EAU 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	GR
Perform semen analyses according to the guidelines of the WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn).	A*
Perform further andrological assessment when semen analysis is abnormal in at least two tests.	A*
Adhere to the 2010 WHO Manual for the standardised investigation, diagnosis and management of the infertile male for diagnosis and evaluation of male subfertility.	C

**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, hypergonadotropic hypogonadism is usually present, with elevated 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 and are elevated when spermatogonia are absent or markedly dimin-

ished. Spermatocytic arrest is typically associated with normal FSH.

Testicular biopsy

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

Recommendations	GR
For men who are candidates for sperm retrieval, give appropriate genetic counselling - also when testing for genetic abnormalities was negative.	A
In men with NOA, perform simultaneous testicular biopsy with multiple TESE (or micro TESE) to define spermatogenesis and diagnose ITGCNU.	A

ICSI = intracytoplasmic sperm injection; ITGCNU = intratubular germ cell neoplasma of unclassified type; 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	GR
Obtain standard karyotype analysis in all men with damaged spermatogenesis (spermatozoa < 10 million/mL) who are seeking fertility treatment by IVF.	B
Provide genetic counselling in all couples with a genetic abnormality found in clinical or genetic investigation and in patients who carry a (potential) inheritable disease.	A

For all men with Klinefelter's syndrome, provide long-term endocrine follow-up and androgen replacement therapy, if necessary.	A
Do not test for microdeletions in men with obstructive azoospermia (OA) when ICSI is used because spermatogenesis should be normal.	A
Inform men with Yq microdeletion and their partners who wish to proceed with ICSI that microdeletions will be passed to sons, but not to daughters.	A
In men with structural abnormalities of the vas deferens (unilateral or bilateral absence), test the man and his partner for CFTR gene mutations.	A

IVF = in vitro fertilisation; OA = obstructive azoospermia; FSH = follicle-stimulating hormone; ICSI = intracytoplasmic sperm injection; TESE = testicular sperm extraction; CFTR = transmembrane conductance regulator; 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 (CBAVD or CUAVD). Obstruction in primary infertile men is frequently 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 one to two 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 testis tumours.

Testicular biopsy

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

Recommendations	GR
For azoospermia caused by vasal or epididymal obstruction, perform microsurgical vasovasostomy or tubulovasostomy.	B

Use sperm retrieval techniques, such as MESA, TESE, and PESA only when cryostorage of the material obtained is available.	B

CBAVD = Congenital Bilateral Absence of the Vas Deferens; CUAVD = Congenital Unilateral Absence of the Vas Deferens

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 with the lowest complication rate among the varicocelectomy techniques.

Recommendations	GR
Treat varicoceles in adolescents with progressive failure of testicular development documented by serial clinical examination.	B
Do not treat varicoceles in infertile men who have normal semen analysis and in men with a subclinical varicocele.	A

Treat varicoceles in men with a clinical varicocele, oligospermia and otherwise unexplained infertility in the couple.	A

Hypogonadism

Idiopathic hypogonadotropic hypogonadism

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

Hypergonadotropic hypogonadism

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

Recommendations	GR
Provide testosterone replacement therapy for symptomatic patients with primary and secondary hypogonadism who are not considering parenthood.	A
In men with hypogonadotropic hypogonadism, induce spermatogenesis by an effective drug therapy (hCG/hMG/rFSH).	A*
Do not use testosterone replacement for the treatment of male infertility.	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 may include hypospadias, reduced fertility, increased risk of malignancy, and Leydig cell dysfunction.

Recommendations	GR
Do not use hormonal treatment of cryptorchidism in adults.	A
If undescended testes are corrected in adulthood, perform simultaneous testicular biopsy for detection of ITGCNU (formerly CIS).	B

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

Idiopathic Male Infertility

Recommendation	GR
Use medical treatment of male infertility only for cases of hypogonadotropic hypogonadism.	A
No recommendation can be made for treatment with gonadotropins, anti-oestrogens and antioxidants even for a subset of patients.	B

Male Contraception

Recommendations	GR
Vasectomy is the gold standard for the male contribution to permanent contraception.	A
Cauterisation and fascial interposition are the most effective techniques for the prevention of early recanalisation.	A
Inform patients seeking vasectomy about the surgical method, risk of failure, potential irreversibility, the need for post-procedure contraception until clearance, and the risk of complications.	A*
To achieve pregnancy, MESA/PESA/TESE - together with ICSI is a second-line option for men who decline a vasectomy reversal and those with failed vasectomy reversal surgery.	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 male accessory gland infection 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.

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	GR
Instruct patients with epididymitis that is known or suspected to be caused by *N. gonorrhoeae* or *C. trachomatis* to refer their sexual partners for evaluation and treatment.	B

Germ Cell Malignancy and Testicular Microcalcification (TM)

Recommendations	GR
As for all men, encourage patients with TM and without special risk factors (see below) to perform self-examination because this might result in early detection of TGCT.	B
Do not perform testicular biopsy, follow-up scrotal ultrasound, routine use of biochemical tumour markers, or abdominal or pelvic CT, in men with isolated TM without associated risk factors (e.g. infertility, cryptorchidism, testicular cancer, and atrophic testis).	B
Perform testicular biopsy for 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.	B
If there are suspicious findings on physical examination or ultrasound in patients with TM and associated lesions, perform surgical exploration with testicular biopsy or orchidectomy.	B
Follow men with TGCT because they are at increased risk of developing hypogonadism and sexual dysfunction.	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	GR
Offer aetiological treatments for ejaculatory disorders before performing sperm collection and ART.	B
To treat disorders of ejaculation, offer pharmacological treatment of either dapoxetine on demand (a short-acting SSRI that is the only approved pharmacological treatment for premature ejaculation) or other off-label antidepressants, i.e. daily SSRIs and clomipramine, that are not amenable to on-demand dosing.	A
Alternatively offer topical anaesthetics or tramadol.	A

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

Semen cryopreservation

Recommendations	GR
Offer cryopreservation of semen to all men who are candidates for chemotherapy, radiation or surgical interventions that might interfere with spermatogenesis or cause ejaculatory disorders.	A
Offer simultaneous sperm cryopreservation if testicular biopsies will be performed for fertility diagnosis.	A
If cryopreservation is not available locally, inform patients about the possibility of visiting, or transferring to a cryopreservation unit before therapy starts.	C

Take precautions 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. Do not store samples from men who are positive for hepatitis virus or HIV. It must not be stored in the same container as samples from men who have been tested and are free from infection.	C

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-90-79754-98-4), available to all members of the European Association of Urology at their website, http://www.uroweb.org.