EAU GUIDELINES ON SEXUAL AND REPRODUCTIVE HEALTH

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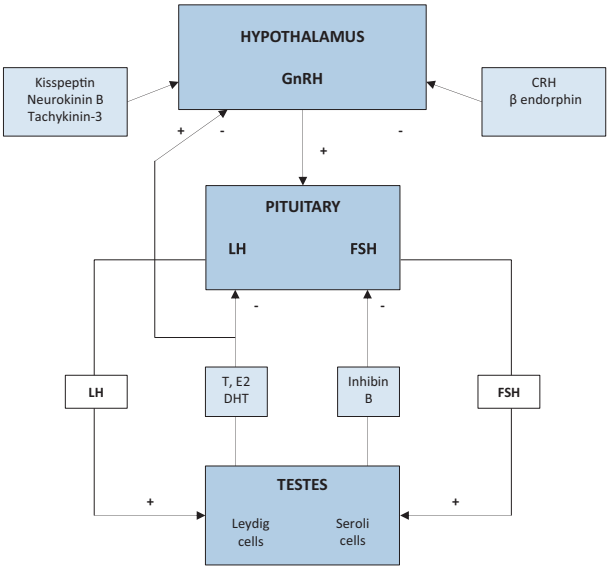
Introduction

The EAU Working Group has published guidelines on Male Sexual and Reproductive Health, combining the former guideline on Male Sexual Dysfunction, Male Infertility and Male Hypogonadism. For priapism refer to the 2018 Male Sexual Dysfunction Guidelines and the 2018 version of the pocket guideline.

Male Hypogonadism

Male Hypogonadism, also known as Testosterone Deficiency, is a disorder associated with decreased functional activity of the testes, with decreased production of androgens and/or impaired sperm production. It may adversely affect multiple organ functions and quality of life (QoL). The prevalence increases with age.

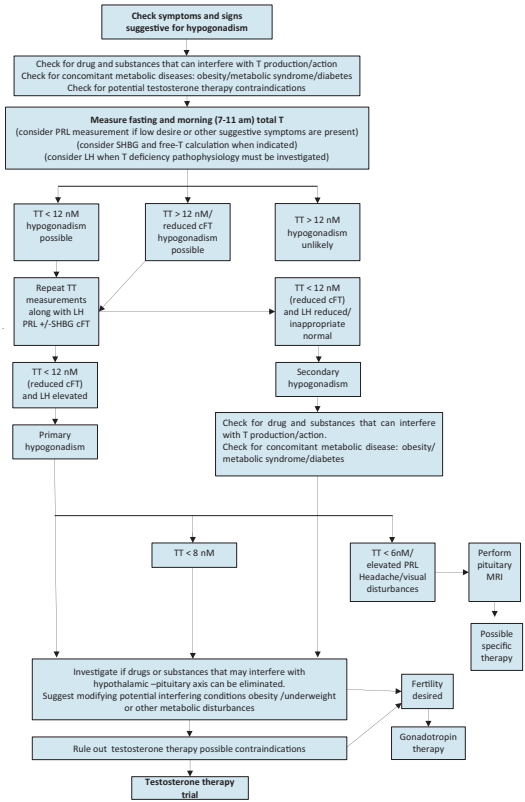
Figure 1: Physiology of testosterone production



GnRH = gonadotropin releasing hormone; LH = luteinising hormone; FSH = follicular stimulating hormone; T = testosterone; E2 = 7-β-estradiol; DHT = dehydroepiandrosterone; CRH = corticotrophin releasing hormone.

Diagnostic evaluation of Late-Onset Hypogonadism

Figure 2: Diagnostic evaluation of Late-Onset Hypogonadism



TT = total testosterone; cFT = calculated free testosterone; PRL = prolactin; SHBG = sex hormone-binding globulin; LH = luteinising hormone; MRI = magnetic resonance imaging.

Recommendations for the diagnostic evaluation of Late-onset Hypogonadism

Recommendations	Strength rating
Check for concomitant diseases, drugs and substances that can interfere with testosterone production/action.	Strong
Total testosterone must be measured in the morning (7.00 and 11.00 hours) and in the fasting state, with a reliable method.	Strong
Repeat total testosterone on at least two separate occasions when below 12 nmol/L and before starting testosterone therapy.	Strong
12 nmol/L total testosterone (3.5 ng/mL) represents a reliable threshold to diagnose late-onset hypogonadism (LOH).	Strong
Consider sex hormone-binding globulin and free-testosterone calculation when indicated.	Strong
Calculated free-testosterone < 225 pmol/L has been suggested as a possible cut off for diagnosis of LOH.	Weak
Analyse luteinising hormone and follicle-stimulating hormone serum levels to differentiate between primary hypogonadism and secondary hypogonadism.	Strong
Consider prolactin (PRL) measurement if low desire (or other suggestive signs/ symptoms) and low or low-normal testosterone is present.	Strong

Perform pituitary magnetic resonance imaging (MRI) in secondary hypogonadism, with elevated PRL or specific symptoms of a pituitary mass and/or presence of other anterior pituitary hormone deficiencies.	Strong
Perform pituitary MRI in secondary severe hypogonadism (total testosterone < 6 nmol/L).	Weak

Recommendations for screening men for Late-onset Hypogonadism

Recommendations	Strength rating
Screen for late-onset hypogonadism (LOH) (including in type 2 diabetes) only in symptomatic men.	Strong
Do not use structured interviews and self-reported questionnaires for systematic screening for LOH as they have low specificity.	Strong

Recommendations for disease management

Recommendations	Strength rating
The use of testosterone therapy in eugonadal men is not indicated.	Strong
Use testosterone therapy as first-line treatment in symptomatic hypogonadal patients with milder erectile dysfuntion (ED).	Strong
Use the combination of phosphodiesterase type 5 inhibitors and testosterone therapy in more severe forms of ED as it may result in better outcomes.	Weak

Use conventional medical therapies for treating severe depressive symptoms and osteoporosis.	Strong
Do not use testosterone therapy to improve body composition, reduce weight and benefit cardio-metabolic profile.	Weak
Do not use testosterone therapy for improving cognition vitality and physical strength in aging men.	Strong

Recommendations for LOH choice of treatment	**Strength rating**
Treat, when indicated, organic causes of hypogonadism (e.g., pituitary masses, hyperprolactinemia, etc.).	Strong
Improve lifestyle and reduce weight (e.g., obesity); withdraw, when possible, concomitant drugs which can impair testosterone production; treat comorbidities before starting testosterone therapy.	Weak
Fully inform the patient about expected benefits and side-effects of any treatment option. Select the testosterone preparation in a joint decision process, only with a fully informed patient.	Strong
The aim of testosterone therapy is to restore serum testosterone concentration to the average normal range for young men.	Weak
Use testosterone gels rather than long-acting depot administration when starting initial treatment, so that therapy can be adjusted or stopped in the case of treatment-related adverse side effects.	Weak

Recommendations on risk factors in testosterone treatment	Strength rating
Fully counsel symptomatic hypogonadal men who have been surgically treated for localised prostate cancer (PCa) and who are currently without evidence of active disease considering testosterone therapy, emphasising the benefits and lack of sufficient safety data on long-term follow up.	Weak
Restrict treatment to patients with a low risk for recurrent PCa (i.e., Gleason score < 8; pathological stage T1-2; pre-operative PSA < 10 ng/mL) and should start after at least one year follow-up with a PSA level < 0.01 ng/mL.	Weak
Safety data on the use of testosterone therapy in men treated for breast cancer are unknown.	Strong
Assess for cardiovascular risk factors before commencing testosterone therapy.	Strong
Assess men with known cardiovascular disease (CVD) for cardiovascular symptoms before testosterone therapy and with close clinical assessment and evaluation during treatment.	Strong
Treat men with hypogonadism and pre-existing CVD, venous-thromboembolism or chronic cardiac failure, who require testosterone therapy with caution, by careful clinical monitoring and regular measurement of haematocrit (not exceeding 54%) and testosterone levels.	Weak

Exclude a family history of venous-thromboembolism before commencing testosterone therapy.	Strong
Monitor testosterone, haematocrit at three, six and twelve months after testosterone therapy initiation, and thereafter annually. A haematocrit more than 54% should require testosterone therapy withdrawal and phlebotomy. Re-introduce testosterone therapy at a lower dose once the haematocrit has normalised and consider switching to topical testosterone preparations.	Strong

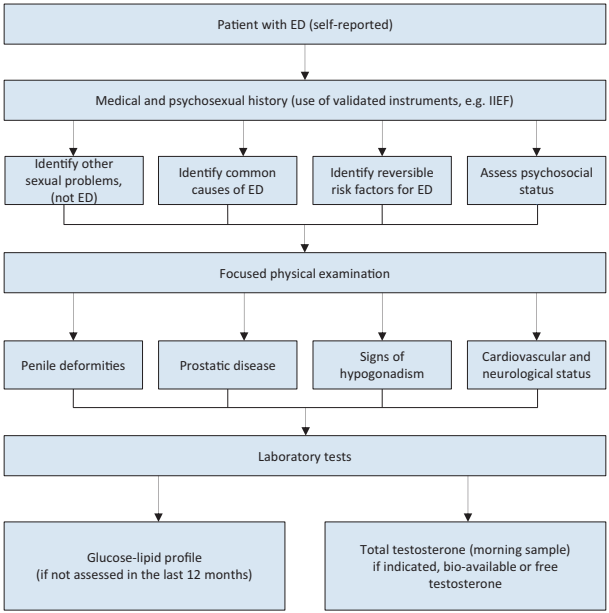
Erectile dysfunction

Introduction

Erectile dysfunction is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance. Erectile dysfunction may affect physical and psychosocial health and may have a significant impact on the QoL of sufferers and their partners. There is increasing evidence that ED can also be an early manifestation of coronary artery and peripheral vascular disease; therefore, ED should not be regarded only as a QoL issue, but also as a potential warning sign of CVD.

Diagnostic evaluation

Figure 3: Minimal diagnostic evaluation (basic work-up) in patients with erectile dysfunction



ED = erectile dysfunction; IIEF = International Index of Erectile Function.

Table 1: Cardiac risk stratification (based on 2nd Princeton Consensus)

Low-risk category	Intermediate-risk category	High-risk category
Asymptomatic, < 3 risk factors for CAD (excluding sex)	≥ 3 risk factors for CAD (excluding sex)	High-risk arrhythmias
Mild, stable angina (evaluated and/or being treated)	Moderate, stable angina	Unstable or refractory angina
Uncomplicated previous MI	Recent MI (> 2, < 6 weeks)	Recent MI (< 2 weeks)
LVD/CHF (NYHA class I or II)	LVD/CHF (NYHA class III)	LVD/CHF (NYHA class IV)
Post-successful coronary revascularisation	Non-cardiac sequelae of atherosclerotic disease (e.g., stroke, peripheral vascular disease)	Hypertrophic obstructive and other cardio-myopathies
Controlled hypertension		Uncontrolled hypertension
Mild valvular disease		Moderate-to-severe valvular disease

CAD = coronary artery disease; CHF = congestive heart failure; LVD = left ventricular dysfunction; MI = myocardial infarction; NYHA = New York Heart Association.

Table 2: Indications for specific diagnostic tests

Primary ED (not caused by acquired organic disease or psychogenic disorder).
Young patients with a history of pelvic or perineal trauma, who could benefit from potentially curative revascularisation surgery or angioplasty.
Patients with penile deformities which might require surgical correction (e.g., Peyronie's disease, congenital penile curvature).
Patients with complex psychiatric or psychosexual disorders.
Patients with complex endocrine disorders.
Specific tests may be indicated at the request of the patient or their partner.
Medico-legal reasons (e.g., implantation of penile prosthesis to document end stage ED, sexual abuse).

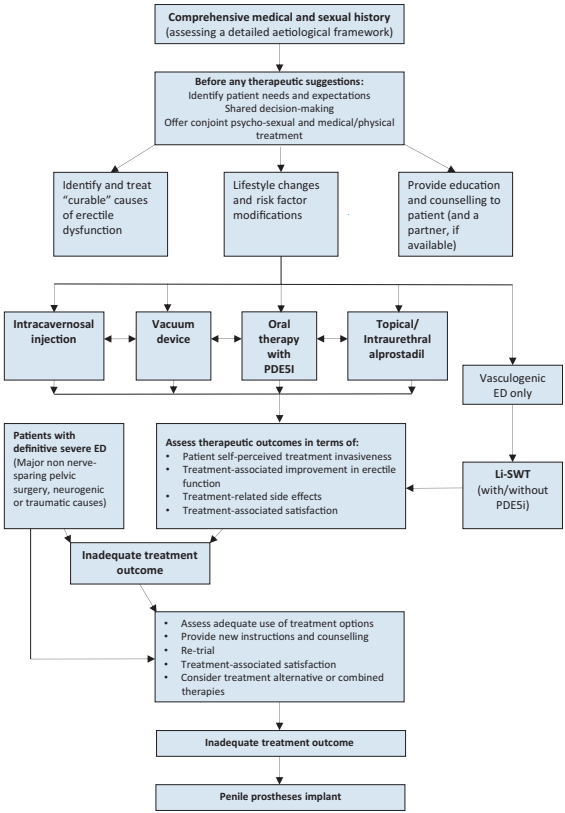
Table 3: Specific diagnostic tests

Nocturnal Penile Tumescence and Rigidity (NTPR) using Rigiscan®
Vascular studies: - Intracavernous vasoactive drug injection - Penile dynamic duplex ultrasonography - Penile dynamic infusion cavernosometry and cavernosography - Internal pudendal arteriography
Specialised endocrinological studies
Specialised psycho-diagnostic evaluation

Recommendations for the diagnosis of erectile dysfunction

Recommendations	Strength rating
Take a comprehensive medical and sexual history in every patient presenting for erectile dysfunction (ED). Consider psychosexual development, including life stressors, cultural aspects, and cognitive/thinking style of the patient regarding their sexual performance.	Strong
Use a validated questionnaire related to ED to assess all sexual function domains (e.g., International Index of Erectile Function [IIEF]) and the effect of a specific treatment modality.	Strong
Include a focused physical examination in the initial assessment of men with ED to identify underlying medical conditions and comorbid genital disorders that may be associated with ED.	Strong
Assess routine laboratory tests, including glucose and lipid profile and total testosterone, to identify and treat any reversible risk factors and lifestyle factors that can be modified.	Strong
Include specific diagnostic tests in the initial evaluation of ED in the presence of the conditions presented in Table 1.	Strong

Figure 4: Management algorithm for erectile dysfunction



ED = erectile dysfunction; PDE5Is = phosphodiesterase type 5 inhibitors ; Li-SWT = low-intensity shockwave treatment.

Table 4: Summary of the key pharmacokinetic data for the four PDE5 inhibitors currently EMA-approved to treat erectile dysfunction*

Parameter	Sildenafil, 100 mg	Tadalafil, 20 mg	Vardenafil, 20 mg	Avanafil, 200mg
C_{max}	560 µg/L	378 µg/L	18.7 µg/L	5.2 µg/L
T_{max} (median)	0.8-1 hours	2 hours	0.9 hours	0.5-0.75 hours
T1/2	2.6-3.7 hours	17.5 hours	3.9 hours	6-17 hours
AUC	1,685 µg.h/L	8,066 µg.h/L	56.8 µg.h/L	11.6 µg.h/L
Protein binding	96%	94%	94%	99%
Bio-availability	41%	NA	15%	8-10%

** Fasted state, higher recommended dose. Data adapted from EMA statements on product characteristics.*

C_{max} = maximal concentration; T_{max} = time-to-maximum plasma concentration; T1/2 = plasma elimination halftime; AUC = area under curve or serum concentration time curve.

Table 5: Common adverse events of the four PDE5 inhibitors currently EMA-approved to treat erectile dysfunction*

Adverse event	Sildenafil	Tadalafil	Vardenafil	Avanafil, 200mg
Headache	12.8%	14.5%	16%	9.3%
Flushing	10.4%	4.1%	12%	3.7%
Dyspepsia	4.6%	12.3%	4%	uncommon

Nasal congestion	1.1%	4.3%	10%	1.9%
Dizziness	1.2%	2.3%	2%	0.6%
Abnormal vision	1.9%		< 2%	None
Back pain		6.5%		< 2%
Myalgia		5.7%		< 2%

** Adapted from EMA statements on product characteristics.*

Table 6: Penile prostheses models available on the market

Semi-rigid prostheses	**Inflatable prostheses**	
	Two-piece	**Three-piece**
AMS Tactra™ [Boston Scientific]	AMS Ambicor™ [Boston Scientific]	Titan™ [Coloplast]
Genesis™ [Coloplast]		Titan OTR NB™ (Narrow base) [Coloplast]
		Titan Zero Degree™
Tube™ [Promedon]		AMS 700 CX™ [Boston Scientific]
ZSI 100™ [Zephyr]		AMS 700 LGX™ [Boston Scientific]
Virilis II™ [Subrini]		AMS 700 CXR™ [Boston Scientific]
		ZSI 475™ [Zephyr]

Recommendations for the treatment of erectile dysfunction

Recommendations	Strength rating
Assess all patients for inadequate/incorrect information about the mechanism of action and the ways in which drugs should be taken, as they are the main causes of a lack of response to phosphodiesterase type 5 inhibitors (PDE5Is).	Weak
Use Cognitive Behaviour Therapy as psychological approach (include the partner) combined with medical treatment to maximise treatment outcomes.	Strong
Discuss with patients undergoing radical prostatectomy (any technique) about the risk of sexual changes other than erectile dysfunction (ED), including libido reduction, changes in orgasm, anejaculation, Peyronie's like disease and penile size changes.	Strong
Initiate lifestyle changes and risk factor modification prior to or at the same time as initiating erectile dysfunction (ED) treatments.	Strong
Treat a curable cause of ED first, when found.	Weak
Use PDE5Is as first-line therapeutic option.	Strong
Use topical/intraurethral alprostadil as an alternative first-line therapy in well-informed patients who do not wish or are not suitable for oral vasoactive therapy. Use topical/ intraurethral alprostadil as an alternative therapy to intracavernous injections in patients who prefer a less-invasive therapy.	Weak

Use low intensity shockwave treatment (LI-SWT) in patients with mild vasculogenic ED or as an alternative first-line therapy in well-informed patients who do not wish or are not suitable for oral vasoactive therapy or desire a curable option.	Weak
Use LI-SWT in vasculogenic ED patients who are poor responders to PDE5Is.	Weak
Use vacuum erection devices as a first-line therapy in well-informed patients with infrequent sexual intercourse and comorbidities requiring non-invasive, drug-free management of ED.	Weak
Use intracavernous injections as an alternative first-line therapy in well-informed patients or as second-line therapy.	Strong
Use implantation of a penile prosthesis if other treatments fail or based upon patient preference.	Strong
Data is inadequate to support the use of any specific regimen for penile rehabilitation after radical prostatectomy.	Strong
Pro-erectile treatments should start at the earliest opportunity after radical prostatectomy/pelvic surgery and other curative treatments for prostate cancer.	Weak

Disorders of ejaculation

Introduction

Ejaculation is a complex physiological process, which is composed of emission and expulsion and is mediated by interwoven neurological and hormonal pathways. Any condition that interferes with these pathways may cause a wide range of ejaculatory disorders.

Table 7: Spectrum of ejaculatory disorders

Premature ejaculation
Retarded or delayed ejaculation
Anejaculation
Painful ejaculation
Retrograde ejaculation
Anorgasmia
Haemospermia

Diagnostic evaluation

Recommendations for the diagnostic evaluation of premature ejaculation

Recommendations	Strength rating
Perform the diagnosis and classification of premature ejaculation (PE) based on medical and sexual history, which should include assessment of intravaginal ejaculatory latency time (IELT) (self-estimated), perceived control, distress and interpersonal difficulty due to the ejaculatory dysfunction.	Strong

Use of stopwatch-measured IELT is not compulsory in clinical practice.	Weak
Use patient-reported outcomes in daily clinical practice.	Weak
Include physical examination in the initial assessment of PE to identify anatomical abnormalities that may be associated with PE or other sexual dysfunctions, particularly erectile dysfunction.	Strong
Do not perform routine laboratory or neuro-physiological tests. They should only be directed by specific findings from history or physical examination.	Strong

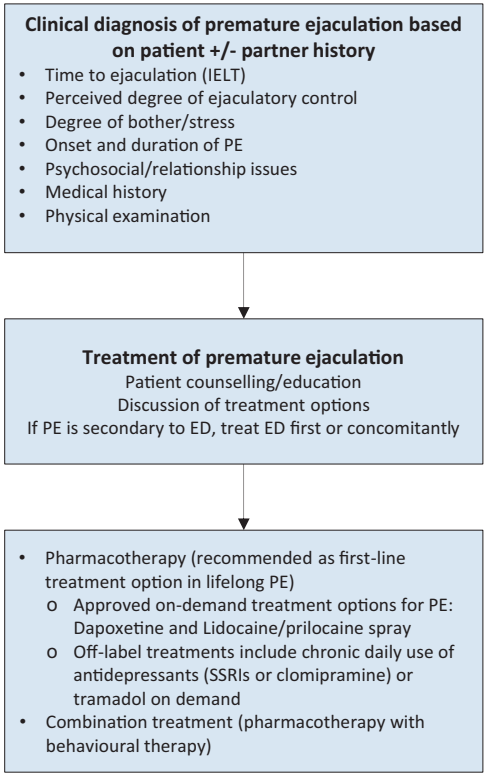
Disease management

Recommendations for the treatment of premature ejaculation

Recommendations	Strength rating
Treat erectile dysfunction (ED), other sexual dysfunction or genitourinary infection (e.g., prostatitis) first.	Strong
Use either dapoxetine or the lidocaine/prilocaine spray as first-line treatments for lifelong premature ejaculation (PE).	Strong
Use off-label topical anaesthetic agents as a viable alternative to oral treatment with selective serotonin re-uptake inhibitor (SSRIs).	Strong
Use tramadol on-demand as a weak alternative to SSRIs.	Weak

Use PDE5Is alone or in combination with other therapies in patients with PE (without ED).	Strong
Use psychological/behavioural therapies in combination with pharmacological treatment in the management of acquired PE.	Weak

Figure 5: Management of premature ejaculation*



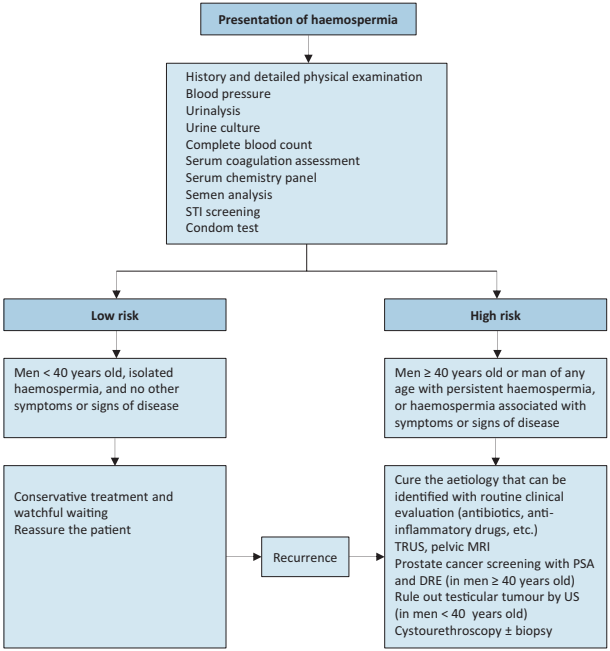
* Adapted from Lue *et al*. 2004.

ED = erectile dysfunction; PE = premature ejaculation; IELT = intravaginal ejaculatory latency time; SSRI = selective serotonin receptor inhibitor.

Recommendations for the management of recurrent haemospermia

Recommendations	Strength rating
Perform a full medical and sexual history with detailed physical examination.	Strong
Men ≥ 40 years of age with persistent haemospermia should be screened for prostate cancer.	Weak
Consider non-invasive imaging modalities (TRUS, MRI) in men ≥ 40 years of age or men of any age with persistent or refractory heamospermia.	Weak
Consider invasive methods such as cystoscopy and vesiculoscopy when the non-invasive methods are inconclusive.	Weak

Figure 6: Management algorithm for haemospermia



STI = sexually transmitted infections; PSA = prostate-specific antigen; DRE = digital rectal examination; US = ultrasonography; TRUS = transrectal ultrasonography; MRI = magnetic resonance imaging.

Low Sexual Desire

Introduction

It has been always a challenge to define sexual desire because of its complex nature and it can be conceptualised in many different ways. According to the ICD-10, lack or loss of sexual desire should be the principal problem and no other sexual problems accompanying it such as erectile dysfunction (ED). In the Diagnostic and Statistical Manual of Mental Disorders-V, male hypoactive sexual desire disorder was defined as "*the persistent or recurrent deficiency (or absence) of sexual or erotic thoughts or fantasies and desire for sexual activity*".

The judgment of deficiency is made by the clinician, taking into account other factors that may affect sexual function, such as age and socio-cultural factors in an individual's life. According to fourth International Consultation on Sexual Medicine (ICSM-IV), the definition of male hypoactive sexual desire disorder was proposed as a *"persistent or recurrent deficiency or absence of sexual or erotic thoughts or fantasies and desire for sexual activity (clinical principle)".*

Table 8: The list of common causes of low sexual desire in men

Androgen deficiency
Hyperprolactinemia
Anger and anxiety
Depression
Relationship conflict
Stroke
Antidepressant therapy
Epilepsy
Post-traumatic stress syndrome
Renal failure
Coronary disease and heart failure

Ageing
HIV
Body-building and eating disorders
Erectile dysfunction
Prostatitis/chronic pelvic pain syndrome

Psychological intervention

Findings on treatment efficacy for psychological intervention are scarce. Accordingly, recommendations must be interpreted with caution. Psychological interventions with a focus on cognitive and behavioural strategies may be beneficial for low sexual desire (LSD) in men. Since both members of a couple may experience age-related changes concurrently and nterdependently, it could be helpful to address the sexual health needs of the aging couple (thus including LSD) as a whole rather than treating the individual patient.

Disease management

Recommendations for the treatment of low sexual desire

Recommendations	Strength rating
Perform the diagnosis and classification of low sexual desire (LSD) based on medical and sexual history, which could include validated questionnaires.	Weak
Include physical examination in the initial assessment of LSD to identify anatomical abnormalities that may be associated with LSD or other sexual dysfunctions, particularly erectile dysfunction.	Weak
Perform laboratory tests to rule out endocrine disorders.	Strong

Modulate chronic therapies which can negatively impact toward sexual desire.	Weak
Replace testosterone if LSD is associated with signs and symptoms of testosterone deficiency.	Strong

Penile curvature

Introduction

Congenital penile curvature (CPC) results from disproportionate development of the tunica albuginea of the corporal bodies and is not associated with urethral malformation. In the majority of cases the curvature is ventral but, can be lateral and rarely dorsal.

Diagnostic evaluation

Taking a medical and sexual history is usually sufficient to establish the diagnosis of CPC. Patients usually present after reaching puberty as the curvature becomes more apparent with erections, and a severe curvature can make intercourse difficult or impossible. Physical examination during erection (autophotograph or after intracavernosal injection of vasoactive drugs) is useful to document curvature and exclude other pathologies.

Disease management

The treatment of this disorder is surgical correction deferred until after puberty. Surgical treatments for congenital penile curvature generally share the same principles as in Peyronie's disease (presented in detail in the next section). Nesbit's procedure with excision of an ellipse of the tunica albuginea is the optimum surgical treatment but many other techniques have been described and employed. Plication techniques are widely used including techniques producing a de-rotation of the corporal bodies. Most of the time, dissection and

mobilisation of the penile dorsal neurovascular bundle are required in order to avoid loss of sensation and ischaemia to the glans penis.

Recommendation for the treatment of congenital penile curvature	Strength rating
Use plication techniques with or without neurovascular bundle dissection (medial/lateral) for satisfactory curvature correction, although there is currently no optimum surgical technique.	Strong

Peyronie's disease

An insult (repetitive microvascular injury or trauma) to the tunica albuginea is the most widely accepted hypothesis on the aetiology of the disease. Abnormal wound healing leads to the remodelling of connective tissue into a fibrotic plaque. Penile plaque formation can result in curvature which, if severe, may impair penetrative sexual intercourse. The most commonly associated comorbidities and risk factors are diabetes, hypertension, dyslipidemias, ischaemic cardiopathy, autoimmune diseases, ED, smoking, excessive consumption of alcohol, low testosterone and pelvic surgery (e.g., radical prostatectomy).

Two phases of the disease can be distinguished. The first is the active inflammatory phase, which may be associated with painful erections and a palpable nodule or plaque in the tunica of the penis; typically, but not invariably, a penile curvature begins to develop. The second is the fibrotic phase with the formation of hard, palpable plaques that can calcify, with stabilisation of the disease and development of the penile deformity.

Diagnostic evaluation

The aim of the initial evaluation is to obtain information on the presenting symptoms and their duration (e.g., pain on erection, palpable nodules, deformity, length and girth and erectile function). It is important to obtain information on the distress caused by the symptoms and the potential risk factors for ED and PD.

Recommendations for the diagnostic evaluation of Peyronie's disease

Recommendations	Strength rating
Take a medical and sexual history of patients with Peyronie's disease (PD), include duration of the disease, pain on erection, penile deformity, difficulty in vaginal intromission due to disabling deformity and erectile dysfunction (ED).	Strong
Take a physical examination, including assessment of palpable plaques, stretched or erect penile length, degree of curvature (self-photography, vacuum-assisted erection test or pharmacological-induced erection) and any other related diseases (e.g. Dupuytren's contracture, Ledderhose disease) in patients with PD.	Strong
Use the intracavernous injection (IC) method to provide an objective assessment of penile curvature with an erection in the diagnostic work-up of PD.	Weak
Use the PD specific questionnaire especially in clinical trials, but mainstream usage in daily clinical practice is not mandatory.	Weak

Do not use ultrasound (US), computerised tomography or magnetic resonance imaging to assess plaque size and deformity in everyday clinical practice.	Weak
Use Doppler US only in the case of diagnostic evaluation of ED, to ascertain penile haemodynamic and vascular anatomy.	Weak

Disease management

Non-operative treatment

Table 9: Conservative treatments for Peyronie's disease

Oral treatments
Non-steroidal anti-inflammatory drugs (NSAIDs)
Phosphodiesterase type 5 inhibitors (PDE5Is)
Intralesional treatments
Verapamil
Nicardipine
Clostridium collagenase
Interferon α2B
Hyaluronic acid
Botulinum toxin
Topical treatments
H-100 gel
Extracorporeal shockwave treatment

Other
Traction devices
Multimodal treatment

Recommendations for the conservative treatment of Peyronie's disease

Recommendations	Strength rating
Offer conservative treatment to patients not fit for surgery or when surgery is not acceptable to the patient.	Strong
Discuss with patients all the available treatment options and expected results before starting any treatment.	Strong
Do not offer oral treatment with vitamin E, potassium para-aminobenzoate (potaba), tamoxifen, pentoxifiline, colchicine and acetyl esters of carnitine to treat Peyronie's disease (PD).	Strong
Non-steroidal anti-inflammatory drugs can be used to treat penile pain in the acute phase of PD.	Strong
Extracorporeal shockwave treatment (ESWT) can be used to treat penile pain in the acute phase of PD.	Weak
Phosphodiesterase type 5 inhibitors can be used to treat concomitant erectile dysfunction or if the deformity results in difficulty in penetrative intercourse in order to optimise penetration.	Weak
Intralesional therapy with interferon alpha-2b may be offered in patients with stable curvature dorsal or lateral > 30° seeking a minimal invasive procedure.	Strong

Intralesional therapy with collagenase of *clostridium histolyticum* may be offered in patients with stable PD and dorsal or lateral curvature > 30°, who request non-surgical treatment, although the placebo effects are high.	Strong
Do not offer intralesional treatment with steroids to reduce penile curvature, plaque size or pain.	Strong
Do not offer ESWT to improve penile curvature and reduce plaque size.	Strong
Penile traction devices and vacuum devices may be offered to reduce penile deformity or as part of a multimodal therapy approach, although outcome data is limited.	Weak

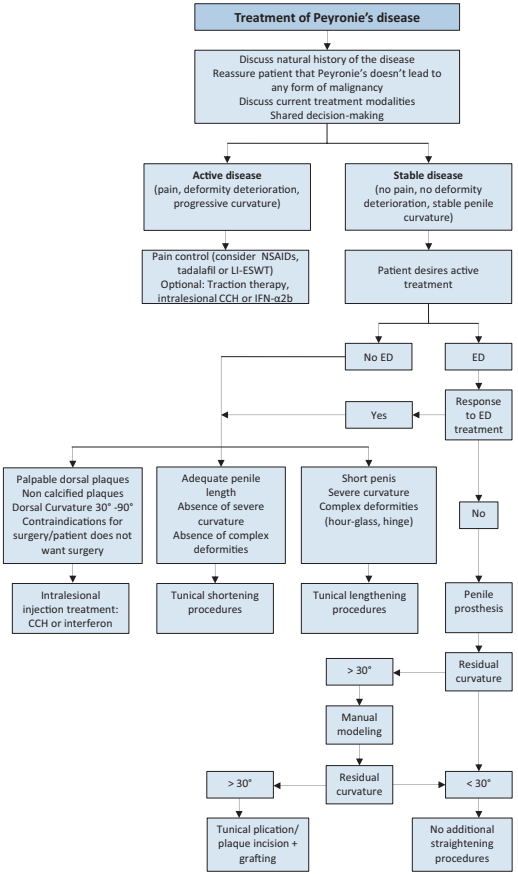
Surgical treatment

Recommendations for the surgical treatment

Recommendations	Strength rating
Perform surgery only when Peyronie's disease (PD) has been stable for at least three months (without pain or deformity deterioration), which is usually the case after twelve months from the onset of symptoms, and intercourse is compromised due to deformity.	Strong
Prior to surgery, assess penile length, curvature severity, erectile function (including response to pharmacotherapy in case of erectile dysfunction [ED]) and patient expectations.	Strong

Use tunical shortening procedures as the first treatment option for congenital penile curvature and for PD with adequate penile length and rigidity, non-severe curvature and absence of complex deformities (hour-glass, hinge). The type of procedure used is dependent on surgeon and patient preference, as no procedure has proven superior to its counterparts.	Weak
Use tunical lengthening procedures for patients with PD and normal erectile function, without adequate penile length, severe curvature or presence of complex deformities (hour-glass, hinge). The type of graft used is dependent on the surgeon and patient factors, as no graft has proven superior to its counterparts.	Weak
Use the sliding techniques with caution, as there is a significant risk of life changing complications (e.g., glans necrosis).	Strong
Do not use synthetic grafts in PD reconstructive surgery.	Strong
Use penile prosthesis implantation, with or without any additional procedure (modeling, plication, incision or excision with or without grafting), in PD patients with ED not responding to pharmacotherapy.	Strong

Figure 7 : Treatment algorithm for Peyronie's disease



ED = erectile dysfunction; Li-ESWT= low-intensity extracorporeal shockwave treatment; US = ultrasound.

Male infertility

Introduction

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

Diagnostic evaluation

A focused evaluation of the male patient must always be undertaken and should include: a medical and reproductive history; physical examination; semen analysis – with strict adherence to WHO reference values for human semen characteristics, and hormonal evaluation. Other investigations (e.g., genetic analysis and imaging) may be required depending on the clinical features and findings on semen analysis.

Semen analysis

A comprehensive andrological examination is always indicated if the semen analysis shows abnormalities when compared to reference values (Table 10).

Table 10: 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 (a+b motility).

Recommendations for the diagnostic work-up of male infertility

Recommendations	Strength rating
Include a parallel assessment of the fertility status, including ovarian reserve, of the female partner during the diagnosis and management of the infertile male, since this might determine decision making in terms of timing and therapeutic strategies (e.g., ART vs. surgical intervention).	Strong
A complete medical history, physical examination and semen analysis are the essential components of male infertility evaluation.	Strong

Prader's orchidometer-derived testis volume is a reliable surrogate of ultrasound-measured testis volume in everyday clinical practice.	Weak
Perform semen analyses according to the WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn) indications and reference criteria.	Strong
Perform a full andrological assessment in all men with couple infertility, particularly when semen analysis is abnormal in at least two consecutive tests.	Strong
In cases of oligozoospermia and azoospermia, a hormonal evaluation should be performed, including a serum total testosterone and Follicle-Stimulating Hormone (FSH)/Luteinising Hormone.	Weak
Offer standard karyotype analysis and genetic counselling to all men with azoospermia and oligozoospermia (spermatozoa < 10 million/mL) for diagnostic purposes.	Strong
Do not test for Y-chromosome micro-deletions in men with pure obstructive azoospermia as spermatogenesis will be normal.	Strong
Y-chromosome microdeletion testing may be offered in men with sperm concentrations of < 5 million sperm/mL, but should be mandatory in men with sperm concentrations of ≤ 1 million sperm/mL.	Strong

Testicular sperm extraction (TESE) (any type) should not be attempted in patients with complete deletions that include the aZFa and aZFb regions, since they are a poor prognostic indicator for retrieving sperm at surgery.	Strong
Inform men with Yq microdeletion and their partners who wish to proceed with intracytoplasmic sperm injection (ICSI) that microdeletions will be passed to sons, but not to their daughters.	Strong
In men with structural abnormalities of the vas deferens (unilateral or bilateral absence with no renal agenesis), test the male and his partner for cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations, which should include common point mutations and the 5T allele.	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 men with Klinefelter Syndrome offer long-term endocrine follow-up and appropriate medical treatment.	Strong
Do not routinely use reactive oxygen species testing in the diagnosis and management of the male partner of an infertile couple.	Weak
Sperm DNA fragmentation testing should be performed in the assessment of couples with recurrent pregnancy loss from natural conception and ART or men with unexplained infertility.	Strong

Perform scrotal ultrasound (US) in patients with infertility, as there is a higher risk of testis cancer.	Weak
A multidisciplinary team discussion concerning invasive diagnostic modalities (e.g., US-guided testis biopsy with frozen section versus radical orchidectomy versus surveillance) should be considered in infertile men with US-detected indeterminate testicular lesions, especially if additional risk factors for malignancy are present.	Weak
Perform transrectal US if a partial or complete distal obstruction is suspected.	Strong
Consider imaging for renal abnormalities in men with structural abnormalities in the vas deferens and no evidence of CFTR abnormalities.	Strong

Special Conditions and Relevant Clinical Entities

Crytorchidism

Cryptorchidism is the most common congenital abnormality of the male genitalia; at one year of age nearly 1% of all full-term male infants have cryptorchidism. Approximately 30% of undescended testes are non-palpable and may be located within the abdominal cavity.

Recommendations	Strength rating
Do not use hormonal treatment for cryptorchidism in post-pubertal men.	Strong

If undescended testes are corrected in adulthood, perform simultaneous testicular biopsy, for the detection of intratubular germ cell neoplasia *in situ* (formerly carcinoma *in situ*).	Strong
Men with unilateral undescended testis and normal hormonal function/spermatogenesis should be offered orchidectomy.	Strong
Men with unilateral or bilateral undescended testis with biochemical hypogonadism and/or or spermatogenic failure (i.e., infertility) may be offered unilateral or bilateral orchidopexy, if technically feasible.	Weak

Germ cell malignancy and male infertility

Testicular germ cell tumour (TGCT) is the most common malignancy in Caucasian men aged 15-40 years, and affects approximately 1% of sub-fertile men. Overall, sperm, cryopreservation is considered standard practice in all patients with cancer and not only those with testicular cancer. As such, it is important to stress that all men with cancer must be offered sperm cryopreservation prior to the therapeutic use of gonadotoxic agents or ablative surgery which may impair spermatogenesis or ejaculation (i.e., chemotherapy; radiation therapy; retroperitoneal surgery). Men with TGCT have decreased semen quality, even before cancer treatment.

Recommendations	Strength rating
Men with testicular microcalcification (TM) should learn 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 (US), measure 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
Testicular biopsy may be offered in infertile men with TM, who belong to one of the following higher risk groups: spermatogenic failure (infertility), bilateral TM, atrophic testes (less than 12 mL), history of undescended testes and TGCT.	Weak
If there are suspicious findings on physical examination or US in patients with TM with associated lesions, perform inguinal surgical exploration with testicular biopsy or offer orchidectomy after multi-disciplinary meeting and discussion with the patient.	Strong
Men treated for TGCT are at increased risk of developing hypogonadism, sexual dysfunction and cardiovascular risk. Men should be managed in a multidisciplinary team setting with a dedicated late effects clinic.	Weak
Sperm cryopreservation should be performed prior to planned orchidectomy, since men with testis cancer may have significant semen abnormalities (including azoospermia).	Weak

Men with testis cancer and azoospermia or severe abnormalities in their semen parameters may be offered onco-testicular sperm extraction (TESE) at the time of radical orchidectomy.	Weak

Varicocele

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

- male subfertility;
- failure of ipsilateral testicular growth and development;
- symptoms of pain and discomfort;
- hypogonadism.

Recommendations	Strength rating
Treat varicocele in adolescents with ipsilateral reduction in testicular volume and evidence of progressive testicular dysfunction.	Weak
Do not treat varicocele in infertile men who have normal semen analysis and in men with a subclinical varicocele.	Weak
Treat infertile men with a clinical varicocele, abnormal semen parameters and otherwise unexplained infertility in a couple where the female partner has good ovarian reserve to improve fertility rates.	Strong
Varicocelectomy may be considered in men with raised DNA fragmentation with otherwise unexplained infertility or who have suffered from failed assisted reproductive techniques, including recurrent pregnancy loss, failure of embryo-genesis and implantation failure.	Weak

Male accessory gland infections and infertility

Infections of the male urogenital tract are potentially curable causes of male infertility. The WHO considers urethritis, prostatitis, orchitis and epididymitis to be male accessory gland infections (MAGIs). Semen analysis clarifies whether the prostate is involved as part of a generalised MAGI and provides information regarding sperm quality. In addition, leukocyte analysis allows differentiation between inflammatory and non-inflammatory chronic pelvic pain syndrome.

Recommendations	Strength rating
Treating male accessory gland infections (MAGIs) may improve sperm quality, although it does not necessarily improve the probability of increasing conception.	Weak
Data is insufficient to conclude whether antibiotics and antioxidants for the treatment of infertile men with leukocyto-spermia may improve fertility outcomes.	Weak
Refer sexual partners of patients with accessory sex gland infections that are known or suspected to be caused by sexually transmitted diseases for evaluation and treatment.	Strong

Non-Invasive Male Infertility Management

Idiopathic male infertility and OATS

Oligo-astheno-teratozoospermia (OAT) is a clinical condition, with a reduced number of spermatozoa in the ejaculate, which is also characterised by a reduced motility and morphology; often referred to as OAT syndrome (OATS).

Recommendations	Strength rating
In men with idiopathic oligo-astheno-teratozoospermia, life-style changes including weight loss and increased physical activity, smoking cessation and alcohol intake reduction can improve sperm quality and the chances of conception.	Weak
No clear recommendation can be made for treatment of patients with idiopathic infertility using antioxidants, although anti-oxidant use may improve semen parameters.	Weak
No conclusive recommendations on the use of selective oestrogen receptor modulators in men with idiopathic infertility can be drawn.	Weak
No conclusive recommendations on the use of either steroidal (testolactone) or non-steroidal (anastrozole and letrozole) aromatase inhibitors in men with idiopathic infertility can be drawn, even before testis surgery.	Weak

Hormonal therapy

Recommendations	Strength rating
Hypogonadotropic hypogonadism (secondary hypogonadism), including congenital causes, should be treated with combined human chorionic gonadotropin (hCG) and follicle-stimulating hormone (FSH) (recombinant FSH; highly purified FSH) or pulsed gonadotropin releasing hormone (GnRH) via pump therapy to stimulate spermatogenesis.	Strong
In men with hypogonadotropic hypogonadism, induce spermatogenesis by an effective drug therapy (hCG; human menopausal gonadotropins; recombinant FSH; highly purified FSH).	Strong
The use of GnRH therapy is more expensive and does not offer any advantages when compared to gonadotropins for the treatment of hypogonadotropic hypogonadism.	Strong
In men with idiopathic oligozoospermia and FSH values within the normal range, FSH treatment may ameliorate spermatogenesis outcomes.	Weak
No conclusive recommendations can be given on the use of high dose FSH in men with idiopathic infertility prior (m)TESE and therefore cannot be routinely advocated.	Weak
Do not use testosterone therapy for the treatment of male infertility.	Strong

Provide testosterone therapy for symptomatic patients with primary and secondary hypogonadism who are not considering parenthood.	Strong
In the presence of hyperprolactinaemia dopamine agonist therapy may improve spermatogenesis.	Weak

Invasive Male Infertility Management

Obstructive azoospermia

Obstructive azoospermia (OA) is the absence of spermatozoa in the sediment of a centrifuged sample of ejaculate due to obstruction. Obstructive azoospermia is less common than non-obstructive azoospermia (NOA) and occurs in 20-40% of men with azoospermia. Men with OA usually have a normal FSH, testes of normal size and epididymal enlargement or distension. Of clinical relevance, men with late maturation arrest may present with normal gonadotrophins and testis size and may be only be distinguished from OA at the time of surgical exploration. The vas deferens may be absent bilaterally (CBAVD) or unilaterally (CUAVD). Obstruction in primary infertile men is more frequently present at the epididymal level.

Recommendations	Strength rating
Perform microsurgical vasovasostomy or epididymovasostomy for azoospermia caused by epididymal or vasal obstruction in men with female partners of good ovarian reserve.	Strong

Use sperm retrieval techniques, such as microsurgical epididymal sperm aspiration (MESA), testicular sperm extraction (TESE) and percutaneous techniques (PESA, TESA) either as an adjunct to reconstructive surgery, or if the condition is not amenable to surgical repair, or when the ovarian reserve of the partner is limited or patient preference is not to undertake a surgical reconstruction and the couple prefer to proceed to ICSI treatment directly.	Strong

Non-obstructive azoospermia

Non-obstructive azoospermia (NOA) is defined as the absence of sperm in semen analysis after centrifugation, with usually a normal ejaculate volume. This finding should be confirmed on at least two consecutives semen analyses. The severe deficit in spermatogenesis observed in NOA patients is often a consequence of primary testicular dysfunction or may be related to a dysfunction of the hypothalamus-pituitary-gonadal (HPG) axis.

Recommendations	Strength rating
Patients with non-obstructive azoospermia (NOA) should undergo a comprehensive assessment, including detailed medical history, hormonal profile and genetic tests to investigate the underlying aetiology and associated comorbidities. Genetic counselling is mandatory in couples with genetic abnormalities prior to any assisted reproductive technology (ART) protocols.	Strong

Surgery for sperm retrieval can be performed in men who are candidates for ART (i.e., intracytoplasmic sperm injection). In patients with complete AZFa and AZFb microdeletions surgery is contra-indicated since the chance of sperm retrieval is zero.	Strong
Fine needle aspiration (FNA) and testicular sperm aspiration (TESA) should not be considered the treatments of choice in patients with NOA, given the lower probability of positive sperm retrieval compared to conventional testicular sperm extraction (cTESE) and microdissection TESE (mTESE).	Weak
Fine needle aspiration as a prognostic procedure prior to definitive testicular sperm extraction (any type) in patients with NOA is not recommended for use in routine clinical practice.	Weak
Conventional TESE or mTESE are the techniques of choice for retrieving sperm in patients with NOA.	Weak
No pre-operative biochemical and clinical variables may be considered sufficient and reliable predictors of positive sperm retrieval at surgery in patients with NOA.	Weak
No conclusive recommendations on the routine use of medical therapy (e.g., recombinant follicle-stimulating hormone (FSH); highly purified FSH; human chorionic gonadotrophin (hCG); aromatase inhibitors or selective oestrogen receptor modulators [SERMs]) in patients with NOA can be drawn and are not therefore currently recommended routinely before TESE.	Weak

This short booklet is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-07-3), available to all members of the European Association of Urology at their website, http://www.uroweb.org/guidelines/.