EAU GUIDELINES ON MALE INFERTILITY

(Limited text update March 2018)

A. Jungwirth (Chair), T. Diemer (Vice-Chair), Z. Kopa, C. Krausz, S. Minhas, H. Tournaye

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 impaired 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 one out of four 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

Recommendations	Strength rating
Include the fertility status of the female partner in the diagnosis and management of male sub-fertility because this might determine the final outcome.	Strong
Perform semen analyses according to the guidelines of the WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn).	Strong
Perform further andrological assessment when semen analysis is abnormal in at least two tests.	Strong
Adhere to the 2000 WHO Manual for the standardised investigation, diagnosis and management of the infertile male for diagnosis and evaluation of male sub-fertility.	Weak

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 minutes and a thorough microscopic examination by phase contrast optics at x 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 with or without low levels of testosterone. Generally, the levels of FSH correlate with the number of spermatogonia and are elevated when spermatogonia are absent or markedly diminished. Spermatogenic arrest is typically associated with normal FSH.

Testicular biopsy

Testicular biopsy and simultaneous testicular sperm extraction (TESE) is a therapeutic option in couples considering assisted reproductive techniques (ART) in men with NOA.

Recommendations	Strength rating
For men who are candidates for sperm retrieval, give appropriate genetic counselling even when testing for genetic abnormalities was negative.	Strong
Perform multiple testicular biopsies (TESE or micro-TESE) in men with non-obstructive azoospermia, to define spermatogenesis, cryopreserve sperm and diagnose germ cell neoplasia *in situ*.	Strong

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	Strength rating
Obtain standard karyotype analysis in all men with damaged spermatogenesis (spermatozoa < 10 million/mL) for diagnostic purposes.	Strong
Provide genetic counselling in all couples with a genetic abnormality found on clinical or genetic investigation and in patients who carry a (potential) inheritable disease.	Strong
For all men with Klinefelter's syndrome, provide long-term endocrine follow-up and appropriate medical treatment, if necessary.	Strong
Do not test for microdeletions in men with obstructive azoospermia (OA) since spermatogenesis should be normal.	Strong
Inform men with Yq microdeletion and their partners who wish to proceed with intracytoplasmic sperm injection that microdeletions will be passed to sons, but not to daughters.	Strong
In men with structural abnormalities of the vas deferens (unilateral or bilateral absence with no renal agenesis), test the man and his partner for cystic fibrosis transmembrane conductance regulator gene mutations.	Strong

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 as in Congenital Bilateral Absence of the Vas Deferens (CBAVD) or Congenital Unilateral Absence of the Vas Deferens (CUAVD).

Obstruction in primary infertile men is frequently present at the epididymal level.

Diagnostic evaluation

Clinical examination should follow the investigation and 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 dilated 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 and Inhibin B levels may be normal, but do not exclude a testicular cause of azoospermia (e.g. spermatogenic arrest).

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) or 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	Strength rating
Perform microsurgical vasovasostomy or tubulovasostomy for azoospermia caused by vasal or epididymal obstruction.	Strong
Use sperm retrieval techniques, such as microsurgical epididymal sperm aspiration, testicular sperm extraction and percutaneous epididymal sperm aspiration only when facilities for cryostorage are available.	Strong

Varicocele

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

- failure of ipsilateral testicular growth and development;
- symptoms of pain and discomfort;
- male sub-fertility;
- 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 varicoceles. Current evidence indicates that microsurgical varicocelectomy is the

most effective with the lowest complication rate among the varicocelectomy techniques.

Recommendations	Strength rating
Treat varicoceles in adolescents with ipsilateral reduction in testicular volume and evidence of progressive testicular dysfunction.	Weak
Do not treat varicoceles in infertile men who have normal semen analysis and in men with a subclinical varicocele.	Strong
Treat men with a clinical varicocele, oligo-zoospermia and otherwise unexplained infertility in the couple.	Weak

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 hypothalamic-pituitary-gonadal axis. Stimulation of sperm production requires treatment with human chorionic gonadotropin (hCG) combined with recombinant FSH or urinary FSH or human menopausal gonadotropins (hMGs).

Hypergonadotropic hypogonadism

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

Recommendations	Strength rating
Provide testosterone replacement therapy for symptomatic patients with primary and secondary hypogonadism who are not considering parenthood.	Strong
In men with hypogonadotropic hypogonadism, induce spermatogenesis by an effective drug therapy (human chorionic gonadotropin, human menopausal gonadotropins, recombinant follicle-stimulating hormone (rFSH), highly purified FSH (hpFSH)).	Strong
Do not use testosterone replacement for the treatment of male infertility.	Strong

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	Strength rating
Do not use hormonal treatment of cryptorchidism in adults.	Strong
If undescended testes are corrected in adulthood, perform simultaneous testicular biopsy for detection of intratubular germ cell neoplasia *in situ* (formerly carcinoma *in situ*).	Weak
Provide medical treatment for male infertility in patients with of hypogonadotropic hypogonadism.	Strong
No clear recommendation can be made for treatment of patients with idiopathic infertility using gonadotropins, anti-oestrogens, and antioxidants.	Strong

Male Contraception

Recommendations	Strength rating
Use cauterisation and fascial interposition as they are the most effective techniques for the prevention of early recanalisation.	Strong
Inform patients seeking vasectomy about the surgical technique, risk of failure, potential irreversibility, the need for post-procedure contraception until clearance, and the risk of complications.	Strong
In order to achieve pregnancy, microsurgical epididymal sperm aspiration/ percutaneous epididymal sperm aspiration/ testicular sperm extraction - together with intracytoplasmic sperm injection is a second-line option for men who decline a vasectomy reversal and those with failed vasectomy reversal surgery.	Weak

Male Accessory Gland Infections and Infertility

Diagnostic evaluation

Ejaculate analysis

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

Disease management

Antibiotic therapy is not indicated before culture results are available.

Recommendation	Strength rating
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.	Strong

Germ Cell Malignancy and Testicular Microcalcification (TM)

Recommendations	Strength rating
Encourage men with testicular microcalcification (TM) to perform self-examination even without additional risk factors as this may result in early detection of testicular germ cell tumour (TGCT).	Weak
Do not perform testicular biopsy, follow-up scrotal ultrasound, routine use of biochemical tumour markers, or abdominal or pelvic computed tomography, in men with isolated TM without associated risk factors (e.g. infertility, cryptorchidism, testicular cancer, and atrophic testis).	Strong
Perform testicular biopsy for men with TM, who belong to one of the following high-risk groups: spermatogenic failure, bilateral TM, atrophic testes (less than 12cc), history of undescended testes and TGCT.	Strong
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.	Strong
Follow men with TGCT because they are at increased risk of developing hypogonadism and sexual dysfunction.	Strong

Disorders of Ejaculation

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

Diagnostic evaluation

Diagnostic management includes the following recommended procedures:

- clinical history;
- physical examination;
- post-ejaculatory urinalysis;
- microbiological examination;
- 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	Strength rating
Offer specific treatments for ejaculatory disorders before performing sperm collection and assisted reproduction technique. Premature ejaculation can be treated using dapoxetine (short acting selective serotonin reuptake inhibitor) and/or topical anaesthetics.	Strong

Semen cryopreservation

Recommendations	Strength rating
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.	Strong
Offer simultaneous sperm cryopreservation if testicular biopsies will be performed for fertility diagnosis.	Strong
If cryopreservation is not available locally, inform patients about the possibility of visiting, or transferring to a cryopreservation unit before therapy starts.	Strong
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 in the same container as samples from men who have been tested and are free from infection.	Strong

This short booklet text is based on the more comprehensive EAU Guidelines ISBN 978-94-92671-01-1), available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines.