GUIDELINES ON THE INVESTIGATION AND TREATMENT OF MALE INFERTILITY

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1. Introduction

"Infertility is the inability of a sexually active, non-contracepting couple to achieve pregnancy in one year" (WHO, 1995).

About 25% of couples do not achieve pregnancy within 1 year. Of these couples, 15% seek medical treatment for infertility and fewer than 5% remain childless against their will.

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.

As a urogenital expert, the urologist should examine any male with fertility problems for urogenital abnormalities. This applies to all males diagnosed with reduced sperm quality. A diagnosis is mandatory to initiate appropriate therapy (drugs, surgery, assisted reproduction).

2. Diagnosis

The diagnosis of male infertility must focus on a number of prevalent disorders, such as varicocele, testicular and epididymal abnormalities, obstructions of the genital tract, and anomalies of prostate and seminal vesicles (Table 1). Simultaneous assessment of the female partner is preferable, even if abnormalities are found in the male.

Table 1: The main cause of male infertility

Testicular insufficiency

- Cryptorchidism
- Orchitis (viral)
- Testicular torsion
- Cytotoxic therapy (chemotherapy)
- Radiotherapy
- Genetic causes (Klinefelter's syndrome, Y deletions)

Endocrine disorders

- Kallmann's syndrome
- Prader-Willi syndrome
- Pituitary gland disorders (adenoma, infection)

Obstructions of the male genital tract

- Congenital absence of the vas deferens/epididymis
- Müllerian prostatic cysts
- Epididymal obstructions (infections, congenital)
- After groin or scrotal surgery

Sperm antibodies

Medication, environment, stress, illness

Varicocele

Sexual problems/ejaculation disorders

Idiopathic

Semen analysis

Andrological examination is indicated if semen analysis shows abnormalities (Table 2). Since semen analysis still forms the basis of important decisions concerning appropriate treatment, standardization of the complete laboratory work-up is highly desirable.

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

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

* *Assessment according to Kruger and Menkfeld criteria.*

** *MAR = Mixed antiglobulin reaction*

Frequency semen analyses

If values are normal according to WHO criteria, one test should suffice. Only if the results are abnormal in at least two tests are further andrological tests necessary.

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 oligo-asteno-teratozoospermia (OAT) syndrome. In extreme cases of OAT syndrome (< 1 million spermatozoa/mL), just as with azoospermia, there is an increased incidence of obstruction of the male genital tract and genetic abnormalities.

Hormonal investigation

Endocrine malfunctions are more prevalent in infertile men than in the general population, but are still quite uncommon. Hormonal screening can be limited to determining follicle-stimulating hormone (FSH), luteinizing hormone (LH) and testosterone levels. In men diagnosed with azoospermia or extreme OAT, it is important to distinguish between obstructive and non-obstructive causes. A criterion with reasonable predictive value for obstruction is a normal FSH with bilaterally a normal testicular volume. However, 29% of men with a normal FSH appear to have defective spermatogenesis.

Hypergonadotrophic hypogonadism (elevated FSH/LH)

Primary testicular developmental disorder with an elevated production of gonadotrophins is an isolated failure of spermatogenesis and generally not caused by a disruption of the endocrine system. Causes may be:

- Congenital - Klinefelter's syndrome (sometimes accompanied by gynaecomastia), anorchia, enzyme defects in androgen synthesis and cryptorchididsm.
- Acquired - after orchitis, testicular torsion, castration and cytotoxic therapy.

Hypogonadotrophic hypogonadism (deficient FSH/LH)

Low levels of gonadotrophins due to dysfunction of the pituitary gland or hypothalamus may occur as a result of:

- Congenital anomalies - isolated arrest of FSH and LH secretion (Kallmann's syndrome, accompanied by anosmia), isolated arrest of LH secretion (fertile eunuch), idiopathic hypopituitarism and delayed puberty.
- Acquired anomalies - generally as an expression of a more complex disorder of the pituitary gland or hypothalamus, or iatrogenic (gonadotrophin-releasing hormone [GnRH] agonists and anti-androgens).

If hypogonadotrophic hypogonadism is suspected, the medical examination should include magnetic resonance imaging (MRI) of the pituitary gland and an LHRH stimulation test.

Microbiological assessment

Indications for microbiological assessment include abnormal urine samples, urinary tract infections, 'prostatitis, epididymitis, silent ejaculate infections' (MAGI) and sexually transmitted diseases (STDs). The clinical implications of white blood cells detected in a semen sample are as yet undetermined. However, in combination with a small ejaculate volume, this may point to a (partial) obstruction of the ejaculatory ducts caused by a (chronic) infection of the prostate or seminal vesicles. Genital infections may instigate the production of spermatotoxic free oxygen radicals. Gonorrhoea and *Chlamydia trachomatis* can also cause obstruction of the epididymis and the vas deferens.

Genetic evaluation

A substantial number of andrological fertility disorders that used to be described as idiopathic male infertility will, in fact, have a genetic origin. By taking an extensive family history and carrying out karyotype analysis, a number of these disorders can be detected. This will not only yield a diagnosis, but also allow for appropriate genetic counselling. The latter may be very important with the advent of intracytoplasmic sperm injection (ICSI), because the fertility disorder and possibly the corresponding genetic defect may be transferred to the offspring.

Chromosomal abnormalities are more common in men with extreme OAT and with azoospermia. The most common sex chromosome abnormality is Klinefelter's syndrome (47 XXY), which affects around 10% of men diagnosed with azoospermia. Klinefelter's syndrome is characterized by gynaecomastia and hypergonadotrophic hypogonadism. Occasionally, a eunuchoid phenotype is found, and sometimes psychological disorders. Both testicles are very small and present with tubular sclerosis. In around 60% of all patients, testosterone levels decrease with age, requiring androgen replacement.

In men presenting with extremely poor quality semen, chromosome translocations and deletions can be found, which may be hereditary and which may cause habitual abortion and congenital malformations in the offspring. It is recommended that karyotyping is performed in all men presenting with < 1 million spermatozoa/mL who are candidates for ICSI.

In cases of azoospermia or severe OAT, deletions in the azoospermic factor (AZF) region of the Y chromosome can occur and testing is advised. The prevalence of Y deletions is considerable (around 5%) in this group of patients. A Y dele-

tion means that the defect will be passed on to sons who will then also be infertile

When performing ICSI with surgically-retrieved sperm, based on a diagnosis of congenital bilateral absence of the vas deferens (CBAVD), both the male and the female partners should be checked for mutations in the cystic fibrosis transmembrane regulator (CFTR) gene. Apart from causing cystic fibrosis (CF), this gene is also associated with CBAVD; 85% of all males diagnosed with CBAVD also test positive for one or two CFTR-gene mutations. In cases where the partner is a carrier of a CFTR-mutation, depending on the mutation involved, there is a 25% chance of a child with CF or CBAVD. Genetic counselling is recommended in these cases.

Ultrasonography

Ultrasonography is a useful tool for locating intrascrotal defects. Colour Doppler ultrasound of the scrotum can detect a varicocele in around 30% of infertile males. Testicular tumours can be found in 0.5% of infertile men and testicular microcalcifications, a potentially premalignant condition, are detected in around 5% of infertile males, especially patients diagnosed with a history of cryptorchism.

Transrectal ultrasonography (TRUS) is indicated in men with a low volume of ejaculate (< 1.5 mL) to exclude obstruction of the ejaculatory ducts caused by a midline prostatic cyst or stenosis of the ejaculatory ducts.

Testicular biopsy

Indications for performing a testicular biopsy are azoospermia or extreme OAT in the presence of a normal testicular volume

and normal FSH levels. The biopsy is aimed at differentiating between testicular insufficiency and obstruction of the male genital tract. Pathological classifications are:

- Absence of seminiferous tubules (tubular sclerosis).
- Presence of Sertoli cells only (Sertoli cell only syndrome).
- Maturation arrest - incomplete spermatogenesis, not beyond the spermatocyte stage.
- Hypospermatogenesis - all cell types up to spermatozoa are present, but there is a distinct decline in the number of reproducing spermatogonia.

Carcinoma *in situ* of the testis can be found, especially in men with bilateral microcalcifications in the testes and in men with a history of testicular tumour.

Treatment

Counselling

Sometimes certain 'lifestyle' factors may be responsible for poor semen quality: for example, alcohol abuse, use of anabolic steroids, extreme sports (marathon training, excessive strength sports), and increase in scrotal temperature through thermal underwear, sauna or hot tub use or occupational exposure to heat sources. A considerable number of drugs can affect the spermatogenesis.

Medical (hormonal) treatment

No studies have confirmed that hormonal therapies - such as human menopausal gonadotrophin (HMG)/human chorionic gonadotrophin (HCG), androgen, anti-oestrogens (clomiphene and tamoxifen), prolactin inhibitors (bromocriptine) and steroids - improve pregnancy rates for men with idiopathic

OAT. However, some primarily endocrinological pathologies can be treated medically.

- Low testosterone - testosterone substitution is indicated; substitution exceeding normal physiological values has a negative effect on the spermatogenesis.
- Hypogonadotrophic hypogonadism - pulsatile GnRH, i.v. or s.c.; the usual starting dose is 5 μg, increased if necessary to 10-20 μg, every 90 minutes. Alternatively, HCG 1500 IE and HMG 150 IE (FSH) i.m. twice weekly can be applied.
- Hyperprolactinaemia - dopamine agonists.

In patients with sperm autoantibodies, corticosteroids are not recommended because of serious side effects and unproven lack of efficacy.

Surgical treatment

Varicocele

The treatment of varicocele is a controversial subject in clinical andrology. This controversy is based not only on the actual need to treat varicocele, but also on the significance of varicocele as a cause of disruption in spermatogenesis. The results of a considerable number of non-randomized studies 'support' the idea that varicocele may be a cause of infertility. A recent prospective randomized trial, however, showed no difference in pregnancy rates when treatment of varicocele was compared with counselling. However, smaller series and unpublished studies have shown a benefit in favour of treatment.

A range of surgical and radiological techniques can be used to treat varicocele. Successful treatment will lead to a significant

improvement in semen quality in at least 44% of men treated.

Microsurgery/epididymovasostomy

Only urologists with experience in microsurgery should undertake this procedure. Considering its limited effect on pregnancy rates (20-30%), it is advisable to combine epididymovasostomy with microsurgical epididymal sperm aspiration (MESA), and cryopreserve the harvested spermatozoa for ICSI. The indications for epididymovasostomy include congenital and acquired obstructions at the level of the epididymis, in the presence of a normal spermatogenesis (testicular biopsy).

Vasovasostomy

Vasovasostomy can be performed either macroscopically or microscopically, though the latter is more effective in improving pregnancy rates. The likelihood of initiating pregnancy is inversely proportional to the obstruction interval and becomes less than 50% after 8 years. Important prognostic factors are the development of antisperm antibodies, the quality of the semen and the partner's age. In approximately 20% of men who have undergone a vasovasostomy, sperm quality deteriorates to the level of azoospermia or extreme oligospermia within 1 year. Poor sperm quality and autoantibodies frequently prevent a spontaneous pregnancy and assisted reproduction is indicated.

MESA

MESA in combination with ICSI is indicated when reconstruction (vasovasostomy, epididymovasostomy) cannot be performed or is unsuccessful. An alternative would be percutaneous aspiration of sperm from the caput epididymis (PESA). If a MESA or PESA procedure does not produce

spermatozoa or very low numbers of motile spermatozoa, a testicular biopsy can be performed with testicular sperm extraction (TESE) to be used for ICSI.

Transurethral incision of ejaculatory ducts or midline prostatic cyst

Distal obstructions of the genital tract are commonly caused by infections of the prostatic urethra and the accessory glands, or by a cyst in the midline of the prostate. Treatment of the obstruction by transurethral incision of the cyst or the ejaculatory ducts may lead to an increase in semen quality and, occasionally, spontaneous pregnancy.

Sexual Dysfunction

For treatment of sexual dysfunction, see the EAU Guidelines on Erectile Dysfunction.

Disorders of ejaculation

Retrograde ejaculation and anejaculation can occur:

- In neurological diseases, such as multiple sclerosis, diabetes mellitus (neuropathy) and spinal cord injuries.
- Following prostate surgery, bladder neck surgery, sympathectomy and retroperitoneal surgery, such as lymph node dissections for testicular tumours.
- During antidepressant therapy.

Often no cause for retrograde ejaculation can be found. The diagnosis is based on the medical history and laboratory microscopic assessment of the post-ejaculate urine. Retrograde ejaculation should also be suspected if the ejaculate volume is very low (partial retrograde ejaculation).

Treatment of retrograde ejaculation is basically aimed at removing the cause of the disorder or harvesting spermatozoa from the urine after orgasm.

Anejacualtion can be treated by vibrostimulation or electro-ejaculation techniques. It is possible to induce ejaculation in around 90% of patients with spinal cord injuries, however, the semen quality is often poor with a low number of motile spermatozoa. This accounts for the disappointing results of assisted reproduction techniques, such as intrauterine insemination, in patients with spinal cord injuries. *In vitro* fertilization and ICSI are often required.

This short booklet text is based on the more comprehensive EAU guidelines (ISBN 90-70244-19-5), available to all members of the European Association of Urology at their website - http://www.uroweb.org.