence of the prognostic significance of gr/gr AZFc microdeletions and the development of TGCTs.
- 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.
- It is likely that a son who inherits a microdeletion will in turn have a fertility problem.
- There is some evidence that the gr/gr AZFc microdeletion may increase the risk of testicular cancer, but the actual increase in risk although unknown is probably very small.

4.4.3 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 4). 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 treatment be successful.

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

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

4.5   Cystic fibrosis mutations and male infertility

Cystic fibrosis (CF), a fatal autosomal-recessive disorder, is the most common genetic disease of Caucasians; 4% are carriers of gene mutations involving the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This gene is located on the short arm of chromosome 7. It encodes a membrane protein that functions as an ion channel and also influences the formation of the ejaculatory duct, seminal vesicle, vas deferens and distal two-thirds of the epididymis.

Congenital bilateral absence of the vas deferens (CBAVD) is associated with CFTR mutations and was found in approximately 2% of men with obstructive azoospermia attending a clinic in Edinburgh (59). However, the incidence in men with obstructive azoospermia varies between different countries.

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

There are approximately 1,500 mutations listed on the CFTR database (http://www.genet.sickkids.on.ca/cftr/). There are many 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. In a review of published series of 449 men with CBAVD, the Delta F508 mutation was detected in 244 men, the R117H mutation in 54 men and the W1282X mutation in 37; 63 other mutations were found in between one and nine men, but not all mutations were tested for in all case series (60). It seems likely that as more mutations are defined and tested for, almost all 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 mutations that occur most commonly in a particular community.

Mutations may be found in both copies of the CFTR gene . However, in most men with CBAVD, mutation is found in only one copy. In some of these supposedly heterozygous cases, there may be an unknown second mutation, but there is also another mechanism. In two-thirds of these, a DNA variant – the 5t allele – can be detected in a non-coding region of CFTR (61). Men with CBAVD often have mild clinical stigmata of CF, 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 hetero- or homozygous.

When a man has CBAVD, it is important to test him and his partner for CF 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 having a baby with CF will be 25% if the man is heterozygous and 50% if the man is homozygous. If the female partner is negative for known mutations, her chance of being a carrier of unknown mutations is about 0.4%. In these circumstances, the possibility of her heterozygous partner fathering a child with CF is approximately 1:410.

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

Unilateral absence of the vas deferens is usually associated with ipsilateral absence of the kidney (62) and probably has a different genetic causation. Men with unilateral absence of the vas deferens are usually fertile,

and the condition is most commonly encountered as an incidental finding in the vasectomy clinic. Nevertheless, men with unilateral absence and CF mutations may have the same underlying genetic diseases as men with true CBAVD. It has also been found that men with bilateral absence of vas deferens and renal abnormalities do not have CFTR abnormalities (63).

Tests for CF mutations should be undertaken in men who are found to have unilateral absence of the vas 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 vessel abnormalities and renal abnormalities, such as pelvic kidney.

4.7 Other single gene disorders

There is intense research into genes that control spermatogenesis, and in particular unique Y genes as their products may be targets for non-hormonal contraception. There are now many research publications of candidate genes for spermatogenesis, for example:

- Ubiquitin protease 26 gene (64,65)
- Polymorphisms in the oestrogen receptor gene (66,67)
- Polymorphisms of the gonadotrophin-regulated testicular helicase gene (68)
- UTP14c (69)
- SPAG16L (70)
- BGR-like gene (71)
- SPO11, EIF5A2, ACT (72)
- N372H variant of the BRCA2 gene (73)
- Heat shock transcription factor in AZFb (74).

At present, the clinical application of these findings is limited. It is likely that single gene mutations of these various genes account for only a small proportion of male infertility and therefore the practicality of testing will be constrained by expense and availability of the testing techniques. However, this may change with the advent of cheap gene array testing techniques, which will have the capacity to screen all or most of the known single gene defects with one test.

4.8 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 a fetal abnormality, because ICSI may enable defective sperm to bypass the selective processes of the female genital tract and egg covering. Alternatively, eggs may be fertilized that would otherwise not be fertilized. It is therefore very reassuring that the collected fetal abnormality statistics from ICSI centres do not indicate any increase in congenital malformations compared with the general population. However, the indications for ICSI are constantly being extended to include fertilization with immature sperm forms and it is particularly important to continue to monitor fetal abnormality rates, using detailed subgroup analysis according to the clinical and molecular diagnosis of the father.

4.9 Genetic and DNA abnormalities in sperm

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

4.10 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. Where there is conflict between the wishes of the couple and the interests of the future child, it may be ethically correct to withhold therapy. The best management is to agree treatment with the couple, providing them with full information about the genetic risk.

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

4.11 CONCLUSIONS

New insights into the genetic basis of infertility and the advent of ICSI necessitate a good understanding of genetics by clinicians and the public at large.

Advances in diagnostic modalities will allow identification of the genetic basis of more disorders, as well as providing diagnosis of known disorders at a lower cost, for some of which gene therapy may become practical.

4.12 RECOMMENDATIONS

- Standard karyotype analysis should be offered to all men with damaged spermatogenesis who are seeking fertility treatment by IVF/ICSI (2) (grade A recommendation).
- For men with severely damaged spermatogenesis, testing for Yq microdeletions before ICSI is desirable. However, as these men and their male children are unlikely to have any phenotypic abnormality other than impaired spermatogenesis, it is reasonable to take into account the cost and limitations of current testing methods and to discuss this with the couple (55-58) (grade B recommendation).
- When a man has structural abnormalities of the vas deferens (CBAVD, unilateral absence of the vas), it is important to test him and his partner for CF gene mutations (60) (grade A recommendation).
- Genetic counselling is mandatory in couples with a genetic abnormality found in clinical or genetic investigation and in patients who carry a (potential) inheritable disease (1) (grade A recommendation).

4.13 REFERENCES

1. Griffin DK, Finch KA. The genetic and cytogenetic basis of male infertility. Human Fertil 2005;8(1);19-26.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15823847&query_hl=26&itool=pubmed_docsum
2. Johnson MD. Genetic risks of intracytoplasmic sperm injection in the treatment of male infertility: recommendations for genetic counseling and screening. Fertil Steril 1998;70(3):397-411.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9757865&query_hl=6&itool=pubmed_docsum
3. van Assche EV, Bonduelle M, Tournaye H, Joris H, Verheyen G, Devroey P, Van Steirteghem A, Liebaers I. Cytogenetics of infertile men. Hum Reprod 1996;11(Suppl 4):1-24.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9147109&query_hl=9&itool=pubmed_docsum
4. Chandley AC. Chromosomes. In: Hargreave TB (ed). *Male Infertility*. Berlin: Springer-Verlag, 1994, pp. 149-164.
5. Clementini E, Palka C, Lezzi I, Stuppia L, Guanciali-Franchi P, Tiboni GM. Prevalence of chromosomal abnormalities in 2078 inferitle couples referred for assisted reproduction technologies. Hum Reprod 2005;20(2):437-442.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15567875&query_hl=13&itool=pubmed_docsum
6. Baccetti B, Collodel G, Marzella R, Moretti E, Piomboni P, Scapigliati G, Serafini F. Ultrastructural studies of spermatozoa from infertile males with Robertsonian translocations and 18, X, Y aneuploidies. Hum Reprod 2005;20(8):2295-2300.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15878922&query_hl=15&itool=pubmed_docsum
7. Martin RH. The risk of chromosomal abnormalities following ICSI. Hum Reprod 1996;11(5):924-925.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8671360&query_hl=19&itool=pubmed_docsum
8. Gianaroli L, Magli MC, Cavallini G, Grippa A, Nadalini M, Bernardini L, Menchini Fabris GF, Voliani S, Ferraretti AP. Frequency of aneuploidy in sperm from patients with extremely severe male factor infertility. Hum Reprod 2005;20(8):2140-2152.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15845594&query_hl=23&itool=pubmed_docsum
9. Pang MG, Kim YJ, Lee SH, Kim CK. The high incidence of meiotic errors increases with decreased sperm count in severe male factor infertilities. Hum Reprod 2005;20(6):1688-1694.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15734753&query_hl=1&itool=pubmed_docsum

10.   Machev N, Gosset P, Viville S. Chromosome abnormalities in sperm from infertile men with normal somatic karyotypes: teratozoospermia. Cytogenet Genome Res 2005;111(3-4):352-357.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=16192715&query_hl=3&itool=pubmed_docsum

11.   Miharu N. Chromosome abnormalities in sperm from infertile men with normal somatic karyotypes: oligozoospermia. Cytogenet Genome Res 2005;111(3-4):347-351.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=16192714&query_hl=5&itool=pubmed_docsum

12.   Wang C, Baker HW, Burger HG, De Kretser DM, Hudson B. Hormonal studies in men with Klinefelter's syndrome. Clin Endocrinol (Oxf) 1975;4(4):399411.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=1157343&query_hl=10&itool=pubmed_docsum

13.   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(8):1644-1649.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=8921109&query_hl=12&itool=pubmed_docsum

14.   Chevret E, Rousseaux S, Monteil M, Usson Y, Cozzi J, Pelletier R, Sele B. Increased incidence of hyperhaploid 24 XY spermatozoa detected by three-colour FISH in a 46,XY/47,XXY male. Hum Genet 1996;97(2):171-175.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=8566948&query_hl=14&itool=pubmed_docsum

15.   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(8):1638-1643.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=8921108&query_hl=16&itool=pubmed_docsum

16.   Lenz P, Luetjens CM, Kamischke A, Kuhnert B, Kennerknecht I, Nieschlag E. Mosaic status in lymphocytes of infertile men with or without Klinefelter syndrome. Hum Reprod 2005;20(5):1248-1255.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=15665007&query_hl=18&itool=pubmed_docsum

17.   Cozzi J, Chevret E, Rousseaux S, Pelletier R, Benitz V, Jalbert H, Sele B. Achievement of meiosis in XXY germ cells: study of 543 sperm karyotypes from an XY/XXY mosaic patient. Hum Genet 1994;93(1):32-34.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=8270252&query_hl=21&itool=pubmed_docsum

18.   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(4):474-477.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=9099836&query_hl=23&itool=pubmed_docsum

19.   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(1):124-127.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=9512242&query_hl=26&itool=pubmed_docsum

20.   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(1):203-205.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=9435442&query_hl=30&itool=pubmed_docsum

21.   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.

22.   Ichioka K, Utsunomiya N, Kohei N, Ueda N, Inoue K, Terai A. Adult onset of declining spermatogenesis in a man with nonmosaic Klinefelter's syndrome. Fertil Steril 2006;85(5):1511.e1-2.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=16616747&query_hl=2&itool=pubmed_docsum

23.   Gonsalves J, Turek PJ, Schlegel PN, Hopps CV, Weier JF, Pera RA. Recombination in men with Klinefelter syndrome. Reproduction 2005;130(2):223-229.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=16049160&query_hl=4&itool=pubmed_docsum

24. 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(6344):529-536.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=1922361&query_hl=6&itool=pubmed_docsum

25. Santen RJ, Paulsen CA. Hypogonadotropic eunuchoidism. I. Clinical study of the mode of inheritance. J Clin Endocrinol Metab 1973;36(1):47-54.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=4404632&query_hl=10&itool=pubmed_docsum

26. Miyagawa Y, Tsujimura A, Matsumiya K, Takao T, Tohda A, Koga M, Takeyama M, Fujioka H, Takada S, Koide T, Okuyama A. Outcome of gonadotropin therapy for male hypogonadotropic hypogonadism at university affiliated male infertility centers: a 30-year retrospective study. J Urol 2005;173(6):2072-2075.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15879837&query_hl=15&itool=pubmed_docsum

27. Tincello DG, Saunders PT, Hargreave TB. Preliminary investigations on androgen receptor gene mutations in infertile men. Mol Hum Reprod 1997;3(11):941-943.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9433918&query_hl=17&itool=pubmed_docsum

28. Gottlieb B, Lombroso R, Beitel LK, Trifiro MA. Molecular pathology of the androgen receptor in male (in)fertility. Reprod Biomed Online 2005;10(1):42-48.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=15705293&dopt=Abstract

29. Gonialves J, McElreavey K, Carreiro H, et al. An azoospermic man with a submicroscopic interstitial deletion on the Xp pseudoautosomal region. Hum Reprod (Abstract Book 1)1996;11:158-159.

30. 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(1-2):38-42.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2249473&dopt=Abstract

31. 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)1-13.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2201466&dopt=Abstract

32. Dinauer MC, Orkin SH. Chronic granulomatous disease. Molecular genetics. Hematol Oncol Clin N Am 1988;2(2):225-240.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3292508&dopt=Abstract

33. Horn N, Tonnesen T, Tumer Z. Menkes disease: an X-linked neurological disorder of the copper metabolism. Brain Pathol 1992;2(4):351-362.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1341968&dopt=Abstract

34. 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(1):29-33.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=1301132&query_hl=39&itool=pubmed_docsum

35. 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(8):534-539.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9023089&dopt=Abstract

36. Vogt P, Edelmann A, Kirsch S, Henegariu O, Hirschmann P, Kiesewetter F, Kohn 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 azoospermia factors (AZF) mapped to different subregions in Yq11. Hum Mol Genet 1996;5(7):933-943.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8817327&dopt=Abstract

37. Muslumanoglu MH, Turgut M, Cilingir O, Can C, Ozyurek Y, Artan S. Role of the AZFd locus in spermatogenesis. Fertil Steril 2005;84(2):519-22.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=16084901&query_hl=43&itool=pubmed_docsum

38. Kent-First M, Muallem A, Shultz J, Pryor J, Roberts K, Nolten W, Meisner L, Chandley A, Gouchy G, Jorgensen L, Havighurst T, Grosch J. Defining regions of the Y-chromosome responsible for male infertility and identification of a fourth AZF region (AZFd) by Y-chromosome microdeletion detection. Mol Reprod Dev 1999;53(1):27-41.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=10230814&query_hl=46&itool=pubmed_docsum

39. Hsu CC, Kuo PL, Chuang L, Lin YH, Teng YN, Lin YM. Uniform deletion junctions of complete azoospermia factor region c deletion in infertile men in Taiwan. Asian J Androl 2006;8(2):205-211.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=16491273&query_hl=51&itool=pubmed_docsum

40. Hopps CV, Mielnik A, Goldstein M, Palermo GD, Rosenwaks Z, Schlegel PN. Detection of sperm in men with Y chromosome microdeletions of the AZFa, AZFb and AZFc regions. Hum Reprod 2003;18(8):1660-1665.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=12871878&query_hl=54&itool=pubmed_docsum

41. Sargent CA, Boucher CA, Kirsch S, Brown G, Weiss B, Trundley A, Burgoyne P, Saut N, Durand C, Levy N, Terriou P, Hargreave T, Cooke H, Mitchell M, Rappold GA, Affara NA. The critical region of overlap defining the AZFa male infertility interval of proximal Yq contains three transcribed sequences. IJ Med Genet 1999;36(9):670-677.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=10507722&query_hl=58&itool=pubmed_docsum

42. Foresta C, Moro E, Rossi A, Rossato M, Garolla A, Ferlin A. Role of the AZFa candidate genes in male infertility. J Endocrinol Invest 2000;23(10):646-651.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=11097428&query_hl=60&itool=pubmed_docsum

43. Kamp C, Huellen K, Fernandes S, Sousa M, Schlegel PN, Mielnik A, Kleiman S, Yavetz H, Krause W, Kupker W, Johannisson R, Schulze W, Weidner W, Barros A, Vogt PH. High deletion frequency of the complete AZFa sequence in men with Sertoli-cell-only syndrome. Mol Hum Reprod 2001;7(10):987-994.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=11574668&query_hl=64&itool=pubmed_docsum

44. Vogt PH. AZF deletions and Y chromosomal haplogroups: history and update based on sequence. Hum Reprod Update 2005;11(4):319-336.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=15890785&query_hl=67&itool=pubmed_docsum

45. Teng YN, Lin YM, Sun HF, Hsu PY, Chung CL, Kuo PL. Association of DAZL haplotypes with spermatogenic failure in infertile men. Fertil Steril 2006;86(1):129-135.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=16730721&query_hl=69&itool=pubmed_docsum

46. 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(4):383-393.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7670487&do pt=Abstract

47. Lynch M, Cram DS, Reilly A, O'Bryan MK, Baker HW, de Kretser DM, McLachlan RI. The Y chromosome gr/gr subdeletion is associated with male infertility. Mol Hum Reprod 2005;11(7):507-512.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=16123079&query_hl=75&itool=pubmed_docsum

48. Nathanson KL, Kanetsky PA, Hawes R, Vaughn DJ, Letrero R, Tucker K, Friedlander M, Phillips KA, Hogg D, Jewett MA, Lohynska R, Daugaard G, Richard S, Chompret A, Bonaiti-Pellie C, Heidenreich A, Olah E, Geczi L, Bodrogi I, Ormiston WJ, Daly PA, Oosterhuis JW, Gillis AJ, Looijenga LH, Guilford P, Fossa SD, Heimdal K, Tjulandin SA, Liubchenko L, Stoll H, Weber W. Rudd M, Huddart R, Crockford GP, Forman D, Oliver DT, Einhorn L, Weber BL, Kramer J, McMaster M, Greene MH, Pike M, Cortessis V, Chen C, Schwartz SM, Bishop DT, Easton DF, Stratton MR, Rapley EA. The Y deletion gr/gr and susceptibility to testicular germ cell tumor. Am J Hum Genet 2005;77(6):1034-1043.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16380914&query_hl=79&itool=pubmed_docsum

49. Dewan S, Puscheck EE, Coulam CB, Wilcox AJ, Jeyendran RS. Y-chromosome microdeletions and recurrent pregnancy loss. Fertil Steril 2006;85(2):441-445.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16595224&query_hl=84&itool=pubmed_docsum

50. Kobayashi K, Mizuno K, Hida A, Komaki R, Tomita K, Matsushita I, Namiki M, Iwamoto T, Tamura S, Minowada S, 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(1):1965-1967.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7661932&query_hl=90&itool=pubmed_docsum

51. Kent-First MG, Kol S, Muallem A, Blazer S, Itskovitz-Eldor J. Infertility in intracytoplasmic sperm injection-derived sons. Lancet 1996;348(9023):332.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8709700&query_hl=95&itool=pubmed_docsum

52. Stuppia L, Gatta V, Calabrese G, Guanciali Franchi P, 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(5):566-570.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9654206&query_hl=98&itool=pubmed_docsum

53. 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(3):503-508.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9130751&query_hl=101&itool=pubmed_docsum

54. 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(12):3332-3337.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9886509&query_hl=104&itool=pubmed_docsum

55. 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(9):2320-2322.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10469702&query_hl=107&itool=pubmed_docsum

56. Lee SH, Ahn SY, Lee KW, Kwack K, Jun HS, Cha KY. Intracytoplasmic sperm injection may lead to vertical transmission, expansion, and de novo occurrence of Y-chromosome microdeletions in male fetuses. Fertil Steril 2006;85(5):1512-1515.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16566932&query_hl=111&itool=pubmed_docsum

57   Kent-First M, Muallem A. Development of a large highly diagnostic panel of multiplexed sequence tagged sites (STSs) which cover key regions on human Yq: its application in fertile and infertile zoospermic and oligozoospermic) populations. Proceedings of the Second International Workshop on the Y Chromosome. Organized by the National Institutes of Health USA and Human genome organization, Medical Research Council, UK. Asilomar Conference Centre, Pacific Grove, California, Sept 17-20, 1995, pp. 24-25.

58. 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.

59. 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(1):74-77.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9043501&dopt=AbstractI

60. 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(9):669-677.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9239681&dopt=Abstract

61. 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(22):1475-1480.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7739684&dopt=Abstract

62. Drake MJ, Quinn FM. Absent vas deferens and ipsilateral multicystic dysplastic kidney in a child. Br J Urol 1996;77(5):756-757.

63. 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(8935):1473-1474.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7968122&dopt=Abstract

64. Paduch DA, Mielnik A, Schlegel PN. Novel mutations in testis-specific ubiquitin protease 26 gene may cause male infertility and hypogonadism. Reprod Biomed Online (2005 Jun);10(6):747-754.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15970005&query_hl=1&itool=pubmed_docsum

65. Stouffs K, Lissens W, Tournaye H, Van Steirteghem A, Liebaers I. Possible role of USP26 in patients with severely impaired spermatogenesis. Eur J Hum Genet 2005;13(3):336-340.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15562280&query_hl=4&itool=pubmed_docsum

66. Aschim EL, Giwercman A, Stahl O, Eberhard J, Cwikiel M, Nordenskjold A, Haugen TB, Grotmol T, Giwercman YL. The RsaI polymorphism in the estrogen receptor-beta gene is associated with male infertility. J Clin Endocrinol Metab 2005;90(9):5343-5348.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15998774&query_hl=9&itool=pubmed_docsum

67. Guarducci E, Nuti F, Becherini L, Rotondi M, Balercia G, Forti G, Krausz C. Estrogen receptor alpha promoter polymorphism: stronger estrogen action is coupled with lower sperm count. Hum Reprod 2006;21(4):994-1001.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16396937&query_hl=11&itool=pubmed_docsum

68. A Z Zhang S, Yang Y, Ma Y, Lin L, Zhang W. Single nucleotide polymorphisms of the gonadotrophin-regulated testicular helicase (GRTH) gene may be associated with the human spermatogenesis impairment. Hum Reprod 2006; 21(3):755-759.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16293649&query_hl=13&itool=pubmed_docsum

69. Rohozinski J, Lamb DJ, Bishop CE. UTP14c is a recently acquired retrogene associated with spermatogenesis and fertility in man. Biol Reprod 2006;74(4):644-651.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16354793&query_hl=16&itool=pubmed_docsum

70. Zhang Z, Kostetskii I, Tang W, Haig-Ladewig L, Sapiro R, Wei Z, Patel AM, Bennett J, Gerton GL, Moss SB, Radice GL, Strauss JF 3rd. Deficiency of SPAG16L causes male infertility associated with impaired sperm motility. Biol Reprod 2006;74(4):751-759.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16382026&query_hl=26&itool=pubmed_docsum

71. Zheng Y, Zhou ZM, Min X, Li JM, Sha J. Identification and characterization of the BGR-like gene with a potential role in human testicular development/spermatogenesis. Asian J Androl 2005;7(1):21-32.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15685348&query_hl=30&itool=pubmed_docsum

72. Carrell DT, De Jonge C, Lamb DJ. The genetics of male infertility: a field of study whose time is now. Arch Androl 2006;52(4):269-274.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16728342&query_hl=32&itool=pubmed_docsum

73.   Zhoucun A, Zhang S, Yang Y, Ma Y, Zhang W, Lin L. The common variant N372H in BRCA2 gene may be associated with idiopathic male infertility with azoospermia or severe oligozoospermia. Eur J Obstet Gynecol Reprod Biol 2006;124(1):61-64.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16257105&query_hl=34&itool=pubmed_docsum

74.   Tessari A, Salata E, Ferlin A, Bartoloni L, Slongo ML, Foresta C. Characterization of HSFY, a novel AZFb gene on the Y chromosome with a possible role in human spermatogenesis. Mol Hum Reprod 2004;10(4):253-258.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=14985478&query_hl=36&itool=pubmed_docsum

75.   Greco E, Romano S, Iacobelli M, Ferrero S, Baroni E, Minasi MG, Ubaldi F, Rienzi L, Tesarik J. ICSI in cases of sperm DNA damage: beneficial effect or oral antioxidant treatment. Hum Reprod 2005;20(9):2590-2594.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15932912&query_hl=38&itool=pubmed_docsum

76.   Zini A, Meriano J, Kader K, Jarvi K, Laskin CA, Cadesky K. Potential adverse effect of sperm DNA damage on embryo quality after ICSI. Hum Reprod 2005;20(12);3476-3480.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16123087&query_hl=40&itool=pubmed_docsum

77.   Zini A, Blumenfeld A, Libman J, Willlis J. Beneficial effect of microsurgical varicocelectomy on human sperm DNA integrity. Hum Reprod 2005;20(4):1018-1021.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15608026&query_hl=42&itool=pubmed_docsum

5.   OBSTRUCTIVE AZOOSPERMIA

5.1   Definition

Obstructive azoospermia means the absence of both spermatozoa and spermatogenetic cells in semen and post-ejaculate urine due to bilateral obstruction of the seminal ducts. Obstructive azoospermia is less common than NOA and occurs in 15-20% of men with azoospermia. Common causes of obstructive azoospermia are summarized in Table 5.

Table 5: A classification of obstructive azoospermia on the basis of ductal obstruction due to congenital and acquired causes

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

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

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

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

Congenital epididymal obstruction usually manifests as congenital bilateral absence of the vas deferens (CBAVD), which is associated with at least one mutation of the CF gene in 82% of cases (5). This form is often accompanied by absence of the distal part of the epididymis and seminal vesicle agenesis (see section 4 Genetic disorders in infertility). Other congenital forms of obstruction (dysjunction between efferent ductules and corpus epididymis, agenesis/atresia of a short part of the epididymis) are rare.

Congenital forms also include chronic sinopulmonary infections (Young's syndrome) (6), in which 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 section 11 Male accessory gland infections). Acute or chronic traumas may result in epididymal damage (9).

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

5.2.3   Vas deferens obstruction
Vas deferens obstruction is the most common cause of acquired obstruction following vasectomy for sterilization, with reports of subsequent germ cell impairment and fibrosis (11,12). About 2-6% of these men request vasectomy reversal. Of those undergoing vasovasostomy, 5-10% appear to have epididymal blockage due to tubule rupture, making epididymovasostomy mandatory (see section 10 Male contraception). Vasal obstruction may also occur after herniotomy (13). Polypropylene mesh herniorrhaphy seems to induce a fibroblastic response able to entrap, or obliterate, the vas deferens (14).

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

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

Cystic obstructions are usually congenital (i.e. Müllerian duct cyst or urogenital sinus/ejaculatory duct cysts) and are medially located in the prostate between the ejaculatory ducts. In urogenital sinus anomalies, one or both ejaculatory ducts empty into the cyst (17), while in Müllerian duct anomalies, ejaculatory ducts are laterally displaced and compressed by the cyst (18).

Paramedian or lateral intraprostatic cysts are Wolffian in origin and rarely found in clinical practice (19).

Post-inflammatory obstructions of the ejaculatory duct are usually secondary to acute, non-acute or chronic urethroprostatitis (20).

Congenital or acquired complete obstructions of the ejaculatory ducts are commonly associated with low semen volume, decreased or absent seminal fructose and acid pH. The seminal vesicles are usually dilated (anterior-posterior diameter > 15 mm) (20,21).

5.2.5   Functional obstruction of the distal seminal ducts
This might be attributed to local neuropathy (22). Because of the vasographic patterns of ampullovesicular atony or of ejaculatory duct hypertony, this abnormality seems to be very often associated with urodynamic dysfunctions. Although it has been observed in patients suffering from juvenile diabetes and in polycystic kidney disease (23), no relevant pathology has been found in most cases described. Results of semen analysis vary between azoospermia, cryptozoospermia and severe OAT syndrome.

5.3   Diagnostic management
5.3.1   Clinical history
Clinical history taking should follow the suggestions for investigation of infertile men (see section 2 Investigations), including asking about the presence of:

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

5.3.2 Clinical examination
This follows the suggestions for investigation of the infertile man. The following findings are indicative for obstructive azoospermia:
- At least one testis > 15 mL volume (although a smaller testicular volume may be found in some patients with obstructive azoospermia and concomitant partial testicular failure)
- Enlarged and hardened epididymis
- Nodules in the epididymis or vas deferens
- Absence or partial atresia of the vas
- Signs of urethritis
- Prostatic abnormalities.

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

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

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

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

Transurethral ultrasound (TRUS) must be performed on patients with a low seminal volume and in whom distal obstruction is suspected. If possible, TRUS should be performed at high resolution and with high-frequency (7 MHz) biplane transducers. Seminal vesicle enlargement (anterior-posterior diameter 15 mm) (21) and roundish, anechoic areas in the seminal vesicle (24) are TRUS anomalies more often associated with ejaculatory duct obstruction, especially when semen volume is 1.5 mL. Other known anomalies in cases of obstructive azoospermia are Müllerian duct cysts or urogenital sinus/ejaculatory duct cysts (20) and ejaculatory duct calcifications (25). TRUS may also be applied to aspirate seminal vesicle fluid (26).

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

5.3.6 Testicular biopsy
This may be indicated to exclude spermatogenic failure in selective cases. The same surgical procedure may also be used to extract testicular spermatozoa (i.e. TESE) for cryopreservation and subsequent ICSI, when surgical recanalization cannot be performed or has failed. A scoring system for testicular biopsies is given in Table 6 (27).

Table 6: Scoring system for testicular biopsies (Johnsen score) (27)

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

5.4 Treatment

5.4.1 Intratesticular obstruction

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

5.4.2 Epididymal obstruction

Microsurgical epididymal sperm aspiration (MESA) (28) is indicated in men with CBAVD. Retrieved spermatozoa are usually used for ICSI. In general, one MESA procedure provides sufficient material for several ICSI cycles (29). For sperm recovery, there is limited evidence that a micropuncture with nerve stimulation may be preferable to a simple MESA technique as it produces higher pregnancy and fertilisation rates (30). In patients with azoospermia due to acquired epididymal obstruction, end-to-end or end-to-side microsurgical epididymovasostomy is recommended: microsurgical intussusception vasoepididimostomy seems to be the most favourable technique (31).

Reconstruction may be done unilaterally or bilaterally; patency and pregnancy rates are usually higher with bilateral reconstruction. Before performing microsurgery, it is important to check that there is full patency downstream of the epididymis. Anatomical recanalization following surgery may require 3-18 months. Before performing microsurgery (and also in all cases where recanalization is impossible), epididymal spermatozoa should be aspirated and cryopreserved to be used for ICSI in case of surgical failure (29).

Patency rates range between 60% and 87% (32-34) and cumulative pregnancy rates between 10% and 43%. Recanalization success rates may be adversely affected by pre-operative and operative findings, such as concomitant abnormal testicular histology, absence of sperm in the spermatic fluid on sectioning the small epididymal tubules and wide fibrosis of the epididymis.

The finding of motile or immotile spermatozoa at the level of the anastomosis does not appear to be related to the patency rate, but moving from the corpus to the caput epididymidis has a significant adverse effect upon patency and pregnancy outcome. Spermatozoa need to pass through at least part of the epididymis to mature and be able to fertilize oocytes in a natural cycle. Concomitant presence of ultrasonographic abnormalities in the prostate and seminal vesicles is also associated with a less favourable outcome (10).

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 (35) (see section 10 Male contraception).

5.4.3 Proximal vas obstruction

Proximal vas obstruction after vasectomy requires microsurgical vasectomy reversal (see section 10 Male contraception). Vasovasostomy must also be performed in the rare cases of proximal vasal obstructions (iatrogenic, post-traumatic, post-inflammatory). When spermatozoa are absent in the intraoperative vas fluid, a secondary epididymal obstruction may be present, especially if the seminal fluid of the proximal vas has a thick 'toothpaste' appearance. Microsurgical vasoepididymostomy is indicated.

5.4.4 Distal vas deferens obstruction

Large bilateral vas defects resulting from involuntary vas excision during hernia surgery in early childhood or previous orchidopexy are usually incorrectable (16). In these cases, one can resort to proximal vas deferens sperm aspiration (36) or TESE/MESA to be used for ICSI. In large monolateral vas defects associated with contralateral testicular atrophy, the vas of the atrophic testis can be used for a crossover vasovasostomy or vasoepididymostomy.

5.4.5   Ejaculatory duct obstruction

The treatment of ejaculatory duct obstruction depends on the aetiology. In large post-inflammatory obstruction and when one or both ejaculatory ducts empty into an intraprostatic midline cyst, transurethral resection of the ejaculatory ducts (TURED) (20,37) can be performed. Resection may remove part of the verumontanum. In cases of obstruction due to a midline intraprostatic cyst, incision or unroofing of the cyst is required (20). Intraoperative TRUS makes this procedure safer and more effective. If distal seminal tract evaluation is carried out at the time of the procedure, installation of methylene blue dye into the vas may be helpful to document opening of the ducts.

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

In cases of functional obstruction of the distal seminal ducts, TURED often fails to improve the sperm output. Spermatozoa may then be retrieved by antegrade seminal tract washout (37). Spermatozoa retrieved by any of the aforementioned surgical techniques should always be cryopreserved for assisted reproductive procedures.

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

5.6   RECOMMENDATIONS
- In cases of azoospermia due to epididymal obstruction a scrotal exploration with MESA and cryopreservation of the spermatozoa should be performed together with a microsurgical reconstruction (35) (grade B recommendation).

5.7   REFERENCES

1.   Hendry WF. Azoospermia and surgery for testicular obstruction. In: Hargreave TB (ed). *Male Infertility*. Berlin, Springer-Verlag: 1997, pp. 319-336.
2.   Hendry WF, Parslow JM, Stedronska J. Exploratory scrototomy in 168 azoospermic males. Br J Urol 1983;55(6):785-791.
      http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=6652453&dopt=Abstract
3.   Jequier AM. Obstructive azoospermia: a study of 102 patients. Clin Reprod Fertil 1985;3(1):21-36.
      http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3978535&dopt=Abstract
4.   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(9):3110-3114.
      http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9745412&dopt=Abstract
5.   Oates RD, Amos JA. The genetic basis of congenital bilateral absence of the vas deferens and cystic fibrosis. J Androl 1994;15(1):1-8.
      http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8188533&dopt=Abstract
6.   Handelsman DJ, Conway AJ, Boylan LM, Turtle JR. Young's syndrome: obstructive azoospermia and chronic sinopulmonary infections. New Engl J Med 1984;310(1):3-9.
      http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=6689737&dopt=Abstract
7.   Silber SJ, Grotjan HE. Microscopic vasectomy reversal 30 years later: a summary of 4010 cases by the same surgeon. J Androl 2004;25(6):845-859.
      http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15477352&query_hl=123&itool=pubmed_docsum

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(5):239-245.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2132475&dopt=Abstract

9. Matthews GJ, Schlegel PN, Goldstein M. Patency following microsurgical vasoepididymostomy and vasovasostomy: temporal considerations. J Urol 1995;154(6):2070-2073.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7500460&query_hl=126&itool=pubmed_docsum

10. 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(4):1410-1412.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9751365&dopt=Abstract

11. Raleigh D, O'Donnell L, Southwick GJ, de Kretser DM, McLachlan RI. Stereological analysis of the human testis after vasectomy indicates impairment of spermatogenic efficiency with increasing obstructive interval. Fertil Steril 2004;81(6):1595-1603.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15193483&query_hl=14&itool=pubmed_docsum

12. McVicar CM, O'Neill DA, McClure N, Clements B, McCullough S, Lewis SEM. Effects of vasectomy on spermatogenesis and fertility outcome after testicular sperm extraction combined with ICSI. Hum Reprod 2005;20(10): 2795-2800.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15958397&query_hl=16&itool=pubmed_docsum

13. Sheynkin YR, Hendin BN, Schlegel PN, Goldstein M. Microsurgical repair of iatrogenic injury to the vas deferens. J Urol 1998;159(1):139-141.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9400456&query_hl=128&itool=pubmed_docsum

14. Shin D, Lipshultz LI, Goldstein M, Barme GA, Fuchs EF, Nagler HM, McCallum SW, Niederberger CS, Schoor RA, Brugh VM 3rd, Honig SC. Herniorrhaphy with polypropylene mesh causing inguinal vasal obstruction: a preventable cause of obstructive azoospermia. Ann Surg 2005;241(4):553-558.
http://ww\w.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15798455&query_hl=12&itool=pubmed_docsum

15. Schlegel PN, Shin D, Goldstein M. Urogenital anomalies in men with congenital absence of the vas deferens. J Urol 1996;155(5):1644-1648.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8627844&dopt=Abstract

16. Borovikov A. Treatment of large vasal defects. In: Goldstein M (ed). *Surgery of Male Infertility*. Philadelphia: WB Saunders, 1995, pp. 77-95.

17. Elder JS, Mostwin JL. Cyst of the ejaculatory duct/urogenital sinus. J Urol 1984;132(4):768-771.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=6471229&dopt=Abstract

18. Schuhrke TD, Kaplan GW. Prostatic utricle cysts (Mullerian duct cysts). J Urol 1978;119(6):765-767.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=26814&dopt=Abstract

19. Surya BV, Washecka R, Glasser J, Johanson KE. Cysts of the seminal vesicles: diagnosis and management. Br J Urol 1988;62(5):491-493.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3208033&dopt=Abstract

20. Schroeder-Printzen I, Ludwig M, Kohn F, Weidner W. Surgical therapy in infertile men with ejaculatory duct obstruction: technique and outcome of a standardized surgical approach. Hum Reprod 2000;15(6):1364-1368.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10831570&dopt=Abstract

21. Kuligowska E, Baker CE, Oates RD. Male infertility: role of transrectal US in diagnosis and management. Radiology 1992;185(2):353-360.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1410338&dopt=Abstract

22. 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(3):165-179.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3125711&dopt=Abstract

23. Hendry WF, Rickards D, Pryor JP, Baker LR. Seminal megavesicles with adult polycystic kidney disease. Hum Reprod 1998;13(6):1567-1569.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9688393&dopt=Abstract

24. Colpi GM, Negri L, Nappi RE, Chinea B. Is transrectal ultrasonography a reliable diagnostic approach in ejaculatory duct sub-obstruction? Hum Reprod 1997;12(10):2186-2191.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9402280&dopt=Abstract

25. Meacham RB, Hellerstein DK, Lipshultz LI. Evaluation and treatment of ejaculatory duct obstruction in the infertile male. Fertil Steril 1993;59(2):393-397.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8425637&dopt=Abstract

26. Jarow JP. Seminal vesicle aspiration of fertile men. J Urol 1996;156(3):1005-1007.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8709296&dopt=Abstract

27. 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(1):2-25.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=5527187&dopt=Abstract

28. 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(3):525-528.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3410105&dopt=Abstract

29. Schroeder-Printzen I, Zumbe G, Bispink L, Palm S, Schneider U, Engelmann U, Weidner W. Microsurgical epididymal sperm aspiration: aspirate analysis and straws available after cryopreservation in patients with non-reconstructable obstructive azoospermia. MESA/TESE Group Giessen. Hum Reprod 2000;15(12):2531-2535.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11098022&dopt=Abstract

30. Van Peperstraten A, Proctor ML, Johnson NP, Philipson G. Techniques for surgical retrieval of sperm prior to ICSI for azoospermia. Cochrane Database Syst Rev 2006 Jul 19;3:CD002807. DOI: 10.1002/14651858.CD002807.pub2. Date of Most Recent Substantive Amendment: 16 May 2006.
http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD002807/frame.html

31. Chan PT, Brandell RA, Goldstein M. Prospective analysis of outcomes after microsurgical intussusception vasoepididymostomy. BJU Int 2005;96(4):598-601.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16104917&query_hl=18&itool=pubmed_docsum

32. Matthews GJ, Schlegel PN, Goldstein M. Patency following microsurgical vasoepididymostomy and vasovasostomy: temporal consideration. J Urol 1995;154(6):2070-2073.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7500460&dopt=Abstract

33. 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-sid epididymovasostomy. Urology 1997;49(4):590-595.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9111630&dopt=Abstract

34. Kim ED, Winkel E, Orejuela F, Lipshultz LI. Pathological epididymal obstruction unrelated to vasectomy: results with microsurgical reconstruction. J Urol 1998;160(6 Pt 1):2078-2080.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9817328&dopt=Abstract

35. Kolettis PN, Thomas AJ Jr. Vasoepididymostomy for vasectomy reversal: a critical assessment in the era of intracytoplasmic sperm injection. J Urol 1997;158(2):467-470.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9224325&dopt=Abstract

36.   Ruiz-Romero J, Sarquella J, Pomerol JM. A new device for microsurgical sperm aspiration. Andrologia
        1994;26(2):119-120.
        http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8042769&do
        pt=Abstract
37.   Colpi GM, Negri L, Patrizio P, Pardi G. Fertility restoration by seminal tract washout in ejaculatory duct
        obstruction. J Urol 1995;153(6):1948-1950.
        http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7752365&do
        pt=Abstract

6.   VARICOCELE

6.1   Introduction
Varicocele is a common abnormality (see section 2 Investigations) with the following andrological implications:
•   Failure of ipsilateral testicular growth and development
•   Symptoms of pain and discomfort
•   Infertility.

6.2   Classification
The following classification of varicocele (1,2) is useful in clinical practice.
•   Subclinical: Not palpable or visible at rest or during Valsalva manoeuvre, but demonstrable by special
        tests (reflux found upon Doppler examination) (3).
•   Grade 1: Palpable during Valsalva manoeuvre but not otherwise.
•   Grade 2: Palpable at rest, but not visible.
•   Grade 3: Visible and palpable at rest.

6.3   Diagnosis
The diagnosis of varicocele has been defined by the WHO (2). The consensus is that diagnostic procedure and
classification of a varicocele, including analysis, have to follow these accepted criteria (2).
        The diagnosis of varicocele is made by clinical examination and may be confirmed by colour Doppler
analysis. In centres where treatment is performed by antegrade or retrograde sclerotherapy or embolization, the
diagnosis is additionally confirmed by X-ray.

6.4   Basic considerations
Various studies have been conducted on the epidemiologyof varicocele, its association with male infertility and
whether treatment is beneficial.
•   Varicocele is a physical abnormality present in 20-24% of the adult male population (4,5). It is more
        common in men of infertile marriages, affecting 25% of those with abnormal semen analysis (6).
•   The incidence of pain and discomfort associated with varicocele is 2-10% (7). Treatment to relieve
        symptoms is often recommended, but there have been few outcome studies; however, most urologists
        accept discomfort as a valid indication.
•   The exact association between reduced male fertility and varicocele is not known, but analysis of the
        WHO data (8) clearly indicates that varicocele is related to semen abnormalities, decreased testicular
        volume and decline in Leydig cell function.
•   Two prospective randomized studies showed increased ipsi- and contralateral testis growth in
        adolescents who had received varicocele treatment compared with those who did not (9,10). A cohort
        follow-up study, which took serial measurements of testicular size in children, showed that varicocele
        halted testicular development. However, following treatment for varicocele, catch-up growth occurred
        to the expected growth percentile (11).
•   A series of studies suggested that altered endocrine profiles in men with varicocele might predict
        those who would benefit from treatment (12,13).
•   Five prospective randomized studies of varicocele treatment in adults gave conflicting results (6,14-
        18), with the largest study indicating benefit (16,18). The externally randomized study involved 10
        centres 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 significantly more effective than delaying treatment
        for 1 year with regard to achieving pregnancy and the pregnancy rate per menstrual cycle
        (fecundability). However, a meta-analysis of the five trials indicated no benefit (common odds ratio
        was 0.85% (95% CI: 0.49-1.45) (19).

- The only prospective randomized study of treatment of subclinical varicocele failed to show that therapy benefited fertility (20).
- Analysis of the large WHO infertility study (21) indicated that there was an excess of couples where both partners had factors associated with reduced fertility compared with the expected rate of coincidence in the general population. This implied that a minor cause of impaired fertility, such as varicocele, will only manifest in couples in which the female partner also has reduced fertility.

The studies mentioned above were summarized in a recent review (22), criticising the recent Cochrane analyses of randomized controlled trials on varicocele treatment and pregnancies (23). The authors concluded that the Cochrane meta-analysis conclusions should not support guidelines recommendation against varicocele treatment in subfertile patients. Data from ongoing studies should provide more information on this topic.

6.5 Treatment

Several treatment modalities can be chosen (Table 7). The type of intervention is mainly dependent on the therapist's experience. Although laparoscopic varicocelectomy is feasible, it needs to be justified in terms of cost effectiveness.

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

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

6.6 CONCLUSIONS

- Current information supports the hypothesis that in some men the presence of varicocele is associated with progressive testicular damage from adolescence onwards and consequent reduction in fertility. However, in infertile couples this impaired fertility potential will only be manifest if female fertility is also reduced.
- Although treatment of varicocele in adolescents may be effective, there is a significant risk of overtreatment.

6.7 RECOMMENDATIONS

- Varicocele treatment is recommended for adolescents who have progressive failure of testicular development documented by serial clinical examination (9,10) (grade B recommendation).
- 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 (9,10) (grade B recommendation).
- Reviews of randomized clinical trials have raised doubts about the benefit of varicocele treatment in subfertle men. Varicocele treatment for infertility should not be done unless there has been full discussion with the infertile couple about the uncertainties of treatment benefit (19,22,23) (grade B recommendation).

6.8 REFERENCES

1. Hudson RW, Perez Marrero RA, Crawford VA, McKay DE. Hormonal parameters in incidental varicoceles and those causing infertility. Fertil Steril 1986;45(5):692-700.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3084304&dopt=Abstract
2. World Health Organization. *WHO Manual for the Standardized Investigation, Diagnosis and Management of the Infertile Male*. Cambridge: Cambridge University Press, 2000.
3. Dhabuwala CB, Hamid S, Moghissi KS. Clinical versus subclinical varicocele: improvement in fertility after varicocelectomy. Fertil Steril 1992;57(4):854-857.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=1555699&query_hl=2&itool=pubmed_docsum
4. Pfeiffer D, Berger J, Schoop C, Tauber R. A Doppler-based study on the prevalence of varicocele in German children and adolescents. Andrologia 2006; 38(1):13-19.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16420237&query_hl=5&itool=pubmed_docsum
5. Hargreave TB. Varicocele. In: Hargreave, TB (ed). *Male Infertility*. Berlin: Springer-Verlag, 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(2):347-353.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7769060&dopt=Abstract
7. Peterson AC, Lance RS, Ruiz HE. Outcomes of varicocele ligation done for pain. J Urol 1998;159(5):1565-1567.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9554356&dopt=Abstract
8. [No authors listed.] The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. World Health Organization. Fertil Steril 1992;57(6):1289-1293.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1601152&dopt=Abstract
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(4):756-762.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1426322&dopt=Abstract
10. Paduch DA, Niedzielski J. Repair versus observation in adolescent varicocele: a prospective study. J Urol 1997;158(3 Pt 2):1128-1132.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9258155&dopt=Abstract
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(2):299-304.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8690120&dopt=Abstract
13. Kass EJ. Pediatric varicocele. In: O'Donnell B, Koff SA (eds). *Pediatric Urology*. Oxford: Butterworth Heinemann, 1996, pp. 608-617.
14. Nilsson S, Edvinsson 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(6):591-596.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=534846&dopt=Abstract

15. Breznik R, Vlaisavljevic V, Borko E. Treatment of varicocele and male fertility. Arch Androl 1993;30(3):157-160.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8498867&dopt=Abstract

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(1):120-124.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7805900&dopt=Abstract

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(8):2147-2150.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9756286&query_hl=135&itool=pubmed_docsum

18. Hargreave TB. Varicocele: overview and commentary on the results of the WHO varicocele trial. 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, Collins JA. Assessment of efficacy of varicocele repair for male subfertility: a systematic review. Lancet 2003;361(9372):1849-1852.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12788571&dopt=Abstract

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(5):1636-1638.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8627841&query_hl=22&itool=pubmed_docsum

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. Ficarra V, Cerruto MA, Liguori G, Mazzoni G, Minucci S, Tracia A, Gentile V. Treatment of varicocele in subfertile men: The Cochrane review - a contrary opinion. Eur Urol 2006;49(2):258-263.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16426727&query_hl=24&itool=pubmed_docsum

23. Evers JL, Collins JA. Surgery or embolisation for varicocele in subfertile men. Cochrane Database Syst Rev 2004;(3):CD000479.
http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD000479/frame.html

24. Sigmund G, Bahren W, Gall H, Lenz M, Thon W. Idiopathic varicoceles: feasibility of percutaneous sclerotherapy. Radiology 1987;164(1):161-168.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3588899&dopt=Abstract

25. Seyferth W, Jecht E, Zeitler E. Percutaneous sclerotherapy of varicocele. Radiology 1981;139(2):335-340.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7220877&query_hl=28&itool=pubmed_docsum

26. Lenk S, Fahlenkamp D, Gliech V, Lindeke A. Comparison of different methods of treating varicocele. J Androl 1994;15(Suppl):34S-37S.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7721674&dopt=Abstract

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(4):642-646.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9352706&dopt=Abstract

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(2):425-431.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8596844&dopt=Abstract

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(7-8):533-536. [Italian]
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8975158&dopt=Abstract

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. Goldstein M (ed). *Surgery of Male Infertility*. Philadelphia, USA, WB Saunders, 1995, pp. 169-172.
33.   McDougall E. Minimally invasive therapy. J Urol 1995;153(3 Pt 1):712-713.
        http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7861516&dopt=Abstract
34.   Miersch WD, Schoeneich G, Winter P, Buszello H. Laparoscopic varicocelectomy: indication, technique and surgical results. Br J Urol 1995;76(5):636-638.
        http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8535687&dopt=Abstract
35.   Tan SM, Ng FC, Ravintharan T, Lim PH, Chng HC. Laparoscopic varicocelectomy: technique and results. Br J Urol 1995;75(4):523-528.
        http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7788264&dopt=Abstract

7.   HYPOGONADISM

7.1   Introduction

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

Table 8: The symptoms and signs of hypogonadism debuting before and after completion of puberty

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

The aetiological and pathogenetic mechanisms behind male hypogonadism can be divided into three main categories.
1.   Primary (hypergonadotropic) hypogonadism due to testicular failure
2.   Secondary (hypogonadotropic) hypogonadism caused by insufficient gonadotrophin releasing hormone (GnRH) and/or gonadotrophin secretion
3.   Androgen insensitivity (end-organ resistance).
The most common conditions within these three categories are given in Table 9.

Table 9: Disorders with male hypogonadism. Modified from Nieschlag et al. (1)

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

Secondary (hypothalamic or pituitary origin) (hypogonadotropic state with secondary hypogonadism)
- Idiopathic hypogonadotropic hypogonadism (including Kallmann's syndrome)
- Delay of puberty
- Hyperprolactinaemia
- Drugs/anabolic steroids

Target organ resistance to androgens
- Testicular feminization
- Reifenstein's syndrome

See section 4 Genetic disorders in infertility.

7.2 Hypogonadotropic hypogonadism: aetiology, diagnosis and therapeutic management

Primary hypogonadotropic hypogonadism is caused either by hypothalamic or pituitary diseases. The failure of hormonal regulation can easily be determined (2). Endocrine deficiency leads to a lack of spermatogenesis and testosterone secretion due to decreased secretion patterns of luteinizing hormone (LH) and FSH. The therapy of choice depends on whether the goal is to achieve normal androgen levels or to achieve fertility.

Normal androgen levels and subsequent development of secondary sex characteristics (in cases of onset of hypogonadism before puberty) and eugonadal state can be achieved by androgen replacement only. However, stimulation of sperm production requires treatment with human chorionic gonadotrophin (hCG) combined with recombinant FSH. In the rare cases of 'fertile eunuchs' having sufficient production of FSH but not LH, treatment with hCG only may be sufficient to stimulate sperm production and to achieve normal testosterone levels (3).

If hypogonadotropic hypogonadism is hypothalamic in origin, an alternative to hCG treatment is therapy with pulsatile GnRH (4). In patients who have developed hypogonadism prior to puberty and not been treated with gonadotropins or GnRH, 1-2 years of therapy may be necessary to achieve sperm production. Once pregnancy has been induced, patients can return to testosterone substitution.

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

7.3 Hypergonadotropic hypogonadism: aetiology, diagnosis and therapeutic management

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

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

The laboratory diagnosis of hypergonadotropic hypogonadism is based on decreased serum

testosterone and increased LH levels (2). Testosterone levels should be evaluated in view of the concentration of the serum concentration of sex hormone binding globulin (SHBG). Based on levels of total testosterone and SHBG, free and bioavailable testosterone can be calculated (www. issam.ch). Due to diurnal variation, blood sampling for testosterone assessment should be done before 10 am. The existing guidelines for androgen replacement are mainly based on total testosterone levels and testosterone supplementation is only indicated in men with levels consistently lower than normal (< 12 nmol/L [300 ng/dL]). Injectable, oral and transdermal testosterone preparations are available for clinical use (2). The best preparation is the one that maintains serum testosterone levels as close to physiological concentrations as possible (11).

7.4 CONCLUSIONS

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

7.5 RECOMMENDATIONS

- Effective drug therapy is available to achieve fertility in men with hypogonadotropic hypogonadism (4) (grade A recommendation).
- Male infertility may be accompanied by hypogonadism (6) (grade B recommendation).

7.6 REFERENCES

1. Nieschlag E, Behre HM. *Testosterone: Action, Deficiency, Substitution*. 2nd edn. Berlin: Springer Verlag, 1998.
2. World Health Organization. *WHO manual for the Standardized Investigation, Diagnosis and Management of the Infertile Male*. Cambridge: Cambridge University Press, 2000.
3. 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(6):1144-1151.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3372679&dopt=Abstract
4. Schopohl J, Mehltretter G, von Zumbusch R, Eversmann T, von Werder K. Comparison of gonadotropin-releasing hormone and gonadotropin therapy in male patients with idiopathic hypothalamic hypogonadism. Fertil Steril 1991;56(6):1143-1150.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1743335&dopt=Abstract
5. Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E. Klinefelter's syndrome. Lancet 2004;364(9430):273-283.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15262106&query_hl=50&itool=pubmed_docsum
6. Andersson AM, Jorgensen N, Frydelund-Larsen L, Rajpert-De Meyts E, Skakkebaek NE. Impaired Leydig cell function in infertile men: a study of 357 idiopathic infertile men and 318 proven fertile controls. J Clin Endocrinol Metab 2004;89(7):3161-3167.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15240588&query_hl=53&itool=pubmed_docsum
7. Manning M, Junemann KP, Alken P. Decrease in testosterone blood concentrations after testicular sperm extraction for intracytoplasmic sperm injection in azoospermic men. Lancet 1998;352(9121):37.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9800753&dopt=Abstract
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(4):375-385.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1924650&dopt=Abstract
9. Daniell HW. Osteoporosis after orchiectomy for prostate cancer. J Urol 1997;157(2):439-444.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8996327&dopt=Abstract
10. Finkelstein JS. Androgens and bone metabolism. In: Nieschlag E, Behre HM (eds). *Testosterone: Action, Deficiency, Substitution*. 2nd edn. Berlin: Springer-Verlag, 1998, pp. 187-207.
11. Nieschlag E, Wang C, Handelsman DJ, Swerdloff RS, Wu F, Einer-Jensen N, Waites G. *Guidelines for the Use of Androgens in Men*. Geneva: WHO, 1992.

8. CRYPTORCHIDISM

8.1 Introduction

Cryptorchidism is the most frequent congenital abnormality of the male genitalia and is found in 2-5% newborn boys. This figure is dependent on the gestational age, with premature boys having a higher frequency of cryptorchidism, and age post partum. At the age of 3 months, the incidence is reduced spontaneously to 1-2%. Approximately 20% of undescended testes are non-palpable and may be located within the abdominal cavity.

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

8.2 Incidence of cryptorchidism

The Caucasian population has a three-fold higher incidence of cryptorchidism compared to African-Americans. Even between Caucasians, significant differences in the risk of this malformation was found, the condition being significantly more common among Danish compared to Finish newborns (2). Premature babies reveal a much higher incidence than fullterm babies. Scorer examined more than 3,000 newborns in London. The incidence of cryptorchidism in boys weighing > 2,500 g was 2.7%, whereas in premature boys weighing < 2,500 g the corresponding number was 21%. At the age of 3 months, spontaneous descence occurred in most boys and the incidence rate declined to 0.9 and 1.7%, respectively (3).

8.3 Testicular descent and maldescent

The process of testicular descent has two distinct phases: a) transabdominal; and b) inguinal.

During 'transabdominal descence', development of the gubernaculum and genitoinguinal ligament plays an important role. The antiMüllerian hormone additionally regulates the transabdominal descence of the testis. Induction of the gubernaculum is dependent on functional Insl3 gene in mice (4). This gene is expressed in Leydig cells, and its targeted deletion causes bilateral cryptorchidism with free-moving testes and genital ducts (5). There are other gene families, e.g. the homeobox (HOX) genes and GREAT gene, which are important for the development of genital organs and may be associated with testicular maldescence (6,7).

8.4 Hormonal control of testicular descent

Maldescence can be caused by two hormonal factors: hypogonadism and androgen insensitivity. Also, the increasing incidence of reproductive abnormalities in human males may be explained by an increased oestrogen exposure during gestation (8). Some pesticides and synthetic chemicals are known to act as hormonal modulators, often possessing oestrogenic activity (xeno-oestrogens) (9). The oestrogenic and antiandrogenic properties of these chemicals may cause hypospadia, cryptorchidism, reduction of sperm density, and an increase in the incidence of testicular tumours in animal models by receptor-mediated mechanisms or direct toxic effects (10).

8.5 Pathophysiological effects in maldescended testes

8.5.1 Degeneration of germ cells

It is established that the degeneration of germ cells in maldescended testes becomes apparent after the first year. Depending on the different position of the testis, the degenerative changes are variable (11). During the second year of life, the number of germ cells clearly starts to decline. In 10-45% of affected patients, a complete loss of germ cells can be detected. Early treatment is therefore recommended to conserve spermatogenesis, especially in bilateral cases. Surgical treatment is the most effective and reliable method of bringing testes into the scrotum, but hormone treatment with either hCG or GnRH analogues can be considered, particularly in cases where testes are located in the high scrotal position (12).

8.5.2 Relationship with fertility

Semen parameters are often impaired in men with a history of cryptorchidism (13). It has been suggested that surgical treatment performed during the first or second year of life has a positive effect on subsequent fertility (14). However, definitive proof of the protective effect of early orchidopexy is lacking. Paternity in men with a history of unilateral cryptorchidism is almost equal (89.7%) to paternity in men without cryptorchidism (93.7%). In men with unilateral cryptorchidism, paternity seems independent of the age of orchidopexy, preoperative

testicular location and testicular size (15). However, it cannot be excluded that a history of unilateral cryptorchidism may result in a reduced fertility potential, i.e. not affecting paternity but causing a prolonged time to pregnancy.

In men with bilateral cryptorchidism, oligozoospermia can be found in 31% and azoospermia in 42%. In cases of bilateral cryptorchidism, the rate of paternity is only 35-53%.

8.5.3 Germ cell tumours
Cryptorchidism is a risk factor for testicular cancer development and is associated with testicular microcalcification and carcinoma *in situ* (CIS) of the testis. In about 5-10% of testicular cancers, there is a history of cryptorchidism (16). The risk of a germ cell tumour is 3.6-7.4 times higher than in the general population, and 2-6% of men with a history of cryptorchidism will develop a testicular tumour (16). So far, there is a lack of evidence for a protective effect of early orchidopexy (17).

8.6 Treatment of undescended testes
8.6.1 Hormonal treatment
In randomized, controlled trials for the efficacy and side-effects of hCG and GnRH treatment, a large variation in success rates have been reported. The corresponding figures in all randomized trials were 21%, 19% and 4% for GnRH, hCG and placebo, respectively (12). A meta-analysis of 33 studies published between 1958 and 1990 by Pyorala et al. (18) showed that the success rate was best in prescrotal and high scrotal testes. Non-palpable testes rarely descend as a result of hormonal treatment.

The current hormonal protocol for high scrotal testes is three hCG injections given once per week. The dose is 1,500 IU per injection for children at ages 1-3 years, 3,000 IU at ages 4-6 years, and 5,000 IU at ages 6-15 years. The recommended age for this treatment is 12-18 months. In a patient with bilateral impalpable testes, a hCG stimulation test can be performed. The presence of testes is confirmed by a rise in testosterone level. Inhibin B is produced by the Sertoli cells of the testis and can be a good indicator for testicular function in children (19).

Hormonal treatment is generally considered safe, with only a few side-effects. However, some studies have indicated an increased risk of interstitial fibrosis and germ cell apoptosis following hCG treatment (20). Early adverse effects include penile growth, pain in the genital region, pain at the site of injection and psychological changes due to androgen effects.

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

If not corrected by adulthood, an undescended testis should not be removed. A biopsy at the time of orchidopexy (see page 55) can reveal the presence of CIS and thereby prevent a malignant tumour.

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

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

8.7 RECOMMENDATIONS
- The success rate of hormonal treatment of cryptorchidism has only been shown for prescrotal and high scrotal testes.
- Non-palpable testes rarely descend by hormonal treatment (18) (grade B recommendation).
- If corrected in adulthood, a testicular biopsy for detection of CIS is recommended at the time of the orchidopexy to exclude the risk of tumour development (16) (grade B recommendation).

8.9 REFERENCES

1. Skakkebaek NS, Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. Hum Reprod 2001;16(5):972-978.
    http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11331648&dopt=Abstract

2. Boisen KA, Kaleva M, Main KM, Virtanen HE, Haavisto AM, Schmidt IM, Chellakooty M, Damgaard IN, Mau C, Reunanen M, Skakkebaek NE, Toppari J. Difference in prevalence of congenital cryptorchidism in infants between two Nordic countries. Lancet 2004;363(9417):1264-1269.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15094270&query_hl=59&itool=pubmed_docsum

3. Heyns CF, Hutson JM. Historical review of theories on testicular descent. J Urol 1995;153(3 Pt 1):754-767.
    http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7861531&dopt=Abstract

4. Scorer CG. The descent of the testis. Arch Dis Child 1964;39:605-609.
    http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14230757&dopt=Abstract

5. Nguyen MT, Showalter PR, Timmons CF, Nef S, Parada LF, Baker LA. Effects of orchiopexy on congenitally cryptorchid insulin-3 knockout mice. J Urol 2002;168(4 Pt 2):1779-1783; discussion, 1783.
    http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12352358&dopt=Abstract

6. Lewis AG, Pecha BR, Smith EP, Gardner BJ, Hsieh-Li HM, Potter SS, Sheldon CA. Early orchidopexy restores fertility in Hoxa 11 gene knockout mouse. J Urol 2003;170:302-305.
    http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12796710&dopt=Abstract

7. Gorlov IP, Kamat A, Bogatcheva NV, Jones E, Lamb DJ, Truong A, Bishop CE, McElreavey K, Agoulnik AI. Mutations of the GREAT gene cause cryptorchidism. Hum Mol Genet 2002;11(19):2309-2318.
    http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12217959&dopt=Abstract

8. Hadziselimovic F, Geneto R, Emmons LR. Elevated placental estradiol: a possible etiological factor of human cryptorchidism. J Urol 2000;164(5):1694-1695.
    http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11025750&dopt=Abstract

9. Hosi S, Loff S, Witt K, Niessen K, Waag KL. Is there a correlation between organochlorine compounds and undescended testes? Eur J Pediatr Surg 2000;10(5):304-309.
    http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11194541&dopt=Abstract

10. Toppari J, Larsen JC, Christiansen P, Giwercman A, Grandjean P, Guillette LJ Jr, Jegou B, Jensen TK, Jouannet P, Keiding N, Leffers H, McLachlan JA, Meyer O, Muller J, Rajpert-De Meyts E, Scheike T, Sharpe R, Sumpter J, Skakkebaek NE. Male reproductive health and environmental xenoestrogens. Environ Health Perspect 1996;104(Suppl 4):741-803.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8880001&query_hl=68&itool=pubmed_docsum

11. Garcia J, González N, Gómez ME, Plaza L, Sanchez J, Alba J. Clinical and anatomopathological study of 2000 cryptorchid testes. Br J Urol 1995(6);75:697-701.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7613821&query_hl=71&itool=pubmed_docsum

12. Christiansen P, Muller J, Buhl S, Hansen OR, Hobolth N, Jacobsen BB, Jorgensen PH, Kastrup KW, Nielsen K, Nielsen LB. Hormonal treatment of cryptorchidism - hCG or GnRH - a multicentre study. Acta Paediatr 1992;81(8):605-608.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=1356527&query_hl=74&itool=pubmed_docsum

13. Yavetz H, Harash B, Paz G, Yogev L, Jaffa AJ, Lessing JB, Homonnai ZT. Cryptorchidism: incidence and sperm quality in infertile men. Andrologia 1992;24(5):293-297.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=1356318&query_hl=77&itool=pubmed_docsum

14. Wilkerson ML, Bartone FF, Fox L, Hadziselimovic F. Fertility potential: a comparison of intra-abdominal and intracanalicular testes by age groups in children. Horm Res 2001;55(1):18-20.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=11423737&query_hl=80&itool=pubmed_docsum

15. Miller KD, Coughlin MT, Lee PA. Fertility after unilateral cryptorchidism: paternity, time to conception, pretreatment testicular location and size, hormone and sperm parameters. Horm Res 2001; 55(5):249-253.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11740148&d opt=Abstract

16. Giwercman A, Bruun E, Frimodt-Moller C, Skakkebaek NE. Prevalence of carcinoma in situ and other histopathological abnormalities in testes of men with a history of cryptorchidism. J Urol 1989;142(4):998-1001.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=2571738&query_hl=84&itool=pubmed_DocSum

17. Pike MC, Chilvers C, Peckham MJ. Effect of age at orchidopexy on risk of testicular cancer. Lancet 1986;1(8492):1246-1248.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=2872394&query_hl=86&itool=pubmed_docsum

18. Pyorala S, Huttunen NP, Uhari M. A review and meta-analysis of hormonal treatment of cryptorchidism. J Clin Endocrinol Metab 1995;80(9):2795-2799.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=7673426&query_hl=88&itool=pubmed_docsum

19. Andersson AM. Inhibin B in the assessment of seminiferous tubular function. Baillieres Best Pract Res Clin Endocrinol Metab 2000;14(3):389-397.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=11517906&query_hl=92&itool=pubmed_docsum

20. Kaleva M, Arsalo A, Louhimo I, Rapola J, Perheentupa J, Henriksen K, Toppari J. Treatment with human chorionic gonadotrophin for cryptorchidism: clinical and histological effects. Int J Androl 1996;19(5):293-298.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=8985778&query_hl=99&itool=pubmed_docsum

21. Jones PF. Approaches to orchidopexy. Br J Urol 1995;75(6):693-696.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=7613820&query_hl=101&itool=pubmed_docsum

9. IDIOPATHIC MALE INFERTILITY

9.1 Introduction

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

9.2 Empirical treatments

A wide variety of empirical drug approaches have been used (Table 10). However, there is little scientific evidence for an empirical approach (1). Criteria for the analysis of all therapeutic trials have been re-evaluated. There is consensus that only randomized, controlled trials, with 'pregnancy' as the outcome parameter, can be accepted for efficacy analysis. The use of recombinant human FSH in patients with idiopathic oligozoospermia, but with normal FSH and inhibin B, may be a debatable choice in the future to improve spermatogenesis (1).

Table 10:   **Empirical therapy of idiopathic oligo-astheno-teratozoospermia (OAT) syndrome‡**

Therapeutic approaches	EAU recommendations
Hormonal	
• GnRH	Contradictory results
	Not controlled trials (2)
	Further trials are needed
• hCG/hMG	Lack of efficacy
	Not recommended
• FSH	Efficacy not yet shown
	Further trials are needed (3)
• Androgens	Lack of efficacy
	Not recommended
• Anti-oestrogens (clomiphene citrate, tamoxifen-testosterone undecanoate)	Potentially effective (4)
	Use must be counterbalanced against possible side-effects (5). Further studies are needed
Non-hormonal	
• Kinin-enhancing drugs	Unproven efficacy
	Clinical trials only
• Bromocriptine	Lack of efficacy
	Not recommended
• Antioxidants	May benefit selected patients
	Clinical trials only
• Mast cell blockers	Some efficacy shown
	Further evaluation needed
	Clinical trials only
• Alpha-blockers	Lack of efficacy
	Not recommended
• Systemic corticosteroids	Lack of efficacy
	Patients with high levels of antisperm antibodies should enter an ART programme
• Magnesium supplementation	Unproven efficacy (4)
	Not recommended

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

9.3   RECOMMENDATIONS
- Medical treatment of male infertility can only be advised in cases of hypogonadotrophic hypogonadism (1) (grade A recommendation).
- Drugs are usually ineffective in the treatment of idiopathic male infertility (grade B recommendation).

9.4   REFERENCES

1.   Foresta C, Bettella A, Spolaore D, Merico M, Rossato M, Ferlin A. Suppression of the high endogenous levels of plasma FSH in infertile men are associated with improved Sertoli cell function as reflected by elevated levels of plasma inhibin B. Hum Reprod 2004; 19(6):1431-1437.
       http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15117900&query_hl=12&itool=pubmed_docsum
2.   Matsumiya K. [New method of endocrine therapy for male infertility.] Hinyokika Kiyo 2004; 50(8):541-543. [Japanese.]
       http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15471073&query_hl=15&itool=pubmed_docsum
3.   Paradisi R, Busacchi P, Seracchioli R, Porcu E, Venturoli S. Effects of high doses of recombinant human follicle-stimulating hormone in the treatment of male factor infertility: results of a pilot study. Fertil Steril 2006;86(3):728-731.
       http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16782097&query_hl=17&itool=pubmed_docsum

4.	Adamopoulos DA, Pappa A, Billa E, Nicopoulou S, Koukkou E, Michopoulos J. Effectiveness of combined tamoxifen citrate and testosterone undecanoate treatment in men with idiopathic oligozoospermia. Fertil Steril 2003;80(4):914-920.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14556812&dopt=Abstract
5.	Hussein A, Ozgok Y, Ross L, Niederberger C. Clomiphene administration for cases of nonobstructive azoospermia: a multicenter study. J Androl 2005;26(6):787-791; discussion, 792-793.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16291975&query_hl=21&itool=pubmed_docsum

# 10.	MALE CONTRACEPTION

## 10.1	Introduction
It is more precise to discuss the 'male contribution to contraception' rather than 'male contraception', because men do not conceive. The development of male contraceptive methods is important because up to 40% of women have an unmet need for family planning, with approximately 80 million women every year having unintended or unwanted pregnancies. Some 45 million unintended pregnancies are terminated each year, with unsafe abortions killing an estimated 68,000 women every year (1).

Three of the four methods of male contraception have been in use for 100s of years (i.e. condoms, periodic abstinence and withdrawal). The typical first-year failure rates of traditional male methods are high (withdrawal 19%, periodic abstinence 20%, and condoms between 3 and 14%) compared to the failure rates of 0.1-3% for modern reversible female methods (2).

For men to take more responsibility for family planning, male contraceptive methods have to be effective, reversible, acceptable and cheap.
Biomedical research is attempting to (3):
- Prevent sperm production (through use of androgens, progestogen and GnRH in various combinations)
- Interfere with the ability of sperm to mature and carry out fertilization by using an epididymal approach to create a hostile environment for sperms
- Produce better barrier methods; polyurethane condoms can be used by those with latex allergy, but have higher breakage rates (4)
- Produce an antisperm contraceptive vaccine (5)
- Inhibit sperm-egg interactions.

All these approaches remain experimental, but the method nearest to being generally available clinically is hormonal male contraception. This method is based on the suppression of gonadotrophins and the use of testosterone substitution to maintain male sexual function and bone mineralization and to prevent muscle wasting (6). Various contraceptive regimens have been developed and tested, including testosterone monotherapy, androgen/progestin combinations, testosterone with GnRH analogues, and selective androgen- and progestin-receptor modulators. There are racial differences in the response to androgens alone. However, a combination of testosterone with progestogin has resulted in complete suppression of spermatogenesis in all races and provided contraceptive efficacy equivalent to female hormonal methods (7). Phase 3 clinical trials of depot preparations of androgen/progestin combinations are in progress.

## 10.2	Vasectomy
Vasectomy is an effective method of permanent male surgical sterilization (8). Before the procedure is performed, the couple should be given accurate information about the benefits and risks. An Australian telephone survey found that 9.2% of respondents said they regretted having a vasectomy (9).

### 10.2.1	Surgical techniques
There are various techniques. The least invasive approach to the vas is the no-scalpel vasectomy approach (10), which is also associated with a low rate of complications (11). The most effective occlusion technique seems to be cauterization of the lumen of the vas and fascial interposition (12-14). Most techniques can be safely performed as an outpatient procedure under local anaesthesia.

### 10.2.2	Complications
Acute local complications include haematoma, wound infection and epididymitis in up to 5% of all cases (15). Long-term complications, such as chronic testicular pain (16), must be discussed with the patient. Epididymal

tubal damage is common, with the consequent development of sperm granuloma and time-dependent secondary epididymal obstruction setting a limit to vasectomy reversal.

Vasectomy does not significantly alter spermatogenesis and Leydig cell function. The volume of ejaculate remains unchanged. Potential systemic effects of vasectomy, including atherosclerosis, have not been proven, and there is no evidence of a significant increase of any systemic disease after vasectomy. In a meta-analysis, Bernal-Delgado et al. could not detect an increased rate of prostate cancer in men who underwent vasectomy (17).

10.2.3 Vasectomy failure

Using an effective occlusion technique, the risk of recanalization after vasectomy should be less than 1% (12). No motile spermatozoa should be detected 3 months after vasectomy. Persistent motility is a sign of vasectomy failure and the need to repeat the procedure. A 'special clearance' can be given to men who continue to produce non-motile spermatozoa up to 1 year after vasectomy (18). Patients should be informed preoperatively that long-term re-canalization, although rare, may occur (19).

10.2.4 Counselling

Counselling has to address the following items concerning vasectomy.
- It should be considered irreversible.
- It has a low complication rate. However, because vasectomy is an elective operation, even small risks should be explained as men may wish to consider these before giving their consent.
- It has a low, but existing, failure rate.
- Couples should be advised to continue with other effective contraception until clearance is achieved.
- All available data indicate that vasectomy is safe and not associated with any serious, long-term side-effects (15) (level of evidence: 2a).
- Fascial interposition and cauterization seem to give a higher efficacy (12-14) (level of evidence: 2a).

10.3 Vasectomy reversal

A wide range of surgical success rates has been published for vasectomy reversal (up to 90%), depending on the time elapsed after vasectomy, type of vasectomy (e.g. open-ended or sealed), type of reversal (vasovasostomy or vasoepididymostomy) and whether reversal was unilateral or bilateral. Although there have been no randomized, controlled trials that compare macrosurgery (loops) and microsurgery, there is consensus that microsurgical techniques with the help of magnification and smaller suture materials should be applied (20).

10.3.1 Length of time since vasectomy

Vasovasostomy results have shown patency rates (up to 90%) superior to pregnancy rates. The longer the interval from vasectomy to reversal, the lower the pregnancy rates. Belker et al. (21) reported results in 1,469 men who had undergone microsurgical vasectomy reversal. Patency and pregnancy rates, respectively, were 97% and 76% for an interval up to 3 years after vasectomy, 88% and 53% for 3-8 years, 79% and 44 % for 9-14 years and 71% and 30% for 15 years or longer.

10.3.2 Epididymovasostomy

The chance of secondary epididymal obstruction increases with time after vasectomy. If this has occurred, epididymovasostomy is needed to reverse the vasectomy (see section 5 Obstructive azoospermia).

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

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

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

10.5 RECOMMENDATIONS

- All available data indicate vasectomy is safe and not associated with any serious, long-term side-effects (15) (grade A recommendation).
- Fascial interposition and cauterization seem to give a higher efficacy (12-14) (grade B recommendation).
- Consultation has to include information about the surgical method, risk of failure, irreversibility, need for post-procedure contraception until clearance, and the risk of complications.
- Other methods of male contraception have high failure rates or are still experimental (e.g. hormonal approach).
- Microsurgical vasectomy reversal is a low-risk and (cost-)effective method of restoring fertility (grade B recommendation).
- Sperm aspiration together with ICSI is a second-line option for selective cases and in cases of failed vaso-vasostomy.

10.6 REFERENCES

1. *Reproductive Health Strategy*. Reproductive Health Research World Health Organisation, Geneva. Adopted at the 57th World Health Assembly, 2004.
http://www.who.int/reproductive-health/publications/strategy.pdf
2. Handelsman D, Waites G. Tradional methods. In: Schill W, Comhaire F, Hargreave T (eds). Andrology for the Clinician. Berlin: Springer Verlag, 2006, pp. 122-124.
3. Griffin D, Ringheim K. Male hormonal contraception. What prospects exist and how acceptable are they? Plan Parent Chall 1996;2:20-24.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12291936&%20dopt=Abstract
4. Gallo MF, Grimes DA, Lopez LM, Schulz KF. Non-latex versus latex male condoms for contraception. Cochrane Database Syst Rev (2006)(1):CD003550.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=16437459&dopt=Abstract
5. Naz RK. Antisperm immunity for contraception. J Androl 2006;27(2):153-159.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16474022&query_hl=110&itool=pubmed_docsum
6. Matthiesson KL, McLachlan RI. Male hormonal contraception: concept proven, product in sight? Hum Reprod Update 2006;12(4):463-482.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16597629&query_hl=112&itool=pubmed_docsum
7. Handelsman DJ, Waites GMH. Hormonal male contraception. In: Schill W, Comhaire F, Hargreave T (eds). *Andrology for the Clinician*. Berlin: Springer Verlag, 2006, pp. 520-524.
8. Schwingl PJ, Guess HA. Safety and effectiveness of vasectomy. Fertil Steril 2000;73)5):923-936.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10785217&dopt=Abstract
9. Holden CA, McLachlan RI, Cumming R, Wittert G, Handelsman DJ, de Kretser DM, Pitts M. Sexual activity, fertility and contraceptive use in middle-aged and older men: Men in Australia, Telephone Survey (MATeS). Hum Reprod 2005: 20(12):3429-3434.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16172145&query_hl=116&itool=pubmed_docsum
10. Li SQ, Goldstein M, Zhu J, Huber D. The no-scalpel vasectomy. J Urol 1991;145(2):341-344.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1988727&dopt=Abstract
11. Nirapathpongporn A, Huber D, Krieger N. No-scalpel vasectomy at the King's birthday vasectomy festival. Lancet 1990;335(8694);894.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=1969992&query_hl=120&itool=pubmed_docsum
12. Sokal, D, Irsula, B, Hays M, Chen-Mok M, Barone MA: Investigator Study Group. Vasectomy by ligation and excision, with or without fascial interposition: a randomized controlled trial. BMC Med. 2004 31;2:6.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15056388&query_hl=122&itool=pubmed_docsum

13. Barone MA, Irsula B, Chen-Mok M, Sokal DC: Investigator Study Group. Effectiveness of vasectomy using cautery. BMC Urol 2004;19;4:10.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15260885&query_hl=124&itool=pubmed_docsum

14. Sokal DC, Irsula B, Chen-Mok M, Labrecque M, Barone MA. A comparison of vas occlusion techniques: cautery more effective than ligation and excision with fascial interposition. BMC Urol 2004;27;4(1):12.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15509302&query_hl=127&itool=pubmed_docsum

15. Schwingl PJ, Guess HA. Safety and effectiveness of vasectomy. Fertil Steril 2000;73(5):923-936.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10785217&dopt=Abstract

16. Christiansen CG, Sandlow JI. Testicular pain following vasectomy: a review of postvasectomy pain syndrome. J Androl 2003;24(3):293-298.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12721203&dopt=Abstract

17. Bernal-Delgado E, Latour-Perez J, Pradas-Arnal F, Gomez-Lopez LI. The association between vasectomy and prostate cancer: a systematic review of the literature. Fertil Steril 1998;70(2):191-200.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9696205&dopt=Abstract

18. Davies AH, Sharp RJ, Cranston D, Mitchell RG. The long-term outcome following 'special clearance' after vasectomy. Br J Urol 1990;66(2):211-212.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2390708&dopt=Abstract

19. Verhulst APM, Hoekstra JW. Paternity after bilateral vasectomy. BJU Int 1999;83:280-282.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10233494&%20dopt=Abstract

20. Schroeder-Printzen I, Diemer T, Weidner W. Vasovasostomy. Urol Int 2003;70(2):101-107.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12592037&dopt=Abstract

21. 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(3):505-511.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1997700&dopt=Abstract

22. Pavlovich CP, Schlegel PN. Fertility options after vasectomy: a cost-effectiveness analysis. Fertil Steril 1997;67(1):133-141.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8986698&dopt=Abstract

23. Heidenreich A, Altmann P, Engelmann UH. Microsurgical vasovasostomy versus microsurgical epididymal sperm aspiration/testicular extraction of sperm combined with intracytoplasmic sperm injection. A cost-benefit analysis. Eur Urol 2000;37(5):609-614.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10765102&dopt=Abstract

11. MALE ACCESSORY GLAND INFECTIONS (MAGIS)

11.1 Introduction

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

11.2 Urethritis

Infectious, sexually acquired urethritis may be caused by a variety of pathogens, most commonly by *Chlamydia trachomatis, Ureaplasma urealyticum*, and *Neisseria gonorrhoea* (4). Non-infectious causes of urethritis include

irritations due to allergic reactions, trauma and manipulations. Urethral discharge and bladder voiding problems are the predominant symptoms of acute urethritis.

11.2.1 Diagnosis and treatment
Diagnosis is based on the analysis of urethral smear and first-voided urine (VB1). Evidence of $\geq$ 4 granulocytes per microscopic high-power field (x1000) in an urethral smear, or of 15 granulocytes per microscopic field (x400) in the smear of the sediment of 3 mL VB1, has been considered pathognomonic (4). In urethritis, defined by inflammatory discharge, semen analysis for disorders of male fertility is not possible as the anterior urethra is full of infectious and inflammatory material that hampers any useful analysis (5).

The impact of urethritis on semen quality and fertility has not really been proven due to contamination of the ejaculate with inflammatory material from the urethra.

The negative influence of sexually transmitted micro-organisms on sperm function is still 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 verumontanum, both of which may lead to ejaculatory disturbances and central obstruction of the seminal pathway (2).

Treatment of sexually transmitted diseases is standardized by the guidelines of the Centers of Disease Control and Prevention in Atlanta (GA, USA) (9). As the aetiology of acute urethritis is usually unknown at the time of diagnosis, empirical therapy directed against potential pathogens is suggested. This involves giving a single dose of a fluoroquinolone followed by a 2-week regimen of doxycycline. Treatment is effective both for gonococcal and (co-existing) chlamydial/ureaplasmal infections.

11.3 Prostatitis
Prostatitis represents the most common urological diagnosis in men under the age of 50 years (10). Traditionally, the disease has been classified into four clinical entities:
* Acute bacterial prostatitis (ABP) and prostatic abscess as a sequela/complication of ABP
* Chronic bacterial prostatitis (CBP)
* Non- or abacterial prostatitis (NBP)
* Prostatodynia.

To improve the definition and understanding of the prostatitis syndrome, a new classification system has been proposed by the National Institute of Health (NIH) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Washington DC, USA (10) (Table 11).

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

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

CPPS = Chronic pelvic pain syndrome.

11.3.1 Microbiology
Acute bacterial prostatitis (NIH I), CBP (NIH II) and more significantly, prostatic abscesses are clinically relevant, but uncommon, diseases. The commonest causes of bacterial prostatitis are gram-negative bacteria, predominantly strains of *Escherichia coli* (11). However, the role of gram-positive bacteria in bacterial prostatitis is controversial. Although enterococci may cause bacterial prostatitis and associated recurrent urinary tract infection (UTI), the importance of other gram-positive bacteria in chronic prostatitis is doubtful (11), as is that of *C. trachomatis* and *Mycoplasma*, particularly *U. urealyticum*, (11-15). Hidden bacteria may be aetiologically involved in patients with chronic idiopathic prostatitis after exclusion of typical bacterial infection (16).

Detection of bacteria by molecular techniques has not been evaluated definitively.

11.3.2 Diagnosis

Symptom evaluation must be done by means of standardized scores, especially the new NIH symptom score (17). Other investigative procedures include laboratory diagnosis of CBP using the four-specimen test for bacterial localization (10,11). The test measures sequential quantitative bacteriological cultures of the urethra, bladder urine and prostatic secretions, both in espressed prostatic excretion (EPS) and urine after prostatic massage (12). Simplified techniques compare bacterial and leukocyte counts in the urine before and after prostatic massage (18). Screening of bladder voiding and imaging analysis of the prostate gland are clinical procedures that need to be integrated.

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

11.3.3 Ejaculate analysis

An ejaculate analysis (see section 2 Investigations) helps to clarify whether the prostate is part of a generalized infection of the accessory sex glands (MAGI) and provides information about sperm quality. In addition, leukocyte analysis allows differentiation between inflammatory and non-inflammatory CPPS (NIH IIa vs. NIH IIIb).

11.3.4 Microbiological findings

After exclusion of urethritis and bladder infection, $\geq 10^6$ 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 considered a significant bacteriospermia. Usually, various micro-organisms are cultured from the genital tract of men seen in infertility clinics with more than one strain of bacteria in most cases (1). The time when samples are obtained influences the positive rate of micro-organisms in semen and the frequency of isolation of different strains (19).

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

By analogy with *Mycoplasma, U. urealyticum* appears to be pathogenic in high concentrations only ($\geq 10^3$ cfu/mL ejaculate). No more than about 10% of samples analyzed for ureaplasma exceed this concentration (20). Normal colonization of the urethra hampers the clarification of 'mycoplasmal-associated' urogenital infections using samples such as the ejaculate (15).

11.3.5 White blood cells

The clinical significance of an increased concentration of white blood cells (WBC) or leukocytes in the ejaculate is highly controversial (21). It seems to be generally accepted that infection is indicated only by an increased level of leukocytes (particularly polymorphonuclear leukocytes) and their products (e.g leukocyte elastase) secreted into the seminal fluid. Most leukocytes are neutrophilic granulocytes, as suggested by the specific staining of the peroxidase reaction (2). Although most authors consider leukocytospermia to be a sign of inflammation, it is not necessarily associated with bacterial or viral infections (7). This is in accordance with earlier findings that elevated leukocyte numbers are not a natural cause of male infertility (22).

According to WHO classification, $> 1 \times 10^6$ WBC per mL have been defined as leukospermia. Only two studies have analyzed alterations of WBC in the ejaculate of patients with proven prostatitis (23,24). Both studies demonstrated a higher number of leukocytes compared to men without inflammation (CPPS, type NIH IIIb).

11.3.6 Sperm quality

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

11.3.7 Seminal plasma alterations

Seminal plasma elastase is accepted as a biochemical indicator of polymorphonuclear lymphocyte activity in the ejaculate (1,28,29), with a suggested cut-off level of about 600 ng/mL (1). Various cytokines are involved in inflammation and may influence sperm function, and several studies have 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).

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

11.3.9 Sperm antibodies
Serum antibodies to sperm antigens are not useful in the diagnosis of immune infertility. Early reports stated an association between increased levels of sperm antibodies in serum and NBP (36,37). However, except in cases of suspected chlamydial infections (38), only a history of vasectomy seems to be predictive of sperm antibody formation (39).

11.3.10 Reactive oxygen species
It is generally accepted that reactive oxygen species may be increased in chronic urogenital infections associated with increased leukocyte numbers (40). However, the biological significance in prostatitis remains unclear (1).

11.3.11 Therapy
Treatment of chronic prostatitis is normally targeted at relieving symptoms (10,41). Andrologically, therapy for altered semen composition in male adnexitis is aimed at:
- Reduction or eradication of micro-organisms in prostatic secretions and semen
- Normalization of inflammatory parameters, such as leukocytes and secretory parameters
- Possible improvement of sperm parameters to counteract fertility impairment (42).

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

Only antibiotic therapy of CBP (NIH II) has provided symptomatic relief, eradication of micro-organisms and a decrease in cellular and humoral inflammatory parameters in urogenital secretions. The use of alpha-blockers for symptom relief is controversial.

Although antibiotic procedures may improve sperm quality (42), there is no convincing evidence that treatment of chronic prostatitis increases the probability of conception (1,43).

11.4 Orchitis and epididymo-orchitis
11.4.1 Introduction
Orchitis is an inflammatory lesion of the testis associated with a predominantly WBC exudate inside and outside the seminiferous tubules, potentially resulting in tubular sclerosis. The inflammation causes pain and swelling. Chronic inflammatory alterations in the seminiferous tubules disrupt the normal process of spermatogenesis and cause alterations both in sperm number and quality (44).

It is generally accepted that orchitis may also be an important cause of spermatogenetic arrest (45), which may be reversible in most cases. Testicular atrophy may develop as a result of tubular sclerosis (45).

11.4.2 Diagnosis
Patients with epididymo-orchitis usually present with unilateral scrotal pain (46). Diagnosis is based on the past medical history and palpation. Ultrasonography usually indicates a swollen, enlarged testis. The sonographic feature of the tissue does not allow any differential diagnosis (47).

11.4.3 Ejaculate analysis
Ejaculate analysis, including leukocyte analysis, indicates persistent inflammatory activity. In many cases, especially in acute epididymo-orchitis, transiently decreased sperm counts and reduced forward motility can be observed (44,46). Obstructive azoospermia due to complete obstruction is considered a rare complication.

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

11.4.4 Therapy
Only the therapy of acute bacterial epididymo-orchitis and of specific granulomatous orchitis is standardized (45) (Table 12). Several regimens are thought to improve the inflammatory lesion. Unfortunately, therapies using corticosteroids and non-steroidal antiphlogistic substances, such as diclofenac, indomethacin, and acetylsalicylic acid have not been evaluated for their andrological outcome (47). A further therapeutic trial involves using GnRH treatment to prevent the deleterious effects of inflammation on spermatogenesis (49). In

mumps orchitis, systemic interferon alpha-2b therapy has been reported to prevent testicular atrophy and azoospermia (50). In idiopathic granulomatous orchitis, surgical removal of the testis appears to be the therapy of choice.

Table 12: Treatment of epididymo-orchitis

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

11.5 Epididymitis

11.5.1 Introduction

Inflammation of the epididymis causes pain and swelling that is located unilaterally and usually with acute onset. The testicle is involved in the inflammatory process in most cases known as epididymo-orchitis.

Among sexually active men under 35 years of age epididymitis is most often caused by *C. trachomatis* or *N. gonorrhoea* (Table 12) (51,52). Sexually transmitted epididymitis is usually accompanied by urethritis. Non-sexually transmitted epididymitis is associated with UTI. This type occurs more often in men aged over 35 years, those who have recently undergone urinary tract instrumentation or surgery, and those who have anatomical abnormalities (52).

11.5.2 Diagnosis

In acute epididymitis, inflammation and swelling usually begin in the tail of the epididymis, and may spread to involve the rest of the epididymis and testicular tissue (46). Although men with epididymitis due to sexually transmitted micro-organisms always have a history of sexual activity, exposure may have occurred 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 (51,52). Intracellular gram-negative diplococci on the smear correlate with the presence of *N. gonorrhoea*. Only WBCs on urethral smear are indicative of non-gonorrhoeal urethritis; *C. trachomatis* will be isolated in approximately two-thirds of these patients (53).

11.5.3 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 (46,48,51). Ipsilateral low-grade orchitis (54,55) has been discussed as the cause of this slight impairment in sperm quality (Table 13) (56).

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

Table 13: Acute epididymitis and impact on sperm parameters

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

11.5.4 Treatment

Antibiotic therapy is indicated before culture results are available (Table 12). Treatment of epididymitis will result in:

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

    Patients who have epididymitis known or suspected to be caused by *N. gonorrhoea* or *C. trachomatis* should be instructed to refer sex partners for evaluation and treatment (60).

11.6 CONCLUSIONS

- Urethritis and prostatitis are not always associated with male subfertility 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 micro-organisms; it has no positive effect on inflammatory alterations and/or cannot reverse functional deficits and anatomical dysfunctions.

11.7 RECOMMENDATIONS

- As the aetiology of acute urethritis is unknown in most cases at the time of diagnosis, empirical therapy is suggested with a single dose of a fluoroquinolone, followed by a 2-week regimen of doxycycline. Treatment is effective both for gonococcal and (co-existing) chlamydial/ureaplasmal infections (9) (grade B recommendation).
- Only antibiotic therapy of (chronic) bacterial prostatitis has proved to be efficacious in providing symptomatic relief, eradication of micro-organisms, and a decrease in cellular and humoral inflammatory parameters in urogenital secretions (61-64) (grade B recommendation).
- Although antibiotic procedures for MAGIs may provide improvement in sperm quality, therapy does not necessarily enhance the probability of conception (1,43) (grade B recommendation).
- Patients who have epididymitis known or suspected to be caused by *N. gonorrhoea* or *C. trachomatis* should be instructed to refer sex partners for evaluation and treatment (60) (grade B recommendation).

11.8 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(5):421-432.
   http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10582781&dopt=Abstract
2. World Health Organization. *WHO Manual for the Standardized Investigation, Diagnosis and Management of the Infertile Male*. Cambridge: 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):1-13.
   http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8468091&dopt=Abstract
4. Schiefer HG. Microbiology of male urethroadnexitis: diagnostic procedures and criteria for aetiologic classification. Andrologia 1998;30(Suppl 1):7-13.
   http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9629437&dopt=Abstract
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(2):205-213.
   http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9240243&dopt=Abstract
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(2):315-319.
   http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9696227&dopt=Abstract

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(1):209-213.
       http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7776428&dopt=Abstract

10.   Nickel JC. Prostatitis: myths and realities. Urology 1998;51(3):362-366.
       http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9510337&dopt=Abstract

11.   Naber KG, Weidner W. Chronic prostatitis - an infectious disease? J Antimicrob Chemother 2000;46(2):157-161.
       http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10933636&dopt=Abstract

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):S119-125.
       http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2055646&dopt=Abstract

13.   Bruce AW, Reid G. Prostatitis associated with Chlamydia trachomatis in 6 patients. J Urol 1989;142(4):1006-1007.
       http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2677408&dopt=Abstract

14.   Taylor-Robinson D. Evaluation and comparison of tests to diagnose Chlamydia trachomatis genital infections. Hum Reprod 1997;12(11 Suppl):113-120.
       http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9433967&dopt=Abstract

15.   Taylor-Robinson D. Infections due to species of Mycoplasma and Ureaplasma: an update. Clin Infect Dis 1996;23(4):671-684; quiz 683-684.
       http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8909826&dopt=Abstract

16.   Krieger JN, Riley DE, Roberts MC, Berger RE. Prokaryotic DNA sequences in patients with chronic idiopathic prostatitis. J Clin Microbiol 1996;34(12):3120-3128.
       http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8940458&dopt=Abstract

17.   Litwin MS, McNaughton-Collins M, Fowler FJ Jr, Nickel JC, Calhourn EA, Pontari MA, Alexander RB, Farrar JT, O'Leary MP. The National Institutes of Health chronic prostatitis symptom index: development and validation of a new outcome measure. Chronic Prostatitis Collaboration Research Network. J Urol 1999;162(2):369-375.
       http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10411041&dopt=Abstract

18.   Ludwig M, Schroeder-Printzen I, Ludecke 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(2):175-177.
       http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10688073&dopt=Abstract

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(6):1227-1231.
       http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8671429&dopt=Abstract

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(1):5-9.
       http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3883615&dopt=Abstract

21.   Aitken RJ, Baker HW. Seminal leukocytes: passengers, terrorists or good samaritans? Hum Reprod1995;10(7):1736-1739.
       http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8582971&dopt=Abstract

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(6):1069-1075.
       http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8243688&query_hl=48&itool=pubmed_docsum

23. Krieger JN, Berger RE, Ross SO, Rothman I, Muller CH. Seminal fluid findings in men with nonbacterial prostatitis and prostatodynia. J Androl 1996;17(3):310-318.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8792222&dopt=Abstract

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(3):173-183.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1872650&dopt=Abstract

25. Giamarellou H, Tympanidis K, Bitos NA, Leonidas E, Daikos GK. Infertility and chronic prostatitis. Andrologia 1984;16(5):417-422.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=6496959&query_hl=160&itool=pubmed_docsum

26. Christiansen E, Tollefsrud A, Purvis K. Sperm quality in men with chronic abacterial prostatovesiculitis verified by rectal ultrasonography. Urology 1991;38(6):545-549.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=1746084&query_hl=164&itool=pubmed_docsum

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(6):1109-1116.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8194626&query_hl=167&itool=pubmed_docsum

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(5):331-334.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1765569&dopt=Abstract

29. Wolff H. The biologic significance of white blood cells in semen. Fertil Steril 1995;63(6):1143-1157.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7750580&dopt=Abstract

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(7):1476-1479.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9262280&dopt=Abstract

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(1):135-139.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8752625&dopt=Abstract

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(4):653-655.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8046017&dopt=Abstract

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(12):3161-3165.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8822435&dopt=Abstract

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(5):744-749.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9801092&dopt=Abstract

35. Comhaire F, Verschraegen G, Vermeulen L. Diagnosis of accessory gland infection and its possible role in male infertility. Int J Androl 1980;3(1):32-45.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7409893&dopt=Abstract

36. Jarow JP, Kirkland JA Jr, Assimos DG. Association of antisperm antibodies with chronic nonbacterial prostatitis. Urology 1990;36(2):154-156.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2385884&dopt=Abstract

37. Witkin SS, Zelikovsky G. Immunosuppression and sperm antibody formation in men with prostatitis. J Clin Lab Immunol 1986;21(1):7-10.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3543373&dopt=Abstract

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(5):1070-1074.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7657743&dopt=Abstract

39. Jarow JP, Sanzone JJ. Risk factors for male partner antisperm antibodies. J Urol 1992;148(6):1805-1807.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1433613&dopt=Abstract

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(6):699-707.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9016401&query_hl=64&itool=pubmed_docsum

41. Schaeffer AJ. Clinical practice. Chronic prostatitis and chronic pelvic pain syndrome. N Engl J Med 2006;355(16): 1690-1698.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=17050893&query_hl=222&itool=pubmed_docsum

42. 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.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9629448&dopt=Abstract

43. 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(2):91-98.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3539821&dopt=Abstract

44. 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):1-13.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8468091&dopt=Abstract

45. Diemer T, Desjardins C. Disorders of Spermatogenesis. In: Knobil E, Neill JD (eds). *Encyclopedia of Reproduction*. Vol 4. San Diego: Academic Press, 1999, pp. 546-556.

46. [No authors listed.] Association of Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases: National guideline for the management of epididymo-orchitis. Sex Transm Infect 1999;75(Suppl 1): S51-53.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10616385&query_hl=195&itool=pubmed_docsum

47. Weidner W, Garbe C, Weissbach L, Harbrecht J, Kleinschmidt K, Schiefer HG, Friedrich HJ. [Initial therapy of acute unilateral epididymitis using ofloxacin. II. Andrological findings.] Urologe A 1990;29(5):277-280. [German]
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2120839&dopt=Abstract

48. Weidner W, Krause W. Orchitis. In: Knobil E, Neill JD (eds). *Encyclopedia of Reproduction*. Vol. 3. San Diego: Academic Press, 1999, pp. 92-95.

49. 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(8):2072-2078.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8567844&dopt=Abstract

50. Ruther U, Stilz S, Rohl E, Nunnensiek C, Rassweiler J, Dorr U, Jipp P. Successful interferon-alpha 2, a therapy for a patient with acute mumps orchitis. Eur Urol 1995;27(2):174-176.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7744163&query_hl=70&itool=pubmed_docsum

51. 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(6):750-754.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=379366&dopt=Abstract

52. Berger RE. Epididymitis. In: Holmes KK, Mardh PA, Sparling PF et al. (eds). Sexually Transmitted Diseases. New York: McGraw-Hill, 1984, pp. 650-662.

53. Weidner W, Schiefer HG, Garbe C. Acute nongonococcal epididymitis. Aetiological and therapeutic aspects. Drugs 1987;34 (Suppl 1):111-117.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3481311&dopt=Abstract

54. Nilsson S, Obrant KO, Persson PS. Changes in the testis parenchyma caused by acute non-specific epididymitis. Fertil Steril 1968;19:748-757.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=5676481&dopt=Abstract

55. Osegbe DN. Testicular function after unilateral bacterial epididymo-orchitis. Eur Urol 1991;19(3):204-208.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1855525&dopt=Abstract

56. 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(5):421-432.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10582781&dopt=Abstract

57. Ludwig G, Haselberger J. [Epididymitis and fertility. Treatment results in acute unspecific epididymitis.] Fortschr Med 1977;95(7):397-399. [German]
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=849851&dopt=Abstract

58. Haidl G. Macrophages in semen are indicative of chronic epididymal infection. Arch Androl 1990;25(1):5-11.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2389992&dopt=Abstract

59. 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(5):329-336.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2283178&dopt=Abstract

60. Robinson AJ, Grant JB, Spencer RC, Potter C, Kinghorn GR. Acute epididymitis: why patient and consort must be investigated. Br J Urol 1990;66(6):642-645.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2265337&dopt=Abstract

61. Schneede P, Tenke P, Hofstetter AG. Urinary Tract Infection Working Group of the Health Care Office of the European Association of Urology. Sexually transmitted diseases (STDs) - a synoptic overview for urologists. Eur Urol 2003;44(1):1-7.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12814668&dopt=Abstract

62. Schaeffer AJ, Weidner W, Barbalias GA, Botto H, Bjerklung-Johansen TE, Hochreiter WW, Krieger JN, Lobel B, Naber KG, Nickel JC, Potts JM, Tenke P, Hart C. Summary consensus statement: diagnosis and management of chronic prostatitis/chronic pelvic pain syndrome. Eur Urol 2003;(Suppl 2):1-4.

63. Alexander RB, Propert KJ, Schaeffer AJ, Landis JR, Nickel JC, O'Leary MP, Pontari MA, McNaughton-Collins M, Shoskes DA, Comiter CV, Datta NS, Fowler JE Jr, Nadler RB, Zeitlin SI, Knauss JS, Wang Y, Kusek JW, Nyberg LM Jr, Litwin MS; Chronic Prostatitis Collaborative Research Network. Ciprofloxacin or tamsulosin in men with chronic prostatitis/chronic pelvic pain syndrome: a randomized, double-blind trial. Ann Intern Med 2004;141(8):581-589.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15492337&query_hl=215&itool=pubmed_docsum

64. Nickel JC, Narayan P, McKay J, Doyle C. Treatment of chronic prostatitis/chronic pelvic pain syndrome with tamsulosin: a randomized double blind trial. J Urol 2004;171(4):1594-1597.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15017228&query_hl=218&itool=pubmed_docsum

12. GERM CELL MALIGNANCIES AND TESTICULAR MICROCALCIFICATIONS

12.1 Germ cell malignancies and male infertility

Testicular germ cell cancer (TGCC) is the most common malignancy in Caucasian males aged between 15 and 40 years and affects about 1% of subfertile males. The lifetime risk of TGCC varies between ethnic groups and from country to country. The highest annual incidence occurs in Caucasians, varying from 10 per 100,000 in, for example, Denmark and Norway to 2 per 100,000 in Finland and the Baltic countries. It is generally accepted that seminomas and non-seminomas are always preceded by CIS, and that CIS will eventually progress to an invasive cancer if not treated (1,2).

The most convincing evidence for a general decline in male reproductive health in humans is the increase in testicular cancer noted over the recent past in several Western countries (3). The incidence of testicular cancer has increased in almost all countries which have reliable cancer registers – at least in the Caucasian population (4). It has also been observed that both cryptorchidism and hypospadias are associated with an increased risk of testicular cancer, based on the observation that men with cryptorchidism and/or hypospadias are overrepresented among patients with testicular cancer.

Dysgenic testes have an increased risk of developing testicular cancer in adulthood. These cancers seem to arise from premalignant gonocytes or CIS cells (5). Testicular microlithiasis can be associated with both germ cell tumours and CIS of the testis.

12.2 Testicular germ cell cancer and reproductive function.

Men with TGCT have decreased semen quality, even prior to a cancer diagnosis (6). Orchidectomy implies a risk of azoospermia in these men, with sperm found in the ejaculate before the tumour-bearing testis has been removed. Semen cryopreservation prior to orchidectomy should therefore be considered (see section 14 Semen cryopreservation). Treatment of TGCT tmay imply an additional impairment of semen quality (7).

As well as spermatogenic failure, TGCT patients have Leydig cell dysfunction, even in the contralateral testis (8). The risk of hypogonadism may therefore be increased in men treated for TGCT. Obtaining pretreatment levels of testosterone, SHBG, LH and oestradiol, may help in disclosing post-treatment hypogonadism. Long-term follow up of TGCT men with low normal androgen levels should be considered as they may be at risk for developing hypogonadism due to age-related decrease in testosterone production (9).

12.3 Testicular microlithiasis

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

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

Testicular microcalcification is a condition found in testis at risk for malignant development. The reported incidence of TM in men with germ cell malignancy is 6-46% (15-17), and it has therefore been suggested that TM should be considered premalignant. However, it remains to be established whether TM is present before development of invasive TGCT, and whether TM might be an indicator for the preinvasive stage of TGCTs, known as carcinoma *in situ* (CIS). Testicular biopsies of men with TM have found a higher prevalence of CIS, especially in men with bilateral microlithiasis (18). On the other hand, TM is found most often in men with a benign testicular condition and the microcalcifications itself are not malignant.

Further investigation of the association between TM and CIS would require testicular biopsies to be carried out in large series of men without signs of a TGCT. Available data, however, indicate that a finding of TM in high-risk patients (e.g. patients referred due to infertility and/or cryptorchidism) warrants follow up by repeated ultrasound and/or testicular biopsy for detection of CIS.

12.4 RECOMMENDATIONS

- It is recommended that either a testicular biopsy or a follow-up scrotal ultrasound should be performed in men with TM and a history of male infertility, cryptorchidism or testicular cancer and in men with atrophic testis to rule out CIS of the testis (17,18) (grade B recommendation).
- It is important to encourage and educate these patients about self-examination, since this may result in early detection of germ cell tumours.
- In case of suspicious findings on physical examination or ultrasound in patients with TM and associated lesions, a surgical exploration with testicular biopsy or orchidectomy should be considered.
- Testicular biopsy, follow-up scrotal ultrasound or the routine use of biochemical tumour markers, abdominal and pelvic computed tomography scanning does not seem to be justified for men with isolated TM without associated risk factors (male infertility, cryptorchidism, testicular cancer, atrophic testis) (11) (grade B recommendation).
- Men with TGCT are at increased risk of developing hypogonadism, which should be considered in follow up of these patients (9) (grade B recommendation).

12.5 REFERENCES

1. Skakkebaek NE. Carcinoma in situ of the testis: frequency and relationship to invasive germ cell tumours in infertile men. Histopathology 1978;2(3):157-170.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=27442&query_hl=225&itool=pubmed_docsum

2. von der Maase H, Rorth M, Walbom-Jorgensen S, Sorensen BL, Christophersen IS, Hald T, Jacobsen GK, Berthelsen JG, Skakkebaek NE. Carcinoma in situ of contralateral testis in patients with testicular germ cell cancer: study of 27 cases in 500 patients. Br Med J 1986;293(6559):1398-401.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=3026550&query_hl=230&itool=pubmed_docsum

3. Jacobsen R, Bostofte E, Engholm G, Hansen J, Olsen JH, Skakkebaek NE, Moller H. Risk of testicular cancer in men with abnormal semen characteristics: cohort study. BMJ 2000;321(7264):789-792.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=11009515&query_hl=232&itool=pubmed_docsum

4. Huyghe E, Matsuda T, Thonneau P. Increasing incidence of testicular cancer worldwide: a review. J Urol 2003;170(1):5-11.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12796635&d opt=Abstract

5. Giwercman A, Muller J, Skakkebaek NE. Carcinoma in situ of the undescended testis. Semin Urol 1988;6(2):110-119.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2903524&do pt=Abstract

6. Petersen PM, Skakkebaek NE, Vistisen K, Rorth M, Giwercman A. Semen quality and reproductive hormones before orchiectomy in men with testicular cancer. J Clin Oncol 1999;17(3):941-947.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=10071288&query_hl=237&itool=pubmed_docsum

7. Eberhard J, Stahl O, Giwercman Y, Cwikiel M, Cavallin-Stahl E, Lundin KB, Flodgren P, Giwercman A. Impact of therapy and androgen receptor polymorphism on sperm concentration in men treated for testicular germ cell cancer: a longitudinal study. Hum Reprod 2004;19(6):1418-1425.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=15105386&query_hl=240&itool=pubmed_docsum

8. Willemse PH, Sleijfer DT, Sluiter WJ, Schraffordt Koops H, Doorenbos H. Altered Leydig cell function in patients with testicular cancer: evidence for bilateral testicular defect. Acta Endocrinol (Copenh) 1983;102(4):616-624.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=6133401&query_hl=242&itool=pubmed_docsum

9. Nord C, Bjoro T, Ellingsen D, Mykletun A, Dahl O, Klepp O, Bremnes RM, Wist E, Fossa SD. Gonadal hormones in long-term survivors 10 years after treatment for unilateral testicular cancer. Eur Urol 2003;44(3):322-328.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=12932930&query_hl=245&itool=pubmed_docsum

10.   Parra BL, Venable DD, Gonzalez E, Eastham JA. Testicular microlithiasis as a predictor of intratubular germ cell neoplasia. Urology 1996;48(5):797-799.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8911532&dopt=Abstract

11.   Peterson AC, Bauman JM, Light DE, McMann LP, Costabile RA. The prevalence of testicular microlithiasis in an asymptomatic population of men 18 to 35 years old. J Urol 2001;166(6):2061-2064.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11696707&query_hl=249&itool=pubmed_docsum

12.   von Eckardstein S, Tsakmakidis G, Kamischke A, Rolf C, Nieschlag E. Sonographic testicular microlithiasis as an indicator of premalignant conditions in normal and infertile men. J Androl 2001;22(5):818-824.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11545295&query_hl=252&itool=pubmed_docsum

13.   Thomas K, Wood SJ, Thompson AJ, Pilling D, Lewis-Jones DI. The incidence and significance of testicular microlithiasis in a subfertile population. Br J Radiol 2000;73(869):494-497.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10884745&query_hl=257&itool=pubmed_docsum

14.   Pierik FH, Dohle GR, van Muiswinkel JM, Vreeburg JT, Weber RF. Is routine scrotal ultrasound advantageous in infertile men? J Urol 1999;162(5):1618-1620.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=10524881&query_hl=260&itool=pubmed_docsum

15.   Derogee M, Bevers RF, Prins HJ, Jonges TG, Elbers FH, Boon TA. Testicular microlithiasis, a premalignant condition: prevalence, histopathologic findings, and relation to testicular tumor. Urology 2001;57(6):1133-1137.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11377326&dopt=Abstract

16.   Miller FN, Sidhu PS. Does testicular microlithiasis matter? A review. Clin Radiol 2002;57(10):883-890.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12413911&query_hl=263&itool=pubmed_docsum

17.   Giwercman A, Muller J, Skakkebaek NE. Prevalence of carcinoma in situ and other histopathological abnormalities in testes from 399 men who died suddenly and unexpectedly. J Urol 1991;145(1):77-80.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1984105&dopt=Abstract

18.   de Gouveia Brazao CA, Pierik FH, Oosterhuis JW, Dohle GR, Looijenga LH, Weber RF. Bilateral testicular microlithiasis predicts the presence of the precursor of testicular germ cell tumors in subfertile men. J Urol 2004;171(1):158-160.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14665866&dopt=Abstract

13.   DISORDERS OF EJACULATION

13.1   Definition

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

13.2   Classification and aetiology

13.2.1   Anejaculation

Anejaculation is the complete absence of an antegrade or retrograde ejaculation. It is caused by a failure of emission of semen from the seminal vesicles, the prostate and the ejaculatory ducts into the urethra (1). True anejaculation is usually associated with a normal orgasmic sensation. Occasionally (e.g. in incomplete spinal cord injuries), this sensation may be altered or decreased. True anejaculation is always connected with central or peripheral nervous system dysfunctions or with drugs (2) (Table 14).

Table 14: Aetiologies of anejaculation

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

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

13.2.3   Delayed ejaculation
Delayed ejaculation is the condition in which abnormal stimulation of the erected penis is necessary to obtain an orgasm with ejaculation (1). It may be considered a slight form of anorgasmia: both can be found alternately 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) or pharmacological (antidepressants, antihypertensives, antipsychotics).

13.2.4   Retrograde ejaculation
Retrograde ejaculation is the total, or sometimes partial, absence of an antegrade ejaculation due to semen passing backwards through the bladder neck into the bladder. Patients experience a normal or decreased orgasmic sensation, except in paraplegia. Partial antegrade ejaculation must not be confused with the secretion of bulbo-urethral glands. The causes of retrograde ejaculation can be subdivided as shown in Table 15.

Table 15: Aetiology of retrograde ejaculation

Neurogenic causes	Pharmacological causes
• Spinal cord injury	• Antihypertensives
• Cauda equina lesions	• Alpha1-adrenoceptor antagonists
• Multiple sclerosis	• Antipsychotics
• Autonomic neuropathy (juvenile diabetes)	• Antidepressants
• Retroperitoneal lymphadenectomy	
• Sympathectomy	
• Colorectal and anal surgery	

Urethral causes	Bladder neck incompetence
• Ectopic ureterocele	• Congenital defects/dysfunction of hemitrigone
• Urethral stricture	• Bladder extrophy
• Urethral valves or verumontaneum hyperplasia	• Bladder neck resection
• Congenital dopamine beta-hydroxylase deficiency	• Prostatectomy

13.2.5   Asthenic ejaculation
Asthenic ejaculation, also defined as partial ejaculatory incompetence or 'éjaculation baveuse' (5), is characterized by an altered propulsive phase with a normal emission phase. The orgasmic sensation is reduced and the typically rhythmical contractions associated with ejaculation are missing, while in asthenic ejaculation due to urethral obstruction, these contractions are present. Asthenic ejaculation is generally due to the neurogenic or urethral pathologies already listed in Table 15. Asthenic ejaculation does not usually alter semen quality.

13.2.6   Premature ejaculation
Premature ejaculation is the inability to control ejaculation for a 'sufficient' length of time during vaginal

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

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

13.3 Diagnosis
Diagnostic management includes the following recommended procedures.

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

13.3.2 Physical examination
A genital and rectal examination are conducted, including evaluation of the prostate, bulbocavernosus reflex and anal sphincter tone. Minimal neurological tests include:
* Sensitivity of scrotum, testes and perineum
* Cremasteric and abdominal cutaneous reflex
* Leg osteotendinous and plantar reflexes.

13.3.3 Post-ejaculatory urinalysis
Post-ejaculatory urinalysis will determine if there is total or partial retrograde ejaculation.

13.3.4 Microbiological examinations
Initial, mid-stream urine, EPS and/or urine after prostatic massage are cultured for evidence of prostatic infection. In cases of increased leukocytes in semen, semen culture is also suggested (8).

13.3.5 Optional diagnostic work up
This may include:
* Neurophysiological tests (bulbocavernosus evoked response and dorsal nerve somatosensory evoked-potentials)
* Tests for autonomic neuropathies (i.e. appreciation of temperature regulation in the feet)
* Psychosexual evaluation
* Videocystometry
* Cystoscopy
* Transrectal ultrasonography
* Uroflowmetry
* Vibratory stimulation of the penis.

13.4 Treatment
The treatment of infertility due to disorders of ejaculation is rarely aetiological, and generally consists of retrieving spermatozoa to be used in assisted reproduction techniques (ART). In decision-making, the following aspects must be considered:
* Age of patient and of his partner
* Psychological problems in the patient and his partner
* Couple's willingness and acceptance of the different fertility procedures
* Associated pathologies
* Psychosexual counselling.

13.5 Aetiological treatments
If possible, stop any pharmacological treatments that are interfering with ejaculation. Tamsulosin can be

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

13.6 Symptomatic treatments

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

13.6.2 Retrograde ejaculation
In the absence of spinal cord injury, anatomical anomalies of the urethra, or pharmacological agents, an attempt must be made with drug treatment to induce antegrade ejaculation (Table 16). Alternatively, the patient can be encouraged to ejaculate when his bladder is full to increase bladder neck closure (11).

Table 16: Drug therapy for retrograde ejaculation
- Ephedrine sulfate, 10-15 mg 4 times a day (12)
- Midodrin, 5 mg 3 times a day (13)
- Brompheniramine maleate, 8 mg twice a day (14)
- Imipramine, 25-75 mg 3 times a day (15)
- Desipramine, 50 mg every second day (16)

Sperm collection from post-orgasmic urine for use in ART is suggested if:
- Drug treatment is ineffective or intolerable due to side-effects
- When the patient has a spinal cord injury
- Drug therapy inducing retrograde ejaculation cannot be interrupted.

Sperm retrieval is timed to coincide with the partner's ovulation. Urine must be alkalinized (pH 7.2-7.8) and osmolarity must be 200-300 mOsmol/kg. The patient is asked to have intercourse or to masturbate. Within 10 minutes after ejaculation, urine must be voided and centrifuged, and the pellet resuspended in 0.5 mL Tyrode's or Ham's F-10 medium and immediately inseminated (17). As an alternative, a catheter may be applied to the bladder and 10-50 mL Tyrode's or Ham's F-10 medium instilled into the bladder. The patient must ejaculate, and a second catheterization is performed immediately to retrieve spermatozoa. The latter treatment minimizes the contact between spermatozoa and urine (18). If the biological sperm preparation is not of sufficient quality for intrauterine insemination, the couple must undergo in-vitro reproductive procedures (i.e. ICSI) with fresh or cryopreserved spermatozoa.

13.6.3 Anejaculation
Drug treatment for anejaculation due to lymphadenectomy and neuropathy is not very effective. Nor is psychosexual therapy in anorgasmic subjects. In all these cases and in spinal cord injured men, vibrostimulation (i.e. the application of a vibrator to the penis) is first-line therapy.

In anejaculation, vibrostimulation evokes the ejaculation reflex (19). It requires an intact lumbosacral spinal cord segment. Complete injuries and injuries above T10 show a better response to vibrostimulation. Once the safety and efficacy of this procedure has been assessed, patients can manage themselves in their own home. Intravaginal insemination via a 10 mL syringe during ovulation can be performed. If the quality of semen is poor, or ejaculation is retrograde, the couple may enter an IVF programme. If vibrostimulation has failed, electroejaculation is the therapy of choice (20). Electroejaculation is an electric stimulation of the periprostatic nerves via a probe inserted into the rectum, which seems unaffected by reflex arc integrity. Anaesthesia is required except in cases of complete spinal cord injury. In 90% of patients, electrostimulation induces ejaculation, which is retrograde in one-third of them. Semen quality is often poor and most couples must resort to IVF programmes (21).

When electroejaculation fails or cannot be performed, sperm retrieval from the seminal ducts may be achieved by sperm aspiration from the vas deferens (22) (see section 5 Obstructive azoospermia) or seminal tract washout (23).

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

13.7 CONCLUSIONS

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

13.8 RECOMMENDATIONS

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

13.9 REFERENCES

1. Buvat J. Glossaire. [Les perturbations de l'éjaculation.] In: Buvat J, Jouannet P (eds). [*L'éjaculation et ses Perturbations*]. Lyon-Villeurbanne: SIMEP, 1984, p. 9. [French] [Ejaculation and its disruptions]
2. Wang R, Monga M, Hellstrom WJG. 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. Berlin: Springer-Verlag, 1997, pp. 319-336.
4. Yachia D. Our experience with penile deformations: incidence, operative techniques, and results. J Androl 1994;15(Suppl):63S-68S.
   http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7721682&dopt=Abstract
5. Chapelle PA. [Séquelles génito-sexuelles du paraplégique.] 2-Neuro-physiologie. Tempo Medical 1982;103:67-70. [French] [Sexual consequences of spinal cord injury]
6. Vallancien G, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1,274 European men suffering from lower urinary tract symptoms. J Urol 2003;169(6):2257-2261.
   http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12771764&dopt=Abstract
7. Hermabessiere J, Bouquet de la Joliniere J, Buvat J. [L'éjaculation douloureuse. Recherche de causes organiques.] In: Buvat J, Jouannet P (eds). *L'éjaculation et ses perturbations*. Lyon-Villeurbanne: SIMEP, 1984, pp. 129-134. [French] [Painful ejaculation. Researching organic causes]
8. Abdel-Hamid IA, El Naggar EA, El Gilany AH. Assessment of as needed use of pharmacotherapy and the pause-squeeze technique in premature ejaculation. Int J Impot Res 2001;13(1):41-45.
   http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11313839&dopt=Abstract
9. Perimenis P, Gyftopoulos K, Ravazoula P, Athanassopoulos A, Barbalias G. Excessive verumontanum hyperplasia causing infertility. Urol Int 2001;67(2):184-185.
   http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11490221&dopt=Abstract
10. Demyttenaere K, Huygens R. Painful ejaculation and urinary hesitancy in association with antidepressant therapy: relief with tamsulosin. Eur Neuropsychopharmacol 2002;12(4):337-341.
    http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12126873&dopt=Abstract
11. 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(5):572-576.
    http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=720646&dopt=Abstract
12. Gilja I, Parazajder J, Radej M, Cvitkovic P, Kovacic M. Retrograde ejaculation and loss of emission: possibilities of conservative treatment. Eur Urol 1994;25(3):226-228.
    http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8200405&dopt=Abstract
13. Jonas D, Linzbach P, Weber W. The use of midodrin in the treatment of ejaculation disorders following retroperitoneal lymphadenectomy. Eur Urol 1979;5(3):184-187.
    http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=87324&dopt=Abstract

14. Schill WB. Pregnancy after brompheniramine treatment of a diabetic with incomplete emission failure. Arch Androl 1990;25(1):101-104.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2389987&dopt=Abstract

15. Brooks ME, Berezin M, Braf Z. Treatment of retrograde ejaculation with imipramine. Urology 1980;15(4):353-355.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7190335&dopt=Abstract

16. Hendry WF. Disorders of ejaculation: congenital, acquired and functional. Br J Urol 1998;82(3):331-341.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9772867&dopt=Abstract

17. 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: Academic Press, 1986, pp. 599-617.

18. Hotchkiss RS, Pinto AB, Kleegman S. Artificial insemination with semen recovered from the bladder. Fertil Steril 1954;6(1):37-42.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=13220644&dopt=Abstract

19. Brindley GS. Reflex ejaculation under vibratory stimulation in paraplegic men. Paraplegia 1981;19(5):299-302.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7279433&dopt=Abstract

20. Elliott S, Rainsbury PA. Treatment of anejaculation. In: Colpi GM, Balerna M (eds). *Treating Male Infertility: New Possibilities*. Basel: Karger AG, 1994, pp. 240-254.

21. Denil J, Kuczyk MA, Schultheiss D, Jibril S, Kupker W, Fischer R, Jonas U, Schlosser HW, Diedrich K. Use of assisted reproductive techniques for treatment of ejaculatory disorders. Andrologia 1996;28(Suppl 1):43-51.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9082877&dopt=Abstract

22. Waldinger MD. The neurobiological approach to premature ejaculation. J Urol 2002;168(6):2359-2367.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12441918&dopt=Abstract

23. Jankowicz E, Drozdowski W, Pogumirski J. [Idiopathic autonomic neuropathy (pandysautonomia).] Neurol Neurochir Pol 2001;35(3):439-452. [Polish]
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11732267&dopt=Abstract

24. Maurer CA, Z'Graggen K, Renzulli P, Schilling MK, Netzer P, Buchler MW. Total mesorectal excision preserves male genital function compared with conventional rectal cancer surgery. Br J Surg 2001;88(11):1501-1505.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11683749&dopt=Abstract

14. SEMEN CRYOPRESERVATION

14.1   Definition
Cryopreservation is the storage of biological material at low subzero temperatures, such as -80°C or -196°C (the boiling point of liquid nitrogen). At these low temperatures, biochemical processes of cell metabolism are slowed or interrupted, while at -196°C, the biochemical reactions that lead to cell death are effectively stopped.

14.2   Introduction
Cryopreservation was first developed in the 1940s by veterinarians for farm animals and adapted for human sperm in the 1950s. The first pregnancy obtained using cryopreservation was in 1954 (1). In fertility practice, current clinical indications for cyropreservation include storage of sperm, testicular and ovarian tissue and early embryos.

14.3   Indications for storage
Storage of sperm is available in many clinics for some or all of the following indications:

- Prior to potentially sterilising cancer chemotherapy or radiotherapy (2).
- Prior to any potentially sterilising chemotherapy for any other non-malignant disease, e.g. Behçet's disease.
- Prior to surgery that will, or may, interfere with fertility, e.g. bladder neck surgery in a younger man. Removal of the second testicle in a man with bilateral testicular malignancy, etc.
- For men with progressive decrease in semen quality due to diseases carrying an associated risk of subsequent azoospermia (i.e. pituitary macroadenomas, craniopharyngiomas, empty sella syndrome, chronic nephropathies, uncontrolled diabetes mellitus, multiple sclerosis).
- For men with paraplegia, after sperm have been obtained by electroejaculation.
- For men with psychogenic anejaculation, after sperm have been obtained either by electroejaculation or a sperm retrieving procedure.
- After gonadotrophin treatment has induced spermatogenesis in men with hypogonadotropic hypogonadism.
- For men with NOA, the chance of finding sperm using micro-TESE is approximately 60-70%. Cryopreservation can be used to separate sperm collection from ICSI and thus to avoid unnecessary hyperstimulation of the female partner. It may also be used to avoid repeated sperm retrieval procedures.
- In any situation where sperm have been obtained by a sperm retrieving procedure, e.g. after failed vasectomy reversal, or in some cases of epididymal obstruction not amenable to surgery.
- For storage of sperm prior to vasectomy. This service is offered by a limited number of clinics as an insurance policy against change of mind or circumstances.
- For storage of donor sperm. Cryopreservation and a 3-6 months' quarantine period reduce the risk of transmission of infection from sperm donors. In most countries, fresh sperm are no longer used.

14.4   Precautions and techniques

14.4.1   Freezing and thawing process
Available techniques are not yet optimal as damage occurs to cells during cyropreservation and during prolonged storage. Most damage occurs during freezing and thawing. The major causes of damage during freezing are ice crystal formation and cell dehydration causing cell wall disruption and intracellular organelles. Sperm morphology, motility and vitality decrease significantly after thawing, while cryopreservation increases the damage done to sperm DNA (3-5,6). Further damage may be caused by contamination of samples with micro-organisms and high levels of superoxide radicals (7,8). To reduce ice crystal formation, a cryopreservation solution is added prior to freezing. There are various commercially available cryopreservation solutions, most of which contain varying proportions of glycerol and albumen. After freezing, the tissues are immersed in liquid nitrogen.

Various techniques have been developed to try to reduce damage caused by freezing and thawing.
Rapid method (9,10): The sample is held in the vapour phase for 10 min before being plunged into liquid nitrogen.
Slow method (11): The sample is gradually cooled in the vapour phase for about 40 min.
Using a programmable automatic freezing machine, which is pre-set to cool at a rate of between 1-10°C/min.

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

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

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

14.4.3   Testing for infections and preventing cross-contamination
Sperm storage in straws in widely used. Large numbers of straws are stored in canisters with the straws bathed in a pool of liquid nitrogen. Micro-organism contamination of the pool of liquid nitrogen results in

contamination of the outside of all the straws. The most widely used safeguard is to accept samples for storage only from patients whose semen samples have been tested for infection and shown to be safe. Donor samples should be tested for viral infections (hepatitis B and C, HIV) and sexually transmitted infections (*C. trachomatis, gonorrhoea*, syphilis).

Until the test results are known, samples must be stored in an individual quarantine vessel (15) (http://www.hfea.gov.uk/cps/rde/xchg/SID-3F57D79B-1F88B22E/hfea/hs.xsl/576.html). Some laboratories use the additional safeguard of double-wrapping the straws before freezing, but this is an extra cost. It may also interfere with the freezing process, reducing the quality of the samples on thawing. In some centres, there is also cytomegalovirus (CMV) testing with separate storage facilities for CMV-negative and CMV-positive samples.

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

14.4.4   Fail-safe precautions to prevent loss of stored materials
Any laboratory undertaking long-term storage of human biological materials should have procedures that guard against accidental loss of material caused by storage vessel failure. This is particularly important for sperm stored prior to sterilising cancer chemotherapy because in such cases there may be no opportunity to obtain further sperm. The level of precaution will depend on the cost and resources available to the laboratory, but if possible the following safeguards should be in place. All in-use storage vessels should be fitted with an alarm system activated by a rising temperature or liquid nitrogen leakage. The alarm system should alert a laboratory staff member, according to a 24-hour 365-day rota. Ideally, there should be a spare storage container into which samples can be transferred following a vessel failure.

14.4.5   'Orphan' samples
In malignancy and some other situations, years may pass before stored samples are required. Inevitably, during this time, the owners of some samples may become untraceable or die, leaving behind 'orphan' samples for which the owner can no longer be contacted. The duty of the laboratory and the legal ownership of these samples can create considerable problems.

It is best to obtain consent about what to do with the sample in the event of death or untraceability from the owner of the sample at the time of, or very shortly after, storage. Some countries legally require such consent. Choices available for the owner of the sample depend on the laws of the country and may or may not be appropriate in all situations. They include:
*   A request that the sample should be destroyed
*   Use of the sample by their wife or partner
*   Use of the sample in research
*   Donation of the sample to help another infertile couple.

14.5   Biological aspects
Cryopreservation induces deterioration of the seminal quality. After the sample has been thawed, motility (16) and morphology (17,18) appear worsened, including mitochondrial acrosomal and sperm tail damage (19). Recent studies confirm some correlation between these parameters. Sperm freezing decreases motility by 31%, morphology by 37%, and mitochondrial activity by 36% (9). Motility seems to be best correlated with IVF capacity of the thawed sample. Further improvement can be achieved by selecting out the subpopulation of sperm with the best motility and DNA integrity and freezing these sperm in seminal plasma, making this the optimal procedure (13).

14.6   CONCLUSIONS
*   The purpose of sperm cryopreservation is to secure future pregnancies by assisted reproduction techniques.
*   Cryopreservation techniques are far from optimal and future efforts are needed to improve the outcome of sperm banking.
*   Cryopreservation should be compulsorily explained and suggested in case of specific pathologies or before making a patient undergo surgery, chemotherapy or radiotherapy that might damage his reproductive integrity.
*   If testicular biopsies are indicated, carrying out sperm cryopreservation as part of the same procedure is strongly advised.

14.7 RECOMMENDATIONS

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

14.8 REFERENCES

1. Bunge RG, Keettel WC, Sherman JK. Clinical use of frozen semen; report of four cases. Fertil Steril 1954;5(6):520-529.
    http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=13210484&dopt=Abstract
2. Saito K, Suzuki K, Iwasaki A, Yumura Y, Kubota Y. Sperm cryopreservation before cancer chemotherapy helps in the emotional battle against cancer. Cancer 2005;104(3):521-524.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15968690&query_hl=20&itool=pubmed_docsum
3. Desrosiers P, Legare C, Leclerc P,Sullivan R. Membranous and structural damage that occur during cryopreservation of human sperm may be time-related events. Fertil Steril 2006;85(6):1744-1752.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=16643911&query_hl=23&itool=pubmed_docsum
4. Donnelly ET, McClure N, Lewis SE. Cryopreservation of human semen and prepared sperm: effects on motility parameters and DNA integrity. Fertil Steril 2001;76(5):892-900.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=11704107&query_hl=26&itool=pubmed_docsum
5. Chohan KR, Griffin JT, Carrell DT. Evaluation of chromatin integrity in human sperm using acridine orange staining with different fixatives and after cryopreservation. Andrologia 2004;36(5):321-326.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15458552&query_hl=28&itool=pubmed_docsum
6. Askari HA, Check JH, Peymer N, Bollendorf A. Effect of natural antioxidants tocopherol and ascorbic acids in maintenance of sperm activity during freeze-thaw process. Arch Androl 1994;33(1):11-15.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7979804&query_hl=30&itool=pubmed_docsum
7. Smith KD, Steinberger E. Survival of spermatozoa in a human sperm bank. Effects of long-term storage in liquid nitrogen. J Am Med Assoc 1973;223(7):774-777.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=4739258&query_hl=133&itool=pubmed_docsum
8. Agarwal A, Said TM. Oxidative stress, DNA damage and apoptosis in male infertility: a clinical approach. BJU Int 2005;95(4):503-507.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=15705068&query_hl=37&itool=pubmed_docsum
9. Grischenko VI, Dunaevskaya AV, Babenko VI. Cryopreservation of human sperm using rapid cooling rates. Cryo Letters 2003;24(2):67-76.
    http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=12819827&query_hl=39&itool=pubmed_docsum
10. Sherman JK, Bunge RG. Observations on preservation of human spermatozoa at low temperatures. Proc Soc Exp Biol Med 1953;82(4):686-688.
    http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=13055973&dopt=Abstract

11. Sawada Y, Ackerman D, Behrman SJ. Motility and respiration of human spermatozoa after cooling to various low temperatures. Fertil Steril 1967;18(6):775-781.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=6073928&query_hl=43&itool=pubmed_docsum

12. Henry MA, Noiles EE, Gao D, Mazur P, Critser JK. Cryopreservation of human spermatozoa. IV. The effects of cooling rate and warming rate on the maintenance of motility, plasma membrane integrity, and mitochondrial function. Fertil Steril 1993;60(5):911-918.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8224279&do pt=Abstract

13. Bahadur G, Ling KL, Hart R, Ralph D, Wafa R, Ashraf A, Jaman N, Mahmud S, Oyede AW. Semen quality and cryopreservation in adolescent cancer patients. Hum Reprod 2002;17(12):3157-3161.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12456617&d opt=Abstract

14. Hallak J, Hendin BN, Thomas AJ Jr, Agarwal A. Investigation of fertilizing capacity of cryopreserved spermatozoa from patients with cancer. J Urol 1998;159(4):1217-1220.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=9507838&query_hl=49&itool=pubmed_docsum

15. Clarke GN. Sperm cryopreservation: is there a significant risk of cross-contamination? Hum Reprod 1999;14(12):2941-2943.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10601075&d opt=Abstract

16. O'Connell M, McClure N, Lewis SE. The effects of cryopreservation on sperm morphology, motility and mitochondrial function. Hum Reprod 2002;17(3):704-709.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11870124&d opt=Abstract

17. Woolley DM, Richardson DW. Ultrastructural injury to human spermatozoa after freezing and thawing. J Reprod Fertil 1978;53(2):389-394.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=567693&dopt =Abstract

18. Watson PF. Recent developments and concepts in the cryopreservation of spermatozoa and the assessment of their post-thawing function. Reprod Fertil Dev 1995;7(4):871-891.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8711221&do pt=Abstract

19. Donnelly ET, McClure N, Lewis SE. Cryopreservation of human semen and prepared sperm: effects on motility parameters and DNA integrity. Fertil Steril 2001;76(5):892-900.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_ui ds=11704107&query_hl=56&itool=pubmed_docsum

15. LEVELS OF EVIDENCE AND GRADES OF GUIDELINE RECOMMENDATIONS

Table 17: Levels of evidence (1)

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

Table 18: Grades of guideline recommendations (1)

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

15.1   REFERENCES

1.   **Agency for Health Care Policy and Research**. Clinical Practice Guidelines Development, Methodological Perspectives. US Department of Health and Human Services, Public Health Service, Washington DC,1992, pp. 115-127.

16. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations

ABP	acute bacterial prostatitis
ART	assisted reproduction techniques
CAG	cytosine-adenine-guanosine
CBAVD	congenital bilateral absence of the vas deferens
CBP	chronic bacterial prostatitis
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator gene
CIS	carcinoma *in situ*
CMV	cytomegalovirus
CPPS	chronic pelvic pain syndrome
CFTR	cystic fibrosis transmembrane conductance regulator
EPS	espressed prostatic excretion
FISH	(multicolour) fluorescent *in situ* hybridization
HIV	human immunodeficiency virus
FSH	follicle-stimulating hormone
GnRH	gonadotrophin-releasing hormone
hCG	human chorionic gonadotrophin
hMG	human menopausal gonadotrophin
IBT	immunobead test
ICSI	intracytoplasmic sperm injection
IL-6	interleukin-6
IVF	in-vitro fertilization
LH	luteinizing hormone
MAGI	male accessory gland infection
MAR	mixed antiglobulin reaction
MESA	microsurgical epididymal sperm aspiration
NBP	non- or abacterial prostatitis
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institute of Health
NOA	non-obstructive azoospermia
OA	obstructive azoospermia
OAT	oligo-astheno-teratozoospermia [syndrome]
SHBG	sex hormone binding globulin
SSRIs	selective serotonin reuptake inhibitors
STS	sequence tagged sites
TESE	testicular sperm extraction
TEFNA	testicular fine needle aspiration
TGCT	testicular germ cell tumour
TM	testicular microlithiasis
TRUS	transurethral ultrasound
TURED	transurethral resection of the ejaculatory ducts
WBC	white blood cells
VB1	first-voided urine