GUIDELINES FOR THE INVESTIGATION AND TREATMENT OF MALE INFERTILITY

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Definition

"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 less than 5% remain unwillingly childless.

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, so that appropriate treatment can be given.

Diagnosis

The diagnosis of male fertility must focus on a number of prevalent disorders (Table 1). Simultaneous assessment of the

female partner is preferable, even if abnormalities are found in the male since WHO data show that in one out of four couples who consult with fertility problems, both male and female partners have abnormalities.

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-Willy 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

Semen analysis forms the basis of important decisions concerning appropriate treatment. Semen analysis should be performed in a laboratory adhering to national quality control standards (Table 2).

Table 2: Overview of standard values for semen analysis according to 2006 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*
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 of semen analyses

If values are normal according to WHO criteria, one test should suffice. Only if the results are abnormal, semen analysis should be repeated twice more. 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/or 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)

Impaired spermatogenesis associated with elevated levels of gonadotrophins is a common problem and are 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 cryptorchidism
- 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 are rare and 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 more complex disorders 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) or a computed tomography (CT) scan of the pituitary gland

Microbiological assessment

Indications for microbiological assessment include abnormal urine samples, urinary tract infections, 'male accessory gland 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 genital tract.

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. 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. An Y deletion 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 partner should be tested for mutations in the cystic fibrosis trans-membrane 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. Karyotyping is recommended in all men presenting with < 1 million spermatozoa/mL and who are candidates for ICSI.

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. Tissue may be cryopreserved for future ICSI attempts.

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.

Testicular biopsy can also be performed as part of a therapeutic process in patients with clinical evidence of non-obstructive azoospermia who decide to undergo ICSI.

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 - improved pregnancy rates in 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 – HCG and HMG i.m. twice weekly
- Hyperprolactinaemia - dopamine agonists.

In patients with sperm autoantibodies, high-dose corticosteroids, although effective, are not recommended because of serious side effects.

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 Cochrane review of randomized studies showed no benefit in terms of pregnancy from varicocele ligation. There is, however, evidence of improved semen measurements and further

data from large randomized trials are needed. 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 40-50% 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 vaso-epididymostomy with microsurgical epididymal sperm aspiration (MESA), and cryopreserve the harvested spermatozoa for ICSI.

The indications for vaso-epididymostomy include 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. Other important prognostic factors are the quality of the semen after the procedure and the partner's age. In approximately 15% 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 sometimes sperm antibodies prevent a spontaneous pregnancy and assisted reproduction is indicated.

MESA

MESA in combination with ICSI is indicated when reconstruction (vasovasostomy, vaso-epididymostomy) cannot be performed or is unsuccessful. An alternative would be percutaneous aspiration of spermatozoa from the caput epididymis (PESA). If a MESA or PESA procedure does not produce 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. Long-term results, however, are disappointing.

Sexual Dysfunction

For treatment of sexual dysfunction, see EAU Guidelines on Male Sexual 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.

Anejaculation 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.