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, 2000). About 15% of couples do not achieve pregnancy within 1 year and seek medical treatment for infertility. 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 medical advise and 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 1 out of 4 couples who consult with fertility problems, both male and female partners have pathological findings.

Table 1: Reasons for a reduction in male infertility

- Congenital factors (cryptorchidism and testicular dysgenesis, congenital absence of the vas deferens);
- Acquired urogenital abnormalities (obstructions, testicular torsion, testicular tumour, orchitis);
- Urogenital tract infections;
- Increased scrotal temperature (e.g. as a consequence of varicocele);
- Endocrine disturbances;
- Genetic abnormalities;
- Immunological factors;
- Systemic diseases;
- Exogenous factors (medications, toxins, irradiation, lifestyle factors);
- Idiopathic (40-50% of cases).

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: Lower reference limits (5th centiles and their 95% confidence intervals) for semen characteristics

(WHO Manual for Semen Analysis, 5th edn, 2010)

Parameter	Lower reference limit
Semen volume (mL)	1.5 (1.4-1.7)
Total sperm number (10^6 per ejaculate)	39 (33-46)
Sperm concentration (10^6 per mL)	15 (12-16)
Total motility (Progressive and Non-progressive, %)	40 (38-42)
Progressive motility (%)	32 (31-34)
Vitality (live spermatozoa, %)	58 (55-63)
Sperm morphology (normal forms, %)	4 (3.0-4.0)
Other consensus threshold values	
pH	≥ 7.2
Peroxidase-positive leukocytes (10^6 per mL)	< 1.0
MAR test (motile spermatozoa with bound particles, %)	< 50
Immunobead test (motile spermatozoa with bound beads, %)	< 50
Seminal zinc (µmol/ejaculate)	≥ 2.4
Seminal fructose (µmol/ejaculate)	≥ 13
Seminal neutral glucosidase (mU/ejaculate)	≥ 20

Frequency of semen analyses

If values are normal according to WHO criteria, one test should suffice. If the results are abnormal, semen analysis should be repeated. It is important to distinguish between oligozoospermia (< 15 million spermatozoa/mL), asthenozoospermia (< 40% motile spermatozoa), and teratozoospermia (< 4% normal forms). Quite often, all three pathologies occur simultaneously as oligo-astheno-teratozoospermia (OAT) syndrome. In extreme cases of OAT syndrome (< 1 million spermatozoa/mL), just as with azoospermia, there is an increased incidence of genetic abnormalities and obstruction of the male genital tract.

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), luteinising hormone (LH), and testosterone levels in case of abnormal semen parameters. 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 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 it is due to primary testicular failure. Causes include:

- congenital – Klinefelter's syndrome, anorchia, cryp-

torchidism (dysgenesis), Y chromosome microdeletions;
- acquired – after orchitis, testicular torsion, testicular tumour, systemic illness, 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 – idiopathic hypogonadotrophic hypogonadism, Kallmann syndrome (accompanied by anosmia);
- acquired anomalies – acquired hypothalamic/pituitary gland diseases (tumour, granulomatous illness, hyperprolactinemia);
- exogenous factors – drugs (anabolic steroids, obesity, irradiation).

If unexplained hypogonadotrophic hypogonadism is present, 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. Although antibiotic procedures for MAGI might provide improvement in sperm quality, therapy does not necessarily enhance the probability of conception.

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 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 characterised by hypergonadotrophic hypogonadism. Occasionally, a eunuchoid phenotype is found and gynaecomastia is present. Both testicles are very small and present with tubular sclerosis. In around 60% of all patients, testosterone levels decrease with age requiring androgen replacement. Karyotyping is recommended in all men who are candidates for ICSI due to OAT.

In men presenting with 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. The presence of a 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 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 mandatory 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 2-5% 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

Testicular biopsy is mainly performed as part of a therapeutical process in non-obstructive azoospermic patients (testicular sperm retrieval) who decide to undergo ICSI. It is advised that tissue that contains spermatozoa is cryopreserved for future ICSI attempts. Indications for performing a diagnostic testicular biopsy in infertile patients are limited to patients with azoospermia 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. It is advised that tissue that contains spermatozoa is 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 – spermatogenesis arrested at different stages (spermatogonia, spermatocytes, or spermatides);
- 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 risk factors for testicular germ cell tumours (male infertility, cryptorchidism, history of a testicular tumour, atrophy of the testis) and microcalcifications in the testes.

Treatment

Counselling

Sometimes certain 'lifestyle' factors may be responsible for poor semen quality: for example, heavy smoking, alcohol abuse, use of anabolic steroids, extreme sports (marathon training, excessive strength sports), and an 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, have improved pregnancy rates in men with idiopathic OAT. However, some primarily endocrinological pathologies can be treated medically, including:

- Low testosterone: testosterone substitution, however, can have a negative effect on the spermatogenesis. Anti-estrogen therapy may be a better alternative for substitution, f.i. Tamoxifen 10 mg 2dd.
- Hypogonadotrophic hypogonadism: start HCG 1500 IU sc. 3 times per week and add HMG or rFSH 75-150 IU im 3 times per week after 6 months if azoospermia persists.
- Hyperprolactinaemia, with dopamine agonists.

In patients with sperm autoantibodies, high-dose corticosteroids could be effective, but 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 mainly based on the actual need to treat varicocele in infertile men. There is evidence of improved semen parameters after successful varicocele treatment. 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. Although treatment of varicocele in adolescents may be effective, there is a significant risk of over-treatment, since many of the boys will show to be fertile later in life without varicocele treatment.

A Cochrane meta-analysis of all randomised studies of varicocele treatment in infertile men showed no benefit in terms of pregnancy from varicocele ligation. This meta-analysis also included studies of men with normal semen analysis and men with a subclinical varicoceles: in these studies there appeared to be no benefit from treatment over observation. Varicocele repair, however, may be effective in men who have a subnormal semen analysis, clinical varicocele and otherwise unexplained infertility. Further randomised studies are needed to confirm that this subgroup of infertile couples will benefit from treatment.

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 vasoepididymostomy 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 in men with obstructive azoospermia 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.

TESE

In about 50% of men with non-obstructive azoospermia (NOA), spermatozoa can be found in the testis that can be

used for ICSI. Most authors recommend taking several testicular samples. A good correlation is seen between diagnostic biopsy histology and the likelihood of finding mature sperm cells during testicular sperm retrieval and ICSI. No clear relationship has been found between successful sperm harvesting and FSH, inhibin B or testicular volume. In case of AZFa and AZFb microdeletions, no spermatozoa can be retrieved. Testicular sperm extraction is the technique of choice and shows excellent repeatability. Microsurgical testicular sperm extraction may increase retrieval rates.

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 electroejaculation 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 fertilisation and ICSI are often required.

This short booklet text is based on the more comprehensive EAU guidelines (978-90-79754-70-0), available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines/online-guidelines/.