GUIDELINES ON MALE INFERTILITY

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Introduction

'Infertility is the inability of a sexually active, non-contracepting couple to achieve spontaneous pregnancy in one year.' (World Health Organization 2000).

Epidemiology and aetiology

About 15% of couples do not achieve pregnancy within one year and seek medical treatment for infertility.

Male fertility can be reduced as a result of:

- congenital or acquired urogenital abnormalities;
- malignancies;
- urogenital tract infections;
- increased scrotal temperature (e.g. as a consequence of varicocele);
- endocrine disturbances;
- genetic abnormalities;
- immunological factors.

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.

Diagnostic evaluation

The diagnosis of male fertility should 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 data show that in 1 out of 4 couples both male and female partners have pathological findings.

Semen analysis

A comprehensive andrological examination is indicated if semen analysis shows abnormalities compared with reference values (Table 1).

Table 1: Lower reference limits (5th centiles and their 95% CIs) for semen characteristics

Parameter	Lower reference limit (range)
Semen volume (mL)	1.5 (1.4-1.7)
Total sperm number (10^6/ejaculate)	39 (33-46)
Sperm concentration (10^6/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)
Other consensus threshold values pH	> 7.2
Peroxidase-positive leukocytes (10^6/mL)	< 1.0
Optional investigations	
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

CIs = confidence intervals; MAR = mixed antiglobulin reaction NP = non-progressive; PR = progressive.

It is important to differentiate between the following:

- oligozoospermia: spermatozoa < 15 million/mL;
- asthenozoospermia: < 32% progressive motile spermatozoa;

- teratozoospermia: < 4% normal forms.

Recommendations for the diagnostic evaluation of male infertility	GR
According to WHO criteria, andrological investigations are indicated if semen analysis is abnormal in at least two tests to define a diagnosis.	A*
Diagnosis and evaluation of male subfertility according to the WHO Manual for the standardised investigation, diagnosis and management of the infertile male is recommended.	C
Semen analysis must follow the guidelines of the WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn.).	A*
The WHO laboratory manual proposes reference values based on fertility, hence, these reference values do not allow to classify a man as being infertile.	A

**Upgraded following panel consensus.*

PRIMARY SPERMATOGENIC FAILURE

Diagnostic evaluation

Routine investigations include semen analysis and hormonal determinations. Other investigations may be required depending on the individual situation.

Semen analysis

In non-obstructive azoospermia (NOA), semen analysis shows normal ejaculate volume and azoospermia after centrifugation. A recommended method is semen centrifugation at 3000 g for 15 min and a thorough microscopic examination by phase contrast optics at ×200 magnification of the pellet. All samples can be stained and re-examined microscopically.

Hormonal determinations

In men with testicular deficiency, hypergonadotrophic hypogonadism is usually present, with high levels of follicle-stimulating hormone (FSH) and luteinising hormone (LH), and sometimes low levels of testosterone. Generally, the levels of FSH correlate with the number of spermatogonia: elevated when spermatogonia are absent or markedly diminished.

Testicular biopsy

Testicular biopsy can be part of intracytoplasmic sperm injection (ICSI) treatment in patients with clinical evidence of NOA.

Recommendations for testicular deficiency	GR
Men who are candidates for sperm retrieval must receive appropriate genetic counselling.	A
Men with NOA can be offered TESE with cryopreservation of the spermatozoa to be used for ICSI.	A
To increase the chances of positive sperm retrieval in men with NOA, TESE (microsurgical or multiple) should be used.	A
Testicular biopsy is the best procedure to define the histological diagnosis and retrieve sperm in the same procedure. Spermatozoa have to be cryopreserved for use in ICSI.	A
For patients with NOA who have spermatozoa in their testicular biopsy, ICSI with fresh or cryopreserved spermatozoa is the only therapeutic option.	A

ICSI = intracytoplasmic sperm injection; TESE = testicular sperm extraction; NOA = non-obstructive azoospermia.

GENETIC DISORDERS IN INFERTILITY

Current routine clinical practice is based on the screening of genomic DNA from peripheral blood samples, however, screening of chromosomal anomalies in spermatozoa is also

feasible and can be performed in selected cases.

Recommendations for genetic disorders in male infertility	GR
From a diagnostic view point, standard karyotype analysis should be offered to all men with damaged spermatogenesis (spermatozoa < 10 million/mL) who are seeking fertility treatment by IVF.	B
Genetic counselling is mandatory in couples with a genetic abnormality found in clinical or genetic investigation and in patients who carry a (potential) inheritable disease.	A
All men with Klinefelter's syndrome need long-term endocrine follow-up and usually require androgen replacement therapy.	A
Testing for microdeletions is not necessary in men with OA (with normal FSH) when ICSI is used because spermatogenesis should be normal.	A
Men with severely damaged spermatogenesis (spermatozoa < 5 million/mL) should be advised to undergo Yq microdeletion testing for both diagnostic and prognostic purposes. Yq microdeletion also has important implications for genetic counselling.	A
If complete AZFa or AZFb microdeletions are detected, micro-TESE should not be performed because it is extremely unlikely that any sperm will be found.	A
If a man with Yq microdeletion and his partner wish to proceed with ICSI, they should be advised that microdeletions will be passed to sons, but not to daughters.	A
When a man has structural abnormalities of the vas deferens (unilateral or bilateral absence), he and his partner should be tested for CF gene mutations.	A

IVF = in vitro fertilisation; OA = obstructive azoospermia; FSH = follicle-stimulating hormone; ICSI = intracytoplasmic

sperm injection; TESE = testicular sperm extraction; CF = cystic fibrosis.

OBSTRUCTIVE AZOOSPERMIA

Obstructive azoospermia (OA) is the absence of spermatozoa and spermatogenetic cells in semen and post-ejaculate urine due to obstruction. Sometimes, the vas deferens is absent. Obstruction in primary infertile men is often present at the epididymal level.

Diagnostic evaluation

Clinical examination should follow suggestions for the diagnostic evaluation of infertile men. The following findings indicate OA:

- At least one testis with a volume > 15 mL, although a smaller volume may be found in some patients with OA and concomitant partial testicular failure.
- Enlarged and hardened epididymis.
- Nodules in the epididymis or vas deferens.
- Absence or partial atresia of the vas.

Semen analysis

At least two examinations must be carried out at an interval of 1-2 months, according to the WHO. When semen volume is low, a search must be made for spermatozoa in urine after ejaculation. Absence of spermatozoa and immature germ cells in semen smears suggest complete seminal duct obstruction.

Hormone levels

Serum FSH levels may be normal, but do not exclude a testicular cause of azoospermia.

Ultrasonography

In addition to physical examination, a scrotal ultrasound may be helpful in finding signs of obstruction (e.g., dilatation of rete testis, enlarged epididymis with cystic lesions, or absent vas deferens) and may demonstrate signs of testicular dysgenesis (e.g., non-homogeneous testicular architecture and microcalcifications) and associated ITGCN.

Testicular biopsy

In selected cases, testicular biopsy may be indicated to exclude spermatogenic failure. Testicular biopsy should be combined with extraction of testicular spermatozoa (i.e. TESE) for cryopreservation.

Recommendation for obstructive azoospermia	GR
In azoospermia caused by epididymal obstruction, scrotal exploration with microsurgical epididymal sperm aspiration and cryopreservation of spermatozoa should be performed. Microsurgical reconstruction should be performed, if applicable. Results of reconstructive microsurgery depend on the cause and location of the obstruction, and the surgeon's expertise.	B
In azoospermia caused by epididymal obstruction, reconstructive procedures can include tubulovastomy.	B
Sperm retrieval techniques, such as MESA, TESE, and PESA, should be used additionally. These methods should be applied only, when cryostorage of the material obtained is available.	B

VARICOCELE

Varicocele is a common abnormality which may be associated with the following andrological conditions:

- Failure of ipsilateral testicular growth and development.
- Symptoms of pain and discomfort.
- Male subfertility.
- Hypogonadism.

Diagnostic evaluation

The diagnosis of varicocele is made by clinical examination and should be confirmed by colour Duplex analysis. In centres where treatment is carried out by antegrade or retrograde sclerotherapy or embolisation, diagnosis is additionally confirmed by X-ray.

Disease management

Several treatments are available for varicocele. Current evidence indicates that microsurgical varicocelectomy is the most effective and least morbid method among the varicocelectomy techniques.

Recommendations for varicocele	GR
Varicocele treatment is recommended for adolescents with progressive failure of testicular development documented by serial clinical examination.	B
No evidence indicates benefit from varicocele treatment in infertile men who have normal semen analysis or in men with subclinical varicocele. In this situation, varicocele treatment cannot be recommended.	A
Varicocele repair should be considered in case of a clinical varicocele, oligospermia, infertility duration of ≥ 2 years and otherwise unexplained infertility in the couple.	A

HYPOGONADISM

Idiopathic hypogonadotrophic hypogonadism

Idiopathic hypogonadotrophic hypogonadism is characterised by low levels of gonadotropins and sex steroid in the absence of anatomical or functional abnormalities of the hypothalamic-pituitary-gonadal axis.

Hypergonadotrophic hypogonadism

Many conditions in men are associated with hypergonadotrophic hypogonadism and impaired fertility (e.g. anorchia, maldescended testes, Klinefelter's syndrome, trauma, orchitis, systemic diseases, testicular tumour, varicocele etc).

Recommendations for hypogonadism	GR
Effective drug therapy is available to achieve fertility in men with hypogonadotrophic hypogonadism.	A*
Testosterone replacement is strictly contraindicated for the treatment of male infertility (low levels of FSH and LH.	A*

**Upgraded following panel consensus.*
FSH = follicle-stimulating hormone; LH = luteinising hormone.

CRYPTORCHIDISM

The aetiology of cryptorchidism is multifactorial, involving disrupted endocrine regulation and several gene defects. It has been postulated that cryptorchidism may be a part of the so-called testicular dysgenesis syndrome (TDS), which is a developmental disorder of the gonads caused by environmental and/or genetic influences early in pregnancy. Besides cryptorchidism, TDS includes hypospadias, reduced fertility, increased risk of malignancy, and Leydig cell dysfunction.

Recommendations for cryptorchidism	GR
Hormonal treatment of cryptorchidism in adults is not recommended.	A
Early orchidopexy (6-12 months of age) might be beneficial for testicular development in adulthood.	B
If undescended testes are corrected in adulthood, testicular biopsy for detection of ITGCNU (formerly CIS) is recommended at the time of orchidopexy.	B

CIS = carcinoma in situ; ITGCNU = intratubular germ cell neoplasia of unclassified type.

IDIOPATHIC MALE INFERTILITY

Recommendation for idiopathic male infertility	GR
Medical treatment of male infertility is recommended only for cases of hypogonadotrophic hypogonadism.	A

MALE CONTRACEPTION

Recommendations for male contraception	GR
Vasectomy meets best the criteria for the male contribution to contraception, with regard to efficacy, safety and side-effects. Cauterisation and fascial interposition are the most effective techniques.	A
Patients seeking consultation about vasectomy must be informed about the surgical method, risk of failure, irreversibility, the need for post-procedure contraception until clearance, and the risk of complications.	A*
Microsurgical vasectomy reversal is a low-risk and (cost-) effective method of restoring fertility.	B
MESA/PESA/TESE and ICSI should be reserved for failed vasectomy reversal surgery.	A

For couples wanting to achieve pregnancy, sperm aspiration together with ICSI is a second-line option for selected cases and those with failed vasovasostomy.	B

**Upgraded following panel consensus*
MESA = microsurgical epididymal sperm aspiration;
PESA = percutaneous epididymal sperm aspiration;
TESE = testicular sperm extraction; ICSI = intracytoplasmic sperm injection.

MALE ACCESSORY GLAND INFECTIONS AND INFERTILITY

Diagnostic evaluation

Ejaculate analysis

Ejaculate analysis clarifies whether the prostate is involved as part of a generalised MAGI and provides information about sperm quality.

Microbiological findings

After exclusion of urethritis and bladder infection, $>10^6$ peroxidase-positive white blood cells (WBCs) per millilitre of ejaculate indicate an inflammatory process. In this case, a culture should be performed for common urinary tract pathogens.

Disease management

Treatment of chronic prostatitis is usually targeted at relieving symptoms. The aims of therapy for altered semen composition in male adnexitis are:

- reduction or eradication of microorganisms in prostatic secretions and semen;
- normalisation of inflammatory (e.g., leukocytes) and secretory parameters;
- improvement of sperm parameters to counteract fertility impairment.

EPIDIDYMITIS

Inflammation of the epididymis causes unilateral pain and swelling, usually with acute onset.

Diagnostic evaluation

Ejaculate analysis

Ejaculate analysis according to WHO criteria, might indicate persistent inflammatory activity.

Disease management

Antibiotic therapy is indicated before culture results are available.

Recommendation for male accessory gland infections	GR
Patients with epididymitis that is known or suspected to be caused by N. gonorrhoeae or C. trachomatis must be instructed to refer their sexual partners for evaluation and treatment.	B

GERM CELL MALIGNANCY AND TESTICULAR MICROCALCIFICATION

Recommendations for germ cell malignancy and testicular microcalcification	GR
As for all men, patients with TM and without special risk factors (see below) should be encouraged to perform self-examination because this might result in early detection of TGCT.	B
Testicular biopsy should be offered to men with TM, who belong to one of the following high-risk groups: infertility and bilateral TM, atrophic testes, undescended testes, a history of TGCT, or contralateral TM.	B

If there are suspicious findings on physical examination or ultrasound in patients with TM and associated lesions, surgical exploration with testicular biopsy or orchidectomy should be considered.	B
Testicular biopsy, follow-up scrotal ultrasound, routine use of biochemical tumour markers, or abdominal or pelvic CT, are not justified in men with isolated TM without associated risk factors (e.g., infertility, cryptorchidism, testicular cancer, and atrophic testis).	B
Men with TGCT are at increased risk of developing hypogonadism and sexual dysfunction and should therefore be followed up.	B

TM = testicular microlithiasis; TGCT = testicular germ cell tumour; CT = computed tomography.

DISORDERS OF EJACULATION

Disorders of ejaculation are uncommon, but important causes of male infertility.

Diagnostic evaluation

Diagnostic management includes the following recommended procedures.

1. Clinical history
2. Physical examination
3. Post-ejaculatory urinalysis
4. Microbiological examination
5. Optional diagnostic work-up

This diagnostic work-up can include:

- neurophysiological tests (bulbocavernosus evoked response and dorsal nerve somatosensory evoked potentials);
- tests for autonomic neuropathy;
- psychosexual evaluation;

- videocystometry;
- cystoscopy;
- transrectal ultrasonography;
- uroflowmetry;
- vibratory stimulation of the penis.

Disease management

The following aspects must be considered when selecting treatment:

- Age of patient and his partner.
- Psychological problems of the patient and his partner.
- Couple's willingness and acceptance of different fertility procedures.
- Associated pathology.
- Psychosexual counselling.

Recommendations for disorders of ejaculation	GR
Aetiological treatments for ejaculatory disorders should be offered before sperm collection and ART is performed.	B
Premature ejaculation can be treated successfully with either topical anaesthetic creams or a short acting SSRI.	A
In men with spinal cord injury, vibrostimulation and electro-ejaculation are effective methods of sperm retrieval.	B

ART = assisted reproduction technique; SSRIs = selective serotonin reuptake inhibitors.

Semen cryopreservation

Recommendations for semen cryopreservation	GR
Cryopreservation of semen should be offered to all men who are candidates for chemotherapy, radiation or surgical interventions that might interfere with spermatogenesis or cause ejaculatory disorders.	A
If testicular biopsies are indicated, sperm cryopreservation is strongly advised.	A
If cryopreservation is not available locally, patients should be advised about the possibility of visiting, or transferring to the nearest cryopreservation unit before therapy starts.	C
Consent for cryopreservation should include a record of the man's wishes for his samples if he dies or is otherwise untraceable.	C
Precautions should be taken to prevent transmission of viral, sexually transmitted or any other infection by cryostored materials from donor to recipient, and to prevent contamination of stored samples. These precautions include testing of the patient and the use of rapid testing and quarantine of samples until test results are known. Samples from men who are positive for hepatitis virus or HIV must not be stored in the same container as samples from men who are free from infection.	C

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-90-79754-80-9), available to all members of the European Association of Urology at their website, http://www.uroweb.org.