European Urology

European Urology 42 (2002) 313–322

EAU Guidelines on Male Infertility☆

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Accepted 3 July 2002

Keywords: Male infertility; Azoospermia; Oligozoospermia; Vasectomy; Refertilisation; Varicocele; Hypogonadism; Urogenital infections; Genetic disorders

1. Andrological investigations and spermatology

Ejaculate analysis and the assessment of andrological status have been standardised by the World Health Organisation (WHO). Advanced diagnostic spermatological tests (computer-assisted sperm analysis (CASA), acrosome reaction tests, zona-free hamster egg penetration tests, sperm-zona pellucida bindings tests) may be necessary in certain diagnostic situations [1,2].

2. Idiopathic oligoasthenoteratozoospermia

Most men presenting with infertility are found to have idiopathic oligoasthenoteratozoospermia (OAT). It is diagnosed according to WHO criteria. However, other factors, such as duration of the couple's infertility, previous pregnancy history and the age of the female partner are better predictors of pregnancy than sperm quality [3,4].

2.1. Treatment

A wide variety of empiric drug approaches have been tried (Table 1). Assisted reproductive techniques, such as intrauterine insemination, in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) are also used. However, the effect of any infertility treatment must be weighed against the likelihood of spontaneous conception. In untreated infertile couples, the prediction scores for live births are 62% to 76%. Furthermore, the scientific evidence for empirical approaches is low. Criteria for the analysis of all therapeutic trials have been re-evaluated. There is consensus that only randomised controlled trials, with 'pregnancy' as the outcome parameter, can accepted for efficacy analysis.

3. Genetic disorders[1]

Chromosomal abnormalities are more common in infertile men than in fertile men. Standard karyotype analysis should be offered to all men with damaged spermatogenesis who are seeking fertility treatment by IVF or ICSI. Fluorescent in situ hybridisation (FISH) analysis of spermatozoa is a research investigation [5–7].

☆ Regarding each section, selected references are offered for further reading. The complete list of references used to establish these guidelines is found in the full-length version of the "EAU Guidelines on Male Infertility" presented at the XVIth EAU Annual Congress, Geneva, Switzerland (ISBN 90-806179-3-9), or the EAU website www. uroweb.org.

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0302-2838/02/$ – see front matter
PII: S0302-2838(02)00367-6

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Table 1
Empiric therapy of idiopathic oligoasthenoteratozoospermia (OAT)[a]

Therapeutic approaches	EAU recommendations
Hormonal	
GnRH	Contradictory results. Not controlled trials. Not recommended.
hCG/hMG	Lack of efficacy. Not recommended.
FSH	Lack of efficacy. Further trials needed.
Androgens	Lack of efficacy. Not recommended.
Antioestrogens (clomiphene citrate, tamoxifen)	Possible small effect. Use must be counterbalanced by potential side-effects.
Non-hormonal	
Kinin-enhancing drugs	Unproven efficacy. Use in clinical trials only.
Bromocriptine	Lack of efficacy. Not recommended.
Antioxidants	May benefit selected patients. Use in clinical trials only.
Mast cell blockers	Some efficacy shown. Further evaluation needed. Use in clinical trials only.
α-Blockers	Lack of efficacy. Not recommended.
Systemic corticosteroids	Lack of efficacy. Patients with high levels of antisperm antibodies should enter an ICSI protocol.
Assisted reproductive techniques	
Intrauterine insemination	
IVF/ICSI	

FSH: follicle-stimulating hormone; GnRH: gonadotrophin-releasing hormone; hCG: human chorionic gonadotrophin; hMG: human menopausal gonadotrophin; ICSI: intracytoplasmic sperm injection; IVF: in vitro fertilisation.
[a] Also based in parts on the recommendations of the "Infertility Guidelines Group" of the Royal College of Obstetricians and Gynaecologists, London, 1998.

3.1. Sex chromosomal abnormalities

3.1.1. Klinefelter's syndrome (47XXY) and variants (46XY or 47XXY mosaicism)

This is the most common sex chromosome abnormality. These men have an increased risk of producing 47XXY spermatozoa. Pre-implantation diagnosis or amniocentesis and karyotyping should be done in IVF/ICSI, and embryos with Klinefelter's karyotype should not be implanted.

3.2. Autosomal abnormalities

Where an autosomal karyotypic abnormality is already known, or found to be present, in the male partner, all couples requesting fertility treatment should be offered genetic counselling (see Section 3.5).

3.3. Genetic defects

3.3.1. X-linked genetic disorders and male fertility

X-linked recessive disorders manifest in males and are carried by daughters. X-linked disorders associated with infertility include Kallman's syndrome and Reifenstein's syndrome (androgen insensitivity). Many X-linked disorders have phenotypic abnormalities, e.g. retinitis pigmentosa, Menkes' syndrome, but do not affect fertility. Couples should receive appropriate genetic counselling (see Section 3.5).

3.3.2. Y genes and male infertility

Defects in the Y gene are associated with impaired or absent spermatogenesis. If fertility is possible, the defect will be passed to sons. Y microdeletion analysis is desirable in men with severely damaged spermatogenesis, who are seeking IVF/ICSI. The techniques are becoming widespread in IVF/ICSI units, but have not been standardised. If a man is found to have microdeletions and the couple wishes to proceed with ICSI, they can be advised that microdeletions will be passed to sons but not daughters. Patients who have autosomal defects resulting in severe phenotypic abnormalities and infertility will already be under medical care. Any fertility problem should be managed within that context.

3.4. Cystic fibrosis mutations and male infertility

Cystic fibrosis (CF) is a fatal autosomal recessive disorder. It is the most common genetic disease of Caucasians; 1 in 25 are carriers of gene mutations involving the CF transmembrane conductance regulator gene (CFTR).

3.4.1. Men with congenital bilateral absence of vas deferens (CBAVD)

Carrier status in men of the CFTR gene is associated with CBAVD. Thus, if a male has CBAVD, both he, and his partner, must be tested for CF mutations. If the female partner is also found to be a carrier, the couple must be carefully counselled about the risks of proceeding with ICSI using the husband's sperm (see Section 3.5). Although unilateral absence of the vas deferens probably has a different genetic cause, there have been reports of some men having CF mutations and these men should be tested as for men with CBAVD.

3.5. Genetic counselling and ICSI

The main difficulties will occur if there is a conflict of interest between the wishes of the couple and the interests of a future child. The best initial management is to give full information to the couple, who should then decide whether to proceed or not. However, there is often a greatly increased likelihood of a future child inheriting a genetic disorder. If the decision is taken to proceed, it is important for the couple to appreciate fully what may be in store for them and their child. Preimplantation diagnosis with replacement only of normal embryos, or if not available, amniocentesis and the possibility of termination, should also be considered.

4. Primary spermatogenic failure

Primary spermatogenic failure (Table 2) is defined as any spermatogenic alteration caused by reasons other than hypothalamic–pituitary diseases. Severe forms of primary spermatogenic failure present clinically as non-obstructive azoospermia [8,9].

4.1. Diagnosis

In non-obstructive azoospermia, semen analysis shows normal ejaculate volume and azoospermia after several centrifugations. The serum level of FSH is mainly correlated with the number of spermatogonia. There is no correlation between FSH levels and the presence of sperm in testicles with non-obstructive azoospermia. The measurement of luteinising hormone (LH) and testosterone should be considered in patients with clinical signs of hypogonadism. For genetic studies see Section 3.

Table 2
Causes of primary spermatogenic failure and underlying clinical entities

Aetiology
Congenital
Maldescended testes
Other chromosomic alterations
Complete and focal germ cell aplasia (either congenital or acquired: maldescended testes, irradiation, cytostatic drugs, etc.)
Post-inflammatory (orchitis)
Systemic diseases (liver cirrhosis, renal failure)
Varicocele
Idiopathic
Acquired (trauma, testicular torsion, tumour, surgery)
Klinefelter's syndrome
Germ cell aplasia
Spermatogenic arrest
Exogenous factors (medications, toxics, irradiation, heat, etc.)
Testicular tumour
Surgeries that can damage vascularisation of the testes

Testicular biopsy is indicated in patients without obvious factors, i.e. they have a normal FSH and normal testicular volume, to differentiate between obstructive and non-obstructive azoospermia. Some azoospermic patients may present with both obstructive and spermatogenic pathologies and increased serum FSH levels. Testicular biopsy may also be indicated in patients with clinical evidence of non-obstructive azoospermia, who request ICSI. Testicular biopsy is a simple, outpatient procedure performed under local anaesthesia, as an open or percutaneous biopsy or by testicular fine-needle aspiration. Several testicular samples should be taken because of regional differences. There is a good correlation between diagnostic biopsy histology and the likelihood of finding mature sperm cells. Any type of testicular biopsy should provide sufficient material to cryopreserve sperm for future ICSI cycles.

4.2. Testicular morphology

Severe forms of altered spermatogenesis are complete sclerosis; complete aplasia of germ cells (Sertoli cell-only syndrome [SCOS] or Del Castillo syndrome) and complete spermatogenic arrest at the spermatocyte level. Infrequently, spermatogenic arrest is seen at the spermatogonia or round spermatid level. Less severe forms include hypospermatogenesis, partial spermatogenic arrest, focal SCOS and mixed patterns. In focal spermatogenesis, mature cells are produced by localised seminiferous tubules. About 50–60% of men with non-obstructive azoospermia have some seminiferous tubules with spermatozoa that can be used for ICSI.

4.3. Treatment

The only treatment for patients with non-obstructive azoospermia is testicular sperm retrieval, to be used either fresh or cryopreserved in ICSI. Karotyping and Y microdeletion analysis are necessary to identify the implications for a future child. If genetic anomalies are detected, the couple will need genetic counselling (see Section 3).

4.3.1. Testicular sperm extraction (TESE) techniques

Open biopsy including microsurgical techniques and fine-needle aspiration are the two main techniques for sperm retrieval from the testicle. In non-obstructive azoospermia, multiple TESE or testicular punctions have been associated with focal inflammation and haematoma, as well as impaired testicular blood flow. In small testes, an intermittent decrease in serum testosterone levels is debated. Of 616 TESE reported procedures, 373 (60.6%) yielded sperm for ICSI. The

mean fertilisation rate was 52.5% (38.6–69%) and the mean pregnancy rate was 29.2% (11.3–31%). In most series, successful testicular sperm retrieval and ICSI was not associated with the patient's age, aetiology of infertility, testicular volume, serum FSH levels and histopathology, or whether sperm was fresh or cryopreserved.

5. Obstructive azoospermia

Obstructive azoospermia is the absence of both spermatozoa and spermatogenetic cells in semen and post-ejaculate urine (see Section 1) because of a complete obstruction of seminal ducts. Total obstruction of the seminal ducts is often accompanied by gonadal secretory dysfunction. Permanent absence of spermatozoa in the semen results in male infertility [10–13].

5.1. Proximal obstruction

Intratesticular obstruction occurs in 15% of obstructive azoospermia. Congenital obstruction is less common than acquired obstruction (post-inflammatory or post-traumatic). Epididymal obstruction is the most common cause of obstructive azoospermia. It usually manifests as bilateral corpus and/or CBAVD, which is associated with CF gene mutation (see Section 3). In Young's syndrome, a mechanical blockage is caused by debris within the proximal epididymal lumen. Acquired epididymal obstruction occurs most often following acute (gonococcal) and subclinical (e.g. chlamydial) epididymitis (see Section 10). Proximal vas deferens obstruction is the most frequent cause of acquired obstruction following vasectomy for sterilisation (see Section 6). Herniotomy may also result in vasal obstruction.

5.2. Distal obstruction

Ejaculatory duct obstruction occurs in about 1–3% of obstructive azoospermia, and is either cystic or post-inflammatory. Cystic obstructions are usually congenital cysts that occur in the prostate between the ejaculatory ducts. Post-inflammatory obstructions of the ejaculatory duct are rare and usually secondary to urethroprostatitis. Congenital or acquired complete obstructions of the ejaculatory ducts are associated with low semen volume, decreased or absent seminal fructose and acid pH. Seminal vesicles are usually dilated (anterior–posterior diameter >15 mm). Functional obstruction of the distal seminal ducts may be associated with local neuropathy urodynamic dysfunction, juvenile diabetes and polycystic kidney disease.

5.3. Investigations

The history and examination should follow the investigation of infertile men (see Section 1). A semen volume of less than 1.5 ml, acid pH and low fructose levels suggest an ejaculatory duct obstruction or CBAVD. When semen volume is low, spermatozoa in urine after ejaculation must always be searched for to rule out an ejaculatory disorder. Serum FSH levels may be normal, but this does not exclude a testicular cause of azoospermia, e.g. spermatogenic arrest. Transrectal ultrasonography (TRUS) must be performed, especially when the semen volume is $\leq$1.5 ml. Seminal vesicle enlargement (anterior–posterior diameter $\geq$15 mm), roundish, anechoic areas in the seminal vesicles and median intraprostatic cysts are typical. Distal seminal tract evaluation has to consider the anatomical permeability of the seminal ducts below the proximal vas deferens. Each vas deferens may be microsurgically cannulated with consecutive saline injection; if the saline solution passes through, vasography is not needed. The injected solution passed into the bladder is recovered through a Foley catheter, and spermatozoa are searched for and counted (seminal tract washout). Testicular biopsy can be added when concomitant pathology is suspected. In addition, the procedure may be used to extract testicular spermatozoa (TESE) for cryopreservation and subsequent ICSI (see Section 4).

5.4. Management

5.4.1. Intratesticular obstruction

TESE or fine-needle aspiration should be used to retrieve spermatozoa for immediate use in ICSI or cryopreservation (see Section 4).

5.4.2. Epididymal obstruction

Microsurgical epididymal sperm aspiration (MESA) or TESE are mandatory in CBAVD. Retrieved spermatozoa are generally used for ICSI, with one MESA procedure usually providing material for several ICSI cycles. In patients with azoospermia due to acquired epididymal obstruction, end-to-side microsurgical epididymovasostomy must be performed. Reconstruction may be done uni- or bilaterally, with higher patency and pregnancy rates associated with bilateral surgery. Before performing microsurgery, the epididymis must be checked for full patency downstream. It may take 3–18 months for anatomical recanalisation to occur following surgery. Before performing microsurgery, epididymal spermatozoa should be aspirated and cryopreserved for ICSI in case of surgical failure. Patency rates of 60–87% and cumulative pregnancy rates of 10–43% have been obtained. Late failure

occurs in 10–21% of recanalisations, due to abnormal testicular histology, absence of sperm in the epididymal fluid, fibrosis of the epididymis and abnormalities in the prostate.

5.4.3. Vas obstruction

Vas obstruction after vasectomy requires microsurgical vasectomy reversal (see Section 6). Proximal vas deferens sperm aspiration or TESE/MESA may be possible in cases of concomitant epididymal obstruction. The routinely use of sperm reservoirs is not recommended.

5.4.4. Ejaculatory duct obstruction

Transurethral resection of the ejaculatory ducts (TURED) is recommended in post-inflammatory obstruction, when one or both ejaculatory ducts empty into an intraprostatic midline cyst. Complications associated with TURED include retrograde ejaculation due to bladder neck injury, and also urine reflux into the seminal pathways (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 functional obstruction of the distal seminal ducts, antegrade seminal tract washout should be used to retrieve spermatozoa. Spermatozoa retrieved by any of the aforementioned surgical techniques should always be cryopreserved for assisted reproductive procedures.

5.5. Conclusions

Results of reconstructive microsurgery depend on the cause and location of the obstruction and the expertise of the surgeon. Standardised procedures include vasovasostomy, epididymovasostomy and TURED. In addition, sperm retrieval techniques can be used (MESA, TESE, testicular fine-needle aspiration). However, the consensus is that these methods should only be used if cryopreservation is available.

6. Vasectomy and vasectomy reversal

Vasectomy is the most effective method of permanent surgical sterilisation. A man undergoing vasectomy should be interested in permanent surgical contraception. Initial discussion should include both the failure rate and the possibility of vasectomy reversal. The most appropriate technique should be chosen. One standard technique is cauterisation and ligation of the vasal lumina. Fascial interposition between the vasal ends is recommended [14–16].

6.1. Complications

Local complications include haematoma (1% of cases), wound infection and epididymitis. Chronic testicular pain may develop. Vasectomy does not significantly alter spermatogenesis and Leydig cell function. Epididymal tubular damage ('blow-out') is common, leading to sperm granuloma. Antisperm antibodies are typical in the follow-up. Ejaculate volume is unchanged. All available data indicate vasectomy is safe and not associated with any serious, long-term side-effects.

6.2. Vasectomy failure

Vasectomy has a failure rate of less than 1%. Paternity as a result of recanalisation (including very rarely long-term recanalisation) can occur at any time after vasectomy and does not depend on the surgical procedure. No motile spermatozoa should be detected 6–8 weeks after vasectomy. If azoospermia fails to occur, repeat vasectomy.

6.3. Preoperative patient counselling

Patients must be aware that vasectomy is not irreversible and of its complications and failure rate. Normal contraceptive methods must be used post-surgery until there is evidence of azoospermia.

6.4. Vasectomy reversal

There are no standardised criteria for the results of vasectomy reversal. A wide range of surgical success rates have been published up to 90%. Personal experience with a particular technique is an important factor in success. Although there are no randomised, controlled trials, reports from case series indicate better results with microsurgery compared with loop surgery. It is therefore strongly recommended that microsurgical vasectomy reversal is the standard method used. Reported vasovasostomy results have shown patency rates (up to 90%) superior to pregnancy rates. The reason for this discrepancy is unclear. However, the longer the interval from vasectomy to reversal, the lower the pregnancy rates. The necessity for epididymovasostomy in some cases after vasectomy has been discussed previously (see Section 5).

6.5. Treatment of post-vasectomy infertility

Microsurgical vasectomy reversal was compared with epididymal or testicular sperm retrieval and ICSI. Compared with a calculated 29% delivery rate for MESA and ICSI, the data provide strong evidence for the better outcome of simple vasectomy reversal compared to sperm retrieval and ICSI. In addition, in contrast to ICSI, conception follows normal inter-

course without intervention and its associated risks for the female partner. MESA/TESE and ICSI should be reserved for failed surgery or cases not amenable to surgical reconstruction.

7. Special problems (1): hypogonadism

Men with hypogonadism usually present with symptoms of androgen deficiency. Hypogonadotrophic hypogonadism may sometimes result in infertility. Disorders with male hypogonadism are given in Table 3 [17,18].

7.1. Hypogonadotrophic hypogonadism

Hypogonadotrophic hypogonadism is caused by hypothalamic or pituitary diseases. Endocrine deficiency leads to a lack of spermatogenesis and testosterone secretion due to decreased secretion patterns of LH and FSH. Drug therapy is effective in achieving fertility. The therapy of choice is hCG treatment; hMG may be added later, depending on initial testicular volume. For hypogonadotrophic hypogonadism that is hypothalamic in origin, treatment with pulsatile GnRH for one year is as effective as gonadotrophins in stimulating spermatogenesis. Once pregnancy has been achieved, patients return to testosterone substitution therapy (see Section 7.3).

7.2. Hypergonadotrophic hypogonadism

In younger men, common conditions associated with hypergonadotrophic hypogonadism are testicular disorders (Table 3). Hypertrophic hypogonadism may also occur after extensive testicular biopsy to recover sperm for IVF/ICSI; the risk is almost certainly increased in men with Klinefelter's syndrome, who are already at risk for spontaneous hypogonadism with ageing. Laboratory diagnosis of hypergonadotrophic hypogonadism is based on decreased serum testosterone and increased LH levels. Additional prolactin measurement is suggested.

7.3. Treatment

There is general agreement that patients with primary or secondary hypogonadism should receive testosterone substitution therapy. 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. The best preparation is the one that maintains serum testosterone levels as close to physiological concentrations as possible.

Table 3
Disorders with male hypogonadism[a]

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

[a] Adapted from [18].

8. Special problems (2): varicocele

Varicocele is a common condition (Table 4). Diagnosis is by clinical examination. A doubtful diagnosis may be confirmed by colour Doppler ultrasound or, in some centres, radiography [19,20].

Varicocele has been associated with the following andrological problems: failure of ipsilateral testicular growth and development, infertility, reduced testosterone in older men and symptoms of pain and discomfort. In some men, the presence of a varicocele is thought to be associated with progressive testicular damage from adolescence onwards, resulting in reduced male fertility. However, the man's reduced fertility will only manifest as an infertile couple if the female partner's fertility is also reduced.

8.1. Treatment

The treatment modalities are: sclerotherapy (antegrade, retrograde), embolisation, and open surgery, including microsurgical dissection. Choice of therapy is mainly influenced by the therapist's experience. Although laparoscopic varicocelectomy is also feasible, it still needs to be justified in terms of cost-effectiveness.

Table 4
Clinical classification of varicocele

Grading	Feature
Subclinical	Not palpable or visible either at rest or during Valsalva manoeuvre, but can be demonstrated by special tests (reflux on Doppler examination)
Grade 1	Palpable during a Valsalva manoeuvre but not otherwise
Grade 2	Palpable at rest but not visible
Grade 3	Visible and palpable at rest

8.1.1. Indications for treatment

Treatment is recommended in adolescents if serial clinical examination shows progressive failure of testicular development. Treatment is probably recommended in adolescents with ipsilateral testicular atrophy. Treatment may be indicated in adolescents in whom varicocele is associated with an exaggerated response to gonadotrophin-releasing hormone (GnRH). There is no evidence to indicate that varicocele treatment benefits adolescents in the absence of either ipsilateral testicular atrophy or endocrine abnormalities. It is general clinical urological practice to recommend varicocele treatment for adolescents and adults with symptoms.

According to meta-analysis of randomised clinical trials, varicocele ligation for infertility does not improve fertility. However, there are case reports showing restoration of fertility. Thus, varicocele ligation for infertility should only be carried out after discussing fully the uncertain benefits of treatment. It may be worth selecting subgroups of men with infertile marriages, according to endocrine measurements. New methods of endocrine measurement, e.g. inhibin B measurement, may be helpful. Observational evidence suggests that older men with varicocele may have lower testosterone levels than those without varicocele. However, there are no clinical trials to address whether varicocele ligation helps restore testosterone levels. By the time, these changes become manifest, damage is almost certainly irreversible. In the absence of local symptoms of pain and discomfort, treatment of varicocele in older men with low testosterone levels is not recommended.

9. Special problems (3): cryptorchidism[2]

The association between testicular maldescent and infertility has been well known for a long time [21,22].

9.1. Impact on fertility

Among men who have untreated unilateral cryptorchidism (and still cryptorchid on semen analysis), between 50 and 70% are azoospermic or oligozoospermic. In contrast, almost all men with untreated bilateral cryptorchidism are infertile. Although the mechanisms for impaired fertility in these cases are not completely understood, the following alterations have been discussed aetiologically: decreased number of tubules containing spermatogonia, decreased number of spermatogonia per tubule, mild concomitant hypogonadotrophic hypogonadal situation, damaging effects on the contralateral testis, induction of sperm antibodies, epididymal malformations.

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

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

10. Special problems (4): urogenital infections[3]

Infections of the male urogenital tract are potentially correctable causes of male infertility. A generalised inflammatory disease has been defined as male accessory gland infection by WHO. Male urogenital infections include urethritis, prostatitis, orchitis and epididymitis [23–25].

10.1. Urethritis

In urethritis, the anterior urethra is full of infectious and inflammatory material. Due to contamination of the ejaculate with this inflammatory material, the impact of urethritis on semen quality and fertility is not really proven. A negative influence of sexually transmitted microorganisms on sperm function is a matter of debate. Obstruction has been claimed to impair fertility, either as a normal urethral stricture or as a lesion in the posterior urethra in the area of the veromontanum, both of which can lead to ejaculatory disturbances. Treatment is standardised by the guidelines of the Centers of Disease Control and Prevention. The impact upon fertility is unknown.

[2] As cryptorchidism is discussed in the EAU Guidelines on paediatric urology, Chapter 2, p. 7–10, only the impact on fertility disorders will be reviewed here (EAU Guidelines published at the time of the XVIth EAU Annual Congress in Geneva, ISBN 90-806179-3-8).

[3] As male genital infections are discussed in the UIT Guidelines, only the impact on fertility disorders will be reviewed here (EAU Guidelines for the management of urinary and male genital tract infections. Eur Urol 2000;40:576–88).

Table 5
Classification of the prostatitis syndrome from the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK)

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

10.2. Prostatitis

Prostatitis is the most common urological diagnosis in men aged under 50 years. A new classification system including semen analysis is given in Table 5.

10.2.1. Ejaculate analysis

Ejaculate analysis is part of the new classification (Table 5) and helps to clarify whether the prostate is part of a generalised infection of the accessory sex glands and also gives the semen quality. Leukocyte analysis allows differentiation between inflammatory and non-inflammatory CPPS.

10.2.2. White blood cells

According to WHO classification, $>1\times10^6$ white blood cells per ml are defined as leukocytospermia. The great majority of leukocytes are neutrophilic granulocytes. The clinical significance of an increased concentration of white blood cells in the ejaculate is highly controversial. This debate reflects earlier findings that elevated leukocyte numbers are not a natural cause of male infertility.

10.2.3. Microbiological findings

In evidence of $\geq10^6$ peroxidase-positive white blood cells per ml ejaculate (see above), a culture for common urinary tract pathogens should be performed. A concentration of $\geq10^3$ cfu/ml of urinary tract pathogens in the ejaculate is significant bacteriospermia.

10.2.4. Semen quality

Deteriorative effects of chronic prostatitis on sperm density, motility and morphology are debated contradictory, recent data do not confirm a decisive role of chronic prostatitis for male infertility.

10.2.5. Seminal plasma alterations

Seminal plasma elastase is a biochemical indicator of granulocyte activity in the ejaculate. Various cytokines, involved in inflammation, may influence sperm function. Sex gland infections can impair their excretory function. Decreased quantities of citric acid, phosphatase, fructose, zinc and α-glutamyltransferase activity in seminal plasma have been evaluated as disturbed prostatic secretory parameters and reduced fructose concentration as an indicator of impaired vesicular function.

10.2.6. Sperm antibodies

Post-inflammatory seminal plasma antibodies to sperm antigens do not play a decisive role in immune infertility.

10.2.7. Reactive oxygen species

Levels may be increased in chronic urogenital infections associated with increased leukocyte numbers. However, their biological significance in prostatitis remains unclear.

10.3. Treatment

Treatment of chronic prostatitis is normally targeted at relieving symptoms. Therapy for altered semen composition in male adnexitis is aimed at reduction or eradication of microorganisms in prostatic secretions and semen, normalisation of inflammatory parameters, possible improvement of sperm parameters to counteract fertility impairment. Although antibiotic procedures may improve sperm quality, therapy does not always enhance the probability of conception.

11. Special problems (5): orchitis and epididymitis

11.1. Orchitis

Orchitis is an inflammatory lesion of the testicle, associated with a predominantly leukocytic exsudate, inside and outside the seminiferous tubules, resulting in tubular sclerosis. Chronic inflammatory changes alter both sperm number and quality. Orchitis is an

Table 6
Classification of epididymo-orchitis

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

Table 7
Treatment of epididymo-orchitis

Condition	Therapy
Acute bacterial epididymo-orchitis	
N. gonorrhoeae	Tetracyclines
C. trachomatis	Tetracyclines
E. coli, Enterobacteriaceae	Fluoroquinolones
Mumps orchitis	Inteferon α-2b
Non-specific chronic epididymo-orchitis	Steroidal and non-steroidal antiphlogistic substances Gonadotrophin-releasing hormone
Granulomatous (idiopathic) orchitis	Semicastration
Specific orchitis	According to therapy of underlying diseases

important cause of spermatogenetic arrest, which may be reversible, and of testicular atrophy. Orchitis is classified according to aetiology (Table 6).

11.1.1. Diagnosis

Ejaculate analysis, including leukocyte analysis, indicates persistent inflammatory activity. Especially in acute epididymo-orchitis, there is transiently decreased sperm counts and reduced forward motility. Obstructive azoospermia due to complete bilateral epididymal obstruction is a rare complication. Mumps orchitis may result in bilateral testicular atrophy and testicular azoospermia. When granulomatous orchitis is suspected, sperm-bound autoantibodies occur.

11.1.2. Treatment

Only the antibiotic therapy of acute bacterial epididymo-orchitis and of specific granulomatous orchitis is standardised (Table 7). Several regimens are thought to improve the inflammatory lesion and to be beneficial for the risks of infertility. Unfortunately, corticosteroids and non-steroidal antiphlogistic substances, i.e. diclofenac, indomethacin and acetylsalicylic acid, have not been evaluated as to their andrological outcome. gonadotrophin-releasing hormone has been used with the aim of prevention of spermatogenesis.

11.2. Epididymitis

Inflammation of the epididymis is almost unilateral and relatively acute in onset. In many cases, the testicle is involved in the inflammatory process known as epididymo-orchitis (Table 6).

11.2.1. Diagnosis

11.2.1.1. Ejaculate analysis. In acute epididymo-orchitis semen analysis is not recommended. In chronic epididymitis, ejaculate analysis, including leukocyte count, may indicate persistent inflammatory activity. In many cases, transiently decreased sperm counts and forward motility are observed. Ipsilateral low-grade orchitis has been discussed as the cause of this slight impairment in sperm quality. Development of stenosis in the epididymal duct, reduction of sperm count and azoospermia are important in the follow-up of bilateral epididymitis (see Section 5). The true prevalence of azoospermia after unilateral epididymitis is unclear.

11.2.2. Treatment

Antibiotic therapy is indicated before culture results are available (Table 7). Treatment should resultin a microbiological cure of infection, improvement of signs and symptoms, prevention of transmission to others and a decrease in potential complications, e.g. inflammatory obstructive lesion. Patients with epididymitis, known or suspected to be caused by *N. gonorrhoeae* or *C. trachomatis*, should be instructed to refer sex partners for evaluation and treatment.

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