

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 spontaneous pregnancy in one year.'
(WHO, 1995).

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

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. due to varicocele)
Endocrine disturbances
Genetic abnormalities
Immunological factors (autoimmune diseases)
Systemic diseases (diabetes, renal and liver insufficiency, cancer, hemochromatosis)
Exogenous factors (medications, toxins, irradiation)
Lifestyle factors (obesity, smoking, drugs, anabolic steroids)
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 95% confidence intervals) for semen characteristics*

Parameter	Lower reference limit (95% CI)
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 (PR+NP, %)	40 (38-42)
Progressive motility (PR, %)	32 (31-34)
Vitality (live spermatozoa, %)	58 (55-63)
Sperm morphology (normal forms, %)	4 (3.0-4.0)
<i>Other consensus threshold values</i>	
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

*WHO Manual for Semen Analysis, 5th edn, 2010.

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), astheno-

zoospermia (< 40% motile spermatozoa) and teratozoospermia (< 4% normal forms). Quite often, all three pathologies occur at the same time, i.e. 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/or 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 the levels of follicle stimulating hormone (FSH), luteinizing hormone (LH) and testosterone in cases of abnormal semen parameters. In men diagnosed with azoospermia or extreme OAT, it is important to distinguish between obstructive and non-obstructive causes. Criteria with a reasonable predictive value for non-obstruction are a normal FSH with bilaterally normal testicular volume. However, 29% of infertile 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 is due to primary testicular failure. Causes include:

- Congenital – Klinefelter's syndrome, anorchia, cryptorchidism, testicular 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 – isolated hypogonadotrophic hypogonadism (iHH), syndromic KK, Kallmann's syndrome, Prader-Willi syndrome
- Acquired anomalies – acquired hypothalamic/pituitary gland diseases (malignant CNS tumours, pituitary adenoma, hyperprolactinaemia, granulomatous illness, hemochromatosis)
- Exogenous factors – drugs (anabolic steroids, obesity, irradiation).

If unexplained hypogonadotrophic hypogonadism is present, the medical examination should include magnetic resonance imaging (MRI) 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 spermatoxic free oxygen radicals. *Neisseria gonorrhoea* and *Chlamydia trachomatis* infections can also cause obstruction of the genital tract. Although antibiotic procedures for MAGI

might provide improvement in sperm quality, therapy does not necessarily increase the probability of conception.

Genetic evaluation

A substantial number of andrological fertility disorders that used to be described as idiopathic male infertility have a genetic origin. An extensive family history and karyotype - and Y chromosome deletion analysis will detect a number of these disorders, not only providing a diagnosis, but also enabling appropriate genetic counselling. The latter may be very important with the advent of intracytoplasmic sperm injection (ICSI), because genetic defects may be transferred and a balanced translocation of the infertile father may become unbalanced in the offspring.

Chromosomal abnormalities are more common in men with OAT and with azoospermia, and karyotyping is recommended in these men both for diagnosis purposes and for genetic counselling. The most common sex chromosome abnormality is Klinefelter's syndrome (47, XXY), which affects around 14% of men diagnosed with azoospermia. Klinefelter's syndrome is characterized by hypergonadotrophic hypogonadism which may be associated with eunuchoid features and/or gynaecomastia. Both testicles are very small due to extensive tubular sclerosis. In around 60% of all patients, testosterone levels decrease with age requiring androgen replacement.

Furthermore, chromosome translocations and deletions can be found, which may be hereditary and cause habitual abortion and congenital malformations in the offspring. In cases of azoospermia or severe OAT, there may be deletions in the

azoospermic factor (AZF) region of the Y chromosome 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 to sons, who will then also be affected by spermatogenic disturbances or failure.

When performing ICSI with surgically retrieved sperm or ejaculated spermatozoa, based on a diagnosis of congenital bilateral/unilateral absence of the vas deferens (CAVD), 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 CAVD; 85% of all males diagnosed with CAVD also test positive for two *CFTR*-gene mutations when the entire gene is sequenced. 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 CAVD. 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 subfertile males. Testicular tumours can be found in 0.5%, and testicular microcalcifications (a potentially premalignant condition) are detected in around 2–5% of subfertile males, especially patients diagnosed with a history of cryptorchidism. 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 usually performed as part of a therapeutic process in azoospermic patients (testicular sperm retrieval) who decide to undergo ICSI. Indications for performing a diagnostic testicular biopsy could be 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. It is advised that, during the procedure, tissue that contains spermatozoa is cryopreserved for future ICSI attempts.

In addition, testicular biopsies are performed to detect carcinoma *in situ* of the testis in infertile men with testicular microcalcifications and risk factors for testicular cancer (i.e. male infertility, cryptorchidism, history of a testicular tumour, testicular atrophy).

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.

Treatment

Counselling

'Lifestyle' factors can impair semen quality, e.g. 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 spermatogenesis.

Medical (hormonal) treatment

Antioxidant treatment (folic acid, vitamin E, zinc, selenium) have a positive influence on semen quality and some improvement of spontaneous pregnancy rates. 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: clomiphene citrate 50 mg/day or tamoxifen 20 mg/day
- Hypogonadotrophic hypogonadism: start HCG 1500 IU subcutaneously 3 times per week, and add HMG or FSH 75–150 IU intramuscularly 3 times per week, until spermatogenesis occurs
- Hyperprolactinaemia: dopamine agonists.

In patients with sperm autoantibodies, high-dose corticosteroids

teroids, although effective, are not recommended because of serious side-effects.

Surgical treatment

Varicocele

The treatment of varicocele is a controversial subject, mainly based on whether there is an 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. In cases of normal semen analysis and in men with a subclinical varicocele, there appears to be no benefit from treatment compared with observation. Varicocele repair, however, seems effective in couples in whom the men has oligozoospermia, a clinical varicocele and otherwise unexplained infertility.

Microsurgery/vasovasostomy and epididymovasostomy

Only urologists with experience in microsurgery should undertake these procedures using an operating microscope. 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 successful vasovasostomy, sperm quality deteriorates to the level of azoospermia or extreme oligospermia within 1 year.

Sometimes an epididymal obstruction coexists, especially in men with a long interval between vasectomy and vasovasostomy. In these men a vaso-epididymostomy is indicated. Considering that a vaso-epididymostomy has a limited effect on pregnancy rates (20–30%), it is advisable to combine this procedure 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). Poor sperm quality and sometimes sperm antibodies after successful vasectomy repair may prevent spontaneous pregnancy and assisted reproduction is indicated.

MESA/TESE

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, testicular sperm extraction (TESE) can be applied. In about 50–60% of men with non-obstructive azoospermia (NOA), spermatozoa can be found in the testis. Some authors recommend taking several testicular samples, while others advocate microsurgical harvesting of spermatozoa. So far, no clinical or laboratory parameter has been shown to be useful in predicting sperm harvesting in men with NOA. In case of AZFa and AZFb microdeletions, no spermatozoa can be retrieved.

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 (TURED) may lead to an increase in semen quality and, occasionally, spontaneous pregnancy. Long-term results, however, are disappointing.

Disorders of ejaculation

Retrograde ejaculation and anejaculation can occur:

- In neurological diseases, e.g. multiple sclerosis, diabetes mellitus (neuropathy) and spinal cord injuries
- Following prostate surgery, bladder neck surgery, sympathectomy and retroperitoneal surgery, e.g. 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 and increased rates of DNA fragmentation. This accounts for the disappointing results of assisted reproduction techniques in these men. Testicular sperm extraction (TESE), in-vitro fertiliation and ICSI are often required.

This short booklet text is based on the more comprehensive EAU guidelines (978-90-79754-83-0), available to all members of the European Association of Urology at their website - <http://www.uroweb.org>.