EAU Guidelines on

Sexual and Reproductive Health

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European Association of Urology

TABLE OF CONTENTS PAGE

1. INTRODUCTION

1.1 Aims and Objectives

The European Association of Urology (EAU) Sexual and Reproductive Health Guidelines aim to provide a comprehensive overview of the medical aspects relating to sexual and reproductive health in adult men. These Guidelines cover the former EAU Guidelines on Male Sexual Dysfunction, Male Infertility and Male Hypogonadism.

It must be emphasised that guidelines present the best evidence available to the experts. However, following guideline recommendations will not necessarily result in the best outcome. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions - while taking personal values and preferences/individual circumstances of patients into account. Guidelines are not mandates and do not purport to be a legal standard of care.

1.2 Panel Composition

The EAU Sexual and Reproductive Health Guidelines Panel consists of an international multi-disciplinary group of urologists, endocrinologists and a psychologist. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guideline/sexual-and-reproductive-health/.

1.3 Available Publications

A quick reference document, the Pocket Guidelines, is available. This is an abridged versions that may require consultation together with the full-text version. A number of scientific publications are also available. All documents can be viewed through the EAU website: http://www.uroweb.org/guideline/sexual-and-reproductive-health/.

1.4 Publication History

The EAU Sexual and Reproductive Health Guidelines were first published in 2020. This 2024 document presents a limited update of the 2023 publication.

1.5 Changes in the Guideline for 2024

The 2024 Sexual and Reproductive Health Guidelines have undergone a major revision and restructuring of the full text as well as a review of all recommendations.

2. METHODOLOGY

2.1 Methods

Recommendation within the Guidelines are developed by the panels to prioritise clinically important care decisions. The strength of each recommendation is determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and the nature and variability of patient values and preferences. This decision process, which can be reviewed in the strength rating forms which accompany each guideline statement, addresses a number of key elements:

1. the overall quality of the evidence which exists for the recommendation [1];
2. the magnitude of the effect (individual or combined effects);
3. the certainty of the results (precision, consistency, heterogeneity and other statistical or study related factors);
4. the balance between desirable and undesirable outcomes;
5. the impact and certainty of patient values and preferences on the intervention

Strong recommendations typically indicate a high degree of evidence quality and / or a favourable balance of benefit to harm and patient preference. Weak recommendations typically indicate availability of lower quality evidence, and/or equivocal balance between benefit and harm, and uncertainty or variability of patient preference [2].

Additional information can be found in the general Methodology section of this print, and online at the EAU website: http://www.uroweb.org/guideline/. A list of associations endorsing the EAU Guidelines can also be viewed online at this address.

2.2 Review

The EAU Sexual and Reproductive Health Guidelines were peer-reviewed prior to publication in 2020. The new priapism section was reviewed prior to publication in 2021. In 2023 the newly added section on penile size abnormalities and dysmorphophobia was reviewed prior to publication. The Panel would like to acknowledge the contribution of Dr. Miguel Ricou from the Department of Community Medicine, Information and Health Decision Sciences at the Faculty of Medicine, University of Porto, Portugal, for his expertise and time in reviewing the penile size abnormalities and dysmorphophobia section from a bioethics perspective.

3. MALE HYPOGONADISM

3.1 Definition, epidemiology and classification of male hypogonadism

3.1.1 ***Definition***

Male hypogonadism is a clinical syndrome which comprises of symptoms with or without signs and biochemical evidence of testosterone deficiency. Hypogonadism is associated with decreased testicular function and production of androgens and/or impaired sperm production [3]. This may be caused by impaired testicular function (hypergonadotropic hypogonadism or primary hypogonadism) or as a result of inadequate stimulation of the testes by the hypothalamic-pituitary axis (hypogonadotropic hypogonadism or secondary hypogonadism) (Table 1) or uncommonly by reduced ability of testosterone to stimulate the androgen receptor at the cellular level. Hypogonadism can adversely affect multiple organ functions and quality of life (QoL) [3, 4]. This chapter specifically addresses the management of adult male hypogonadism also called late-onset hypogonadism (LOH). Some insights related to congenital or pre-pubertal hypogonadism are also provided.

3.1.2 ***Epidemiology***

The prevalence of LOH increases with age, with the major causes being obesity, other comorbidities (e.g., diabetes) and overall poor health [5]. The incidence of hypogonadism has been reported to be between 12.3 and 11.7 cases per 1,000 people per year [6, 7]. Aging accounts for a low percentage of hypogonadism, as there is only a small gradual decline in testosterone, up to the age of 80 years, in healthy ageing men [5]. In men aged 40-79 years, the incidence of symptomatic hypogonadism varies between 2.1 and 5.7% [6, 8, 9].

There is a high prevalence of LOH within specific populations, including patients with obesity, type 2 diabetes (T2DM), metabolic syndrome (MetS), cardiovascular diseases (CVD), chronic obstructive pulmonary disease (COPD), renal disease and cancer [9]. In particular low testosterone levels are relatively common in men with T2DM [10, 11] and in those with metabolic derangements.

Klinefelter syndrome, a trisomy associated with a 47, XXY karyotype, is the most prevalent genetic cause of primary hypogonadism, with a global prevalence of 1/500-1,000 live male births [12-15]. However, < 50% of individuals with Klinefelter syndrome are diagnosed during their lifetime [16].

3.1.3 ***Classification***

Male hypogonadism can be classified according to the aetiology into primary hypogonadism or secondary hypogonadism (Table 1) [3, 17]. A compensated or subclinical form of hypogonadism, characterised by normal testosterone serum levels and elevated luteinising hormone (LH) production, has also been reported [18]; the clinical significance of this condition is unclear [18-21].

The classification of hypogonadism has also been divided into two broad categories: 'Classical/Organic' and 'Functional, often but not correctly identified as LOH [58]. The clinical effects of testosterone deficiency are however common to all patients independent of the cause of the hypogonadism; although, they may vary in severity or as a result of age of onset (see below). Classical hypogonadism includes: congenital or acquired diseases causing structural and/or irreversible impairment of the pituitary and/or testes. Functional hypogonadism is diagnosed on the absence of any recognised organic alterations in the HPG axis and it is mainly a consequence of comorbidities, affecting the Hypothalamic-Pituitary-Testicular (HPT) axis and should be treated first by resolving or improving any underlying conditions (e.g., anorexia in younger male subjects). Late onset hypogonadism, conversely represents even a broader clinical entity including adulthood onset forms which can have either organic or functional origin and can be primary or secondary [22] (see below). Late onset hypogonadism is frequently diagnosed in the absence of an identifiable classical cause of hypogonadism, which becomes more prevalent with age, usually occurring, but not exclusively, in men aged > 40 years. By definition LOH must comprise both persistent specific symptoms and biochemical evidence of testosterone deficiency [3, 23].

Finally, hypogonadism can also result from several conditions leading to reduced sensitivity/insensitivity to testosterone and its metabolites [3].

The current guidelines maintain a classification of Primary and Secondary Hypogonadism, with special reference to LOH.

The classification, based on the aetiology of hypogonadism, allows clinicians to adequately select appropriate treatment. In patients with secondary hypogonadism, both fertility and testosterone normalisation can be theoretically achieved with adequate treatment, whereas in primary hypogonadism only testosterone therapy can be considered [3, 17] (Table 1). However, it should also be recognised that symptoms and signs of hypogonadism can be similarly independent of the site of origin of the disease. Conversely, the age of onset of hypogonadism can influence the clinical phenotype [24]. Accordingly, early onset, such as that occurring during foetal life, the clinical phenotype can span from an almost complete female phenotype (e.g., complete androgen insensitivity or enzymatic defects blocking androgen synthesis) to various defects in virilisation. In the case of a pre- or peri-pubertal appearance of hypogonadism due to a milder central (isolated hypogonadotropic hypogonadism [IHH]) or a peripheral defect (such as in Klinefelter syndrome), there may be delayed puberty with an overall eunuchoid phenotype. Finally, when hypogonadism arises post-puberty, particularly with advancing age, symptoms may manifest subtly and frequently overlap with the natural ageing process, leading to confusion [24].

Table 1: Classification of male hypogonadism

PRIMARY HYPOGONADISM (hypergonadotropic hypogonadism)	
Congenital or developmental disorders	
Common causes	*Uncommon causes*
• Klinefelter syndrome	• Rare chromosomal abnormalities - (XX male, 47 XYY and 48 XXYY syndrome • 21 Trisomy (Down syndrome) • Noonan syndrome • Autosomal translocations1 • Defects of testosterone biosynthesis • CAH (testicular adrenal rest tumours) • Disorders of sex development (gonadal • dysgenesis) • LHR gene mutations • Myotonic dystrophy (including type I and II) • Uncorrected cryptorchidism (including INSL3 • and LGR8 mutations) • Bilateral congenital anorchia • Sickle cell disease • Adreno-leukodystrophy
Acquired disorders	
Drug-induced	*Localised problems*
• Chemotherapy agents • Alkylating agents • Methotrexate • Testosterone synthesis inhibitors - Ketoconazole, Aminoglutethimide, Mitotane and Metyrapon	• Bilateral surgical castration or trauma • Testicular irradiation • Orchitis (including mumps orchitis) • Autoimmune testicular failure • Testicular Torsion • Alcohol/Cirrhosis • Environmental Toxins
Systemic diseases/conditions with hypothalamus/pituitary impact	
• Chronic systemic diseases* • Chronic organ failure* • Glucocorticoid excess (Cushing syndrome)* • Ageing* • HIV	• Malignancies – Lymphoma and Testis cancer • Spinal cord injury • Vasculitis • Infiltrative diseases (amyloidosis; leukaemia)

SECONDARY HYPOGONADISM (hypogonadotropic hypogonadism)	
Congenital or developmental disorders	
Common causes	*Uncommon causes*
• Haemochromatosis*	• Combined hormone pituitary deficiency • Idiopathic hypogonadotropic hypogonadism • IHH with variants: Normosmic IHH, Kallmann syndrome, isolated LH β gene mutations and Prader-Willi syndrome
Acquired disorders	
Drug-induced	*Localised problems*
• Oestrogens • Testosterone or androgenic anabolic steroids • Progestogens (including cyproterone acetate) • Hyperprolactinemia-induced drugs • Opiates - GnRH agonist or antagonist and glucocorticoids	• Traumatic brain injury • Pituitary neoplasm (micro/macro-adenomas) • Hypothalamus tumours • Pituitary stalk diseases • Iatrogenic - surgical hypophysectomy and pituitary or cranial irradiation • Inflammatory and infectious diseases -lymphocytic hypophysitis; pituitary infections; granulomatous lesions; sarcoidosis; Wegener's granulomatosis; other granulomatosis and encephalitis • Langerhans' histiocytosis • Hyperprolactinaemia, as a consequence of localised problems (hypothalamus-pituitary mass)
Systemic diseases/conditions impacting the hypothalamus/pituitary	
• Chronic systemic diseases* - Type 2 diabetes mellitus/Metabolic Syndrome/metabolic diseases; HIV infection; chronic organ failure; and chronic Inflammatory Arthritis • Glucocorticoid excess (Cushing syndrome)* • Eating disorders* • Endurance exercise • Acute and critical illness • Ageing*	• Spinal cord injury • Transfusion-related iron overload (β-thalassemia)
ANDROGEN RESISTANCE/DECREASED TESTOSTERONE BIOACTIVITY	
Congenital or developmental disorders	
• Aromatase deficiency • Kennedy diseases (spinal and bulbar muscular atrophy) and other extensions of CAG repeats • Partial or complete androgen insensitivity • 5α reductase type II (5aR) deficiency	
Acquired disorders	
Drug-induced	*Localised problems*
• Drug-induced AR blockage - steroidal antiandrogen, cyproterone acetate and spironolactone • Non-steroidal antiandrogen – flutamide, bicalutamide and nilutamide • Drug-induced 5α reductase (5aR) activity blockade – finasteride and dutasteride • Drug-induced ER blockade – clomiphene, tamoxifen and raloxifene • Drug-induced aromatase activity blockade – letrozole, anastrozole and exemestane • Increased Sex Hormone Binding Globulin (SHBG)	• Coeliac disease

** Conditions acting at central and peripheral levels resulting in either primary and secondary hypogonadism.*

[1] Different autosomal translocations can cause rare cases of hypogonadism and infertility.

A brief discussion on the physiology of testosterone production can be found in Appendix 1, online supplementary evidence.

3.2 Comorbidities associated with male hypogonadism

3.2.1 ***Obesity***

Low testosterone levels are common in men with obesity. Male hypogonadism is associated with a greater percentage of fat mass and a lower lean mass compared to men with adequate testosterone levels [25, 26]. Low levels of testosterone are strongly linked to heightened visceral adiposity. Additionally, they result in lipid accumulation in the liver and muscle, correlating with atherosclerosis [25, 26].

3.2.2 ***Metabolic Syndrome/Type 2 Diabetes***

Hypogonadism is frequently associated with MetS or its related components, including central obesity, hyperglycaemia, insulin resistance and dyslipidaemia and arterial hypertension [27].

Several randomised controlled trials (RCTs) have demonstrated that testosterone therapy may improve insulin resistance and hyperglycaemia and lower total and low-density protein
(LDL) cholesterol [28-33]. Testosterone therapy in hypogonadal T2DM improved glycaemic control in some RCTs and registry trials; however, there is no conclusive evidence [29, 34, 35]. A large placebo-controlled RCT, including 1,007 patients with impaired glucose tolerance or newly-diagnosed T2DM and total testosterone < 14 nmol/L showed that testosterone therapy for two years reduced the proportion of patients with T2DM regardless of a lifestyle programme [33]. Similarly, a registry study reported that testosterone therapy was associated in time with remission of T2DM [34]. High-density lipoprotein (HDL)-cholesterol may decrease, remain unchanged or increase with testosterone therapy.

Testosterone therapy in men with MetS and low testosterone has been shown to reduce mortality compared to untreated men [36, 37], although no conclusive evidence is available.

Erectile dysfunction (ED) is common in men with MetS and T2DM (up to 70% of patients). The causes of ED are multi-factorial and 30% of men with ED have co-existing testosterone-deficiency/hypogonadism. Some evidence has suggested that ED is only found in men with T2DM and clearly reduced testosterone levels (< 8 nmol/L or 2.31 ng/mL) [38]. From a pathophysiological perspective, it has been reported that this is because ED is predominantly caused by vascular and neuropathic disease, and therefore not likely in men who do not have established vascular disease. Therefore, men presenting with ED should be screened for MetS. Likewise, patients with ED and diabetes may be offered testosterone measurement.

Placebo-controlled RCTs of testosterone therapy in T2DM have demonstrated improved sexual desire and satisfaction, although data on erectile function were limited [29, 38]. Similar results were derived from a meta-analysis of published trials [39]. Accordingly, a large two-year RCT of testosterone undecanoate vs. placebo showed that testosterone therapy significantly improved sexual function and ED in men with impaired glucose tolerance or newly-diagnosed T2DM low testosterone (< 14 nmol/L) [33].

Testosterone therapy has been associated with a reduced percentage of body fat and increase in lean body mass [40]. Data from a registry study have suggested that testosterone therapy with long-acting intramuscular testosterone undecanoate over eleven years was associated with a substantial but gradual loss of weight, along with a reduction in waist circumference [41]

3.2.3 ***Sars-CoV-2 / COVID-19***

Data seem to suggest that low circulating testosterone levels are more frequently associated with worse clinical outcomes in men with COVID-19 [42-49]. Accordingly, a cohort study, analysing two large academic health systems databases, including 723 men with a history of COVID-19 reported that hypogonadal men had a higher risk of being hospitalised [50]. In addition, a meta-analysis suggested that reduced testosterone levels detected at hospital admission for COVID-19 are associated with a four- five-fold increased risk of being admitted to the Intensive Care Unit (ICU) or dying, after adjustment for potential confounders [51].

Although no information on the role of testosterone therapy in the acute phase of the disease is available currently, data also showed that the hypogonadal patients under testosterone therapy had a reduced risk to be hospitalised after SARS-CoV-2 infection [50]. However, whether or not low testosterone can directly contribute to worse COVID-19 outcomes is still under investigation. The possibility that low testosterone in the acute phase of COVID-19 infection represents an adaptive response mechanism to dampen non-essential activities non

conducive to recovery (physical and sexual activities) by turning off testosterone-dependent functions, cannot be excluded [52, 53]. Accordingly, a meta-analysis showed that secondary or mixed hypogonadism is more frequently observed in the acute phase of the infection [51].

Studies evaluating patients in the recovery phase of COVID-19 have documented either restored [54, 55] or persistently low testosterone levels in the majority of cases [56]. A longitudinal evaluation study showed that during the recovery phase a further improvement of testosterone levels can be observed up to twelve months after COVID-19. Male subjects who have recovered from COVID-19 should be accurately followed-up to exclude any long-term andrological consequences including impairment in sperm and testosterone production [51].

Table 2: Main factors associated with an increase or reduction of SHBG circulating levels

SHBG increase	SHBG decrease
• Drugs: anticonvulsants, oestrogens, thyroid hormone • Hyperthyroidism • Hepatic disease • Ageing • Smoking • AIDS/HIV	• Drugs: growth hormone (GH), glucocorticoids, testosterone, anabolic androgenic steroids • Hypothyroidism • Obesity • Acromegaly • Cushing's disease • Insulin resistance (MetS/T2DM) • Non-alcoholic fatty liver disease (NAFLD), • Nephrotic syndrome

3.3 Late-onset hypogonadism

Testosterone production declines with ageing. The European Male Aging Study (EMAS) reported a 0.4% per annum (log hormone-age) decrease in total testosterone and a 1.3% per annum decline in free testosterone (fT) [5]. Late onset hypogonadism is the term frequently used to describe this phenomenon and the detection of hypogonadism in adulthood. Evidence indicates that several associated diseases and chronic comorbidities can interfere with the HPG axis leading to the development of primary hypogonadism or, more frequently, secondary hypogonadism in adulthood, thus significantly influencing the physiological age-dependent decline of testosterone. Combining the data from three different waves of the Massachusetts Male Aging Study (MMAS), demonstrated that associated comorbidity and obesity significantly decreased, whereas smoking tended to increase total, free and bio-available testosterone concentrations [57]. Data derived from the EMAS confirmed these findings [5, 19]. Based upon these data and other evidence, as previously reported the concept of *functional and organic hypogonadism* has been more recently introduced (see above) [58]. Considering that suppression of HPG axis activity is functional, and potentially reversible by empiric measures, such as weight loss, the need for testosterone therapy has been questioned [58].

3.3.1 Clinical Diagnosis and Evaluation

The mainstay of LOH diagnosis includes signs and symptoms consistent with hypogonadism, coupled with biochemical evidence of low morning serum total testosterone levels on two or more occasions, measured with a reliable assay and in fasting conditions.

3.3.2 History taking

Specific symptoms associated with hypogonadism, including LOH, are shown in Table 3. These symptoms are non-specific and need to be recorded and taken in context with the clinical and biochemical state. Several self-reported questionnaires or structural interviews have been developed for screening of hypogonadism. Although these case-history tools have demonstrated clinical utility in supporting the biochemical diagnosis of hypogonadism, or in the assessment of testosterone therapy outcomes, their specificity remains poor and they should not be used for a systematic screening of hypogonadal men [59]. Headache and/or visual disturbance may indicate a pituitary-related disorder. History of surgical intervention for cryptorchidism or hypospadias must be taken into account as possible signs of congenital defects. Chronic and systemic comorbidities must be comprehensively investigated in every patient. Use of drugs that potentially interfere with the HPG axis should be excluded (Table 1). Acute diseases are associated with development of functional hypogonadism and determination of serum total testosterone levels should be avoided in these conditions; however, the role of testosterone in the case of acute illness remains to be clarified [42, 46, 51, 60]. Fertility issues should be always discussed.

Table 3: Specific symptoms associated with LOH

	Sexual symptoms	Physical symptoms	Psychological symptoms
More specific	• Reduced libido • Erectile dysfunction • Decreased spontaneous/morning erections	• Decreased vigorous activity • Difficulty walking > 1 km • Decreased bending	• Low mood/mood deflection • Decreased motivation • Fatigue
Less specific	• Reduced frequency of sexual intercourse • Reduced frequency of masturbation • Delayed ejaculation	• Hot flushes • Decreased energy • Decreased physical strength/function/ activity	• Concentration difficulties • Sleep disturbances

3.3.3 ***Physical examination***

Since obesity is frequently associated with hypogonadism (mostly functional), the determination of body mass index (BMI) and the measurement of waist circumference are strongly recommended in all individuals. Testicular and penile size, as well as the presence of sexual secondary characteristics can provide useful information regarding overall androgen status. In addition, upper segment/lower segment ratio (n.v. > 0.92) and arm-span to height ratio (n.v. < 1.0) can be useful to identify a eunuchoid body shape, especially in subjects with pre-pubertal hypogonadism or delayed puberty. Finally, digital rectal examination (DRE) should be performed in all subjects to exclude prostate abnormalities before testosterone therapy (any type) or to support suspicion of hypogonadism (in case of reduced volume) [61].

3.3.4 ***Laboratory Diagnostics***

Testosterone levels are produced in a circadian variation, which may persist in ageing men [62, 63]. Testosterone levels are also potentially influenced by food intake [64]; therefore, serum total testosterone should be measured in fasting conditions in the morning (between 07.00 and 11.00 hours). A confirmatory measurement should always be undertaken in the case of a primary pathological value, and before starting any testosterone therapy.

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) represents the most accurate method for sex steroid evaluation; however, standardised automated platform immuno-assays for total testosterone assessment demonstrate a good correlation with LC-MS/MS [65]. Available immuno-assays are not able to provide an accurate estimation of fT; therefore, direct fT evaluation with these methods is not recommended and should be avoided [66]. Equilibrium dialysis is the most accurate method for total testosterone measurement and FT calculation [67]. Alternatively, fT can be derived from specific mathematical calculations using total testosterone as derived by common immunoassays and taking into account serum sex hormone binding globulin (SHBG) and albumin levels [68] (http://www.issam.ch/freetesto.htm).

Data from meta-analyses have shown that testosterone therapy is ineffective when baseline levels are > 12 nmol/L (3.5 ng/mL). Positive outcomes are documented when testosterone levels are < 12 nmol/L, being higher in symptomatic patients with more severe forms of hypogonadism (< 8 nmol/L). Hence, 12 nmol/L should be considered as a possible threshold for starting testosterone therapy in the presence of hypogonadal symptoms [40, 69].

In clinical conditions that may interfere with SHBG levels, evaluation of fT should be considered to better estimate actual androgen levels (Figure 1). Unfortunately, despite its potential clinical value [70], no validated thresholds for fT are available from clinical studies and this represents an area of uncertainty; however, data from the EMAS indicated that fT levels < 220 pmol/L (6.4 ng/dL) increased the likelihood to correct identify hypogonadism as compared with total testosterone level alone, particularly when total testosterone levels are between 8.0 and 11 nmol per litre [8, 71, 72].

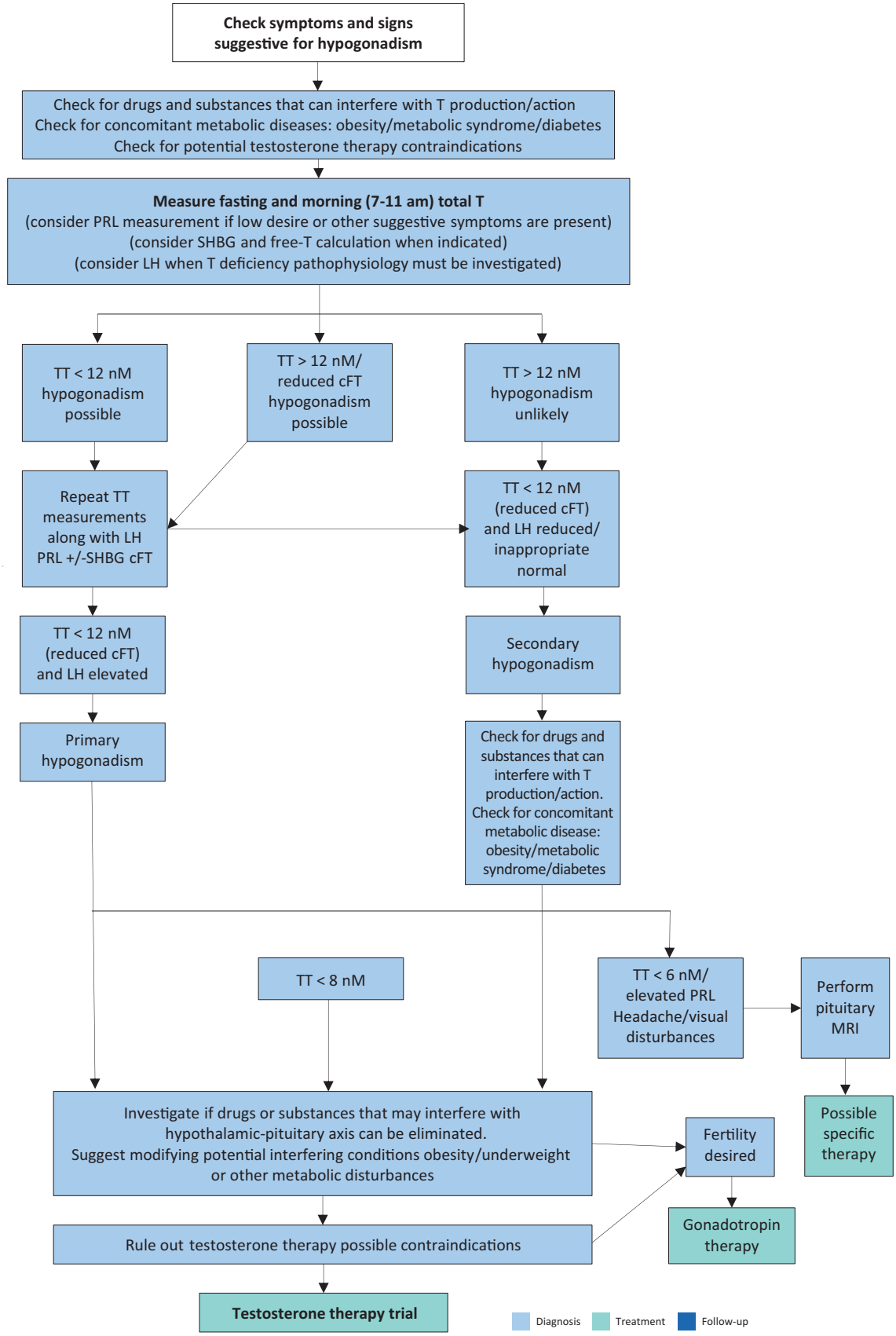
The determination of LH must be performed along with prolactin (PRL) when pathological total testosterone levels are detected, in order to correctly define the underlying conditions and exclude possible organic causes (Figure 1). Follicle-stimulating hormone determination can further support the diagnosis of primary or secondary hypogonadism [21, 73]. Due to its negative influence on libido, PRL can also be considered as first-line screening in patients with reduced sexual desire. In addition, contrast-enhanced pituitary magnetic resonance imaging (MRI) scanning, as well as other pituitary hormone evaluations, is required in the presence of specific symptoms such as visual disturbances, headache and when hyperprolactinemia is confirmed [74, 75]. Limited evidence suggests also performing pituitary MRI in the case of severe hypogonadism (< 6 nmol/L, 1.75 ng/mL) with inadequate gonadotropin levels (Figure 1) [74-76].

3.3.5 *Summary of evidence and recommendations for the diagnostic evaluation and screening of LOH*

Summary of evidence	LE
Sexual symptoms are the most specific symptoms associated with late-onset hypogonadism (LOH).	1a
Diagnosis of LOH should be based on specific signs and symptoms of androgen deficiency, together with consistently low serum testosterone levels.	1a
Total testosterone 12 nmol/L (3.5 ng/mL) represents a reliable threshold to diagnose LOH.	1a
Functional hypogonadism is a consequence of comorbidity/concomitant drugs, which can impair testosterone production in adulthood. The diagnosis of functional hypogonadism is a diagnosis of exclusion, after ruling out organic causes of hypogonadism.	4
Calculated free-testosterone of < 220 pmol/L has been suggested as a possible cut-off to diagnose LOH.	3
Self-reported questionnaires and structural interviews have been developed for screening of hypogonadism but their specificity remains poor.	2a

Recommendations	Strength rating
Diagnostic evaluation	
Check for concomitant diseases, drugs and substances that can interfere with testosterone production/action.	Strong
Measure total testosterone in the morning (between 07.00 and 11.00 hours) and in the fasting state, with a reliable laboratory assay.	Strong
Repeat total testosterone on at least two separate occasions when < 12 nmol/L and before starting testosterone therapy.	Strong
Use 12 nmol/L total testosterone (3.5 ng/mL) as a reliable threshold to diagnose late onset hypogonadism (LOH).	Strong
Measure sex hormone-binding globulin and free-testosterone calculation when indicated	Strong
Analyse luteinising hormone and follicle-stimulating hormone serum levels to differentiate between the different types of hypogonadism.	Strong
Measure prolactin (PRL) levels if evidence of low sexual desire (or other suggestive signs/symptoms) and secondary hypogonadism is present.	Strong
Perform pituitary magnetic resonance imaging (MRI) in secondary hypogonadism, with elevated PRL or symptoms specific of a pituitary mass and/or presence of other anterior pituitary hormone deficiency.	Strong
Perform pituitary MRI in secondary severe hypogonadism (total testosterone < 6 nmol/L).	Weak
Screening	
Screen for late onset hypogonadism (LOH) only in symptomatic men.	Strong
Do not use structured interviews and self-reported questionnaires for systematic screening for LOH as they have a low specificity.	Strong

Figure 1: 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.

3.4 Treatment of Classical and LOH

3.4.1 Indications and contraindications for treatment of hypogonadism

Patients with symptomatic hypogonadism (total testosterone < 12 nmol/L) without specific contraindications are suitable candidates to receive testosterone therapy (Table 4).

Absolute contraindications are untreated breast and prostate cancer (PCa). Similarly, conditions such as cardiovascular events as well as uncontrolled or poorly controlled congestive heart failure should be considered when prescribing testosterone therapy [77]. Conversely, severe lower urinary tract symptoms (LUTS) [International Prostate Symptom Score (IPSS) score > 19] represent a relative contraindication, as there is insufficient data on the long-term effects of testosterone therapy in these patients [66]. A positive family history for venous thromboembolism requires further analysis to exclude a condition of undiagnosed thrombophilia-hypofibrinolysis [78]. These patients need to be carefully counselled prior to testosterone therapy initiation. A haematocrit (HCT) > 54% should require testosterone therapy withdrawal, reduction in dose, change of formulation and venesection depending on the clinical situation to avoid any potential cardiovascular complications. Lower baseline HTC (48-50%) should be carefully evaluated before testosterone therapy initiation, to avoid pathological increases during treatment, especially in high-risk men such as those with COPD or Obstructive Sleep Apnoea Syndrome (OSAS). Accordingly, the Framingham Heart Study showed that HCT > 48% represented a condition associated with increased risk of coronary artery disease (CAD) and mortality and was associated with cardiovascular disorders [79]. Testosterone therapy suppresses gonadotropin and endogenous testosterone secretion as well as spermatogenesis [80]; therefore, testosterone therapy is contraindicated in individuals who desire fertility [81]. Secondary hypogonadism is characterised by low or inappropriately normal gonadotropin levels; therefore, the rationale is to substitute the gonadotropin deficiency with simultaneously FSH and LH analogues, if fertility is desired [82].

Table 4: Main contraindications of testosterone therapy

Absolute contraindications	Locally advanced or metastatic prostate cancer (PCa) Male breast cancer Men with an active desire to have children Haematocrit ≥ 54% Uncontrolled or poorly controlled congestive heart failure
Relative contraindication	IPSS score > 19 Baseline haematocrit 48-50% Familial history of venous thromboembolism

3.4.2 Testosterone therapy outcomes

3.4.2.1 Sexual dysfunction

Sexual concerns are the main symptoms of hypogonadal patients [3, 8, 83, 84]. A consistent body of evidence shows that testosterone therapy in hypogonadal men (total testosterone < 12 nmol/L) may have a beneficial effect on several aspects of sexual life; in contrast, there is no evidence of benefits in using testosterone therapy for treating sexual dysfunction in eugonadal men [69, 85-87]. The beneficial effect on sexual function seems to be more related to testosterone level normalisation than the specific testosterone formulations used [87, 88].

A meta-analysis of placebo-controlled RCTs showed that testosterone therapy significantly improves erectile function (as measured by IIEF-Erectile Function domain score) and that patients with more severe hypogonadism (i.e., total testosterone < 8 nmol/L) are more likely to achieve better improvement than patients with milder hypogonadism (i.e., total testosterone < 12 nmol/L) [69]. Similar results were observed for sexual desire; however, the presence of metabolic comorbidity (such as diabetes and obesity) decreased the magnitude of these improvements. In particular, testosterone therapy alone resulted in a clinically effective outcome only in patients with milder ED [69]. Similar results have also been confirmed in an update analysis [89] and in a recently published Cochrane review [1970]. In line with these data, report from the non-inferiority "Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE)" study, showed in middle-aged and older hypogonadal (total testosterone < 10.4 nmol/L) men with pre-existing or a high risk of CVD, testosterone therapy with gel for two years improved sexual activity, hypogonadal symptoms, and sexual desire, but not erectile function [90].

Other sexual function parameters, such as intercourse, orgasm and overall satisfaction, were all improved compared with placebo [69, 89]. Men with a comorbidity, such as T2DM, usually show modest improvements in terms of sexual function after testosterone therapy and may potentially require concomitant phosphodiesterase type 5 inhibitors (PDE5Is) to improve effectiveness [3, 87]. A meta-analysis including 913 patients derived from eight RCTs suggested that combination therapy (testosterone and PDE5Is) was superior when compared

to PDE5Is alone in improving erectile function [92]. The specific beneficial effect derived from the combined use of testosterone therapy and PDE5Is is unclear [85]. Similarly, information related to the combined use of testosterone therapy with other ED drug therapies is lacking [3, 87].

The Sexual Function Trial of the Testosterone Trials (TTrials) (one of the largest placebo-controlled trials on testosterone therapy) documented consistent improvements in 10 of 12 measures of sexual activities in older (≥ 65 years) hypogonadal men, particularly in frequency of intercourse, masturbation and nocturnal erections (as measured by PDQ-Q4) [93, 1973]. The magnitude in improvement was shown to be proportional to the increase in serum total testosterone, fT and E2 levels, it was not possible to demonstrate a threshold level [94]. A study of 220 men with MetS with or without T2DM also found that sexual function improved in men who reported sexual problems with improvement in IIEF scores, with specific increases in libido and sexual satisfaction [29].

3.4.2.2 Vitality and physical strength

The role of testosterone in stimulating muscle growth and strength is well established. Accordingly, androgenic-anabolic steroids (AAS) have been used as performance-enhancing agents to increase physical performance in competitive sport [95]. In this regard, testosterone therapy in hypogonadal men has been shown to increase muscle mass and reduce fat mass, with limited effects on final weight [40]. Despite this evidence, the role of testosterone therapy in older men with mobility limitations remains unclear. The National Health and Nutrition Examination Survey 1999-2004 [96] was unable to detect any association between overall circulating testosterone levels and the amount of physical activity. However, among non-obese men, those in the highest physical activity tertile were significantly less likely to have low or low-normal testosterone than those in the lowest tertile. Data from TTrials indicated that testosterone therapy did not substantially increase the fraction of men whose six-minute walking distance increased > 50 m or the absolute increase in the distance walked by those enrolled in the physical function trial [93]. However, when the whole population of the TTrials was considered, a significant, although modest, positive effect on these two parameters was reported [93]. Similar data were derived from the Vitality Trial [93]. As support of the aforementioned considerations, a recent meta-analysis including 2043 subjects older than 60 years failed to show a significant improvement of muscle strength of testosterone therapy when compared to placebo [97].

3.4.2.3 Mood and cognition

Several observational studies have documented a relationship between depressive symptoms, reduced QoL and hypogonadism [98, 99]. However, the specific relationship between hypogonadism and the incidence of depression is still unclear [99]. Only a few placebo-controlled RCTs have investigated the role of testosterone therapy in improving depressive symptoms. Data derived from TTrials showed that testosterone therapy improved mood, and depressive symptoms as continuous measures using several instruments [93]. However, the final effect was small in magnitude. In line with this data, the largest meta-analysis of available studies, including 1,890 hypogonadal men (baseline total testosterone < 12 nmol/L or fT < 225 pmol/L) men from 27 RCTs, documented that the positive effect of testosterone therapy was particularly evident in patients with milder symptoms [100]. The BLAST study of testosterone therapy in T2DM reported that those men with depression were less likely to respond with regards to symptoms of sexual dysfunction compared to men without depression [35].

Robust data on the effect of testosterone therapy on QoL are limited. Although recent meta-analyses suggest a significant effect of testosterone therapy over placebo, the magnitude is low and the heterogeneity high, therefore reducing the scientific value of the effect [88, 101].

The role of testosterone therapy in patients with cognitive impairment is even more uncertain. The TTrials evaluated the effect of testosterone therapy in 493 individuals with age-associated memory impairment to assess possible improvement of several aspects of cognitive function. However, results failed to demonstrate any beneficial effect of testosterone therapy in improving cognitive function [93]. Similarly, a meta-analysis involving 17 studies enrolling 1,438 patients with a mean age of 70.4 years and a mean follow-up of 45.6 weeks did not find any effect of testosterone therapy on cognitive domains [102].

3.4.2.4 Body composition and metabolic profile

Late onset hypogonadism is associated with a greater percentage of fat mass and a lesser lean mass compared to testosterone-repleted men [103]. The major effect of low testosterone is to increase visceral adiposity but it also leads to deposition of lipids in the liver and muscle and is associated with atherosclerosis [25]. Some published data have suggested that testosterone therapy reduces percentage body fat and increases lean mass [104]. Testosterone therapy has also been found to decrease waist circumference, body weight and BMI, with these effects more predominant after twelve months of treatment [104-106]. Over two years, the T4DM RCT reported that men on testosterone therapy and a lifestyle programme had a greater reduction in waist circumference, total and abdominal fat mass and an increase in total and arm muscle mass and an increased

strength in the non-dominant hand compared to a lifestyle programme alone [33]. There was a trend toward reduction in body weight although this approached significance but did not reach significance. The latter result is probably compounded by the increase in muscle mass as well as the decrease in fat mass. However, it should be recognised that the results of previous studies are mainly derived from registry and observational trials, which have important limitations due to the risk of selection bias for the non-random assignment of testosterone exposure. Accordingly, data derived from RCTs showed only an improvement of fat mass and lean mass of the same amount without any modifications in body weight [40]. A meta-analysis including seventeen RCTs specifically investigated the role of testosterone therapy on several metabolic parameters in patients with T2DM and/or MetS [39]. In line with what was reported in the general population, testosterone therapy was associated with an improvement in body composition either in T2DM or MetS without any effects on body weight. Similarly positive effects were also observed on fasting glycemia and insulin resistance (HOMA index) whilst more conflicting data were obtained for HbA1c and lipid profile [39].

3.4.2.5 Bone

Evidence suggests that bone mineralisation requires circulating sex steroids within the normal range [107]. The possible association between mild hypogonadism and osteopenia/osteoporosis is weak, whereas severe hypogonadism (total testosterone < 3.5 nM) is frequently associated with bone loss and osteoporosis, independent of patient age [107]. Three independent meta-analyses showed a positive effect of testosterone therapy on bone mineral density (BMD), with the highest effect at the lumber level [108-110]. Interestingly, the latter meta-analysis has provided novel evidence that the role of testosterone on BMD was even higher in patients with diabetes [110], who are at a higher risk of hypogonadism and bone fracture [39, 111, 112]. Similarly, data derived from TTrials and the T4DM studies confirmed that testosterone therapy increased BMD in hypogonadal ageing men [93, 113]. However, available data are insufficient to determine the effect of testosterone therapy alone on the risk of fractures [107]. Recent data from the aforementioned TRAVERSE trial quite surprisingly showed an increased incidence of overall bone fractures among men who have received testosterone therapy compared to those who received placebo [1971]. However, it should be recognized that no difference in major osteoporotic fractures (i.e., hip, wrist, humerus, clinical spine and hip) were observed between groups. Moreover, this observation was derived from patient reports and therefore it deserves to be more specifically adjudicated. In conclusion, it should be recognized that the use of testosterone therapy as an adjunct to anti-resorptive treatment in hypogonadal patients at high risk of fractures has not been established. Therefore, anti-resorptive therapy must be the first-choice treatment in hypogonadal men at high risk for bone fractures. The combination of anti-resorptive treatment and testosterone therapy should be offered only in conjunction with hypogonadism-related symptoms.

3.4.2.6 Summary of evidence and recommendations for testosterone therapy outcome

Summary of evidence	**LE**
Testosterone therapy can improve:	
• Milder forms of ED and libido in hypogonadal men;	1a
• Other sexual symptoms, including intercourse frequency, orgasm and overall satisfaction.	1b
• Body composition and insulin resistance.	1a
• Weight, waist circumference and lipid profile, but the evidence is conflicting.	3
• Mild depressive symptoms in hypogonadal men.	1a
• Bone mineral density, but information related to fracture risk is lacking.	1a

Recommendations	**Strength rating**
Do not use testosterone therapy in eugonadal men.	Strong
Use testosterone therapy as first-line treatment in hypogonadal patients with mild erectile dysfunction (ED).	Strong
Use a combination of phosphodiesterase type 5 inhibitors and testosterone therapy in more severe forms of ED.	Weak
Use conventional medical therapies for severe depressive symptoms and osteoporosis.	Strong
Do not use testosterone therapy to reduce weight and enhance cardio-metabolic status.	Weak
Do not use testosterone therapy to improve cognition vitality and physical strength in ageing men.	Strong

3.4.3 Choice of treatment

3.4.3.1 Lifestyle factors

As reported above, functional hypogonadism is frequently associated with obesity and metabolic disorders [114]. Therefore, weight loss and lifestyle changes should be the first approach for all overweight and obese men with hypogonadism. A previous meta-analysis documented that a low-calorie diet can to revert obesity-associated secondary hypogonadism by increasing total testosterone and fT, reducing oestrogens and restoring normal gonadotropin circulating levels [115]. This was confirmed in an updated meta-analysis showing that the increase in testosterone is significantly associated with weight reduction [116]. Similar results can be obtained through physical activity, which is associated with the duration of scheduled exercise and weight loss obtained [116]. However, it should be recognised that the increase in testosterone levels observed after a low-calorie diet and physical activity is small (1-2 nmol) [115, 116]. In addition, 60-86% of weight lost is regained after three years and 75-121% after five years [117]. Lifestyle changes represent an essential part of the management of obesity; however, some evidence suggests that when compared to lifestyle modifications alone, testosterone therapy-treated obese men benefit most from relief of their symptoms associated with testosterone deficiency, whereas those not treated did not benefit [82]. There is limited evidence to suggest that combination of life-style interventions and testosterone therapy in symptomatic hypogonadal men might result in better outcomes [103]. As described above, the T4DM study has demonstrated that over two-years testosterone therapy with lifestyle intervention was superior to lifestyle intervention alone in reducing waist circumference and total and abdominal fat content. There was no significant reduction in body weight when compared to lifestyle intervention alone [33]. Interestingly, recent data also showed that weight loss obtained thought the use of Glucagon-like peptide-1 analogues analogues can result in better testosterone increases as compared with diet programs alone [1972].

3.4.3.2 Medical preparations

Several testosterone formulations are available (Table 5). Direct comparisons among different testosterone products are still lacking. Candidates for testosterone therapy should be adequately informed about the possible risks and benefits of all available testosterone preparations. The final choice should be based on the clinical situation, testosterone formulation availability, and patient needs and expectations [22, 118].

3.4.3.2.1 Oral formulations

An oral formulation has been available in oleic acid since the 1970s, and has been recently reformulated in a mixture of castor oil and propylene glycol laureate (testosterone undecanoate [TU] caps), to allow the drug to be maintained at room temperature without degradation [22, 118]. The main limitation is related to poor bioavailability, which is strongly dependent on dietary fat content [22, 118]. The US Food and Drug Administration (FDA) approved a new formulation of oral TU in a liquid-filled soft gel capsule, which improved oral availability [119]. Available evidence showed that TU capsule formulations can reach steady 24-hour average serum testosterone levels in more than 80% of hypogonadal men, thus resulting in a significant improvement of all sexual function domains at all time points when compared to baseline along with an excellent safety profile [119]. More recently, the FDA has approved a new oral formulation which contains as carriers Vitamin E, phytosterol esters, polyoxyl 40 hydrogenated castor oil and propylene glycol monolaurate [119]. For all new oral TU formulations a mild increase in arterial blood pressure has been reported. Hence, the FDA has required a black box warning that these drugs can induce a blood pressure increase [119].

Mesterolone is a 5α-dihydrotestosterone (DHT) derivate available for oral administration. Along with DHT, mesterolone cannot be converted to oestrogens and can only be used for a limited period and for specific indications, such as the presence of painful gynaecomastia. However, the lack of a full spectrum of testosterone bioactivity strongly limits its long-term use [22].

3.4.3.2.2 Parenteral formulations

Injectable testosterone preparations can be classified according to their half-lives (Table 5). Testosterone propionate is a short-term ester formulation requiring multiple fractionated doses (usually 50-100 mg, every two to three days), thus representing a major limitation for its use [22, 118]. Cypionate and enanthate-T esters are short-term formulations, requiring administration every two to four weeks. A formulation containing mixed testosterone esters (TU, isocaproate, phenyl propionate, propionate) which has the benefit of a steady release of testosterone into the circulation, is available in some countries. The use of these older formulations is associated with wide fluctuations in plasma testosterone concentrations and is often reported as unpleasant by patients potentially resulting in adverse effects, such as polycythaemia [22, 118, 120]. A longer-lasting TU injectable formulation is widely available [22, 118], with a good safety/benefit profile allowing the maintenance of normal stable testosterone levels at a dose of 1,000 mg initially every twelve weeks, following a six-week loading dose, but can be adjusted to a frequency of ten to fourteen weeks dependent on the trough (pre-injection level) after three to five injections to maintain levels in the therapeutic range (usually > 12 and < 18 nmol/L) [22, 118, 121].

3.4.3.2.3 Transdermal testosterone preparations

Among the available transdermal formulations, testosterone gels represent the most frequently used preparations. The gel is quickly absorbed by the stratum corneum, creating a reservoir within the subcutaneous tissues from where testosterone is continuously delivered for 24 hours, after a single daily application. These formulations have been shown to normalise serum testosterone levels with an excellent safety profile [22, 118]. The introduction of specific devices and skin enhancers has resulted in better skin penetration of the drugs, thus reducing potential adverse effects. Local skin adverse effects are limited when compared to those with traditional testosterone patches, but they potentially allow transference of testosterone during close contact with the skin surface. The risk can be reduced by wearing clothing or by applying the gel on skin surfaces not usually touched (e.g., the inner thigh surface) [22, 118]. To reduce the total amount of gel applied and residual quantities remaining on the skin, new formulations of testosterone gel have been introduced with a testosterone concentration of 1.62-2% [22, 118]. Another transdermal testosterone formulation includes a topical, alcohol-based testosterone (2%) solution, which must be applied to the underarm once daily, using a metered dose applicator [22, 118]. This testosterone formulation is not available in Europe. Testosterone levels should be monitored to optimise the testosterone dose. Blood collection is best taken two to four hours after gel application to use the peak level of testosterone absorbed as a reference for adequate therapeutic levels. Levels of testosterone after application can vary and a repeat measurement may be indicated especially as sometimes, inadvertently, the skin over the venipuncture site can be contaminated by the gel, leading to falsely elevated results.

In some European countries, DHT is available as a hydroalcoholic 2.5% gel. It is rapidly absorbed, reaching a steady state in two to three days [22, 118]. Similar to that reported for mesterolone, DHT is not aromatised but can be useful for treating particular conditions, such as gynaecomastia and microphallus [22, 118].

3.4.3.2.4 Transmucosal formulations

A testosterone buccal system is still available in several countries. It consists of a sustained-release muco-adhesive buccal-testosterone-tablet requiring twice-daily application to the upper gums. The tablet does not dissolve completely in the mouth and must be removed after twelve hours. This formulation has been proven to restore testosterone levels within the physiological range with minimal or transient local problems, including gum oedema, blistering and gingivitis [22, 118].

A gel for intranasal administration is available in some countries, including the USA and Canada. It requires administration two or three times daily using a specific metered-dose pump. The application is rapid, non-invasive, and convenient, and avoids secondary transference observed with other topical products [22, 118]. Preliminary results suggest that intranasal testosterone is associated with lower suppression of Gn levels and with a lower risk of haematocrit increases [122].

3.4.3.2.5 Subdermal depots

The implantation of testosterone pellets, available in a limited number of countries, represents the longest available testosterone formulation lasting from four to seven months. The procedure is invasive and may be unattractive to patients [22, 118].

3.4.3.2.6 Anti-oestrogens

Anti-oestrogens, including selective oestrogen receptor (ER) modulators (SERMs) and aromatase inhibitors (AI) have been suggested as off-label treatments to restore testosterone levels and fertility in men with functional secondary hypogonadism or idiopathic infertility. They work by preventing down-regulation of the HPG axis by oestrogens and for this reason are particularly useful in men with obesity and metabolic disorders [116, 123]. In the latter case, the hypothesis is that the excess of adipose tissue leads to increased aromatase activity and oestrogens levels resulting in impairment of the HPG [114]. Due to their putative mechanism of action, they require an intact HPG axis and cannot work in primary hypogonadism or secondary hypogonadism due to organic damage of the HPG axis. Both types of SERMs, which bind ERs with an agonist or antagonist effect depending upon the target tissue, and AIs, which prevent androgens from being converted into oestrogens by aromatase, have been used in clinical practice [22, 118]. The evidence published so far is poor; all these products are off-label treatments and SERMs, due to their agonistic effect on venous vessels, could predispose men to the development of venous thromboembolism [22, 118]. In this context patients should be warned of the potential increased risk of venous thromboembolism, although data are lacking. Long-term use of these agents can lead to reduced bone density and the development of osteoporosis, potentially increasing fracture risk.

3.4.3.2.7 Gonadotropins

Gonadotropin therapy should be considered the standard in men with secondary hypogonadism who desire paternity (Table 5) [22, 118]. Recombinant hCG (rhCG) and LH (rLH) formulations offer comparable effects to urinary-derived preparations [118]. According to a meta-analysis of the available evidence, hCG should be administered with FSH since combined therapy results in better outcomes. Similar to recombinant hCG, recombinant FSH (rFSH) offers comparable effects to urinary-derived preparations [121].

Table 5: Available preparations for hypogonadism treatment

Formulation	Chemical structure	t ½	Standard dosage	Advantages	Disadvantages
GONADOTROPINS					
Human chorionic gonadotrophin (HCG)					
Extractive	HCG purified from the urine of pregnant women	NA	1,000-2,000 IU 3 times/week	Low cost	Multiple weekly administration
Recombinant	Human recombinant HCG	NA	No data on men	NA	NA
Luteotropic hormone (LH)					
Recombinant	Human recombinant LH	NA	No data on men	NA	NA
Follicle-stimulating hormone (FSH)					
Extractive	FSH purified from urine of pregnant women	NA	75-150 IU 3 times/week	Low cost	Multiple weekly administration
Recombinant	Human recombinant FSH	NA	75-150 IU 3 times/week	NA	Multiple weekly administration
TESTOSTERONE PREPARATIONS					
Oral					
Testosterone undecanoate	17-α-hydroxylester	4 hours	120-240 mg 2-3 times daily	- Reduction of liver involvement - Oral convenience - Modifiable dosage	- Unpredictable absorption depending on dietary fat content - Must be taken with meals
Testosterone undecanoate self-emulsifying delivery system	17-α-hydroxylester	2-5 hours	100-237 mg 2 times daily	- Oral convenience - Modifiable dosage - Quick reversal	- Gastrointestinal side effects - increase in blood pressure
Mesterolone	1α-methyl-4, 5α-dihydro-testosterone	12 hours	50-100 mg 2-3 times daily	- Oral convenience - Modifiable dosage - Useful in gynaecomastia	- Not aromatisable
Parental					
Testosterone enanthate	17-α-hydroxylester	4-5 days	250 mg every 2-3 weeks	- Low cost - Short-acting preparation allowing drug withdrawal in case of adverse effects	- Fluctuations in circulating testosterone levels - Multiple injections - Relative risk of polycythemia
Testosterone cypionate	17-α-hydroxylester	8 days	200 mg every 2-3 weeks		
Testosterone propionate	17-α-hydroxylester	20 hours	100 mg every 2 days		
Testosterone ester mixture*	4-androsten-3-one-17 beta-hydroxy-androst-4-en-3-one	4-5 days	250 mg every 3 weeks		
Testosterone undecanoate in castor oil	17-α-hydroxylester	34 days	1,000 mg every 10-14 weeks *750 mg every 10 weeks	- Steady-state testosterone level without fluctuation - Long-lasting - Less frequent administration	- Pain at the injection site - Long-acting preparation not allowing rapid drug withdrawal in case of adverse effects

Surgical implants	Native testosterone	N/A	4-6 200 mg implants lasting up to 6 months	- Long duration and constant serum testosterone level	- Placement is invasive - Risk of extrusion and site infections
TRANSDERMAL					
Testosterone patches	Native testosterone	10 hours	50-100 mg/ day	Steady-state testosterone level without fluctuation	- Skin irritation - Daily administration
Testosterone gel 1-2%	Native testosterone	6 hours	50-100 mg/ day		- Possible transfer during intimate contact - Daily administration
Underarm testosterone (testosterone solution 2%)	Native testosterone	NA	60-120 mg/ day		
Dihydro-testosterone gel 2.5%	Native dihydro-testosterone	NA	34-70 mg/day	- Steady-state testosterone level without fluctuation - Useful in gynaecomastia	- Possible transfer during intimate contact - Daily administration - Not aromatisable
TRANSMUCOSAL					
Testosterone buccal system	Native testosterone	12 hours	60 mg 3 times daily	Steady-state testosterone level without fluctuation	- Possible oral irritation - Twice-daily dosing - Unpleasant taste
Testosterone nasal	Native testosterone	6 hours	33 mg 3 times daily		- Nasal irritation - Multiple daily administrations

NA = not applicable.
** Testosterone ester mixture - propionate (30mg), phenylpropionate (60mg), isocaproate (60mg), decanoate (100mg)*

3.4.3.2.8 Summary of evidence and recommendations for choice of treatment for LOH

Summary of evidence	**LE**
Weight loss obtained through a low-calorie diet and regular physical activity results in a small improvement in testosterone levels.	1a
Testosterone gels and long-acting injectable testosterone undecanoate preparations provide optimal safety profiles.	1a
Gonadotropin treatment can be used to restore fertility in men with secondary hypogonadism.	1a

Recommendations	**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 that can impair testosterone production; treat other co-morbidities, when possible, before starting testosterone therapy.	Strong
Fully inform patients about the expected benefits and adverse effects of any treatment option. Select the testosterone preparation in a joint decision process, and fully inform patients of the risks and benefits.	Strong
Use testosterone gels rather than long-acting depot administration when starting initial treatment in high-risk men.	Weak

3.5 Safety and follow-up in hypogonadism management

3.5.1 Hypogonadism and fertility issues

Pharmacological management of hypogonadism aims to increase testosterone levels to normal levels which resolve or improve symptoms of hypogonadism. The first choice is to administer exogenous testosterone. However, while exogenous testosterone has a beneficial effect on the clinical symptoms of hypogonadism, it temporarily inhibits gonadotropin secretion by the pituitary gland, resulting in impaired spermatogenesis and sperm cell maturation [124]. Therefore, testosterone therapy is contraindicated in hypogonadal men seeking fertility treatment [81]. When secondary hypogonadism is present, gonadotropin therapy may maintain normal testosterone levels and restore sperm production [3].

3.5.2 Male breast cancer

Studies have documented that breast cancer growth is significantly influenced by testosterone and/or by its conversion to oestradiol (E_2) through different mechanisms and pathways [125]. Accordingly, the use of SERMs still represents an important therapeutic option in the management of this cancer [125]. No information is available on the role of testosterone therapy in patients successfully treated for male breast cancer; therefore, treated and active male breast cancer should be recognised as absolute contraindications for testosterone therapy.

3.5.3 Lower urinary tract symptoms/benign prostatic hyperplasia (BPH)

A trial of 60 patients undergoing testosterone therapy for six months showed no significant differences on post-void residual urine and prostate volume, while storage symptoms as measured by IPSS significantly improved, despite an increase in prostate-specific antigen (PSA) level [126]. A larger pre-treatment prostate volume was a predictive factor of improvement in LUTS. Similarly, a placebo-controlled RCT including 120 hypogonadal (total testosterone < 12 nmol/L) men with MetS and listed for BPH surgery, showed that testosterone therapy did not result in a difference in LUTS severity compared to placebo. Conversely, an improvement in ultrasound markers of inflammation in the expression of several pro-inflammatory genes was found in the treatment active arm [127]. A long-term study of 428 men undergoing testosterone therapy for eight years demonstrated significant improvements in IPSS, no changes in max flow rate (Q_{max}) and residual urine volume, but also a significant increase in prostate volume [128]. Similar data from the Registry of Hypogonadism in Men (RHYME), including 999 patients with a follow-up of three years, did not demonstrate any significant difference in PSA levels or total IPSS in men undergoing testosterone therapy, compared to untreated patients [129]. Similar results were reported in an Italian registry (SIAMO-NOI), collecting data from 432 hypogonadal men from fifteen centres [130]. Meta-analyses have not found significant changes in LUTS between patients treated with testosterone or placebo [131-137]. According to the most recent literature, there are no grounds to discourage testosterone therapy in hypogonadal patients with BPH/LUTS and there is evidence of limited benefit from androgen administration. The only concern is related to patients with severe LUTS (IPSS > 19), as they are usually excluded from RCTs; therefore, limiting the long-term safety data of testosterone therapy in this specific setting [61].

3.5.4 Prostate cancer (PCa)

A considerable number of observational studies have failed to demonstrate any association between circulating higher testosterone levels and PCa [138]. In contrast, studies investigating the relationship between low levels of testosterone and risk of PCa have found that men with very low levels of fT have a reduced risk of developing low-to-intermediate-grade PCa, but have a non-significantly increased chance of developing high-grade PCa [138]. This peculiar pattern was also reported in trials such as the Health Professionals Follow-up Study, the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE), with varying magnitudes of significance [139].

A meta-analysis, including 27 placebo-controlled, RCTs, found no evidence of increased PSA levels following testosterone therapy for one-year. When considering eleven studies reporting on the occurrence of PCa, the meta-analysis found no evidence of increased risk of PCa. However, a one year follow-up may be considered too short to draw firm conclusions on the risks of developing PCa. Furthermore, the analysis was restricted to studies with > 1-year follow-up, but no significant changes in PSA levels nor increased risk of PCa were found [132]. After five-year of median follow-up in three independent registry studies with > 1,000 patients undergoing testosterone therapy, PCa occurrence always remained below the reported incidence rate in the general population [140]. Similar results were reported by a large observational study including 10,311 men treated with testosterone therapy and 28,029 controls with a median follow-up of 5.3 years [141]. The same study, also showed that the risk of PCa was decreased for men in the highest tertile of testosterone therapy cumulative dose exposure as compared with controls [141].

Recently, the TRAVERSE study, a multicenter, randomized, double-blind, placebo-controlled, noninferiority trial involving 5246 men aged 45 to 80 years, who had pre-existing or a high risk of CVD and who have been

treated because of low testosterone levels (i.e., total T < 10.4 nmol/L) associated with reported symptoms of hypogonadism, did not show any difference in terms of PCa incidence or high-grade PCa rate between arms (testosterone therapy vs. placebo) at a mean follow-up, was 33.0± (SD) 12.1 months. Conversely, the same trial showed a significantly greater increase from baseline of total PSA in the treatment group as compared with the placebo arm [77].

With regards to PCa survivors, safety in terms of the risk of recurrence and progression has not yet been established. Limited data are available in the literature, with most case series not providing sufficient data to draw definitive conclusions (e.g., insufficient follow-up, small samples, lack of control arms, heterogeneity in study population and treatment regimen, etc.) [142]. A meta-analysis derived from thirteen studies including 608 patients, of whom 109 had a history of high-risk PCa, with follow-up of 1-189.3 months [143], suggested that testosterone therapy did not increase the risk of biochemical recurrence, but the available evidence is poor, limiting data interpretation [143]. Similar considerations can be derived from another, larger meta-analysis of 21 studies [144]. However, it is important to recognise both meta-analyses demonstrated high heterogeneity among the different studies and included a limited number of subjects. An RCT assessing the safety/benefit ratio of testosterone therapy in hypogonadal men successfully treated with prostatectomy for non-aggressive prostate PCa is currently ongoing [145].

In conclusion, recent literature does not support an increased risk of PCa in hypogonadal men undergoing testosterone therapy. Although it is mandatory to avoid testosterone administration in men with advanced PCa, insufficient long-term prospective data on the safety of testosterone therapy in PCa survivors [144], should prompt caution in choosing to treat symptomatic hypogonadal men in this setting. In particular, patients should receive comprehensive counselling regarding the uncertain long-term effects of testosterone therapy in this context, which necessitates further investigation. Due to the lack of strong evidence-based data on safety, the possible use of testosterone therapy in symptomatic hypogonadal men previously treated for PCa should be fully discussed with patients and limited to low-risk individuals.

3.5.5 ***Cardiovascular Disease***

Evidence suggests that hypogonadal men have an increased risk of CVD [146, 147]. Whether or not LOH is a cause or a consequence of atherosclerosis has not been clearly determined. Late-onset hypogonadism is associated with CV risk factors, including central obesity, insulin resistance and hyperglycaemia, dyslipidaemia, pro-thrombotic tendency and chronic inflammatory state [147]. Atherosclerosis is a chronic inflammatory disease, that releases pro-inflammatory cytokines into the circulation, which are known to suppress testosterone release from the HPG axis. Evidence from RCTs of testosterone therapy in men with MetS and/or T2DM demonstrates some benefit in CV risk, including reduced central adiposity, insulin resistance, total cholesterol and LDL-cholesterol and suppression of circulating cytokines [28-30, 35, 147, 148]. However, due to the equivocal nature of these studies, testosterone therapy cannot be recommended for use outside of treatment of specific symptoms.

Published data show that LOH is associated with an increase in all-cause and CVD-related mortality [7, 149-152]. These studies are supported by a meta-analysis that concluded that hypogonadism is a risk factor for cardiovascular morbidity [136] and mortality [153]. Importantly, men with low testosterone when compared to eugonadal men with angiographically proven coronary disease have twice the risk of earlier death [147]. Longitudinal population studies have reported that men with testosterone in the upper quartile of the normal range have a reduced number of CV events compared to men with testosterone in the lower three quartiles [149]. Androgen deprivation therapy for PCa is linked to an increased risk of CVD and sudden death [154]. Conversely, two long-term epidemiological studies have reported reduced CV events in men with high normal serum testosterone levels [155, 156]. Erectile dysfunction is independently associated with CVD and may be the first clinical presentation in men with atherosclerosis.

The knowledge that men with hypogonadism and/or ED may have underlying CVD should prompt individual assessment of their CV risk profile. Individual risk factors (e.g., lifestyle, diet, exercise, smoking, hypertension, diabetes and dyslipidaemia) should be assessed and treated in men with pre-existing CVD and in patients receiving androgen deprivation therapy. Cardiovascular risk reduction can be managed by primary care clinicians, but patients should be appropriately counselled by clinicians active in prescribing testosterone therapy [83]. If appropriate, patients should be referred to cardiologists for risk stratification and treatment of comorbidity.

No RCTs have provided a clear answer on whether testosterone therapy affects CV outcomes. The TTrial (n=790) conducted in older men [157], the TIMES2 study (n=220) [29], along with the BLAST studies involving men with Metabolic Syndrome (MetS) and Type 2 Diabetes Mellitus (T2DM), as well as the study involving pre-frail and frail

elderly men - all of which lasted for one year, and the T4DM study spanning two years - did not show any increase in Major Adverse Cardiovascular Events (MACE) increase in Major Adverse Cardiovascular Events (MACE) [29, 32, 33, 157, 158]. Randomised controlled trials, between three and twelve months, in men with known heart disease treated with testosterone have not found an increase in MACE, but have reported improvement in cardiac ischaemia, angina and functional exercise capacity [159-161]. A large cohort study (n=20,4857 men) found that neither transdermal gel or intramuscular testosterone was associated with an increased risk of composite cardiovascular outcome in men with or without prevalent CVD (mean follow-up 4.3 years) [162]. The European Medicines Agency (EMA) has stated that 'The Co-ordination Group for Mutual recognition and Decentralisation Procedures-Human (CMDh), a regulatory body representing EU Member States, has agreed by consensus that there is no consistent evidence of an increased risk of heart problems with testosterone in men. However, the product information is to be updated in line with the most current available evidence on safety, and with warnings that the lack of testosterone should be confirmed by signs and symptoms and laboratory tests before treating men with these drugs [163].

Data recently released from the TRAVERSE study confirm the findings of the EMA [77]. The latter is the first double-blind, placebo-controlled, non-inferiority RCT with primary CV safety as an end point. The results showed that testosterone therapy was noninferior to placebo with respect to the incidence of MACE. However, a mild higher incidence of atrial fibrillation, acute kidney injury, and pulmonary embolism was observed in the testosterone group [77]. The latter observations, however, need to be confirmed since previous available data do not support an increased risk of venous thromboembolism [78, 164] or major arrhythmias [165] after testosterone therapy. Similarly, the long-term follow-up (median of 5.1 years since last injection) of the T4DM study showed no differences in self-reported rates of new diagnosis of CVD [166].

In conclusion, current available data from interventional studies suggest that there is no increased risk up to three years of testosterone therapy [167-171]. The currently published evidence has reported that testosterone therapy in men with diagnosed hypogonadism has neutral or beneficial actions on MACE in patients with normalised testosterone levels. The findings could be considered sufficiently reliable for at least a three year course of testosterone therapy, after which no available study can exclude further or long-term CV events [172, 173].

3.5.5.1 Cardiac Failure

Testosterone therapy is contraindicated in men with severe chronic cardiac failure because fluid retention may lead to exacerbation of the condition. Some studies have shown that men with moderate chronic cardiac failure may benefit from low doses of testosterone, which achieve mid-normal range testosterone levels [160, 174, 175]. An interesting observation is that untreated hypogonadism increased the re-admission and mortality rate in men with heart failure [176]. If a decision is made to treat hypogonadism in men with chronic cardiac failure, it is essential that the patient is followed up carefully with clinical assessment and both testosterone and haematocrit measurements on a regular basis.

*3.5.6 **Erythrocytosis***

An elevated haematocrit level is the most common adverse effect of testosterone therapy. Stimulation of erythropoiesis is a normal biological action that enhances the delivery of oxygen to testosterone-sensitive tissues (e.g., striated, smooth and cardiac muscle). Any elevation above the normal range for haematocrit usually becomes evident between three and twelve months after testosterone therapy initiation. However, polycythaemia can also occur after any subsequent increase in testosterone dose, switching from topical to parenteral administration and, development of comorbidity, which can be linked to an increase in haematocrit (e.g., respiratory or haematological diseases).

There is no evidence that an increase of haematocrit up to and including 54% causes any adverse effects. If the haematocrit exceeds 54% there is a testosterone independent, but weak associated rise in CV events and mortality [79, 177-179]. Any relationship is complex as these studies were based on patients with any cause of secondary polycythaemia, which included smoking and respiratory diseases. There have been no specific studies in men with only testosterone-induced erythrocytosis.

As detailed, the TRAVERSE study, which had included symptomatic hypogonadal men aged 45-80 years who had pre-existing or a high risk of CVD, showed a mild higher incidence of pulmonary embolism, a component of the adjudicated tertiary end point of venous thromboembolic events, in the testosterone therapy than in the placebo group (0.9% vs. 0.5%) [77]. However, three previous large studies have not shown any evidence that testosterone therapy is associated with an increased risk of venous thromboembolism [180, 181]. Of those, one study showed that an increased risk peaked at six months after initiation of testosterone therapy, and then declined over the subsequent period [182]. In one study venous thromboembolism was reported in 42 cases

and 40 of these had a diagnosis of an underlying congenital thrombophilia (including factor V Leiden deficiency, prothrombin mutations and homocysteinuria) [183]. A meta-analysis of RCTs of testosterone therapy reported that venous thromboembolism was frequently related to underlying undiagnosed thrombophilia-hypofibrinolysis disorders [78]. In an RCT of testosterone therapy in men with chronic stable angina there were no adverse effects on coagulation, by assessment of tissue plasminogen activator or plasminogen activator inhibitor-1 enzyme activity or fibrinogen levels [184]. Similary, another meta-analysis and systematic review of RCTs found that testosterone therapy was not associated with an increased risk of venous thromboembolism [164]. With testosterone therapy elevated haematocrit levels are more likely to occur if the baseline level is toward the upper limit of normal prior to initiation. Added risks for raised haematocrit on testosterone therapy include smoking or respiratory conditions at baseline. Higher haematocrit is more common with parenteral rather than topical formulations. Accordingly, a large retrospective two-arm open registry, comparing the effects of long-acting testosterone undecanoate and testosterone gels showed that the former preparation was associated with a higher risk of haematocrit levels > 50%, when compared to testosterone gels [185]. In men with pre-existing CVD extra caution is advised with a definitive diagnosis of hypogonadism before initiating testosterone therapy and monitoring of testosterone as well as haematocrit during treatment.

Elevated haematocrit in the absence of comorbidity or acute CV or venous thromboembolism can be managed by a reduction in testosterone dose, change in formulation or if the elevated haematocrit is very high by venesection (500 mL), even repeated if necessary, with usually no need to stop the testosterone therapy.

*3.5.7 **Obstructive Sleep Apnoea***

There is no evidence that testosterone therapy can result in the onset or worsening of sleep apnoea. Combined therapy with Continuous Positive Airway Pressure (CPAP) and testosterone gel was more effective than CPAP alone in the treatment of obstructive sleep apnoea [186]. In one RCT, testosterone therapy in men with severe sleep apnoea reported a reduction in oxygen saturation index and nocturnal hypoxaemia after seven weeks of therapy compared to placebo, but this change was not evident after eighteen weeks' treatment and there was no association with baseline testosterone levels [187].

*3.5.8 **Follow-up***

Testosterone therapy alleviates symptoms and signs of hypogonadism in men in a specific time-dependent manner. The TTrials clearly showed that testosterone therapy improved sexual symptoms as early as three months after initiation [93]. Similar results have been derived from meta-analyses [78, 85]. Hence, the first evaluation should be planned after three months of treatment. Further evaluation may be scheduled at six months or twelve months, according to patient characteristics, as well as results of biochemical testing (see below). Patients at high risk of developing elevated haematocrit should be evaluated every three months during the first year of testosterone therapy and at least every six months thereafter. Accordingly, current guidelines suggest that haematocrit should be maintained below 45% in patients with polycythaemia vera to avoid thromboembolism risk [188]. Similarly, data derived using a multi-institutional database including a large cohort of hypogonadal (total testosterone < 12 nmol/L) men who received testosterone therapy and subsequently did (n=5,887) or did not (n=4,2784) develop polycythaemia (haematocrit > 52%) showed that men who had an increased haematocrit had a higher risk of MACE or venous thromboembolism mostly during the first year of therapy [189]. The risk was even higher when a haematocrit threshold of 54% was considered whilst no risk was observed when a 50% threshold was applied [189]. Table 6 summarises the clinical and biochemical parameters that should be monitored during testosterone therapy.

TTrials were designed to maintain the serum testosterone concentration within the normal range for young men (280–873 ng/dL or 9.6-30 nmol/L) [93]. This approach resulted in a good benefit/risk ratio. A similar approach could be considered during follow-up. The correct timing for the evaluation of testosterone levels varies according to the type of preparation used (Table 5). Testosterone is involved in the regulation of erythropoiesis [120] and prostate growth [61], hence evaluation of PSA and haematocrit should be mandatory before and during testosterone therapy. However, it is important to recognise that the risk of PCa in men aged < 40 years is low. Similarly, the mortality risk for PCa in men aged > 70 years has not been considered high enough to warrant monitoring in the general population [190]. Therefore, any screening for PCa through the determination of PSA and DRE in men aged < 40 or > 70 years during testosterone therapy should be discussed with the patients.

Baseline and, at least, annual glyco-metabolic profile evaluation may be a reasonable consideration, particularly in the management of functional hypogonadism. Testosterone therapy may be beneficial for hypogonadal men with low or moderate fracture risk [107]; therefore, dual energy X-ray absorptiometry (DEXA) bone scan may also be considered at baseline and 18-24 months following testosterone therapy, particularly in patients with more severe hypogonadism [107].

Digital rectal examination may detect prostate abnormalities that can be present even in men with normal PSA values. Hence, DRE is mandatory in all men at baseline and is recommended to be performed at least annually during testosterone therapy, as long as there is no significant increase in PSA velocity.

The decision to stop testosterone therapy or to perform a prostate biopsy due to PSA increase or prostate abnormalities should be based on local PCa guidelines. There is a large consensus that any increase of haematocrit > 54% during testosterone therapy requires therapy withdrawal and phlebotomy to avoid potential adverse effects including venous-thromboembolism and CVD, especially in high-risk individuals. In patients with lower risk of relevant clinical sequelae, the situation can be alternatively managed by reducing testosterone dose and switching formulation along with venesection. A positive family history of venous-thromboembolism should be carefully investigated and the patient counselled about testosterone therapy to avoid/prevent thrombophilia-hypofibrinolysis [78]. Finally, caution should be exercised in men with pre-existing CVD or at higher risk of CVD [77].

Table 6: Clinical and biochemical parameters to be checked during testosterone therapy

Parameters		Year 1 of treatment			After year 1 of treatment	
	Baseline	3 months	6 months	12 months	Annually	18-24 months
Clinical						
Symptoms	X	X	X	X	X	
Body Mass Index	X			X	X	
Waist circumference	X	X		X	X	
Digital rectal examination	X			X	X	
Blood pressure	X	X		X	X	
Biochemistry						
PSA (ng/mL)	X	X	X[2]	X	X	
Haematocrit (%)	X	X	X[1,2]	X	X	
Testosterone	X	X		X	X	
Lipid and glycaemic profile	X			X	X	
Instrumental						
DEXA	X					X

[1]Population with polycythaemia vera or at high risk of secondary polycythaemia (e.g., sleep apnea, morbid obesity, heavy smokers, chronic obstructive pulmonary disease); [2]Prostate cancer survivors.

3.5.9 Summary of evidence and recommendations on safety and monitoring in testosterone treatment

Summary of evidence	LE
Testosterone therapy is contraindicated in men with secondary hypogonadism who desire fertility.	1a
Testosterone therapy is contraindicated in men with active prostate cancer or breast cancer, as these patients are usually excluded from RCTs.	1a
Testosterone therapy does not increase the risk of prostate cancer, but long-term prospective follow-up data are required to validate this statement.	1a
The effect of testosterone therapy in men with severe lower-urinary tract symptoms is limited, as these patients are usually excluded from RCTs.	1a
There is no substantive evidence that testosterone therapy, when replaced to normal levels, results in the development of major adverse cardiovascular events.	1a
There is no evidence of a relationship between testosterone therapy and mild, moderate or CPAP-treated severe sleep apnoea.	1b

Recommendations	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 lack of sufficient safety data on long-term follow-up.	Weak
Restrict treatment to patients with a low risk of recurrent PCa*. Treatment should start after at least one year of follow-up with prostate-specific antigen (PSA) level < 0.01 ng/mL.	Weak
Advise patients that safety data on the use of testosterone therapy in men treated for breast cancer are unknown.	Strong
Assess cardiovascular risk factors before commencing testosterone therapy.	Strong
Assess men with known cardiovascular disease (CVD) for cardiovascular symptoms before initiating testosterone therapy and monitor these men 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 starting testosterone therapy.	Strong
Monitor testosterone, and haematocrit at three, six and twelve months after testosterone therapy initiation, and thereafter annually. A haematocrit > 54% requires testosterone therapy adjustment or withdrawal and venesection if required. Re-introduce testosterone therapy at a lower dose once the haematocrit has normalised and consider switching to topical testosterone preparations.	Strong
Evaluate patients with polycythaemia vera and those with a higher risk of developing elevated haematocrit every three months during the first year of testosterone therapy, and at least every six months thereafter.	Strong
Evaluate total PSA in PCa survivors at three, six and twelve months during the first year of testosterone therapy, and annually thereafter.	Strong

**As for EAU risk groups for biochemical recurrence of localised or locally advanced prostate cancer (see EAU Prostate Cancer Guidelines, 2024)*

4. EPIDEMIOLOGY AND PREVALENCE OF SEXUAL DYSFUNCTION AND DISORDERS OF MALE REPRODUCTIVE HEALTH

4.1 Erectile dysfunction

Epidemiological data have shown a high prevalence and incidence of ED worldwide [191]. Among others, the Massachusetts Male Aging Study (MMAS) [192] reported an overall prevalence of 52% ED in non-institutionalised men aged 40-70 years in the Boston area; specific prevalence for minimal, moderate, and complete ED was 17.2%, 25.2%, and 9.6%, respectively. In the Cologne study of men aged 30-80 years, the prevalence of ED was 19.2%, with a steep age-related increase from 2.3% to 53.4% [193]. The incidence rate of ED (new cases per 1,000 men annually) was 26 in the long-term data from the MMAS study [194] and 19.2 (mean follow-up of 4.2 years) in a Dutch study [195]. In a cross-sectional real-life study among men seeking first medical help for new-onset ED, one in four patients were younger than 40 years, with almost 50% of the young men complaining of severe ED [196]. Differences among these studies can be explained by differences in methodology, ages, and socio-economic and cultural status of the populations studied. The prevalence rates of ED studies are reported in Table 1 online supplementary evidence: https://uroweb.org/guidelines/sexual-and-reproductive-health/publications-appendices.

4.2 Premature ejaculation

The highest prevalence rate of 31% (men aged 18-59 years) was found by the National Health and Social Life Survey (NHSLS), which determines adult sexual behaviour in the USA [197]. Prevalence rates were 30% (18-29 years), 32% (30-39 years), 28% (40-49 years) and 55% (50-59 years), respectively. However, it is unlikely that the premature ejaculation (PE) prevalence is as high as 20-30% based on the relatively low number of men

who seek medical help for PE. These high prevalence rates may be a result of the dichotomous scale (yes/no) in a single question asking if ejaculation occurred too early, as the prevalence rates in European studies have been significantly lower [198]. Two separate observational, cross-sectional surveys from different continents found that the overall prevalence of PE was 19.8 and 25.8%, respectively [199, 200]. Further stratifying these complaints into the classifications defined by Waldinger *et al.*, [201], rates of lifelong PE were 2.3 and 3.18%, acquired PE 3.9 and 4.48%, variable PE 8.5 and 11.38% and subjective PE 5.1 and 6.4%, respectively [199, 200]. Both studies showed that men with acquired PE were more likely to seek treatment compared to men with lifelong PE. The prevalence rates of premature ejaculation as evidenced by the highly discrepant prevalence rates reported in Appendix 2 online supplementary evidence: https://uroweb.org/guidelines/sexual-and-reproductive-health/publications-appendices.

4.3 Other ejaculatory disorders

4.3.1 ***Delayed ejaculation***

Due to its rarity and uncertain definitions, the epidemiology of delayed ejaculation (DE) is not clear [202]. However, several well-designed epidemiological studies have revealed that its prevalence is around 3% among sexually active men [197, 203]. According to data from the NHSLS, 7.78% of a national probability sample of 1,246 men aged 18-59 years reported an inability to achieve climax or ejaculation [197]. In a similar stratified national probability sample survey completed over six months among 11,161 men and women aged 16-44 years in Britain, 0.7% of men reported an inability to reach orgasm [204]. In an international survey of sexual problems among 13,618 men aged 40–80 years from 29 countries, 1.1-2.8% of men reported that they frequently experience inability to reach orgasm [205]. Another study conducted in the United States (USA), in a national probability sample of 1,455 men aged 57-85 years, 20% of men reported an inability to climax and 73% reported that they were bothered by this problem. [206]. Similar to PE, there are distinctions among lifelong, acquired and situational DE [207]. Although the evidence is limited, the prevalence of lifelong and acquired DE is estimated at 1 and 4%, respectively [208].

4.3.2 ***Anejaculation and Anorgasmia***

Establishing the exact prevalence of anejaculation and anorgasmia is difficult since many men cannot distinguish between ejaculation and orgasm. The rarity of these clinical conditions further hampers the attempts to conduct epidemiological studies. In a report from the USA, 8% of men reported unsuccessfully achieving orgasm during the past year [197].

According to Kinsey *et al.*, [209], 0.14% of the general population has anejaculation. The most common causes of anejaculation were spinal cord injury, diabetes mellitus and multiple sclerosis. Especially in most cases of spinal cord injury, medical assistance is the only way to ejaculate. While masturbation leads to the lowest rates of ejaculation, higher response rates can be obtained with penile vibratory stimulation or acetylcholine esterase inhibitors followed by masturbation in patients with spinal cord injury [210].

4.3.3 ***Retrograde ejaculation***

Similar to anejaculation, it is difficult to estimate the true incidence of retrograde ejaculation (RE). Although RE is generally reported in 0.3-2% of patients attending fertility clinics [211], diabetes may increase these rates by leading to autonomic neuropathy. Autonomic neuropathy results in ED and ejaculatory dysfunctions ranging from DE to RE and anejaculation, depending on the degree of sympathetic autonomic neuropathy involved [212]. In 54 diabetic patients with sexual dysfunction, RE was observed with a 6% incidence [213]. In a controlled trial, RE was observed in 34.6% of diabetic men [214]. A trial reported the rate of RE among 57 type-1-diabetes mellitus patients (aged 18-50 years) was at least 8.8% [215]. Retrograde ejaculation was also reported in studies of patients who had undergone transurethral resection of prostate (TURP) or open prostatectomy due to disrupted bladder neck integrity. A study of the effect of prostatectomy on QoL in 5,276 men after TURP, found that 68% reported post-surgical RE [216]. However, with the development of less invasive techniques, the incidence of RE decreases following the surgical treatment of LUTS [217-221].

4.3.4 ***Painful ejaculation***

Painful ejaculation is a common but poorly understood clinical phenomenon, which is associated with sexual dysfunction. Several studies demonstrated its prevalence to range between 1-10% in the general population [222-224]; however, it may increase to 30-75% among men with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) [225-229]. It should be noted that the design of most of these studies was not scientifically sound and the condition was probably under-reported due to the lack of an evidence-based definition and well-defined prognostic criteria.

*4.3.5 **Haemospermia***

The exact incidence and prevalence of haemospermia is difficult to elucidate due to a number of factors including its covert presentation, usually self-limiting nature and patient embarrassment. The symptoms represent 1-1.5% of all urological referrals and occur in all age groups, with a mean age of 37 years [230, 231]. In a PCa screening study of 26,126 men, aged ≥ 50 years or older than 40 with a history of PCa or of black ethnicity, haemospermia was found in 0.5% on entry to the trial [232].

4.4 Low sexual desire

The global prevalence of low sexual desire in men is 3-28% [205, 233, 234]. Low solitary and dyadic sexual desires have been reported in 68% and 14% of men, respectively [235]. Also, low sexual desire has been observed as a common complaint in gay men, with a prevalence of 19-57% [236, 237]. Despite its relationship with age, low sexual desire has also been reported among young men (18-29 years), with a prevalence of 6-19% [197, 238, 239].

5. MANAGEMENT OF ERECTILE DYSFUNCTION

5.1 Definition and classification

Erectile dysfunction (ED) is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance [240]. Erectile dysfunction may affect psychosocial health and have a significant impact on the QoL of patients and their partner's [192, 241-243]. Erectile dysfunction is commonly classified into three groups based on aetiology: organic, psychogenic and mixed ED. However, this classification should be used, with caution as most cases are actually of mixed aetiology. It has therefore been suggested to use the terms "primary organic" or "primary psychogenic".

5.2 Risk factors

Erectile dysfunction is associated with numerous risk factors including age, diabetes mellitus, dyslipidaemia, hypertension, CVD, obesity, MetS, hyperhomocysteinemia, lack of exercise, smoking and drug use [242, 244-255]. In addition, several therapeutic agents for CVD have been shown to have a detrimental effect on erectile function (EF), whereas newer drugs have exhibited a neutral or even beneficial effect [247, 256, 257]. Other reported risk factors include atrial fibrillation, hyperthyroidism, vitamin D and folic acid deficiency, hyperuricemia, depression and anxiety disorders, chronic kidney and rheumatic disease, COPD, migraine, inflammatory bowel disease and osteoporosis [252, 258-270]. In addition, a growing body of evidence has demonstrated an association between the onset of new ED in men who have had COVID-19 [1974-1976].

Erectile dysfunction is also frequently associated with other urological conditions and procedures including LUTS/BPH and surgery for LUTS/BPH [275-277], chronic pelvic pain syndrome (CPPS) and chronic prostatitis [278], bladder pain syndrome/interstitial cystitis [279], premature ejaculation [280] and urethroplasty surgery for posterior urethral strictures [281].

5.3 Pathophysiology

The pathophysiology of ED may be vasculogenic, neurogenic, anatomical, hormonal, drug-induced and/or psychogenic (Table 7) [282]. In most cases, numerous pathophysiological pathways can co-exist and may all negatively impact EF.

Table 7: Urological conditions associated with ED [282]

Vasculogenic
Recreational habits (i.e., cigarette smoking)
Lack of regular physical exercise
Obesity
Cardiovascular diseases (e.g., hypertension, coronary artery disease, peripheral vasculopathy)
Type 1 and 2 diabetes mellitus; hyperlipidaemia; metabolic syndrome; hyperhomocysteinemia
Major pelvic surgery (e.g., radical prostatectomy) or radiotherapy (pelvis or retroperitoneum)

Neurogenic
Central causes
Degenerative disorders (e.g., multiple sclerosis, Parkinson's disease, multiple atrophy, etc.)
Spinal cord trauma or diseases
Stroke
Central nervous system tumours
Peripheral causes
Type 1 and 2 diabetes mellitus
Chronic renal failure, chronic liver failure
Polyneuropathy
Surgery (major surgery of pelvis/retroperitoneum) or radiotherapy (pelvis or retroperitoneum)
Surgery of the urethra (urethral stricture, open urethroplasty, etc.)
Anatomical or structural
Hypospadias, epispadias; micropenis
Phimosis
Peyronie's disease
Penile cancer (other tumours of the external genitalia)
Hormonal
Diabetes mellitus; Metabolic Syndrome (MeTS)
Hypogonadism (any type)
Hyperthyroidism
Hyper- and hypocortisolism (Cushing's disease, etc.)
Panhypopituitarism and multiple endocrine disorders
Mixed pathophysiological pathways
Chronic systemic diseases (e.g., diabetes mellitus, hypertension, MeTS, chronic kidney disease, chronic liver disorders, hyperhomocysteinemia, hyperuricemia, chronic obstructive pulmonary disease, rheumatic disease)
Psoriasis, gouty arthritis, ankylosing spondylitis, non-alcoholic fatty liver disease, chronic periodontitis, open-angle glaucoma, inflammatory bowel disease, chronic fatigue syndrome, allergic rhinitis, obstructive sleep apnoea, depression
Iatrogenic causes (e.g. TRUS-guided prostate biopsy)
Drug-induced
Antihypertensives (i.e., thiazidediuretics, beta-blockers)*
Antidepressants (e.g., selective serotonin reuptake inhibitors, tricyclics)
Antipsychotics
Antiandrogens (GnRH analogues and antagonists; 5-ARIs)
Recreational drugs (e.g., heroin, cocaine, marijuana, methadone, synthetic drugs, anabolic steroids, excessive alcohol intake)
Psychogenic
Generalised type (e.g., lack of arousal and disorders of sexual intimacy)
Situational type (e.g., partner-related, performance-related issues or due to distress)
Trauma
Penile fracture
Pelvic fracture

GnRH = gonadotropin-releasing hormone; 5-ARIs = 5α-reductase inhibitors.
**A symmetry analysis showed that cardiovascular drugs do not strongly affect the risk of subsequently being prescribed as an anti-erectogenic drug. The analysis only assessed the short-term risk [283].*

5.3.1 Pelvic surgery and prostate cancer treatment

Pelvic surgery, especially for oncological disease (e.g., radical prostatectomy (RP) [284], radical cystectomy [285] and colorectal surgery [286]), may have a negative impact on EF and overall sexual health. Surgery resulting in damage of the neurovascular bundles, that control the complex mechanism of the cavernous erectile response, may result in ED, although NS approaches have been adopted over the last few decades. To date only the surgical treatment of PCa has enough scientific evidence supporting its potential pathophysiological association with ED [287-289]. However, even non-surgical treatments of PCa (i.e., radiotherapy, or brachytherapy) can be associated with ED [287, 290, 291].

The ProtecT trial randomised 1,643 patients to active treatment (RP or RT) or active monitoring for localised PCa and assessed sexual function, including EF, using the EPIC-26 instrument [271]. At baseline, 67% of men reported erections firm enough for sexual intercourse. At the six year follow-up assessment this fell to 30% in the active monitoring group, 27%% in the RT group and 17% in the RP group, respectively.

Radical prostatectomy for the treatment of clinically localised intermediate- or high-risk PCa is a widely performed procedure. Research has shown that 25-75% of men experience post-RP ED [272, 273, 288]. Conversely, the rate of unassisted post-operative EF recovery ranges between 20 and 25% in most studies. These rates have not substantially improved or changed over the past seventeen years, despite growing attention to post-surgical rehabilitation protocols and refinement of surgical techniques [273, 274, 292]. Overall, patient age, baseline EF and surgical volume, with the subsequent ability to preserve the neurovascular bundles, are the main factors in promoting the highest rates of post-operative EF [272, 289, 293, 294]. Regardless of the surgical technique, surgeons' experience clearly impacts on post-operative EF outcome [295]. The surgical approach may also affect post-RP EF, but the current evidence conflicts with one systematic review reporting a significant advantage in favour of RARP compared to open retropubic RP for twelve-month potency rates [296] and two RCTs reporting only a small improvement in EF for RARP or no different in EF between techniques [297, 298].

Erectile dysfunction is also a common problem after both external beam radiation therapy (EBRT) and brachytherapy for PCa. A systematic review and meta-analysis including men treated with EBRT (65%), brachytherapy (31%) or both (4%) showed that the post-treatment prevalence of ED was 34% at one year and 57% at 5.5 years, respectively [299, 300]. Similar findings have been reported for stereotactic radiotherapy with 26-55% of previously sexually functioning patients reporting ED at five years [301].

Recently other modalities have emerged as potential therapeutic options in patients with clinically-localised PCa, including high-intensity focused US (HIFU), cryo-therapeutic ablation of the prostate (cryotherapy), focal padeliporfin-based vascular-targeted photodynamic therapy and focal RT by brachytherapy or CyberKnife®. All these approaches have been reported to have a less-negative impact on EF with many studies reporting a complete recovery at one-year follow-up [302].

5.3.2 Summary of evidence on the epidemiology/aetiology/pathophysiology of ED

Summary of evidence	LE
Erectile dysfunction is common worldwide.	2b
Erectile dysfunction shares common risk factors with cardiovascular disease.	2b
Lifestyle modification (regular exercise and decrease in BMI) can improve erectile function.	1b
Erectile dysfunction is a symptom, not a disease. Some patients may not be properly evaluated or receive treatment for an underlying disease or condition that may be causing ED.	4
Erectile dysfunction is common after RP, irrespective of the surgical technique used.	2b
Erectile dysfunction is common after external radiotherapy and brachytherapy.	2b
Erectile dysfunction is less common after cryotherapy and high-intensity focused US.	2b

5.4 Diagnostic evaluation (basic work-up)

5.4.1 Medical and sexual history

The first step in evaluating ED is always a detailed medical and sexual history of patients and, when available, their partners [303]. Figure 2 lists the minimal diagnostic evaluation (basic work-up) in patients with ED.

A detailed description should be made of the rigidity and duration of both sexually-stimulated and morning erections and problems with sexual desire, arousal, ejaculation, and orgasm [304-306]. Validated psychometric questionnaires, such as the IIEF [307] or its short version (i.e., Sexual Health Inventory for Men; SHIM) [308], help to assess the different sexual function domains (i.e. sexual desire, EF, orgasmic function, intercourse satisfaction, and overall satisfaction), as well as the potential impact of a specific treatment modality. Similarly, structured interviews allow the identification and quantification of the different underlying factors affecting EF [309].

Psychometric analyses also support the use of the Erectile Hardness Score (EHS) for the assessment of penile rigidity in practice and clinical trials research [310].

Patients should always be screened for symptoms of possible hypogonadism, including decreased libido and energy, and fatigue (see Table 3: Specific symptoms associated with LOH).

*5.4.2 **Physical examination***

Every patient must be given a physical examination focused on the genitourinary, endocrine, vascular and neurological systems [311, 312]. A physical examination may reveal unsuspected diagnoses, such as Peyronie's disease (PD), pre-malignant or malignant genital lesions, prostatic enlargement or irregularity/nodularity, or signs and symptoms suggestive of hypogonadism (see Table 3: Specific symptoms associated with LOH).

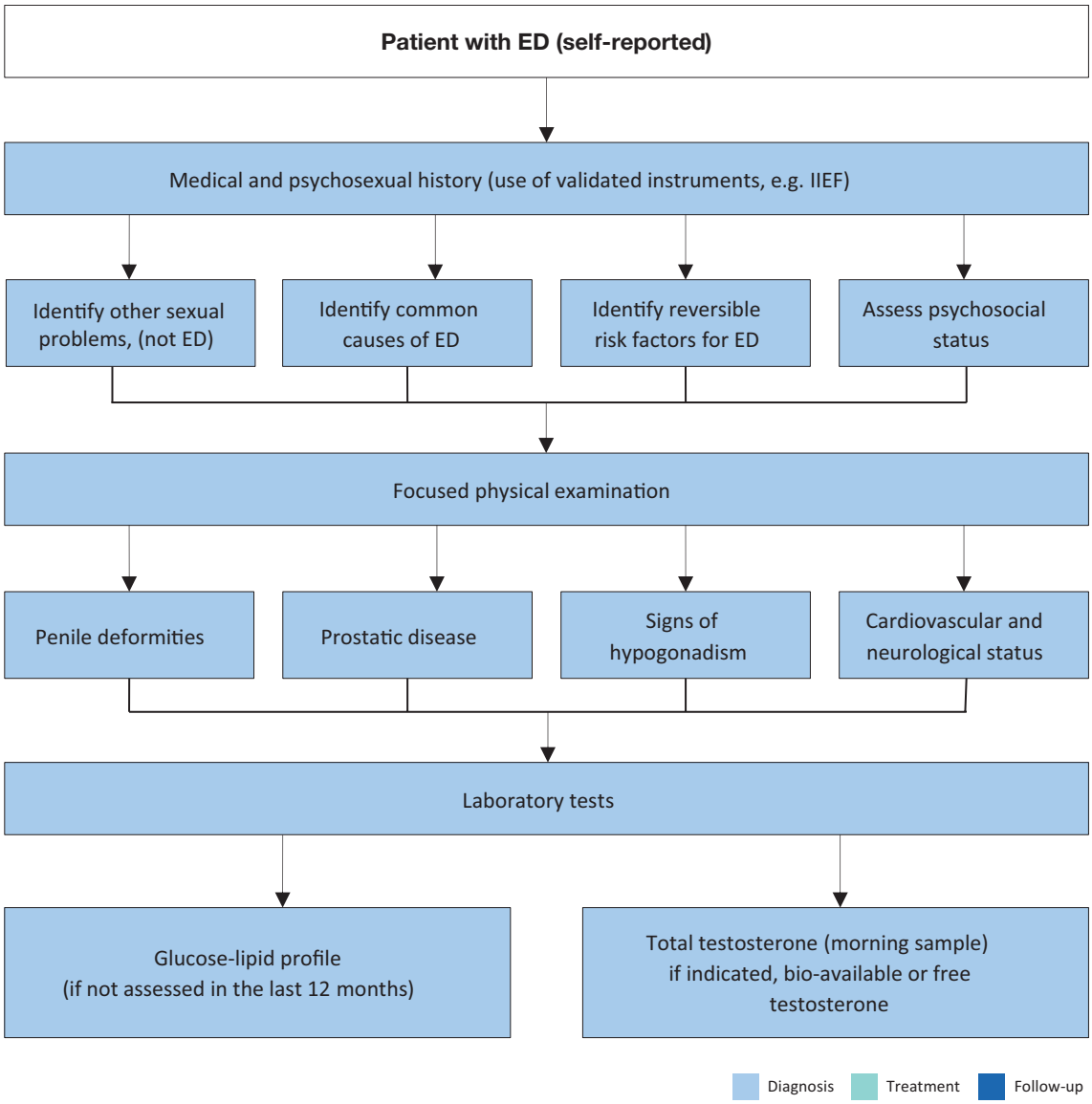
Blood pressure and heart rate should be measured if they have not been assessed in the previous three to six months. Likewise, either BMI calculation or waist circumference measurement should be undertaken to assess patients for comorbid conditions (e.g., MetS).

*5.4.3 **Laboratory testing***

Patients should undergo a fasting blood glucose or haemoglobin A1c and lipid profile measurement if they have not been assessed in the previous twelve months. Hormonal tests should include early morning total testosterone in a fasting state. The bio-available or calculated fT values may sometimes be needed to corroborate total testosterone measurements (see sections 3.2.1 and 3.4.1). Additional laboratory tests may be considered in selected patients with specific signs and associated symptoms (e.g., total PSA) [313], PRL and LH [314]). Although physical examination and laboratory evaluation of most men with ED may not reveal the exact diagnosis, clinical and biochemical evaluation presents an opportunity to identify comorbid conditions [312].

Figure 2: Minimal diagnostic evaluation (basic work-up) in patients with ED

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



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

5.4.4 Cardiovascular system and sexual activity: the patient at risk

Patients who seek treatment for sexual dysfunction have a high prevalence of CVDs. Overall, ED can improve the sensitivity of screening for asymptomatic CVD in men with diabetes [315, 316]. Erectile dysfunction significantly increases the risk of CVD, coronary heart disease, stroke and atrial fibrillation [317]. Longitudinal data from an observational population-based study of 965 men without CVD showed that younger men (especially those < 50 years) with transient and persistent ED have an increased Framingham CVD risk [318].

The current EAU Guidelines on the diagnosis and treatment of men with ED have been adapted from the recommendations from the Princeton Consensus conferences on sexual dysfunction and cardiac risk published in 2012 [319]. Over time, the Princeton Consensus (Expert Panel) Conference is dedicated to optimising sexual function and preserving cardiovascular health [319-322]. Accordingly, patients with ED have been stratified into three cardiovascular risk categories (Table 8), which can still be used as the basis for a treatment algorithm for initiating or resuming sexual activity (Figure 3): low-risk patients do not need cardiac testing or evaluation before initiation or resumption of sexual activity or therapy for sexual dysfunction; intermediate risk patients, according to the results of testing, may be moved to either the high- or low-risk group; high-risk individuals should be referred for cardiac assessment and treatment. Sexual activity should be stopped until the patient's cardiac condition has been stabilised by treatment.

Table 8: Cardiac risk stratification (based on 2nd and 3rd Princeton Consensus) [319, 322]

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 cardiomyopathies
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.

Figure 3: Treatment algorithm for determining level of sexual activity according to cardiac risk in ED (based on 3rd Princeton Consensus) [319]

[a] *Sexual activity is equivalent to walking 1 mile on the flat in 20 minutes or briskly climbing two flights of stairs in 10 seconds.*

[b] *Sexual activity is equivalent to 4 minutes of the Bruce treadmill protocol.*

5.5 Diagnostic Evaluation (advanced work-up)

Most patients with ED can be managed based on their medical and sexual history; conversely, some patients may need specific diagnostic tests (Table 9).

*5.5.1 **Nocturnal penile tumescence and rigidity test***

The nocturnal penile tumescence and rigidity (NPTR) test applies nocturnal monitoring devices that measure the number of erectile episodes, tumescence (circumference change by strain gauges), maximal penile rigidity, and duration of nocturnal erections. The NPTR assessment should be performed on at least two separate nights. A functional erectile mechanism is indicated by an erectile event of at least 60% rigidity recorded on the tip of the penis that lasts for ≥ 10 minutes [323]. Nocturnal penile tumescence and rigidity monitoring is an approach for objectively differentiating between organic and psychogenic ED (patients with psychogenic ED usually have normal findings in the NPTR test). However, many potential confounding factors (e.g., situational) may limit its routine use for diagnostic purposes [324].

*5.5.2 **Intracavernous injection test***

The intracavernous injection test gives limited information about vascular status. A positive test is a rigid erectile response (unable to bend the penis) that appears within 10 minutes after the intracavernous injection and lasts for 30 minutes [325]. Overall, the test *per se* is inconclusive as a diagnostic procedure and a duplex Doppler study of the penis should be requested, if clinically warranted.

*5.5.3 **Dynamic duplex ultrasound of the penis***

Dynamic duplex ultrasound (US) of the penis is a second-level diagnostic test that specifically studies the haemodynamic pathophysiology of EF. Therefore, in clinical practice, it is usually applied in those conditions in which a potential vasculogenic aetiology of ED (e.g., diabetes mellitus, multiple concomitant CV risk factors and/or overt peripheral vascular disease, renal transplantation and poor responders to oral therapy) is suspected. Peak systolic blood flow > 30 cm/s, end-diastolic velocity < 3 cm/s and resistance index > 0.8 are considered normal [326, 327]. Recent data suggest that duplex scanning as a haemodynamic study may be better at tailoring therapy for ED, such as for low-intensity shock wave treatment (Li-SWT) in men with vasculogenic ED [328]. Further vascular investigation is unnecessary if a duplex US examination is normal.

*5.5.4 **Arteriography and dynamic infusion cavernosometry or cavernosography***

Pudendal arteriography should be performed only in patients who are being considered for penile revascularisation [329]. At present, dynamic infusion cavernosometry or cavernosography are rarely employed as diagnostic methods for evaluating venogenic ED, and there has been concern surrounding the concept of venogenic ED.

*5.5.5 **Psychopathological and psychosocial assessment***

Mental health issues and psychological distress are frequently comorbid with ED [330]. This is most evident for depression and anxiety-related disorders, but may also include transitory states of altered mood (i.e., dysfunctional affective states resulting from a specific life stressor or crisis) [264, 331, 332]. Relationship factors, including lack of satisfaction with the partner, poor sexual relationships, length of the relationship, or feeling emotionally disconnected from the partner during sex, have been related to erectile difficulties and dysfunction [331, 333, 334]. In contrast, intimacy was found to be a protective factor in ED [253, 335]. Additionally, the cognitive factors underpinning organic and non-organic ED (i.e., all dysfunctional thinking styles and expectations about sexuality, poor self-esteem and cognitive distraction from erotic cues) must also be assessed.

Psychosexual assessment in ED cases includes a clinical interview considering all the previous topics [336]. Also, self-reported measures are frequently used within the psychosocial context [337]. A growing amount of data suggests that men who have sex with men (MSM) present specific psychological risks associated with erectile capability regarding anal sex [338]. Therefore, professionals must tailor their assessment in the context of sexual minorities.

Figure 4: Psychopathological and psychosocial assessment

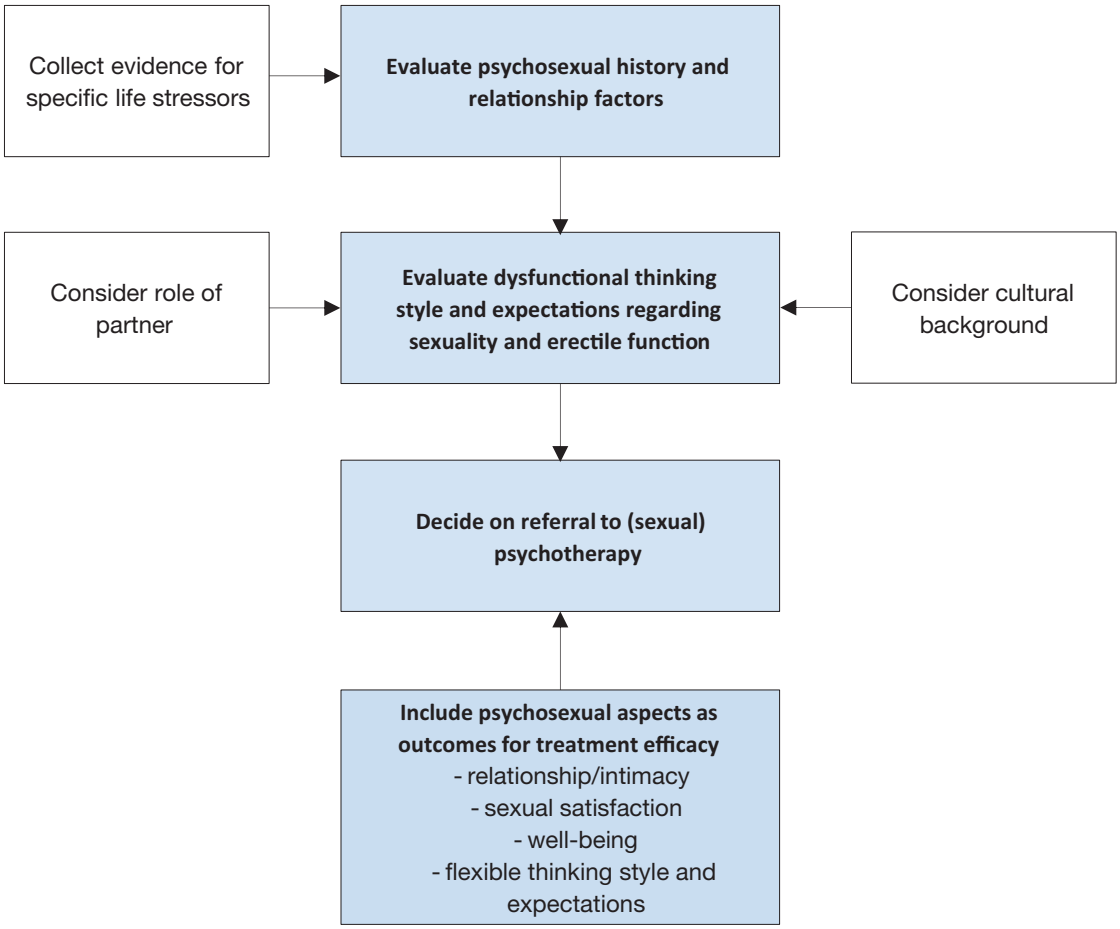


Table 9: Indications for specific diagnostic tests for ED and the specific diagnostic tests

Indications for specific diagnostic tests for ED
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 that might require surgical correction (e.g., Peyronie's disease and 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, and sexual abuse).
Specific diagnostic tests for ED
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

5.5.6 Summary of evidence and recommendations for diagnostic evaluation of ED

Summary of evidence	LE
Medical and sexual history, physical examination and laboratory testing including metabolic and hormonal profile may identify risk factors for ED and may help in defining the ED aetiology.	3
Validated psychometric questionnaires (e.g. IIEF; EHS) are reliable tools to assess ED severity.	3
Specific diagnostic tests could be of help in discerning between vasculogenic, hormonal or psychogenic causes of ED	3

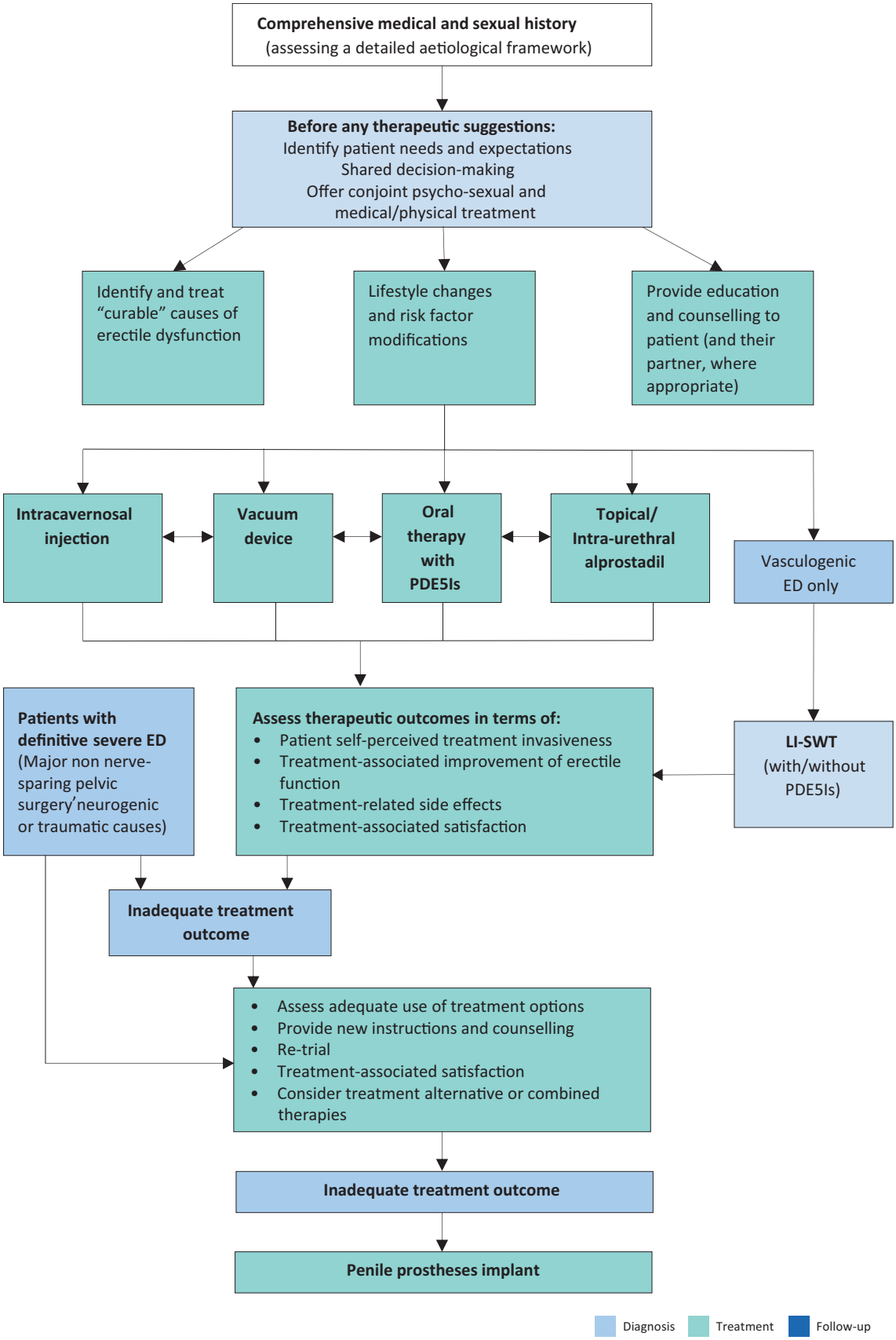
Recommendations	Strength rating
Take a comprehensive medical and sexual history in every patient presenting with erectile dysfunction (ED). Take a targeted psychosexual history, including life stressors, cultural aspects, and cognitive factors regarding patient sexual performance.	Strong
Use a validated questionnaire related to ED to assess all sexual function domains (e.g., International Index of Erectile Function) 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
Evaluate 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 9.	Strong

5.6 Treatment of erectile dysfunction

The Guidelines Panel have developed a comprehensive therapeutic and decision-making algorithm (Figure 5) for treating ED. The treatment algorithm was developed as an alternative to the traditional three-tier concept, to support personalised treatment tailored to individual patients, according to the invasiveness, tolerability and effectiveness of the different therapeutic options and patients' expectations. In this context, patients should be fully counselled with respect to all available treatment modalities.

The majority of men with ED are not treated with cause-specific therapeutic options. This results in a tailored treatment strategy that depends on invasiveness, efficacy, safety and costs, as well as patient preference [339]; therefore, physician-patient dialogue is essential throughout the management of ED. A systematic review has shown a consistent discontinuation rate for all available ED treatment options. This highlights the importance of clinicians understanding patient's beliefs about ED treatment, therapeutic ineffectiveness, adverse effects, quality of intimate relationships and treatment costs all of which were shown to be the most prevalent barriers to treatment use [340].

Figure 5: Management algorithm for erectile dysfunction



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

*5.6.1 **Patient education***

Educational intervention is often the first approach to sexual complaints, and consists of informing patients about the psychological and physiological processes involved in the individual's sexual response, in ways the patient can understand. This baseline approach has been shown to favour sexual satisfaction in men with ED [341]. Accordingly, consultation with the patient should include a discussion of the expectations and needs of the patient's and his sexual partner. It should also review the patient's and partner's understanding of ED and the results of diagnostic tests, and provide a rationale for treatment selection [339].

*5.6.2 **Modifiable risk factors***

Erectile dysfunction may be associated with modifiable or reversible risk factors, including lifestyle or drug-related factors [342]. These factors may be modified either before, or at the same time as, specific therapies are used. Likewise, ED may be associated with concomitant and underlying conditions (e.g., endocrine disorders and metabolic disorders such as diabetes, and some cardiovascular problems such as hypertension) which should always be well-controlled as the first step of any ED treatment [343]. Overall, several studies have shown that lifestyle modifications including physical activity, weight loss and treatment for CVD risk factors and lipid-lowering therapy with statins may be of help in improving sexual function in men with ED [257, 342, 344-349].

*5.6.3 **Phosphodiesterase type 5 inhibitors***

Four potent selective PDE5Is have been approved by the EMA for the treatment of ED [350]. The efficacy of all four PD5EIs in almost every subgroup of patients with ED has been successfully established [350-353]. Efficacy is defined as an erection, with rigidity, sufficient for satisfactory intercourse [343]. In addition, adverse events for the four PDE5Is are generally mild and self-limiting [354-358]. The pharmacokinetic data for all four PDE5Is and their associated adverse events are presented in Tables 10 and 11, respectively. The choice of PDE5I depends on the frequency of intercourse and the patient's personal experience. Two meta-analyses demonstrated that ED patients who prioritise high efficacy should use sildenafil 50 mg whereas those who optimise tolerability should initially use tadalafil 10 mg [351, 359].

5.6.3.1 Sildenafil

Sildenafil is administered in doses of 25, 50 and 100 mg. The recommended starting dose is 50 mg and should be adapted according to the patient's response and adverse effects [360]. The window of effectiveness ranges from 30-60 minutes after administration [360] up to 12 hours [361]. In a 24-week dose-response study, improved erections were reported by 56%, 77% and 84% of general ED patients taking 25, 50 and 100 mg sildenafil, respectively, compared to 25% of men taking placebo [362]. Sildenafil also significantly improved patient scores for IIEF, sexual encounter profile question 2 (SEP2), SEP question 3 (SEP3), General Assessment Questionnaire (GAQ) and treatment satisfaction [362]. Furthermore, an orally disintegrating tablet (ODT) of sildenafil citrate at a dose of 50 mg has been developed, mainly for patients who have difficulty swallowing solid dosage forms.

5.6.3.2 Tadalafil

Tadalafil is administered in on-demand doses of 10 and 20 mg or a daily dose of 5 mg. The recommended on-demand starting dose is 10 mg and should be adapted according to the patient's response and adverse effects [363, 364]. The window of effectiveness ranges from 30 minutes after administration (peak efficacy after approximately 2 hours) up to 36 hours [363]. In a twelve-week dose-response study, improved erections were reported by 67% and 81% of men with ED taking 10 and 20 mg tadalafil, respectively, compared to 35% of men taking placebo [363]. Tadalafil has also been shown to have a net clinical benefit in the short-term on ejaculatory and orgasmic functions in ED patients [365].

Data have also shown that 40% of men aged > 45 years were combined responders for ED and LUTS/BPH when treated with tadalafil 5 mg once daily, with symptom improvement after twelve weeks [366]. Therefore, its use may be considered in both patients with ED only and in patients also complaining of concomitant LUTS, and wishing to benefit from a single therapy [367].

5.6.3.3 Vardenafil

Vardenafil is administered in on-demand doses of 5, 10 and 20 mg. The recommended starting dose is 10 mg and should be adapted according to the patient's response and adverse effects [356]. Vardenafil is effective from 30 minutes after administration [368], with one of three patients achieving satisfactory erections within 15 minutes of ingestion [369]. In a twelve-week dose-response study, improved erections were reported by 66%, 76% and 80% of men with ED taking 5, 10 and 20 mg vardenafil, respectively, compared with 30% of men taking placebo [356, 370]. Vardenafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction. An orodispersable tablet (ODT) formulation of vardenafil has also been released [370]. The efficacy of vardenafil ODT has been demonstrated in several RCTs and did not seem to differ from the regular formulation [371-373].

5.6.3.4 Avanafil

Avanafil is administered in on-demand doses of 50, 100 and 200 mg [357]. The recommended starting dose is 100 mg taken as needed 15-30 minutes before sexual activity and the dose may be adapted according to efficacy and tolerability [357, 358, 374]. In a general ED population the mean percentage of successful sexual attempts resulting in intercourse were 47%, 58% and 59% for the 50, 100 and 200 mg groups, respectively, as compared with 28% for the placebo group [357, 358]. A meta-analysis confirmed that avanafil had comparable efficacy with sildenafil, vardenafil and tadalafil [375].

5.6.3.5 Continuous use of PDE5Is

According to the EMA, a once-daily regimen with tadalafil 2.5 or 5 mg may be considered suitable, based on patients' choice and physicians' judgement. In these patients, the recommended dose is 5 mg, taken once daily at approximately the same time each day. Tadalafil, 5 mg once daily, provides an alternative to on-demand tadalafil for couples who prefer spontaneous rather than scheduled sexual activities or who anticipate frequent sexual activity, with the advantage that dosing and sexual activity no longer need to be linked. Regardless of the type of ED population, there is no clinically significant difference between a tadalafil treatment administered once daily vs. on-demand tadalafil [376]. Overall, treatment with tadalafil 5 mg once daily in men complaining of ED of various severities is well-tolerated and effective [377] and may improve EF among men who have a partial response to on-demand PDE5I therapy [378]. The appropriateness of the continuous use of a daily regimen should be re-assessed periodically [377, 379].

Table 10: Pharmacokinetics data for PDE5Is EMA approved for the treatment of ED*

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%
Bioavailability	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 11: Common adverse events of the four PDE5Is currently EMA-approved to treat ED*

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.*

5.6.3.6 Safety concerns for PDE5Is

5.6.3.6.1 Cardiovascular safety

No RCTs or open-label studies have demonstrated an increase in myocardial infarction rates in patients receiving PDE5Is. None of the PDE5Is have an adverse effect on total exercise time or time-to-ischaemia during exercise testing in men with stable angina [350, 380]. This EAU Guidelines panel agrees to maintain the recommendations provided by the 3rd Princeton Consensus Panel in terms of the prescription of all PDE5Is in patients with CVD or in those with high CV risk [319, 321, 322].

5.6.3.6.2 Contraindications for the concomitant use of organic nitrates and nicorandil

An absolute contraindication to PDE5Is is the concomitant use of any form of organic nitrate or NO donors including recreational use of amyl nitrite or nitrate (poppers). Concomitant use results in cGMP accumulation unpredictable falls in blood pressure and symptoms of hypotension [381-384]. Concurrent use of nicorandil and PDE5Is is contraindicated due to the potential of the nitric oxide donating properties of nicorandil to increase cGMP levels [385].

5.6.3.6.3 Antihypertensive drugs

Co-administration of PDE5Is with antihypertensive agents may result in small additive decreases in blood pressure, which are usually minor [319]. In general, the adverse event profile of a PDE5I is not worsened by a background of antihypertensive medication, even when the patient is taking several antihypertensive agents [386].

5.6.3.6.4 Interactions with α-blockers

Tadalafil 5 mg is currently the only licensed drug for the treatment of both ED and LUTS demonstrating overall good efficacy in relieving urinary symptoms and improving EF [367]. Therefore, treatment with tadalafil 5 mg should be considered in patients suffering from mild to moderate LUTS associated with ED either alone or in combination with α-blockers. Conversely, as both drugs are vasodilators a certain degree of caution has been observed for combination therapy with PDE5Is and alpha-blockers due to the potential cumulative effects on blood pressure described in some studies [361, 369, 387]. However, a meta-analysis concluded that a concomitant treatment with α-blockers [both non-uroselective (e.g., terazosin and doxazosin) and uro-selective (e.g., alfuzosin, tamsulosin and silodosin] and PDE5Is may produce changes in haemodynamic parameters, but it does not increase the rate of adverse events due to hypotension [387]. Therefore, there is no current limitation in the simultaneous use of α-blockers and PDE5I.

5.6.3.7 Management of non- or poor-responders to PDE5Is

The management of non-responders depends upon identifying the underlying cause [388].

Clinicians should begin by ensuring that the medication has been properly prescribed, is being correctly used by the patient and that the patient has been using a licensed medication. Absorption of sildenafil, vardenafil and avanafil can be delayed by high-fat meals [389-391]. Timing is important and patients may be waiting either too short or too long after the medication before attempting sexual intercourse. Studies suggest that patient education can help salvage an apparent non-responder to a PDE5I [388, 392-395]. After emphasising the importance of dose, timing, and sexual stimulation to the patient, EF can be effectively restored following re-administration of the relevant PDE5I [388, 392, 393].

Studies have demonstrated that hypogonadal patients not responding to PDE5Is may improve their response to PDE5Is after initiating testosterone therapy [85, 343, 396]. Therefore, if diagnostic criteria suggestive of testosterone deficiency are present, testosterone therapy may be more appropriate even in ED patients [3, 85].

Limited data suggest that some patients might respond better to one PDE5I than to another [397], raising the possibility that, despite an identical mode of action, switching to a different PDE5I may be beneficial. However, no evidence for this has been reported in the available RCTs [398, 399].

In refractory, complex, or difficult-to-treat cases of ED combination therapy should be considered as a first-line approach. Although the available data are still limited, combining PDE5I with antioxidant agents, Li-SWT or a vacuum erection device (VED) improves efficacy outcomes, without any significant increase in adverse events [400]. Similarly, the association of daily tadalafil with a short-acting PDE5I (such as sildenafil) leads to improved outcomes, without any significant increase in adverse effects [401].

5.6.3.8 Topical/Intraurethral alprostadil

The vasoactive agent alprostadil can be administered inside the urethra in two different formulations. The first delivery method is topical, using a cream that includes a permeation enhancer to facilitate the absorption of alprostadil (200 and 300 µg) via the urethral meatus [402, 403]. Clinical data are still limited. Significant improvement compared to placebo was recorded for IIEF-EF domain score, SEP2 and SEP3 in a broad range of patients with mild-to-severe ED [404]. Adverse effects include penile erythema, penile burning, and pain that usually resolve within two hours of application. Topical alprostadil (VITAROSTM) at a dose of 300 µg is available in some European countries. Recently, a randomised cross-over clinical trial has shown that, compared to the standard administration route, direct delivery within the urethral meatus can increase efficacy and confidence among patients, without increasing adverse effects [405].

The second delivery method is by intra-urethral insertion of a specific formulation of alprostadil (125-1000 µg) in a medicated pellet (MUSE™) [229]. Erections sufficient for intercourse are achieved in 30-65.9% of patients. In clinical practice, it is recommended that intra-urethral alprostadil is initiated at a dose of 500 µg, as it has a higher efficacy than the 250 µg dose, with minimal differences with regards to adverse events. In case of unsatisfactory clinical response, the dose can be increased to 1000 µg [406-408]. Overall, the most common adverse events are local pain (29-41%) and dizziness with possible hypotension (1.9-14%). Penile fibrosis and priapism are rare (< 1%). Urethral bleeding (5%) and urinary tract infections (0.2%) are adverse events related to the mode of administration.

Efficacy rates are significantly lower than for intracavernous pharmacotherapy [409], with 30% adherence to long-term therapy. Intraurethral pharmacotherapy provides an alternative to intracavernous injections in patients who prefer a less-invasive, although less-efficacious treatment.

*5.6.4 **Psychosocial intervention and therapy***

Psychosocial interventions including different modalities (e.g., sexual skills training, marital therapy, psychosexual education) [341], and Cognitive and Behavioural Therapy (CBT - group or couple format), are recommended [336]. Cognitive and Behaviour Therapy is aimed at altering dysfunctional cognitive and behavioural patterns influencing ED, and increasing adjustment during the course of the disorder. The CBT approach combined with medical treatment for ED has received empirical support and is considered an optimal procedure [410].

*5.6.5 **Hormonal treatment***

When clinically indicated, testosterone therapy (intramuscular, transdermal, or oral) can be considered for men with low or low-normal testosterone levels and concomitant problems with their sexual desire, EF and dissatisfaction derived from intercourse and overall sex life (see Section 3.4 for a comprehensive discussion of testosterone therapy) [411].

*5.6.6 **Vacuum erection devices***

Published data report that efficacy, in terms of erections satisfactory for intercourse, is as high as 90%, regardless of the cause of ED and satisfaction rates range between 27% and 94% [412, 413]. Long-term use of VEDs decreases to 50-64% after two years [414]. The most common adverse events include pain, inability to ejaculate, petechiae, bruising, and numbness [413]. Serious adverse events (skin necrosis) can be avoided if patients remove the constriction ring within 30 minutes. Vacuum erection devices are contraindicated in patients with bleeding disorders or on anticoagulant therapy [415, 416]. Vacuum erection devices may be the treatment of choice in well-informed older patients with infrequent sexual intercourse and comorbidity requiring non-invasive, drug-free management of ED [412, 413, 417].

*5.6.7 **Intracavernous injections therapy***

Intracavernous administration of vasoactive drugs was the first medical treatment introduced for ED [395, 418]. Patients may be offered intracavernous injections at every stage of a tailored treatment work-up.

5.6.7.1 Alprostadil

Alprostadil (Caverject™, Edex/Viridal™) was the first and only drug approved for intracavernous treatment of ED [395, 419]. Intracavernous alprostadil is most efficacious as a monotherapy at a dose of 5-40 µg (40 µg may be offered off-label in some European countries). The erection appears after 5-15 minutes and lasts according to the dose injected, but with significant heterogeneity among patients. An office-training programme is required for patients to learn the injection technique. Efficacy rates for intracavernous alprostadil of > 70% have been found in the general ED population, as well as in patient subgroups (e.g., men with diabetes or CVD), with reported satisfaction rates of 87-93.5% in patients and 86-90.3% in partners after the injections [395, 418]. Complications of intracavernous alprostadil include penile pain (50% of patients reported pain only after 11% of total injections), excessively prolonged and undesired erections (5%), priapism (1%), and fibrosis (2%) [395, 418, 420]. Pain is usually self-limited after prolonged use and it can be alleviated with the addition of sodium bicarbonate or local anaesthesia [395, 418, 421]. Cavernosal fibrosis usually clears within a few months after temporary discontinuation of the injection programme. However, tunical fibrosis suggests early onset of Peyronie's disease and may indicate the need to discontinue intracavernous injections indefinitely. Systemic adverse effects are uncommon. The most common is mild hypotension, especially when using higher doses. Contraindications include men with a history of hypersensitivity to alprostadil, men at risk of priapism, and men with bleeding disorders. Despite these favourable data, drop-out rates of 41-68% have been reported for intracavernous pharmacotherapy [395, 418, 422, 423], with most discontinuations occurring within the first two to three months. Careful counselling of patients during the office-training phase as well as close follow-up are important in addressing patient withdrawal from an intracavernous injection programme [424-426].

5.6.7.2 Other vasoactive intracavernous treatments

Table 12 details the available intracavernous injection therapies (compounds and characteristics). Combination therapy enables a patient to take advantage of the different modes of action of the drugs being used, as well as alleviating adverse effects by using lower doses of each drug.

- Papaverine (20-80 mg) was the first oral drug used for intracavernous injections. It is most commonly used in combination therapy because of its high incidence of adverse effects as monotherapy. Papaverine is currently not licensed for the treatment of ED.
- Phentolamine has been used in combination therapy to increase efficacy. As monotherapy, it produces a poor erectile response. Phentolamine is currently not licensed for the treatment of ED.
- Limited data support the use of other drugs, such as vasoactive intestinal peptide (VIP), NO donors (linsidomine), forskolin, potassium channel openers, moxisylyte or calcitonin gene-related peptide, usually combined with the main drugs [427, 428]. Most combinations are not standardised and some drugs have limited availability worldwide.
- Bimix, (papaverine 7.5-45 mg plus phentolamine 0.25-1.5 mg) and Trimix (papaverine 8-16 mg plus phentolamine 0.2-0.4 mg plus alprostadil 10-20 µg), have been widely used with improved efficacy rates, although they have never been licensed for ED [429, 430]. Trimix has the highest efficacy rates, reaching 92%; this combination has similar adverse effects as alprostadil monotherapy, but a lower incidence of penile pain due to lower doses of alprostadil. However, fibrosis is more common (5-10%) when papaverine is used (depending on the total dose).
- Invicorp™: Vasoactive intestinal peptide (25 µg) plus phentolamine mesylate (1-2 mg Invicorp), is a combination of two active components with complementary modes of action. Clinical studies have shown that the combination is effective for intracavernous injections in > 80% of men with ED, including those who have failed to respond to other therapies and, unlike existing intracavernous therapies, is associated with a low incidence of penile pain and a virtually negligible risk of priapism [431].

Overall, despite high efficacy rates, 5-10% of patients do not respond to combination therapy with intracavernous injections.

Table 12: Intracavernous injection therapy - compounds and characteristics

Name	Substance	Dosage	Efficacy	Adverse Events	Comment
Caverject™ or Edex/Viridal™	Alprostadil	5-40 µg/mL	~ 70%	Penile pain, priapism, fibrosis	Easily available
Papaverine	Papaverine	20 - 80 mg	< 55%	Elevation of liver enzymes, priapism, fibrosis	Abandoned as monotherapy
Phentolamine	Phentolamine	0.5 mg/mL	Poor efficacy as monotherapy	Systemic hypotension, reflex tachycardia, nasal congestion, and gastrointestinal upset	Abandoned as monotherapy
Bimix	Papaverine + Phentolamine	30 mg/mL + 0.5 mg/mL	~ 90%	Similar to Alprostadil (less pain)	Not licensed for the treatment of ED
Trimix	Papaverine + Phentolamine + Alprostadil	30 mg/mL + 1 mg/mL + 10 µg/mL	~ 92%	Similar as Alprostadil (less pain)	Not licensed for the treatment of ED
Invicorp™	Vasoactive intestinal peptide (VIP) + Phentolamine	25 µg + 1-2 mg	~ 80%	Similar to Alprostadil without pain	Easily available

5.6.8 ***Innovative treatment modalities***

There are currently several potential novel treatment modalities for ED. Most of these therapeutic approaches require further investigation in large-scale, blinded, placebo-controlled randomised studies to achieve adequate evidence-based and clinically-reliable recommendation grades [432-437].

5.6.8.1 Regenerative medicine therapies

5.6.8.1.1 Shockwave therapy

The use of low-intensity extracorporeal shock wave therapy (Li-SWT) has been increasingly proposed as a treatment for vasculogenic ED over the last decade, and it's the only currently marketed treatment that might offer a cure, which is the most desired outcome for most men suffering from ED [328, 438-445].

Overall, several single-arm trials have shown a beneficial effect of Li-SWT on patient-reported EF, but data from prospective randomised trials are conflicting, and many questions remain to be answered due to the heterogeneity among shockwave generators, type of shockwaves delivered, set-up parameters and treatment protocols [446, 447]. In a trial trying to assess the best treatment parameters, no significant differences were observed between various energy flux density levels; although, a 0.10 mJ/mm^2 seems to perform slightly better than lower energies [448]. Most of the studies have suggested that Li-SWT can significantly increase IIEF and EHS scores in patients with mild vasculogenic ED, although this improvement appears modest and the rates of patients reporting a satisfactory improvement range between 40-80% [328, 446]. Few studies have shown an improvement in penile haemodynamic parameters after Li-SWT, but the clinical meaning of this improvement remains unclear [446, 449]. Likewise, data suggest that Li-SWT could ameliorate erection quality even in patients with severe ED who are either PDE5Is non-responders [443, 450, 451] or inadequate responders [452], thus reducing the immediate need for more invasive treatments. Treatment effect appears to be clinically evident starting from one to three months after treatment completion, with a subsequent progressive decrease of the achieved benefit in terms of EF over time, although some effects could be still detected up to five years after treatment [446, 448, 453]. Data from RCTs suggests that even better results could be achieved by combining Li-SWT with other treatments such as a VED in men with T2DM [454] or daily tadalafil [455, 456].

Findings from a recent meta-analysis showed that LI-ESWT has a positive effect on early recovery of EF in the context of penile rehabilitation of ED after RP. However, the authors clearly outlined that the level of evidence was low; therefore, careful interpretation of the results is required [457-459].

5.6.8.1.2 Platelet-Rich Plasma

Intracavernous injection of platelet-rich plasma (PRP) has been investigated in several prospective and retrospective trials [460-466]. The regenerative effect of PRP is deemed to be exerted through the high concentrations of platelets containing several growth factors including VEGF, EGF, IGF-1, PDGF and FGF [467]. These factors may be responsible for angiogenesis stimulation and stem cell recruitment [467].

In the first RCT investigated the effect of intracavernous injection of PRP for ED, 60 patients with mild to moderate vasculogenic ED were randomised to receive two injections of 10 mL PRP (n=30) or placebo (n=30) [466]. At one, three and six-month follow-up, the rate of patients reporting minimal clinically important difference (MCID) in the IIEF-EF score was significantly higher in the treatment group, with 69% achieving MCID six months after PRP vs. 27% in the placebo group ($p < 0.001$). IIEF-EF scores improved by a mean of 2.7 points at one-month and 3.9 points at six-month assessment after treatment. Regarding safety, no haemorrhagic events or other side effects were reported [466].

A prospective randomized, double-blind, placebo-controlled study was carried out on 109 patients, aged 45-65 years, with mild to moderate ED, following cessation of any ED treatment [468]. At one, three and six months after PRP injections, patients in the PRP group had a significant improvement compared to placebo in terms of IIEF-EF, SEP2 and SEP3. Moreover, at six months post-treatment follow-up, 70% of patients achieved an MCID in the PRP group compared to 16% in the placebo group [468]. Even more recently, a further prospective, randomized, double-blind, placebo-control study on a relatively small cohort of mild to moderate ED patients who have been treated with two PRP injections separated by one month showed that the treatment is safe, but the authors did not find any difference in efficacy between PRP and placebo [469]. Of clinical relevance, patients were allowed to keep PDE5is during the study [469].

As a whole, despite a number of promising results that have been obtained for the treatment of primary organic ED in terms of both efficacy and safety of PRP, the available evidence is still insufficient to provide a recommendation regarding the use of PRP for ED treatment in clinical practice [470]. In this context, an important heterogeneity among studies still exists in terms of timing and dosing regimens, with no consensus regarding the optimal activation method and platelet concentration for each PRP injection, and the need to measure qualitative and quantitative composition of growth factors and cytokines [470, 471]. Therefore, intracavernous injection of PRP should be used only in a clinical trial setting, as larger trials are needed to confirm original findings and define the efficacy and safety of PRP for ED.

5.6.8.1.3 Stem-cells

The use of stem cells as a regenerative treatment for ED is currently under investigation. A systematic review has concluded that five completed human clinical trials have shown promise for stem cell therapy as a restorative treatment for ED [472]. However, data are still insufficient for providing a clinical recommendation.

5.6.8.2 Botulinum Neurotoxin

Botulinum Neurotoxin A (BoNT-A) has been investigated as a possible ED treatment [473]. Two RCTs have investigated the effect of BoNT-A for the treatment of patients with ED who were non-responders to PDE5Is or ICI pro-erectile drugs [474, 475]. One trial randomised 70 patients with ED refractory to PDE5Is to receive a single ICI of 100 UI of BoNT-A or saline [474]. Patients in both groups were instructed to keep using on-demand high-dose PDE5Is. The RCT showed an improvement in EHS and PSV at two weeks post-treatment. At six weeks the treatment group showed a 5 points improvement in the SHIM score vs. no improvement in the placebo group, with 53% of patients reporting an erection hard enough for vaginal penetration [474]. The second trial randomised 176 patients, all non-responders to PDE5Is or ICI trimix, to three treatment groups: BoNT-A 100 UI; BoNT-A 50 UI; or placebo [475]. A significant improvement in SHIM, EHS and SEP scores was reported in both treatment groups with a maximum response rate being reacted three months after treatment. Overall, the RCT showed that up to 40% of patients were able to resume satisfactory sexual activity after treatment [475]. Both trials reported only mild local side-effects with no systemic complications.

Other single-arm, non-controlled studies have confirmed these findings [476, 477]; therefore, showing a promising role for BoNT-A in the treatment of patients who are non-responders to well-established ED therapies. However, at present no recommendation for its use in clinical practice can be provided as larger trials are needed to confirm original findings and define the efficacy and safety of BoNT-A for ED.

5.6.9 ***Herbal medicine and natural supplements***

In recent years there has been an exponential growth in the market of medicinal herbs and natural supplements for the treatment of ED, but with very little available evidence of robust scientific data to support their efficacy and safety. A Cochrane review showed that ginseng may only have trivial effects on erectile function or satisfaction with intercourse compared to placebo when assessed using validated tools [478]. Moreover, data suggested that daily administration of oral L-arginine, only when in combination with PDE5I use, improves sexual function [479].

5.6.10 ***Erectile dysfunction after radical prostatectomy***

The use of pro-erectile drugs following RP is important in achieving post-operative EF and allowing patients to resume sexual activity. Several trials have shown improvements in EF after RP in patients receiving drugs (any therapeutic or prophylactic) for ED. Early compared with delayed EF treatment affects the natural recovery time for EF [480], although there is limited data to support any specific regimen, which is either optimal for penile rehabilitation or may result in the achievement of spontaneous, non-pharmacologically assisted erections [289, 481, 482]. In prospective studies, there is no evidence that penile rehabilitation itself increases the chances of spontaneous recovery of EF in men following nerve-sparing RP (NSRP) [482]. The currently available therapeutic armamentarium follows the treatment algorithm for ED, which is shown in Figure 3.

In this context, PDE5Is have been considered as the first-line therapy in patients who have undergone NS surgery, regardless of the surgical technique used [289, 293]. Several clinical parameters have been identified as potential predictors of PDE5Is outcomes in men undergoing RP, i.e., patient age, baseline EF, and quality of NS technique are key factors in preserving post-RP EF [293, 296, 483].

A Cochrane review analysing data from eight RCTs showed that scheduled PDE5Is may have little or no effect on short-term (up to twelve months) self-reported potency when compared to placebo or no treatment [484]. In this study, a daily PDE5I made little to no difference in short- and long-term EF. The authors conclude that penile rehabilitation strategies using PDE5I following RP do not increase self-reported EF compared to on-demand use.

Intracavernous injections and penile implants have been traditionally suggested as second- and third-line treatments, respectively, when oral PDE5Is are not adequately effective or not suitable for post-operative patients [289, 485]. A meta-analysis showed that the early use of VED has an excellent therapeutic effect on post-RP patients and no serious adverse effects, therefore it should be considered as a therapeutic alternative [486]. Findings from two network meta-analyses showed that combination therapy with VED and PDE5is offers clear advantages over monotherapy, even in post-RP patients; therefore, this combined approach should be considered in the clinical management of ED after RP [487].

Findings from a systematic review suggested that pelvic floor muscle training (PFMT) combined with bio-feedback is a promising alternative to pharmacological treatments, although there is a need for future well-powered, rigorously designed RCTs to draw strong conclusions [488].

5.6.11 Surgical management

5.6.11.1 Surgery for post-traumatic arteriogenic ED

In young patients with pelvic or perineal trauma, surgical penile revascularisation has a 60-70% long-term success rate [416, 489]. The stenosis must be confirmed by penile pharmaco-arteriography. Corporeal veno-occlusive dysfunction is a contraindication to revascularisation.

5.6.11.2 Venous ligation surgery

Venous ligation surgery for veno-occlusive dysfunction is no longer recommended because of poor long-term results [489].

5.6.11.2.1 Penile prostheses

The surgical implantation of a penile prosthesis may be considered in patients who i) are not suitable for different pharmacotherapies or prefer a definitive therapy; and, ii) do not respond to other treatment modalities (Figure 5) [490].

The two currently available classes of penile implants include inflatable (two- and three-piece) and semi-rigid devices (malleable, mechanical and soft flexible) [293, 491-494]. There are currently no head to head studies comparing the different manufacturers' implants, demonstrating superiority of one implant type over another [495]. Patients may prefer the three-piece inflatable devices due to the more "natural" erections obtained, although no prospective RCTs have compared satisfaction rates with both types of implants. The two-piece inflatable prosthesis can be a viable option among patients who are deemed at high-risk of complications with reservoir placements (e.g., previous abdominal surgery). Semi-rigid prostheses result in a firm penis, which may be manually placed in an erect or flaccid state and offer the advantage of a simple implant technique, as well as easy use for the patient [293, 491-493]. Conversely, they can have the disadvantage of unnatural persistent erection and reduced concealability [493, 496]. They may also be an option in men with limited manual dexterity.

There are two main surgical approaches for penile prosthesis implantation: peno-scrotal and infrapubic [492, 493, 496, 497]. A systematic review comparing the satisfaction and complication rates of the different surgical approaches has shown that there is no specific advantage between the two, but rather it is recommended that surgeons have knowledge of both techniques and are capable of tailoring the incision strategy for complex cases [498]. Regardless of the indication, prosthesis implantation has one of the highest satisfaction rates (92-100% in patients and 91-95% in partners) among the treatment options for ED with appropriate counselling [293, 491, 492, 499-507]. Focused psychosexual counselling may improve sexuality and sexual well-being in both patients and their partners after penile implant surgery [508]. There is sufficient evidence to recommend this approach in patients who do not respond to less-invasive treatments due to its high efficacy, safety and satisfaction rate [509].

The two main complications of penile prosthesis implantation are mechanical failure and infection. Several technical modifications of the most commonly used three-piece prostheses (e.g., AMS 700CX/CXR™ and Titan Zero degree™) resulted in mechanical failure rates of < 5% after five years of follow-up [491, 510, 511]. Careful surgical techniques with appropriate antibiotic prophylaxis against Gram-positive and negative bacteria reduced infection rates to 2-3% with primary implantation in low-risk patients and high-volume centres [512-515]. The infection rate may be further reduced to 1-2% by implanting an antibiotic-impregnated prosthesis (AMS Inhibizone™) or hydrophilic-coated prosthesis (Coloplast Titan™) [491, 512, 516-519]. Methods that appear to decrease infection rates include using coated prosthesis and strictly adhering to surgical techniques and protocols that avoid prolonged wound exposure and minimise skin contact (i.e., no-touch technique).
Techniques that might prevent penile prostheses infection but lack definitive evidence include the use of prolonged post-operative antibiotics (> 24 hours), shaving with clippers, and preparation with chlorhexidine-alcohol [520, 521]. Identification and pre-treatment of patients who are colonised with nasal *Staphylococcus aureus* with mupirocin and chlorhexidine before surgery has been shown to reduce the incidence of post-operative surgical site infection from 4.4% to 0.9% RCT [522].

A large database-study has shown that diabetes mellitus is a risk factor for penile prostheses infection, highlighting the need for optimal patient selection [667]. Unfortunately, there are no RCTs determining the ideal and/or correct threshold of glycated haemoglobin that is acceptable prior to implant surgery in diabetic patients [523]. Also, there are no RCTs establishing the optimal or appropriate threshold of glycated haemoglobin deemed acceptable before implant surgery in diabetic patients [524]. A large-cohort, multicentre, retrospective analysis in men with diabetes who received a Coloplast Titan™ implant demonstrated that vancomycin plus gentamicin was the most efficacious combination of antibiotics used for implants dipping in terms of preventing postoperative infection and subsequent explantation and revision [525].

Prosthetic infection requires removal of the prosthesis and antibiotic administration. Alternatively, removal of the infected device with immediate salvage and replacement with a new prosthesis has been described using a wash-out protocol with successful salvages achieved in > 80% of cases [513, 526-528]. An absolute recommendation on how to proceed after explantation in this setting cannot be given and must be focused on the pros and cons of salvage therapy after full consultation with the patient.

Besides infection and mechanical failure, impending implant erosion involving the distal corpora, urethra, or glans can occur in 1-6% of cases after surgery [529]. Similarly, glans ischaemia and necrosis have been reported in about 1.5% of patients [529, 530]. Risk factors for these serious complications are higher in those patients with significant vascular impairment, such as patients with diabetes, or who have undergone concomitant lengthening procedures.

5.6.12 Summary of evidence and recommendations for treatment of ED

Summary of evidence
Lifestyle changes can lead to ED improvement in specific populations.
PDE5Is are associated with significant improvement of erectile function (EF) with a good overall safety profile.
There are no demonstrated differences among different PDE5Is in terms of treatment efficacy.
Topical/intraurethral alprostadil is effective in improving EF but data are still limited.
Vacuum therapy can improve EF with a wide range of treatment satisfaction rate.
Intracavernous injection with alprostadil is an effective treatment for ED; however, it has relatively high treatment drop-out rates.
Low-intensity shockwave therapy can a mild improvement in EF among patients with vasculogenic ED.
Intracavernous injections of PRP have led to a mild improvement of EF among patients with organic ED, but the available evidence is still insufficient to provide a recommendation regarding its use.
BoNT-A has been shown to improve response rate to medical treatment for ED in patients who were non-responsive to oral or injective therapies, but data are still limited.
Penile rehabilitation with PDE5Is after RP does not increase the chance of spontaneous EF recovery.
Penile prosthesis implantation is associated with high satisfaction rate among patients with ED.
There is no difference in terms of efficacy and safety among different penile implants available or surgical approaches used.

Recommendations	**Strength rating**
Fully inform patients of the mechanism of action and how phosphodiesterase type 5 inhibitors (PDE5Is) should be taken, as incorrect use/inadequate information is the main causes of a lack of response to PDE5Is.	Strong
Direct the patient to Cognitive Behaviour Therapy as a psychological approach (include the partner), when indicated, combined with medical treatment to maximise treatment outcomes.	Strong
Discuss with patients undergoing active treatment for prostate cancer (PCa) about the risk of sexual changes other than erectile dysfunction (ED), including sexual desire reduction, changes in orgasm, anejaculation, Peyronie like disease and penile size changes.	Strong
Initiate lifestyle changes and risk factor modification prior to, or at the same time as, initiating ED treatments.	Strong
Use PDE5Is as first-line therapy for the treatment of ED.	Strong

Use intracavernous injections as an alternative first-line therapy in well-informed patients or as second-line therapy.	Strong
Use topical/intra-urethral alprostadil as an alternative first-line therapy in well-informed patients who: • do not wish to have or are not suitable for oral vasoactive therapy; • do not wish to have intracavernous injections; • in patients who prefer a less-invasive therapy.	Weak
Use low-intensity shockwave treatment (Li-SWT) with/without PDE5Is in patients • with mild vasculogenic ED; • as an alternative therapy in well-informed patients who do not wish to have or are not suitable for oral vasoactive therapy; • who are vasculogenic ED patients who are poor responders to PDE5Is	Weak
Use vacuum erection devices in well-informed patients requesting non-invasive, drug-free management of ED.	Weak
Implant a penile prosthesis if other treatments fail or depending upon patient preference. Patients should be fully informed of the benefits and harms associated with the procedure.	Strong
Start pro-erectile treatments at the earliest opportunity after radical prostatectomy/pelvic surgery and other curative treatments for PCa.	Weak

5.7 *Follow-up*

Follow-up is important in order to assess the efficacy and safety of the treatment provided. It is also essential to assess patient satisfaction since successful treatment for ED goes beyond efficacy and safety. Physicians must be aware that there is no single treatment that fits all patients or all situations as described in detail in the previous section.

6. DISORDERS OF EJACULATION

6.1 Introduction

Ejaculation is a complex physiological process that comprises emission and expulsion processes and is mediated by interwoven neurological and hormonal pathways [531]. Any interference with those pathways may cause a wide range of ejaculatory disorders. The spectrum of ejaculation disorders includes premature ejaculation (PE), retarded or delayed ejaculation, anejaculation, painful ejaculation, retrograde ejaculation, anorgasmia and haemospermia.

6.2 Premature ejaculation

6.2.1 Epidemiology

Historically, the main problem in assessing the prevalence of PE has been the lack of a universally recognised definition at the time that surveys were conducted [532]. See Section 4.2 for a comprehensive discussion of the epidemiology of PE.

6.2.2 Pathophysiology and risk factors

The aetiology of PE is relatively unknown, with limited data to support suggested biological and psychological hypotheses, including anxiety [533-536], penile hypersensitivity [537-544] and 5-hydroxytryptamine (HT) receptor dysfunction [545-550]. The classification of PE into four subtypes [201] has contributed to a better delineation of lifelong, acquired, variable and subjective PE [551-553]. It has been hypothesised that the pathophysiology of lifelong PE is mediated by a complex interplay of central and peripheral serotonergic, dopaminergic, oxytocinergic, endocrinological, genetic and epigenetic factors [554]. Acquired PE may occur due to psychological problems - such as sexual performance anxiety, and psychological or relationship problems and/or co-morbidity, including ED, prostatitis, hyperthyroidism and poor sleep quality [555-558]. Variable PE is considered to be a normal variation of sexual function whereas subjective PE can stem from cultural or abnormal psychological constructs [201].

A significant proportion of men with ED also experience PE [205, 559]. High levels of performance anxiety related to ED may worsen PE, with a risk of misdiagnosing PE instead of the underlying ED. According to the National Health and Social Life Survey (NHSLS), the prevalence of PE is not affected by age [197], unlike ED, which increases with age. Premature ejaculation is not affected by marital or income status [197, 560].

However, PE is more common in Black men, Hispanic men, and men from regions where an Islamic background is common [197, 561, 562] and the prevalence may be higher in men with a lower educational level [197, 205]. Other reported risk factors for PE include genetic predisposition [550, 563-566], poor overall health status and obesity [197], prostate inflammation [567-571], hyperthyroidism [555], low prolactin levels [572], high testosterone levels [573], vitamin D and B12 deficiency [574, 575], diabetes [576, 577], MetS [578, 579], lack of physical activity [580], emotional problems and stress [197, 581, 582], depressive symptoms [582], and traumatic sexual experiences [197, 205].

*6.2.3 **Impact of PE on quality of life***

Men with PE are more likely to report low satisfaction with their sexual relationship, low satisfaction with sexual intercourse, difficulty relaxing during intercourse, and less-frequent intercourse [583-585]. Premature ejaculation can have a detrimental effect on self-confidence and the relationship with the partner, and may sometimes cause mental distress, anxiety, embarrassment and depression [583, 586, 587]. Moreover, PE may also affect the partner's sexual functioning and their satisfaction with the sexual relationship decreases with increasing severity of the patient's condition [588-590]. Despite the possible serious psychological and QoL consequences of PE, few men seek treatment [198, 205, 591-594].

*6.2.4 **Classification***

There is still little consensus about the definition and classification of PE [595]. It is now universally accepted that "premature ejaculation" is a broad term that includes several concepts belonging to the common category of PE. The most recent definition comes from the International Classification of Diseases 11th Revision, where PE was renamed as Early Ejaculation [596]: *"Male early ejaculation is characterized by ejaculation that occurs prior to or within a very short duration of the initiation of vaginal penetration or other relevant sexual stimulation, with no or little perceived control over ejaculation. The pattern of early ejaculation has occurred episodically or persistently over a period of at least several months and is associated with clinically significant distress."*

This definition includes four categories: male early ejaculation, lifelong generalised and situational, acquired generalised and situational, and unspecified.

> The Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) [207] and the International Society for Sexual Medicine (ISSM) [597] published definitions for lifelong and acquired PE. These definitions are overlapping, with 3 shared factors (1. Time to ejaculation assessed by IELT; 2. Perceived control; and, 3. Distress, bother, frustration, interpersonal difficulty related to the ejaculatory dysfunction), resulting in a multi-dimensional diagnosis [597].

Two more PE syndromes have been proposed [552]:

- 'Variable PE' is characterised by inconsistent and irregular early ejaculations, representing a normal variation in sexual performance.
- 'Subjective PE' is characterised by subjective perception of consistent or inconsistent rapid ejaculation during intercourse, while ejaculation latency time is in the normal range or can even last longer. It should not be regarded as a symptom or manifestation of true medical pathology [598].

*6.2.5 **Diagnostic evaluation***

Diagnosis of PE is based on the patient's medical and sexual history [599-602]. History should classify PE as lifelong or acquired and determine whether PE is situational (under specific circumstances or with a specific partner) or consistent. Special attention should be given to the duration time of ejaculation, degree of sexual stimulus, impact on sexual activity and QoL, and drug use or abuse. It is also important to distinguish PE from ED. Many patients with ED develop secondary PE caused by the anxiety associated with difficulty in attaining and maintaining an erection [559, 603]. Furthermore, some patients are unaware that loss of erection after ejaculation is normal and may erroneously complain of ED, while the actual problem is PE [594].

6.2.5.1 Intravaginal ejaculatory latency time (IELT)

Although it has been suggested as an objective diagnostic criterion and treatment outcome measure [604, 605], the use of IELT alone is not sufficient to define PE, as there is significant overlap between men with and without PE [606, 607]. Moreover, some men may experience PE in their non-coital sexual activities (e.g., during masturbation, oral sex or anal intercourse); thus, measuring IELT will not be suitable for their assessment. Although PE is apparently less prevalent and less bothersome among men who have sex with men (MSM) [608], many of them may also suffer from PE and IELT cannot be applied to them [609, 610]. Although some studies demonstrated that MSM report longer ejaculation latency time compared to straight men [608], some others failed to demonstrate such a difference [611].

In everyday clinical practice, self-estimated IELT is sufficient [612]. Self-estimated and stopwatch-measured IELT are interchangeable and correctly assign PE status with 80% sensitivity and 80% specificity [613].

Measurement of IELT with a calibrated stopwatch is mandatory in clinical trials. For any drug treatment study of PE, Waldinger *et al.,* suggested using geometric mean instead of arithmetic mean IELT because the distributed IELT data are skewed. Otherwise, any treatment-related ejaculation delay may be overestimated if the arithmetic mean IELT is used instead of the geometric mean IELT [614].

6.2.5.2 Premature ejaculation assessment questionnaires

The need to objectively assess PE has led to the development of several questionnaires based on using PROMs. Only two questionnaires can discriminate between patients who have PE and those who do not:

- Premature Ejaculation Diagnostic Tool (PEDT): A five-item questionnaire based on focus groups and interviews from the USA, Germany, and Spain assesses control, frequency, minimal stimulation, distress and interpersonal difficulty [615]. A total score of > 11 suggests a diagnosis of PE, 9 or 10 suggests a probable diagnosis, and < 8 indicates a low likelihood of PE.

- Arabic Index of Premature Ejaculation (AIPE): A seven-item questionnaire developed in Saudi Arabia assesses sexual desire, hard erections for sufficient intercourse, time to ejaculation, control, satisfaction of the patient and partner, and anxiety or depression [616]. A cut-off score of 30 (range 7-35) discriminates PE diagnosis best. The severity of PE is classified as severe (score: 7-13), moderate (score: 14-19), mild-to-moderate (score: 20-25) and mild (score: 26-30).

Other questionnaires used to characterise PE and determine treatment effects include the Premature Ejaculation Profile (PEP) [607], Index of Premature Ejaculation (IPE) [617] and Male Sexual Health Questionnaire Ejaculatory Dysfunction (MSHQ-EjD) [618]. Currently, their role is optional in everyday clinical practice. The Masturbatory Premature Ejaculation Diagnostic Tool (MPEDT) has also been recently proposed [619], due to fact since PE patients report longer IELTs and lesser bother/distress during masturbation than partnered sex [620]; however, further validation studies are required before the routine use of this questionnaire in this population.

6.2.5.3 Physical examination and investigations

Physical examination may be part of the initial assessment of men with PE. It may include a focused examination of the urological, endocrine and neurological systems to identify underlying medical conditions associated with PE or other sexual dysfunctions, such as endocrinopathy, Peyronie's disease, urethritis or prostatitis. Laboratory or physiological testing should be directed by specific findings from history or physical examination and is not routinely recommended [601].

6.2.5.4 Recommendations for the diagnostic evaluation of PE

Summary of evidence	**LE**
A comprehensive medical history and a thorough physical examination can serve as valuable tools for clinicians in identifying the underlying medical factors contributing to PE.	3
PE can negatively impact self-confidence, strain partner relationships, and potentially lead to emotional distress, anxiety, shame, and depression.	2a
Several questionnaires can be used for the diagnosis of PE (PEDT, AIPE) and for assessing the therapeutic outcomes of PE interventions (PEP).	2b
Although relying on IELT is inadequate for characterizing PE, self-reported IELT proves satisfactory in routine clinical contexts.	3

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 patient-reported outcomes in daily clinical practice.	Weak

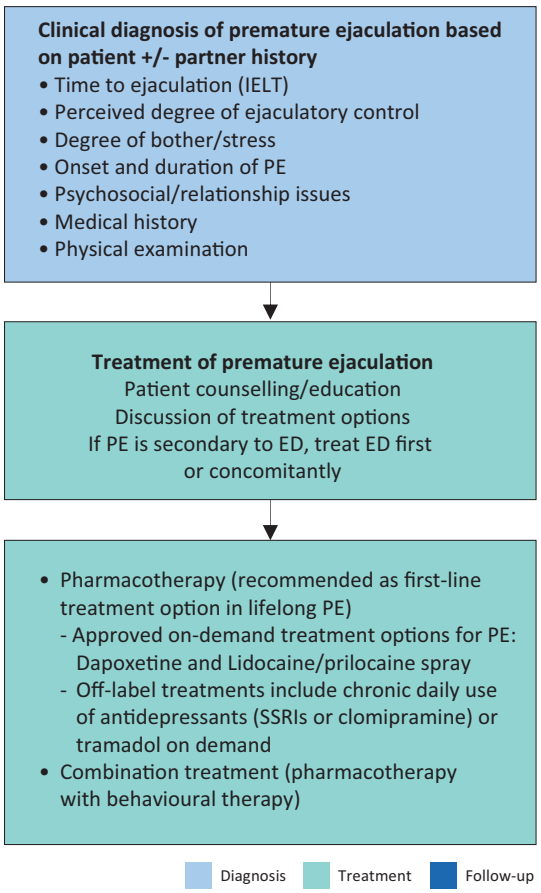
Include physical examination in the initial assessment of PE to identify anatomical abnormalities that may be associated with PE or other sexual dysfunctions, particularly erectile dysfunction.	Strong
Do not perform routine laboratory or physiological tests. They should only be directed by specific findings from history or physical examination.	Strong

6.2.6 Disease management

Before commencing any treatment, it is essential to define the subtype of PE and discuss patient's expectations thoroughly. Pharmacotherapy must be considered the first-line treatment for patients with lifelong PE, whereas treating the underlying cause (e.g., ED, prostatitis, LUTS, anxiety and hyperthyroidism) must be the initial goal for patients with acquired PE [601]. Various behavioural techniques may be beneficial in treating variable and subjective PE [621]. Psychotherapy can also be considered for PE patients who are uncomfortable with pharmacological therapy or in combination with pharmacological therapy [622, 623]. However, there is weak and inconsistent evidence regarding the effectiveness of these psychosexual interventions and their long-term outcomes in PE are unknown [624].

Dapoxetine (30 and 60 mg) is the first on-demand oral pharmacological agent approved for lifelong and acquired PE in many countries, except for the USA [625]. The metered-dose aerosol spray of lidocaine (150 mg/mL) and prilocaine (50 mg/mL) combination is the first topical formulation to be officially approved for on-demand treatment of lifelong PE by the EMA in the European Union [626]. All other medications used in PE are off-label indications [627]. In this context, daily or on-demand use of selective serotonin re-uptake inhibitors (SSRIs) and clomipramine and on-demand topical anaesthetic agents have consistently shown efficacy in PE [628-631]. The long-term outcomes of pharmacological treatments are unknown. An evidence-based analysis of all current treatment modalities was performed. Levels of evidence and grades of recommendation are provided, and a treatment algorithm is presented (Figure 6).

Figure 6: Management of premature ejaculation*

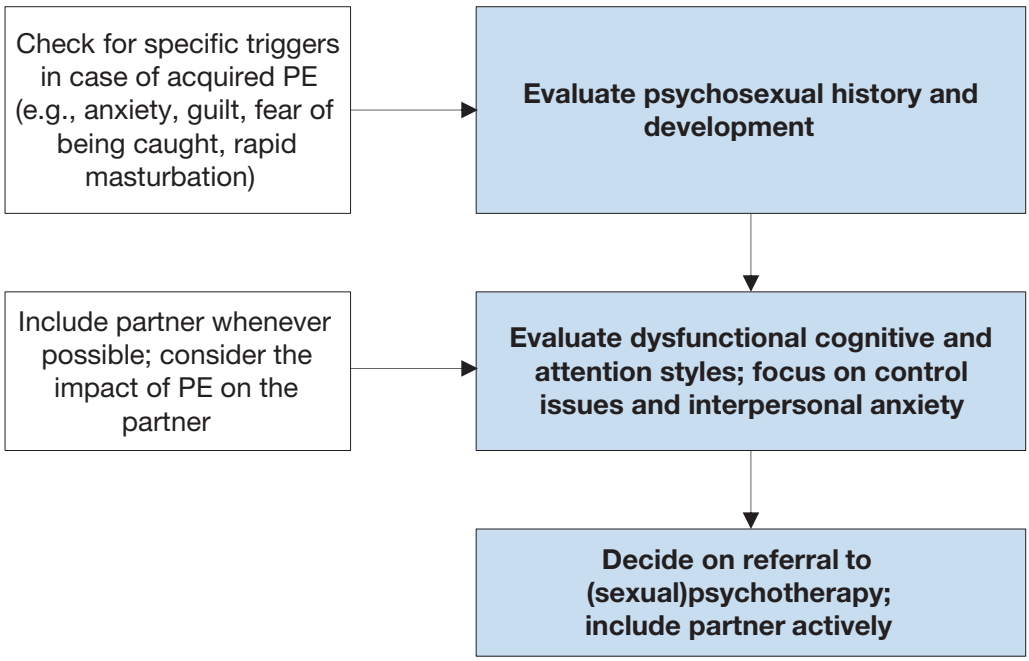


ED = erectile dysfunction; PE = premature ejaculation; IELT = intravaginal ejaculatory latency time; SSRI = selective serotonin receptor inhibitor.

6.2.6.1 Psychological aspects and intervention

Psychosexual interventions, whether behavioural, cognitive, or focused on the couple, are aimed at teaching techniques to control/delay ejaculation, gaining confidence in sexual performance, reducing anxiety, and promoting communication and problem-solving within the couple [621]. Interventions with a focus on sexual education or acceptance may be positive as well [632]. However, psychosexual interventions alone regarding PE lack empirical support. Recent evidence suggests that start-stop exercises, combined with psycho-education and mindfulness techniques improve PE symptoms, as well as PE-associated distress, anxiety and depression [633]. The potential benefits of mindfulness have been reported [634]. Behavioural therapy may be most effective when used to 'add value' to medical interventions. Smartphone-delivered psychological intervention, aimed at improving behavioural skills for ejaculatory delay and sexual self-confidence, has positive effects, supporting E-health in the context of PE [635].

Figure 7: Key aspects of psychosexual evaluation



6.2.6.1.1 Summary of evidence and recommendations for the assessment and treatment (psychosexual approach) of PE

Summary of evidence	**LE**
The incorporation of a psychosexual approach, alongside psycho-educational guidance and mindfulness techniques, ameliorates symptoms of PE and alleviate the associated distress, anxiety, and depression.	2b
The combination of psychosexual approaches and pharmacological treatments yields superior outcomes compared to pharmacological interventions alone.	3

Recommendations for assessment	**Strength rating**
Assess sexual history and psychosexual development.	Strong
Assess anxiety, and interpersonal anxiety; focus on control issues.	Strong
Include the partner if available; check for the impact of PE on the partner.	Strong
Recommendations for treatment (psychosexual approach)	
Use behavioural, cognitive and/or couple therapy approaches in combination with pharmacotherapy. Discuss the use of mindfulness exercises.	Weak

6.2.6.2 Pharmacotherapy

6.2.6.2.1 Dapoxetine

Dapoxetine hydrochloride is a short-acting SSRI with a pharmacokinetic profile suitable for on-demand treatment for PE [636]. It has a rapid T_{max} (1.3 hours) and a short half-life (95% clearance rate after 24 hours) [637, 638]. It is approved for on-demand treatment of PE in European countries and elsewhere, but not in the USA. Both available doses of dapoxetine (30 mg and 60 mg) have shown 2.5- and 3.0-fold increases, respectively, in IELT overall, rising to 3.4- and 4.3-fold in patients with a baseline average IELT < 30 seconds [639].

In RCTs, dapoxetine, 30 mg or 60 mg 1-2 hours before intercourse, was effective at improving IELT and increasing ejaculatory control, decreasing distress, and increasing satisfaction [639]. Dapoxetine has shown a similar efficacy profile in men with lifelong and acquired PE [639, 640]. Treatment-related adverse effects were dose-dependent and included nausea, diarrhoea, thirst, headache and dizziness [640]. Treatment-emergent adverse events (TEAEs) were responsible for study discontinuation in 4% (30 mg) and 10% (60 mg) of subjects [612]. There was no indication of an increased risk of suicidal ideation or suicide attempts and little indication of withdrawal symptoms with abrupt dapoxetine cessation [639, 640]. Dapoxetine is safer than formal anti-depressant compounds used for treatment of PE [641].

A low rate (0.1%) of vasovagal syncope was reported in phase 3 studies [642]. According to the summary of product characteristics, vital orthostatic signs (blood pressure and heart rate) must be measured prior to starting dapoxetine, and dose titration must be considered [643]. The EMA assessment report for dapoxetine concluded that the potentially increased risk for syncope had been proven manageable with adequate risk minimisation measures [644]. No cases of syncope were observed in a post-marketing observational study, which identified patients at risk for the orthostatic reaction using the patient's medical history and orthostatic testing [645].

Many patients and physicians may prefer using dapoxetine in combination with a PDE5I to extend the time until ejaculation and minimise the risk of ED due to dapoxetine treatment. Phase 1 studies of dapoxetine have confirmed that it has no pharmacokinetic interactions with PDE5Is (i.e., tadalafil 20 mg and sildenafil 100 mg) [646]. When dapoxetine is co-administered with PDE5Is, it is well tolerated, with a safety profile consistent with previous phase 3 studies of dapoxetine alone [647]. An RCT, including PE patients without ED, demonstrated that a combination of dapoxetine with sildenafil could significantly improve IELT values and PROs compared with dapoxetine alone or sildenafil alone, with tolerable adverse events [648]. The efficacy and safety of dapoxetine/sildenafil combination tablets for the treatment of PE have also been reported [649].

The discontinuation rates of dapoxetine seem moderate to high [650]. The cumulative discontinuation rates increase over time, reaching 90% at two years after initiation of therapy. The reasons for the high discontinuation rate are cost (29.9%), disappointment that PE was not curable and the on-demand nature of the drug (25%), adverse effects (11.6%), perceived poor efficacy (9.8%), a search for other treatment options (5.5%), and unknown (18.3%) [651]. Similarly, it was confirmed that many patients on dapoxetine treatment spontaneously discontinued treatment, while this rate was reported at 50% for other SSRIs and 28.8% for paroxetine, respectively [652]. In a Chinese cohort study, 13.6% of the patients discontinued dapoxetine due to lack of efficacy (62%), adverse effects (24%), and low frequency of sexual intercourse (14%) [653].

6.2.6.2.2 Off-label use of antidepressants

Selective serotonin re-uptake inhibitors are used to treat mood disorders but can delay ejaculation and therefore have been widely used 'off-label' for PE since the 1990s [654-656]. Commonly used SSRIs include continuous intake of citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, all of which have similar efficacy, whereas paroxetine exerts the most substantial ejaculation delay [604, 657, 658]. A novel 5-HT1A receptor antagonist, GSK958108, significantly delayed ejaculation in a double-blind, placebo-controlled trial [659].

Clomipramine, the most serotoninergic tricyclic antidepressant, was first reported in 1977 as an effective PE treatment [660, 661]. In an RCT, on-demand use of clomipramine 15 mg, two to six hours before sexual intercourse was found to be associated with IELT fold change and significant improvements in PRO measures in the treatment group as compared with the placebo group (4.66 ± 5.64 vs. 2.80 ± 2.19, $P < 0.05$) [662, 663]. The most commonly reported TEAEs were nausea in 15.7% and dizziness in 4.9% of men, respectively [662, 663].

Several meta-analyses suggest SSRIs may increase the geometric mean IELT by 2.6-13.2-fold [664]. Paroxetine is superior to fluoxetine, clomipramine and sertraline [665, 666]. Sertraline is superior to fluoxetine, whereas the efficacy of clomipramine is not significantly different from that of fluoxetine and sertraline. Paroxetine was evaluated in doses of 20-40 mg, sertraline 25-200 mg, fluoxetine 10-60 mg and clomipramine 25-50 mg [664-666].

Ejaculation delay may start a few days after drug intake, but it is more evident after one to two weeks as receptor desensitisation requires time to occur. Although efficacy may be maintained for several years, tachyphylaxis (decreasing response to a drug following chronic administration) may occur after six to twelve months [660]. Common TEAEs of SSRIs include fatigue, drowsiness, yawning, nausea, vomiting, dry mouth, diarrhoea and perspiration; TEAEs are usually mild and gradually improve after two to three weeks of treatment [660, 667]. Decreased libido, anorgasmia, anejaculation and ED have also been reported.

Because of the risk of suicidal ideation or suicide attempts, caution is suggested in prescribing SSRIs to young adolescents aged ≤ 18 years with PE, and to men with PE and a comorbid depressive disorder, particularly when associated with suicidal ideation. Patients should be advised to avoid sudden cessation or rapid dose reduction of daily-dosed SSRIs, which may be related to SSRI withdrawal syndrome [612]. Moreover, PE patients trying to conceive should avoid using these medications because of their detrimental effects on sperm cells [668-672].

6.2.6.2.3 Topical anaesthetic agents

The use of local anaesthetics to delay ejaculation is the oldest form of pharmacological therapy for PE [673]. Several trials [540, 675] support the hypothesis that topical desensitising agents reduce the sensitivity of the glans penis thereby delaying ejaculatory latency, but without adversely affecting the sensation of ejaculation. Meta-analyses have confirmed the efficacy and safety of these agents for the treatment of PE [676]. In a meta-analysis, the efficacy of local anaesthetics was best among the other treatment options including SSRIs, dapoxetine 30 and 60 mg, PDE5Is and tramadol for < 8 weeks of therapy [676].

6.2.6.2.3.1 Lidocaine/prilocaine cream

Lidocaine/prilocaine creams can significantly increase the stopwatch-measured IELT from 1-2 minutes to 6-9 minutes [677, 678]. Although no significant TEAEs have been reported, topical anaesthetics are contraindicated in patients or partners with an allergy to any ingredient in the product. These anaesthetic creams/gels may be transferred to the partner, resulting in vaginal numbness. Therefore, patients are advised to use a condom after applying the cream to their penis. Alternatively, the penis can be washed to clean off any residual active compound prior to sexual intercourse. Since these chemicals may be associated with cytotoxic effects on fresh human sperm cells, couples seeking parenthood should not use topical lidocaine/prilocaine-containing substances [679].

6.2.6.2.3.2 Lidocaine/prilocaine spray

The eutectic lidocaine/prilocaine spray is a metered-dose aerosol spray containing purely base forms of lidocaine (150 mg/mL) and prilocaine (50 mg/mL), which has been officially approved by the EMA for the treatment of lifelong PE [680]. Compared to topical creams, the metered-dose spray delivery system has been proved to deposit the drug in a dose-controlled, concentrated film covering the glans penis, maximising neural blockage and minimising the onset of numbness [681], without absorption through the penile shaft skin [682].

Several studies have demonstrated the efficacy of lidocaine/prilocaine spray in improving both IELT and PROs three sprays administered 5 minutes before sexual intercourse [683, 684]. Published data showed that lidocaine/prilocaine spray increases IELT over time up to 6.3-fold over three months, with a month-by-month improvement through the course of the treatment in long-term studies [685]. A low incidence of local TEAEs in both patients and partners has been reported, including genital hypoaesthesia (4.5% and 1.0% in men and female partners, respectively) and ED (4.4%), and vulvovaginal burning sensation (3.9%), but is unlikely to be associated with systemic TEAEs [686, 687].
Lidocaine-only sprays are also available and found to be effective in the treatment of PE [688, 689].

6.2.6.2.4 Tramadol

Tramadol is a centrally-acting analgesic agent that combines opioid receptor activation and serotonin and noradrenaline re-uptake inhibition. Tramadol is a mild-opioid receptor agonist, but it also displays antagonistic properties on transporters of noradrenaline and 5-HT [690]. This mechanism of action distinguishes tramadol from other opioids, including morphine. Tramadol is readily absorbed after oral administration and has an elimination half-life of 5-7 hours.

Several clinical trials evaluated the efficacy and safety of tramadol ODT (62 and 89 mg) and tramadol HCl in the treatment of PE [691]. Up to 2.5-fold increases in the median IELT have been reported among patients who received on-demand tramadol treatment [692, 693].

Adverse effects were reported at doses used for analgesic purposes (≤ 400 mg daily) and included constipation, sedation and dry mouth. In May 2009, the US FDA released a warning letter about tramadol's potential to cause addiction and difficulty in breathing [694]. The tolerability during the twelve-week study period in men with PE was acceptable [695]. Several other studies have also reported that tramadol exhibits a significant dose-related efficacy along with potential adverse effects during the treatment of PE [692, 693]. The Guidelines Panel considers tramadol as a potential alternative treatment to established first-line therapeutic options in men with PE; however, it should be clearly outlined that the use of tramadol has to be considered with caution since there is a lack of data on the long-term safety of the compound in this setting.

6.2.6.2.5 Phosphodiesterase type 5 inhibitors

Although IELT was not significantly improved, sildenafil increased confidence, the perception of ejaculatory control and overall sexual satisfaction, reduced anxiety and the refractory time to achieve a second erection after ejaculation [696, 697]. Several open-label studies have shown that a combination of PDE5Is and SSRIs is superior to SSRI monotherapy, which has also been recently confirmed by a Bayesian network meta-analysis [676, 698].

6.2.6.2.6 Other drugs

In addition to the aforementioned drugs, there is continuous research into other treatment options. Considering the abundant α1a-adrenergic receptors in seminal vesicles and the prostate and the role of the sympathetic system in ejaculation physiology, the efficacy of selective α-blockers in the treatment of PE has been assessed [699-701]. A study demonstrated that the wake-promoting agent modafinil may be effective in delaying ejaculation and improving PROMs [702]. Decreasing penile sensitivity with glans penis augmentation using hyaluronic acid for the treatment of PE was initially proposed by Korean researchers in 2004 [703]. Since then, it has gained popularity mainly in Asian countries [704, 705]. Randomised controlled studies demonstrated that hyaluronic acid glans injections were safe, with a modest but significant increase in IELT along with improvements in PRO measures [704, 705]. No serious TEAEs were reported related to glans penis injections with hyaluronic acid. However, this procedure may result in serious complications, and more safety studies must be conducted before recommending this treatment to PE patients [706]. Selective dorsal neurectomy has also been suggested for the treatment of PE, mainly by Asian researchers [707-713]. However, considering the irreversible nature of these procedures, more safety data are warranted.

Considering the importance of central oxytocin receptors in the ejaculation reflex, several researchers have assessed the efficacy and safety of oxytocin receptor antagonists in the treatment of PE [714]. Epelsiban [715] and cligosiban [716-719] have been found to be safe and mildly effective in delaying ejaculation, but further controlled trials are needed [718, 719]. Delayed ejaculation was associated with the use of pregabalin, a new generation of gabapentinoids, as a side-effect. On-demand oral pregabalin 150 mg was found to increase the IELTs of patients 2.45 ± 1.43-fold. Treatment-emergent side effects (blurred vision, dizziness, vomiting) were minimal and did not lead to drug discontinuation [720].

The role of other proposed treatment modalities for the treatment of PE, such as penis-root masturbation [721], vibrator-assisted start-stop exercises [633], transcutaneous functional electric stimulation [722, 723], transcutaneous posterior tibial nerve stimulation [724], acupuncture [725-727] and practising yoga [728] need more evidence to be considered in the clinical setting.

*6.2.7 **Summary of evidence and recommendations for the treatment of PE***

Summary of evidence	**LE**
Pharmacotherapy includes either dapoxetine on-demand (an oral short-acting SSRI) and eutectic lidocaine/prilocaine spray (a topical desensitising agent), which are the only approved treatments for PE, or other off-label antidepressants (daily/on-demand SSRIs and clomipramine).	1a
Both on-demand dapoxetine treatment and daily SSRI treatment improve IELT values significantly.	1a
Both on-demand dapoxetine treatment and daily SSRI treatment have generally tolerable side effects when used for the treatment of PE.	1a
Daily/on-demand clomipramine treatments improve IELT values significantly and have generally tolerable side effects when used for the treatment of PE.	1a
Cream and spray forms of lidocaine/prilocaine improve IELT values significantly and have safe a profile.	1b
Tramadol is effective in the treatment of PE but the evidence is still inadequate for its long-term safety profile including addiction potential.	1a

Combination of PDE5Is and SSRIs overtakes SSRI monotherapy in effectiveness.	1a
Hyaluronic acid injections are effective in decreasing penile sensitivity.	2b

Recommendations for assessment	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 oral treatment with daily selective serotonin re-uptake inhibitor (SSRIs) or daily/on-demand clomipramine as a viable alternative for second-line treatments.	Strong
Use off-label tramadol with caution as a viable on-demand third-line treatment alternative to on-demand/daily antidepressants (SSRIs or clomipramine).	Strong
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
Use hyaluronic acid injection with caution as a treatment option for PE compared to other more established treatment modalities.	Weak
Do not perform dorsal neurectomy because more safety data are warranted.	Weak

6.3 Delayed Ejaculation (DE)

6.3.1 ***Definition and classification***

The American Psychiatric Association defines DE as requiring one of two symptoms; marked delay, infrequency or absence of ejaculation on 75-100% of occasions that persists for at least 6 months and causes personal distress [207]. However, in a recent study, while ejaculatory latency and control were significant criteria to differentiate men with DE from those without ejaculatory disorders, bother/distress did not emerge as a significant factor [729]. Similar to PE, there are distinctions among lifelong, acquired and situational DE [207]. A study demonstrated that men with lifelong DE are younger, report greater DE symptomatology, are less likely to have a medical issue or medication that can cause DE and are more likely to masturbate for anxiety/distress reduction than for pleasure as compared with men with acquired delayed ejaculation [730]. Although the evidence is limited, the prevalence of lifelong and acquired DE is estimated at around 1% and 4%, respectively [208].

6.3.2 ***Pathophysiology and risk factors***

The aetiology of DE can be psychological, organic (e.g., incomplete spinal cord lesion or iatrogenic penile nerve damage), or pharmacological (e.g., SSRIs, antihypertensive drugs, or antipsychotics) [731, 732] (Table 18). Other factors that may play a role in the aetiology of DE include tactile sensitivity and tissue atrophy [632]. Although low testosterone level has been considered a risk factor in the past [573, 733], more contemporary studies have not confirmed any association between ejaculation times and serum testosterone levels [734, 735]. Idiosyncratic masturbation and lack of desire for stimuli are also proposed risk factors for DE [736-738].

Table 13: Aetiological causes of delayed ejaculation and anejaculation [739-742]

Ageing Men	Degeneration of penile afferent nerves inhibited ejaculation
Congenital	Mullerian duct cyst Wolfian duct abnormalities Prune Belly Syndrome Imperforate Anus Genetic abnormalities
Anatomic causes	Transurethral resection of prostate Bladder neck incision Circumcision Ejaculatory duct obstruction (can be congenital or acquired)

Neurogenic causes	Diabetic autonomic neuropathy Multiple sclerosis Spinal cord injury Radical prostatectomy Proctocolectomy Bilateral sympathectomy Abdominal aortic aneurysmectomy Para-aortic lymphadenectomy
Infective/Inflammation	Urethritis Genitourinary tuberculosis Schistosomiasis Prostatitis Orchitis
Endocrine	Hypogonadism Hypothyroidism Prolactin disorders Disorders of lipid metabolism
Medication	Antihypertensives; thiazide diuretics Alpha-adrenergic blockers Antipsychotics and antidepressants Alcohol Antiandrogens Ganglion blockers
Psychological	Anxiety Psychoses Acute psychological distress Relationship distress Psychosexual skill deficit Disconnect between arousal and sexual situations Masturbation style

*6.3.3 **Investigation and treatment***

Patients should have a full medical and sexual history performed along with a detailed physical examination when evaluating for DE. Understanding the details of the ejaculatory response, sensation, frequency, and sexual activity/techniques; cultural context and history of the disorder; quality of the sexual response cycle (desire, arousal, ejaculation, orgasm, and refractory period); partner's assessment of the disorder and if the partner suffers from any sexual dysfunction her/himself; and the overall satisfaction of the sexual relationship are all important to garner during history-taking [602]. It is incumbent on the clinician to diagnose medical pathologies that cause or contribute to DE, such as assessing the hormonal milieu, anatomy, and overall medical condition.

6.3.3.1 Psychological aspects and intervention

There is scarce literature on the psychological aspects relating to DE, as well as on empirical evidence regarding psychological treatment efficacy. Studies on psychological aspects have revealed that men with DE show a strong need to control their sexual experiences. Delayed ejaculation is associated with difficulties surrendering to sexual pleasure during sex - i.e., the sense of *letting go* [743] - which denotes a underlying psychological mechanism influencing the reaching of orgasm [744]. As for psychological treatments, these may include, but are not limited to: increased genital-specific stimulation; sexual education; role-playing on his own and in front of his partner; retraining masturbatory practices; anxiety reduction on ejaculation and performance; and, re-calibrating the mismatch of sexual fantasies with arousal (such as with pornography use and fantasy stimulation compared to reality). Masturbation techniques that are either solo or partnered can be considered practice for the "real performance", which can eventually result in greater psychosexual arousal and orgasm for both parties [738]. Although masturbation with fantasy can be harmful when not associated with appropriate sexual arousal and context, fantasy can be supportive if it allows blockage of critical thoughts that may prevent orgasm and ejaculation. Techniques geared towards reducing anxiety are important skills that can help overcome performance anxiety, as this can often interrupt the natural erectile function through orgasmic progression. Referral to a sexual therapist, psychologist or psychiatrist is appropriate and often warranted.

6.3.3.2 *Pharmacotherapy*

Several pharmacological agents, including cabergoline, bupropion, alpha-1-adrenergic agonists (pseudoephedrine, midodrine, imipramine and ephedrine), buspirone, oxytocin, testosterone, bethanechol, yohimbine, amantadine, cyproheptadine and apomorphine have been used to treat DE with varied success [632]. Unfortunately, there is no FDA or EMA-approved medications to treat DE, as most of the cited research is based on case-cohort studies that were not randomised, blinded, or placebo-controlled. Many drugs have been used as primary treatments and/or antidotes to other medications that can cause DE. A survey of sexual health providers demonstrated an overall treatment success of 40% with most providers commonly using cabergoline, bupropion or oxytocin [745]. However, this survey measured the anecdotal results of practitioners. There was no proven efficacy or superiority of any drug due to a lack of placebo-controlled, randomised, blinded, comparative trials [739]. In addition to pharmacotherapy, penile vibratory stimulation (PVS) is also used as an adjunct therapy for DE [746]. Another study that used combined therapy of midodrine and PVS to increase autonomic stimulation in 158 men with spinal cord injury led to ejaculation in almost 65% of the patients [747].

Summary of evidence	**LE**
Delayed ejaculation can be caused by several aetiologies including congenital, anatomic, neurogenic, infective, hormonal, drug-related and psychological.	3
There is not enough evidence to support a definitive treatment for DE.	3

6.4 Anejaculation

6.4.1 ***Definition and classification***

Anejaculation involves the complete absence of antegrade or retrograde ejaculation. It is caused by the failure of semen emission from the seminal vesicles, prostate, and ejaculatory ducts into the urethra [748]. True anejaculation is usually associated with a normal orgasmic sensation and is always associated with central or peripheral nervous system dysfunction or with drugs [749].

6.4.2 ***Pathophysiology and risk factors***

Generally, anejaculation shares similar aetiological factors with DE and retrograde ejaculation (Table 13).

6.4.3 ***Investigation and treatment***

Drug treatment for anejaculation caused by lymphadenectomy and neuropathy, or psychosexual therapy for anorgasmia, is not effective. In all these cases, and in men who have a spinal cord injury, PVS (i.e., application of a vibrator to the penis) is the first-line therapy. In anejaculation, PVS evokes the ejaculation reflex [750], which requires an intact lumbosacral spinal cord segment. If the quality of semen is poor or ejaculation is retrograde, the couple may enter an *in vitro* fertilisation program whenever fathering is desired. If PVS has failed, electro-ejaculation can be the therapy of choice [751]. Other sperm-retrieval techniques may be used when electro-ejaculation fails or cannot be carried out [752]. Anejaculation following either retroperitoneal surgery for testicular cancer or total mesorectal excision can be prevented using unilateral lymphadenectomy or autonomic nerve preservation [753], respectively.

6.5 Painful Ejaculation

6.5.1 ***Definition and classification***

Painful ejaculation is a condition in which a patient feels mild discomfort to severe pain during or after ejaculation. The pain can involve the penis, scrotum, and perineum [754].

6.5.2 ***Pathophysiology and risk factors***

Many medical conditions can result in painful ejaculation, but it can also be an idiopathic problem. Initial reports demonstrated possible associations of painful ejaculation with calculi in the seminal vesicles [755], sexual neurasthenia [756], sexually transmitted diseases (STIs) [754, 757], inflammation of the prostate [228, 758], PCa [759, 760], BPH [226], prostate surgery [761, 762], pelvic radiation [763], herniorrhaphy [764] and antidepressants [765-767]. Further case reports have suggested that mercury toxicity or Ciguatera toxin fish poisoning may also result in painful ejaculation [768, 769]. Psychological issues may also be the cause of painful ejaculation, especially if the patient does not experience this problem during masturbation [770].

6.5.3 ***Investigation and treatment***

Treating painful ejaculation must be tailored to the underlying cause if detected. Psychotherapy or relationship counselling, withdrawal of suspected agents (drugs, toxins, or radiation) [765, 766, 771] or the prescription of appropriate medical treatment (antibiotics, α-blockers or anti-inflammatory agents) may ameliorate painful ejaculation. Behavioural therapy, muscle relaxants, antidepressant treatment, anticonvulsant drugs and/or opioids, and pelvic floor exercises, may be implemented if no underlying cause can be identified [772, 773].

6.5.3.1 Surgical intervention

If medical treatments fail, surgical operations such as TURP, transurethral resection of the ejaculatory duct (TURED) and neurolysis of the pudendal nerve have been suggested [774, 775]. However, there is no strong supporting evidence that surgical therapy improves painful ejaculation: therefore, it must be used with caution.

6.6 Retrograde ejaculation

*6.6.1 **Definition and classification***

Retrograde ejaculation is the total, or sometimes partial, absence of antegrade ejaculation, due to semen passing backwards through the bladder neck into the bladder. Patients may experience a normal or decreased orgasmic sensation. The causes of retrograde ejaculation can be divided into neurogenic, pharmacological, urethral, or bladder neck incompetence [754].

*6.6.2 **Pathophysiology and risk factors***

The process of ejaculation requires complex co-ordination and interplay between the epididymis, vas deferens, prostate, seminal vesicles, bladder neck and bulbourethral glands [776]. Upon ejaculation, sperm are rapidly conveyed along the vas deferens and into the urethra via the ejaculatory ducts. From there, the semen progresses in an antegrade fashion, partly maintained by coaptation of the bladder neck and rhythmic contractions of the periurethral muscles, co-ordinated by a centrally mediated reflex [776]. Closure of the bladder neck and seminal emission is initiated via the sympathetic nervous system from the lumbar sympathetic ganglia and subsequently hypogastric nerve. Prostatic and seminal vesicle secretion, as well as contraction of the bulbo-cavernosal, ischio-cavernosal and pelvic floor muscles are initiated by the S 2-4 parasympathetic nervous system via the pelvic nerve [776].

Any factor that disrupts this reflex and inhibits contraction of the bladder neck (internal vesical sphincter) may lead to retrograde passage of semen into the bladder. These can be broadly categorised as pharmacological, neurogenic, anatomic and endocrinal causes of retrograde ejaculation (Table 14).

Table 14: Aetiology of retrograde ejaculation [754]

Neurogenic	Spinal cord injury Cauda equina lesions Multiple sclerosis Autonomic neuropathy Retroperitoneal lymphadenectomy Sympathectomy or aortoiliac surgery Prostate, colorectal and anal surgery Parkinson´s disease Diabetes mellitus Psychological/behavioural
Urethral	Ectopic ureterocele Urethral stricture Urethral valves or verumontaneum hyperplasia Congenital dopamine β-hydroxylase deficiency
Pharmacological	Antihypertensives, thiazide diuretics α-1-Adrenoceptor antagonists Antipsychotics and antidepressants
Endocrine	Hypothyroidism Hypogonadism Hyperprolactinaemia
Bladder neck incompetence	Congenital defects/dysfunction of hemitrigone Bladder neck resection (transurethral resection of the prostate) Prostatectomy

6.6.3 ***Disease management***

6.6.3.1 Pharmacological

Sympathomimetics stimulate the release of noradrenaline and activate α- and β-adrenergic receptors, resulting in the closure of the internal urethral sphincter, restoring the antegrade flow of semen. The most common sympathomimetics are synephrine, pseudoephedrine hydrochloride, ephedrine, phenylpropanolamine and midodrine [777]. Unfortunately, as time progresses, their effect diminishes [778]. Many studies published about the efficacy of sympathomimetics in the treatment of retrograde ejaculation suffer from small sample size, with some represented by case reports.

An RCT randomised patients to receive one of four α-adrenergic agents (dextroamphetamine, ephedrine, phenylpropanolamine and pseudoephedrine) with or without histamine. The patients suffered from failure of ejaculation following retroperitoneal lymphadenectomy. They found that four days of treatment prior to ejaculation was the most effective and that all the adrenergic agonists restored antegrade ejaculation [777]. In a systematic review, the efficacy of this group of medications was found to be 28% [211]. The adverse effects of sympathomimetics include dryness of mucous membranes and hypertension.

The use of antimuscarinics has been described, including brompheniramine maleate and imipramine, as well as in combination with sympathomimetics. The calculated efficacy of antimuscarinics alone or in combination with sympathomimetics is 22% and 39%, respectively [211]. Combination therapy appears to be more effective, although statistical analysis is not yet possible due to the small sample sizes.

6.6.3.2 Management of infertility

Infertility has been the major concern of patients with retrograde ejaculation. Beyond standard sperm-retrieval techniques, such as testicular sperm aspiration/extraction (TESA/TESE), three different methods of sperm acquisition have been identified for managing infertility in patients with retrograde ejaculation. These include: i) centrifugation and resuspension of post-ejaculatory urine specimens; ii) the Hotchkiss (or modified Hotchkiss) technique; and, iii) ejaculation on a full bladder.

1. *Centrifugation and resuspension.* In order to improve the ambient conditions for the sperm, the patient is asked to increase their fluid intake or take sodium bicarbonate to dilute or alkalise the urine, respectively. Afterwards, a post-orgasmic urine sample is collected by introducing a catheter or spontaneous voiding. This sample is then centrifuged and suspended in a medium. The types of suspension fluids are heterogeneous and can include bovine serum albumin, human serum albumin, Earle's/Hank's balanced salt solution and the patient's urine. The resultant modified sperm mixture can then be used in assisted reproductive techniques. A systematic review of studies in couples in which the male partner had retrograde ejaculation found a 15% pregnancy rate per cycle (0-100%) [211].
2. *Hotchkiss method.* The Hotchkiss method involves emptying the bladder prior to ejaculation, using a catheter, and then washing out and instilling a small quantity of Lactated Ringers to improve the ambient condition of the bladder. The patient then ejaculates, and semen is retrieved by catheterisation or voiding [779]. Modified Hotchkiss methods involve variance in the instillation medium. Pregnancy rates were 24% per cycle (0-100%) [211].
3. *Ejaculation on a full bladder.* The patient is encouraged to ejaculate on a full bladder and semen is suspended in Baker's Buffer. The pregnancy rate in the two studies, which included only five patients, have described results using this technique [780, 781].

6.7 Anorgasmia

6.7.1 ***Definition and classification***

Anorgasmia is the perceived absence of orgasm and can give rise to anejaculation. Regardless of the presence of ejaculation, anorgasmia can be a lifelong (primary) or acquired (secondary) disorder [208].

6.7.2 ***Pathophysiology and risk factors***

Primary anorgasmia starts from a man's first sexual intercourse and lasts throughout his life, while secondary anorgasmia patients should have a normal period before the problem starts [782]. Substance abuse, obesity and some non-specific psychological aspects, such as anxiety and fear, are considered risk factors for anorgasmia. Only a few studies have described anorgasmia alone and generally, it has been considered a symptom linked to ejaculatory disorders, especially with DE, and therefore, they are believed to share the same risk factors. However, psychological factors are for 90% of anorgasmia problems [783]. The causes of delayed orgasm and anorgasmia are shown in Table 15 [782].

Table 15: Causes of delayed orgasm and anorgasmia [782]

Endocrine	Testosterone deficiency Hypothyroidism
Medications	Antidepressants Antipsychotics Opioids
Psychosexual causes	
Hyperstimulation	
Penile sensation loss	

6.7.3 ***Disease management***

The psychological/behavioural strategies for anorgasmia are similar to those for DE. The patient and his partner should be examined physically and psychosexually in detail, including determining the onset of anorgasmia, medication and disease history, penile sensitivity and psychological issues. Adjunctive laboratory tests can also be used to rule out organic causes, such as testosterone, prolactin and TSH levels. Patients who have loss of penile sensitivity require further investigations [782].

6.7.3.1 Psychological/behavioural strategies

Lifestyle changes can be recommended to affected individuals, including changing masturbation style, taking steps to improve intimacy, and decreasing alcohol consumption. Several psychotherapy techniques or their combinations have been offered, including alterations in arousal methods, reduction of sexual anxiety, role-playing an exaggerated orgasm and increased genital stimulation [744, 784]. However, it is difficult to determine the success rates from the literature.

6.7.3.2 Pharmacotherapy

Several drugs have been reported to reverse anorgasmia, including cyproheptadine, yohimbine, buspirone, amantadine and oxytocin [785-790]. However, these reports are generally from case-cohort studies and drugs have limited efficacy and significant adverse effect profiles. Therefore, current evidence is not strong enough to recommend drugs to treat anorgasmia.

6.7.3.3 Management of infertility

If patients fail the treatment methods mentioned above, penile vibratory stimulation, electro-ejaculation or TESE are options for sperm retrieval in anorgasmia cases [782].

6.8 Haemospermia

6.8.1 ***Definition and classification***

Haemospermia is defined as the appearance of blood in the ejaculate. Although it is often regarded as a symptom of minor significance, blood in the ejaculate causes anxiety in many men and may indicate underlying pathology [231].

6.8.2 ***Pathophysiology and risk factors***

Several causes of haemospermia have been acknowledged and can be classified into the following sub-categories; idiopathic, congenital malformations, inflammatory conditions, obstruction, malignancies, vascular abnormalities, iatrogenic/trauma and systemic causes (Table 16) [791].

Table 16: Pathology associated with haemospermia [791-794]

Category	Causes
Congenital	Seminal vesicle (SV) or ejaculatory duct cysts
Inflammatory	Urethritis, prostatitis, epididymitis, tuberculosis, CMV, HIV, Schistosomiasis, hydatid, condyloma of urethra and meatus, urinary tract infections
Obstruction	Prostatic, SV and ejaculatory duct calculi, post-inflammatory, seminal vesicle diverticula/cyst, urethral stricture, utricle cyst, BPH
Tumours	Prostate, bladder, SV, urethra, testis, epididymis, melanoma

Vascular	Prostatic varices, prostatic telangiectasia, haemangioma, posterior urethral veins, excessive sex or masturbation
Trauma/iatrogenic	Perineum, testis, instrumentation, post-haemorrhoid injection, prostate biopsy, vaso-venous fistula
Systemic	Hypertension, haemophilia, purpura, scurvy, bleeding disorders, chronic liver disease, renovascular disease, leukaemia, lymphoma, cirrhosis, amyloidosis
Idiopathic	-

The risk of any malignancy in patients presenting with haemospermia is approximately 3.5% (0-13.1%) [793, 795]. In a study in which 342 patients with haemospermia were included, the most relevant aetiology for haemospermia was inflammation/infection (49.4%) while genitourinary cancers (i.e., prostate and testis) only accounted for 3.2% of the cases [796].

*6.8.3 **Investigations***

As with other clinical conditions, a systematic clinical history and assessment is undertaken to help identify the cause of haemospermia. Although the differential diagnosis is extensive, most cases are caused by infections or other inflammatory processes [231].

The basic examination of haemospermia should start with a thorough symptom-specific and systemic clinical history. The first step is to understand if the patient has true haemospermia. Pseudo-haemospermia may occur as a consequence of haematuria or even suction of a partner's blood into the urethra during copulation [754, 797, 798]. A sexual history should be taken to identify those whose haemospermia may be a consequence of a STI. Recent foreign travel to areas affected by schistosomiasis or tuberculosis should also be considered. The possibility of co-existing systemic diseases such as hypertension, liver disease and coagulopathy should be investigated along with systemic features of malignancy such as weight loss, loss of appetite or bone pain. Examination of the patient should also include measurement of blood pressure, as there have been several case reports suggesting an association between uncontrolled hypertension and haemospermia [799, 800].

Most authors who propose an investigative baseline agree on the initial diagnostic tests, but there is no consensus in this regard [791, 792, 795, 797]. Urinalysis should be performed along with sending the urine for culture and sensitivity testing, as well as microscopy. If tuberculosis or schistosomiasis is the suspected cause, the semen or prostatic secretions should be sent for analysis. A full sexually-transmitted disease screen, including first-void urine as well as serum and genitourinary samples, should be tested for *Chlamydia, Ureaplasma* and Herpes Simplex virus. Using this strategy, it may be possible to find an infectious agent among cases that would have been labelled as idiopathic haemospermia [801].

Serum PSA should be taken in men aged > 40 years who have been appropriately counselled [232]. Blood work, including a full blood count, liver function tests, and a clotting screen should be taken to identify systemic diseases. The question of whether further investigation is warranted depends on clinician judgment, patient age and an assessment of risk factors [791]. Digital rectal examination should also be performed, and the meatus re-examined after DRE for bloody discharge [802]. Detection of a palpable nodule in the prostate is important because an association between haemospermia and PCa has been postulated, although not completely proven.

Magnetic resonance imaging (MRI) is being increasingly used as a definitive means to investigate haemospermia. The multiplanar ability of MRI to accurately represent structural changes in the prostate, seminal vesicles, ampulla of vas deferens, and ejaculatory ducts has enabled the technique to be particularly useful in determining the origin of midline or paramedian prostatic cysts and in determining optimal surgical management [803]. The addition of an endorectal coil can improve diagnostic accuracy for identifying the site and possible causes of haemorrhage [804].

Cystoscopy has been included in most suggested investigative protocols in patients with high-risk features (patients who are refractory to conservative treatment and who have persistent haemospermia). It can provide valuable information as it allows direct visualisation of the main structures in the urinary tract that can be attributed to causes of haemospermia, such as polyps, urethritis, prostatic cysts, foreign bodies, calcifications and vascular abnormalities [805, 806].

With the advancement of optics, the ability to create ureteroscopes of diameters small enough to allow insertion into the ejaculatory duct and seminal vesicles has been made possible [806, 807]. In a prospective study, 106 patients with prolonged haemospermia underwent transrectal US and seminal vesiculoscopy. With both methods combined, the diagnosis was made in 87.7% of patients. When compared head-to-head, the diagnostic yield for TRUS vs. seminal vesiculoscopy was 45.3% and 74.5%, respectively ($P < 0.001$) [808].

Melanospermia is a consequence of malignant melanoma involving the genitourinary tract and is a rare condition that has been described in two case reports [809, 810]. Chromatography of the semen sample can be used to distinguish the two by identifying the presence of melanin if needed.

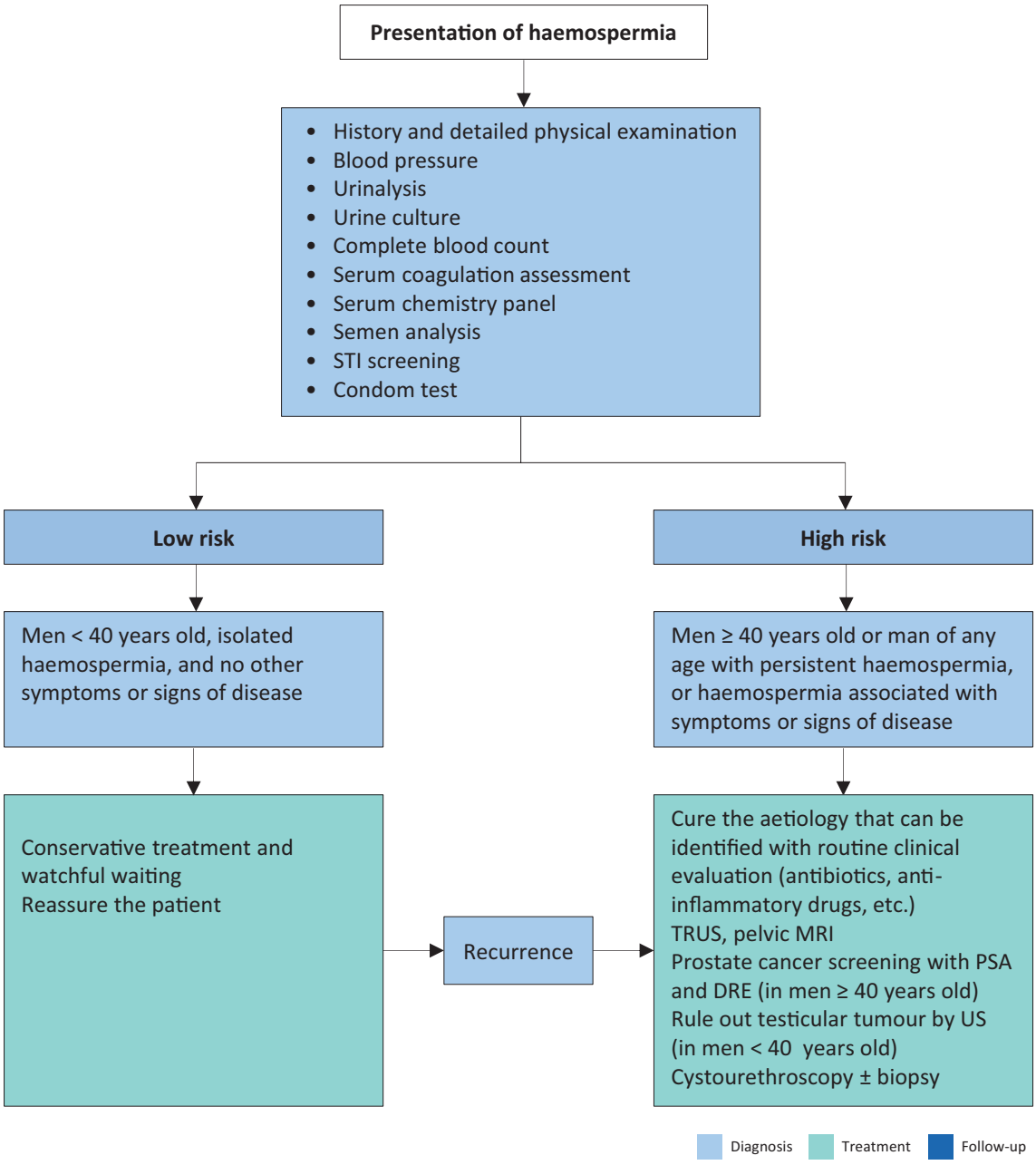
*6.8.4 **Disease management***

Conservative management is generally the primary treatment option when the patients are aged < 40 years and have a single episode of haemospermia. The primary goal of treatment is to exclude malignant conditions like prostate and bladder cancer and treat any other underlying cause. If no pathology is found, then the patient can be reassured [231, 791].

Middle-aged patients with recurrent haemospermia warrant more aggressive intervention. Appropriate antibiotic therapy should be given to patients who have urogenital infections or STIs. Urethral or prostate varices or angiodyplastic vessels can be fulgurated, whereas cysts, either of the seminal vesicles or prostatic urethra, can be aspirated transrectally [231]. Ejaculatory duct obstruction is managed by transurethral incision at the duct opening [811, 812]. Systemic conditions should be treated appropriately [795, 798, 813, 814].

Defining a management algorithm for haemospermia is based on the patient's age and degree of haemospermia. Patients often find blood in the ejaculate alarming, and investigations should be aimed at excluding a serious, despite infrequent, underlying cause (e.g., cancer), while at the same time preventing over-investigation and alleviating patient anxiety. The literature describes a multitude of causes for haemospermia, although many of these are not commonly found after investigation. However, men may be stratified into higher-risk groups according to several factors including: age > 40 years, recurrent or persistent haemospermia, the actual risk for PCa (e.g., positive family history), and concurrent haematuria. Based on the literature, a management algorithm is proposed (Figure 8) [795, 798, 813, 814].

Figure 8: Management algorithm for haemospermia [795, 798, 813, 814]



STI = Sexually transmitted infections; PSA = Prostate specific antigen; DRE = Digital rectal examination; US = Ultrasonography; TRUS = Transrectal ultrasonography; MRI = Magnetic resonance imaging.

6.8.5 *Summary of evidence and recommendations for the investigation and management of haemospermia*

Summary of evidence	LE
While haemospermia has traditionally been attributed to benign causes, it is a potential indicator warranting thorough diagnostic evaluation and, if necessary, targeted treatment.	3
The principal objective of treatment is to rule out malignancies, while addressing any other underlying causes as well.	3

Recommendations	Strength rating
Perform a full medical and sexual history with detailed physical examination.	Strong
Use a risk-stratification system to manage the disease systematically.	Weak

7. LOW SEXUAL DESIRE AND MALE HYPOACTIVE SEXUAL DESIRE DISORDER

7.1 Definition, classification and epidemiology

It has always been a challenge to define sexual desire properly because it has a complicated nature and it can be conceptualised in many different ways. According to the International Classification of Diseases 10th edition (ICD-10), lack or loss of sexual desire should be the principal problem and not other sexual problems accompanying it such as ED [815]. In the DSM-V, male hypoactive sexual desire disorder (HSDD) is defined as "the persistent or recurrent deficiency (or absence) of sexual or erotic thoughts or fantasies and desire for sexual activity". The clinician makes the judgment of deficiency, taking into account factors that affect sexual functioning, such as age and general and socio-cultural contexts of the individual's life [207]. According to the fourth International Consultation on Sexual Medicine (ICSM), the definition of male HSDD was proposed as a "persistent or recurrent deficiency or absence of sexual or erotic thoughts or fantasies and desire for sexual activity (clinical principle)" [816]. Although the exact prevalence of low sexual desire (LSD) is unknown, a prevalence of 4.7% was reported in a survey of a population-based sample of middle-aged German men (n = 12,646) [817].

7.2 Pathophysiology and risk factors

Several aetiological factors are considered to contribute to the pathophysiology of LSD. Levine proposed three components of sexual desire drive (biological), motivation (psychological) and wish (cultural) [818]. However, it is believed that both in the surveys and clinical practice those three components are usually found interwoven [819].

*7.2.1 **Psychological aspects***

The endorsement of negative thoughts during sexual intercourse (i.e., concerns about erection, lack of erotic thoughts, and restrictive attitudes toward sexuality) predicts LSD in men [820, 821]. Furthermore, feeling shame during sexual intercourse, because of negative sexual thoughts (e.g., concern about achieving an erection), characterises men with LSD as opposed to women with the same condition [822]. Psychopathological symptoms stemming from a crisis context negatively impacted male sexual desire [332], as well. In addition, dyadic male sexual desire was best accounted for by sexual satisfaction [823]. It is worth noting that, despite LSD being less common in men than in women [816], it is the most frequent complaint in couples' therapy [824]. Therefore, the role of relationship factors must be addressed. In addition, anxiety proneness has been associated with LSD in men and is expected to shift men's attention from erotic cues to worrying thoughts, thereby decreasing sexual desire [825]. Finally, it is worth noting that current approaches focus on sexual desire discrepancies between partners; the focus on discrepancies rather than on the partner who presents low desire not only reduces stigma, but also provides new opportunities for managing desire in the relationship context [826].

*7.2.2 **Biological aspects***

Testosterone seems to be essential for a man's sexual desire; however, sexual desire does not directly relate to the circulating level of testosterone, especially in older men [827]. The biological and psychological components that take place in the pathophysiology of LSD are shown in Table 22 [819, 828]. In addition to these factors, there is some speculation about the role of the thyroid and oxytocin hormones [555, 829].

Table 22: Common causes of low sexual desire in men [819, 828]

Androgen deficiency
Hyperprolactinaemia
Anger and anxiety
Depression
Relationship conflict
Stroke
Antidepressant therapy
Epilepsy
Post-traumatic stress syndrome

Renal failure
Coronary disease and heart failure
Ageing
HIV infection
Body-building and eating disorders
Erectile dysfunction
Prostatitis/chronic pelvic pain syndrome

*7.2.3 **Risk factors***

In an international survey aimed at estimating the prevalence and correlates of sexual problems in 13,882 women and 13,618 men from 29 countries (Global Study of Sexual Attitudes and Behaviours), risk factors for male LSD were age 60-69 and 70-80 years, poor overall health, vascular diseases, being a current smoker, belief that ageing reduces sex, divorce in the past 3 years, financial problems in the last 3 years, major depression, being worried about the future of a relationship and less than one sexual relation in a week [205]. In a recent study that determined the factors associated with LSD in a large sample of middle-aged German men, PE, ED, and lower urinary tract symptoms were associated with LSD [817]. In contrast, men having more than two children, higher frequency of solo masturbation, perceived importance of sexuality, and higher sexual self-esteem were less likely to have LSD [817].

7.3 Diagnostic work-up

*7.3.1 **Assessment questionnaires***

Sexual Desire Inventory (SDI) evaluates different components influencing the development and expression of sexual desire [830]. This self-administered questionnaire consists of 14 questions that weigh the strength, frequency, and significance of an individual's desire for sexual activity with others and by themselves. The SDI suggests that desire can be split into two categories: dyadic and solitary desire. While dyadic desire refers to "interest in or a wish to engage in sexual activity with another person and desire for sharing and intimacy with another", solitary desire refers to "an interest in engaging in sexual behaviour by oneself and may involve a wish to refrain from intimacy and sharing with others" [830].

*7.3.2 **Physical examination and investigations***

Similar to other forms of sexual dysfunctions, a thorough medical and sexual history must be obtained from men who complain of LSD. The depressive symptoms of the patients must be assessed [831] and relationship problems (e.g., conflict with the sexual partner) must be questioned. In the presence of accompanying symptoms suggestive of endocrinological problems, circulating total testosterone [832], prolactin [833] and thyroid hormones [555] levels can be evaluated.

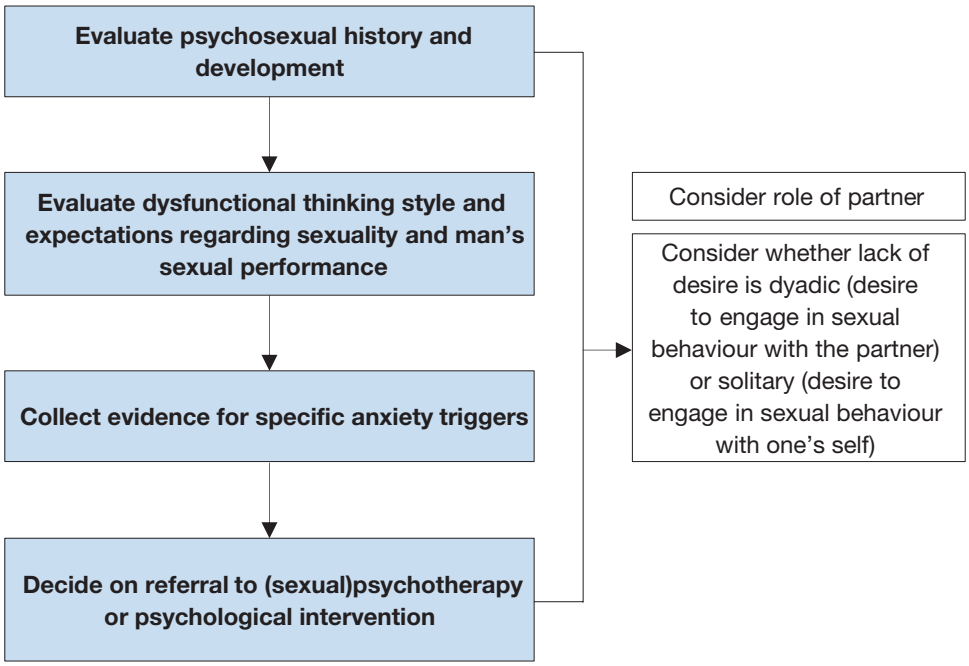
7.4 Disease management

Treatment of LSD should be tailored according to the underlying aetiology.

*7.4.1 **Psychological intervention***

Data on the efficacy of psychological interventions for LSD are scarce. Accordingly, recommendations must be interpreted with caution. Psychological interventions with a focus on cognitive and behavioural strategies may be beneficial for LSD in men [336, 834] (Figure 9). Mindfulness treatments may be a strong candidate, as well [834]. Since both members of a couple may experience age-related changes concurrently and interdependently, it could be helpful to address the sexual health needs of the ageing couple (including LSD) as a whole rather than treating the individual patient [835]. Indeed, psychologists are putting more emphasis on the concept of sexual desire discrepancy. Sexual desire discrepancy is often found in couples or partners, and mirror a natural part of life and partners' dynamics. Clinical approaches based on this lens are less stigmatising as they consider the normal variations in sexual desire that occur throughout the lifespan. This intervention option targets couples distressed by sexual desire discrepancies rather than a single individual targeted as the one presenting low sexual desire [826].

Figure 9: Flow-diagram of psychological evaluation of patients with low sexual desire



7.4.2 ***Pharmacotherapy***

Low sexual desire secondary to low testosterone levels can be treated with different formulations of testosterone. The favourable effect of testosterone therapy on sexual motivation and the presence of sexual thoughts was shown in a meta-analysis [832]. The aim of treatment should be to reach the physiological range of testosterone (see Section 3.3).

Hyperprolactinaemia can also cause LSD and one of the most relevant aetiological factors is prolactin-secreting pituitary adenomas. These adenomas can be easily diagnosed with an MRI of the pituitary gland and can be treated with dopamine agonist agents [836]. The other accompanying endocrine disorders, such as hypothyroidism, hyperthyroidism and diabetes, should be treated accordingly.

Pharmacotherapy can also be used to treat major depression; however, it should be remembered that antidepressants may negatively affect sexual functioning; therefore, antidepressant compounds with less effect on sexual function should be chosen. Psychotherapy can increase the efficacy of pharmacotherapy, especially for patients whose LSD is due to depression [837].

7.5 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
Provide testosterone therapy if LSD is associated with signs and symptoms of testosterone deficiency.	Strong

8. PENILE CURVATURE

8.1 Congenital penile curvature

8.1.1 Epidemiology/aetiology/pathophysiology

Congenital penile curvature (CPC) is a rare condition, with a reported incidence of < 1% [838], although some studies have reported higher prevalence rates of 4-10%, in the absence of hypospadias [839]. Congenital penile curvature results from disproportionate development of the tunica albuginea of the corporal bodies and is not associated with urethral malformation. In most cases, the curvature is ventral, but it can also be lateral or, more rarely, dorsal [840].

8.1.2 Diagnostic evaluation

Taking a medical and sexual history is usually sufficient to establish a diagnosis of CPC. Patients usually present after reaching puberty as the curvature becomes more apparent with erections and sexual activity. The more severe curvatures can make intercourse difficult or impossible. Physical examination and photographic documentation during erection (preferably after intracavernous injection [ICI] of vasoactive drugs) are both mandatory to document the curvature and exclude other pathologies [840].

8.1.3 Disease management

Surgery is the definitive treatment for this disorder and can be deferred until after puberty. However, a survey has suggested that men with untreated ventral penile curvature report more dissatisfaction with penile appearance, increased difficulty with intercourse, and psychological problems; supporting surgical correction of CPC in childhood, although this should be discouraged as penile growth will not have maximised [841]. Surgical treatments for CPC generally share the same principles as in PD. Plication techniques (Nesbit, 16-dot, Yachia, Essed-Schröeder, and others) with or without neurovascular bundle elevation (medial/lateral) and complete penile degloving, have been described [842-851]. Other approaches are based on corporal body de-rotation with different technical refinements that enable correction of a ventral curvature, with reported minimal narrowing and shortening [852-855]. There are no direct comparative studies; therefore, no single technique can be recommended for surgical correction.

8.1.4 Summary of evidence and recommendation for diagnosis and treatment of congenital penile curvature

Summary of evidence	LE
Medical and sexual history are usually sufficient to establish a diagnosis of CPC. Physical examination and photographic documentation during erection (preferably after ICI of vasoactive drugs) are mandatory to document the curvature.	3
Surgery is the only treatment option for CPC, which should be deferred until after puberty and performed at any time in adult life in individuals with significant functional impairment during intercourse.	3

8.1.5 Recommendation for the treatment of congenital penile curvature

Recommendation	Strength rating
Use the Nesbit procedure or plication techniques with or without neurovascular bundle dissection (medial/lateral) for satisfactory curvature correction.	Strong

8.2 Peyronie's Disease

(A discussion on the Aetiology, Risk factors and Pathophysiology of PD can be found in Appendix 4, online supplementary evidence.)

8.2.1 Epidemiology

Epidemiological data on PD are limited. Prevalence rates of 0.4-20.3% have been reported, with a higher prevalence in patients with ED and diabetes [856-864]. A recent survey has indicated that the prevalence of definitive and probable cases of PD in the USA is 0.7% and 11%, respectively, suggesting that PD is an under-diagnosed condition [865]. Peyronie's disease often occurs in older men with a typical age of onset of 50-60 years. However, PD also occurs in younger men (< 40 years), with a reported prevalence of 1.5-16.9% [860, 866, 867].

*8.2.2 **Diagnostic evaluation***

The initial evaluation aims 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. A disease-specific questionnaire (Peyronie's disease questionnaire [PDQ]) has been developed for use in clinical practice and trials. The Peyronie's disease questionnaire measures three domains, including psychological and physical symptoms, penile pain and symptom bother [868].

Clinicians should take a focused history to distinguish between active and stable disease, as this will influence medical treatment and the timing of surgery. Patients who are still likely to have active disease are those with a shorter symptom duration, pain on erection, or a recent change in penile deformity. Resolution of pain and stability of the curvature for at least three months are accepted criteria of disease stabilisation as well as patients' referral for specific medical therapy [869, 870] or surgical intervention, if indicated [871].

The examination should start with a focused genital assessment that is extended to the hands and feet for detecting possible Dupuytren's contracture or Ledderhose scarring of the plantar fascia [872]. A penile examination is performed to assess the presence of a palpable nodule or plaque. There is no correlation between plaque size and degree of curvature [873]. Measurement of the stretched or erect penile length is important because it may have an impact on the subsequent treatment decisions and potential medico-legal implications [874-876].

An objective assessment of penile curvature with an erection is mandatory. This can be obtained by several approaches, including home (self) photography of a natural erection (preferably), using a vacuum-assisted erection test or an ICI using vasoactive agents. However, it has been suggested that the ICI method is superior, as it can induce an erection similar to or better than that which the patient would experience when sexually aroused [877-879]. Computed tomography and MRI have a limited role in the diagnosis of the curvature and are not recommended on a routine basis. Erectile function can be assessed using validated instruments such as the IIEF although this has not been validated in PD patients [880]. Erectile dysfunction is common in patients with PD (30-70.6%) [881, 882]. The presence of ED and psychological factors may also have a profound impact on the chosen treatment strategy [883]. Ultrasound measurement of plaque size is not accurate but may be helpful to assess the presence of the plaque and its calcification and location [884, 885]. Doppler US may be used for the assessment of penile haemodynamics and ED aetiology [882]. In particular to assess penile arterial inflow in the context of the interventional modality to be undertaken (eg plaque incision and grafting) to exclude arteriogenic ED.

8.2.2.1 Summary of evidence and recommendations for diagnosis of Peyronie's disease

Summary of evidence	**LE**
Ultrasound measurement of plaque size is inaccurate and operator-dependent.	3
Doppler US may be used to assess penile haemodynamic and vascular anatomy.	2a
Intracavernous injection method is superior to other methods in providing an objective assessment of penile curvature with an erection.	4

Recommendations	**Strength rating**
Take a medical and sexual history of patients with Peyronie's disease (PD), including duration of the disease, pain on erection, penile deformity, difficulty in vaginal/anal intromission due to the deformity and erectile dysfunction (ED).	Strong
Perform 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 in the diagnostic work-up of PD to provide an objective assessment of penile curvature with an erection.	Weak
Use the PD specific questionnaire especially in clinical trials, but routine use in daily clinical practice is not mandatory.	Weak

Do not use ultrasound (US), computed tomography or magnetic resonance imaging to assess plaque size and deformity in routine clinical practice.	Weak
Use penile Doppler US in the case of diagnostic evaluation of ED, to evaluate penile haemodynamic and vascular anatomy, and to assess location and calcification of plaques, especially prior to surgery.	Weak

*8.2.3 **Disease management***

8.2.3.1 Conservative treatment

Conservative treatment of PD is primarily focused on patients in the early stage of the disease as an adjunct treatment to relieve pain and prevent disease progression or if the patient declines other treatment options during the active phase [871, 872]. Several options have been suggested, including oral pharmacotherapy, intralesional injection therapy, shockwave therapy (SWT) and other topical treatments (Table 16).

The results of the studies on conservative treatment for PD are often contradictory, making it difficult to provide recommendations in everyday, real-life settings [886]. The Guidelines do not recommend the use of oral treatments for PD including pentoxifylline, vitamin E, tamoxifen, procarbazine, potassium para-aminobenzoate (potaba), omega-3 fatty acids or a combination of vitamin E and L-carnitine because of their lack of proven efficacy [871, 887-889]. Studies of these treatments have numerous methodological problems including their uncontrolled nature, the limited number of patients treated, the short-term follow-up and the different outcome measures used [890, 891]. Even in the absence of adverse events, treatment with these agents may delay the use of other more efficacious treatments.

Table 16: Conservative treatments for PD

Oral treatments
Nonsteroidal 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
Other
Traction devices
Multimodal treatment
Extracorporeal shockwave treatment
Vacuum Erection Device

8.2.3.1.1 Oral treatment

Phosphodiesterase type 5 inhibitors

Phosphodiesterase type 5 inhibitors were first suggested as a treatment for PD in 2003 to reduce collagen deposition and increase apoptosis through the inhibition of transforming growth factor (TGF)-b1 [892-894]. The results of a retrospective study of 65 men indicated that treatment with tadalafil was helpful in decreasing helped decrease curvature and remodel septal scars when compared to controls [895]. Another study concluded that sildenafil was able to improve erectile function and pain in PD patients. Thirty-nine patients with PD were divided into two groups receiving vitamin E (400 IU) or sildenafil 50 mg for twelve weeks with significantly better outcomes in pain and mean IIEF scores were seen in the sildenafil group [896]. Findings from a observational retrospective study including patients in the acute phase of PD and ED who had been treated with Tadalafil 5 mg once daily compared to patients with comparable baseline parameters who decided not to take the daily compound (i.e., 108 intervention vs. 83 controls) showed that treated men had lower curvature progression rates at 12 weeks (25.9% vs. 39.7%, p = 0.042) [897]. Similarly, mean SHIM score and PDQ-Overall and PDQ-Penile Pain scores significantly improved in the intervention group ($p < 0.001$).

Nonsteroidal anti-inflammatory drugs
Nonsteroidal anti-inflammatory drugs (NSAIDs) may be offered to patients in active-phase PD to ameliorate penile pain. Pain levels should be periodically reassessed whilst monitoring treatment efficacy.

8.2.3.1.2 Intralesional treatment
Injection of pharmacologically active agents directly into penile plaques represents another treatment option. It allows a localised delivery of a pharmacological agent that provides higher concentrations of the drug inside the plaque. However, delivery of the compound to the target area is difficult to ensure, particularly when a dense or calcified plaque is present.

Calcium channel antagonists: verapamil and nicardipine
The rationale for intralesional use of channel antagonists in patients with PD is based on *in vitro* research [898, 899]. Due to the use of different dosing schedules and the contradictory results obtained in published studies, the evidence is not strong enough to support the clinical use of injected channel blockers verapamil and nicardipine and the results do not demonstrate a meaningful improvement in penile curvature compared to placebo [900-905]. In fact, most of the studies did not perform direct statistical comparisons between these groups.

Collagenase of Clostridium histolyticum
Collagenase of *Clostridium histolyticum* (CCH) is a chromatographically purified bacterial enzyme that selectively targets collagen, the primary component of the PD plaque [906-909]. Intralesional injection of CCH has been used in the treatment of PD since 1985. In 2014 the EMA approved CCH for the non-surgical treatment of the stable phase of PD in men with palpable dorsal plaques in whom abnormal curvature of 30-90o and non-ventrally located plaques are present. It should be administered by a healthcare professional who is experienced and properly trained in the administration of CCH treatment for PD [910, 911]. However, CCH has been officially withdrawn from the European market by its manufacturer. Despite this the evidence and recommendations for CCH have been maintained by the Guidelines for completeness.

The original treatment protocol in all studies consists of two injections of 0.58 mg of CCH 24-72 hours apart every six weeks for up to four cycles. Data from IMPRESS (Investigation for Maximal Peyronie´s Reduction Efficacy and Safety Studies) II and II studies [976], as well as post-approval trials [912], which demonstrated the efficacy and safety of this treatment, are summarised in Table 8.2 online Appendix 5.

The average improvement in curvature was 34% compared to 18.2% in the placebo group. Three adverse events of corporeal rupture were surgically repaired. The greatest chance of curvature improvement was for curvatures between 30° and 60°, longer duration of disease, IIEF > 17, and no calcification [870]. An 18.2% improvement from baseline in the placebo arm was also observed. These findings raise questions regarding the proposed role of plaque injection and penile modelling, regardless of the medication, in improving outcomes in men with PD as the placebo or modelling arm resulted in relatively high curvature reduction compared to the treatment arm.

The conclusion of the IMPRESS I and II studies is that CCH improves PD both physically and psychologically [913]. A *post hoc* meta-analysis of the IMPRESS studies demonstrated better results in patients with curvatures < 60º, > 2 years of onset, no calcification in the plaque and good erectile function [912].

Thereafter, a modified short protocol consisting of administration of a single (0.9 mg, one vial) injection per cycle distributed along three lines around the point of maximum curvature up to three cycles, separated by 4-weekly intervals, has been proposed and rapidly popularised replacing physician modelling with a multi-modal approach through penile stretching, modelling and VED at home [914]. The results from this modified protocol were comparable to the results of the IMPRESS trials and appeared to decrease the cost and duration of treatment, although these studies were non-randomised. However, these results were further explored in a prospective non-randomised multi-centre study [982]. In another large single-arm multi-centre clinical study using the shortened protocol, longer PD duration, greater baseline PC and basal and dorsal plaque location were identified as clinically significant predictors of treatment success [915]. Accordingly, a nomogram developed to predict treatment success after CCH for PD showed that patients with longer PD duration, greater baseline penile curvature and basal plaque location had a greater chance of treatment success [915]; however, these findings need to be externally validated.

Regarding safety concerns, most PD patients treated with CCH experienced at least one mild or moderate adverse event localised to the penis (penile haematoma (50.2%), penile pain (33.5%), penile swelling (28.9%) and injection site pain (24.1%), which resolved spontaneously within 14 days of injection [916]. The adverse reaction

profile was similar after each injection, regardless of the number of injections administered. Serious treatment-emergent adverse events (TEAEs) (0.9%) included penile haematoma and corporeal rupture that require surgical treatment. According to IMPRESS data and the shortened protocol, to prevent serious TEAEs men should be advised to avoid sexual intercourse in the four weeks following injection. Recent preliminary data suggest that treatment in the acute phase of the disease is effective and safe [880, 917-921].

In conclusion, CCH is a safe and established treatment for stable-phase disease wit more recent evidence suggesting that CCH also has a role in affecting the progression of active-phase disease. It should also be noted that there is a large effect of traction or modelling in controlled studies, whilst studies reporting on modified protocols have small numbers of patients and are largely uncontrolled. Therefore, patients should be counselled fully on the efficacy of collagenase and the high cost of treatment.

It has been suggested that those patients with severe curvature may also benefit from CCH injections because of a potential downgrading of the penile curvature: a decrease in curvature may allow for a penile plication procedure instead of a plaque incision and grafting procedure, therefore avoiding the more negative impact on erectile function from plaque incision and grafting. However, further studies are required to validate these initial findings [880, 921].

Interferon α-2b

Intralesional injections (5x10^6 units of IFN-α2b in 10 mL saline every 2 weeks over 12 weeks for a total of six injections) significantly improved penile curvature, plaque size and density, and pain compared to placebo. Additionally, penile blood flow parameters are benefited by IFN-α2b [911, 922, 923]. Regardless of plaque location, IFN-α2b is an effective treatment option. Treatment with IFN-α2b provides a > 20% reduction in curvature in most men with PD, independent of plaque location [924]. Given the mild adverse effects, which include sinusitis and flu-like symptoms, which can be effectively treated with NSAIDs before IFN-α2b injection, and the moderate strength of data available, IFN-α2b is currently recommended for treatment of stable-phase PD.

Steroids, hyaluronic acid and botulinum toxin (botox)

In the only single-blind, placebo-controlled study with intralesional administration of betamethasone, no statistically significant changes in penile deformity, penile plaque size, and penile pain during erection were reported [925]. Adverse effects include tissue atrophy, thinning of the skin and immunosuppression [926]. The effect of hyaluronic acid treatment in patients with PD was investigated in a non-randomised study; intralesional injection of hyaluronic acid was compared to intralesional verapamil in acute phase PD and significant improvement of pain, curvature and IIEF-15 were observed [927]. In an RCT, oral administration of hyaluronic acid combined with intralesional injection was found to be superior to intralesional injection only and an improvement of 7.8±3.9 degrees in curvature and reduction in plaque size of 3.0 mm was observed [928]. There is only a single study evaluating intralesional botox injections in men with PD; therefore, there is insufficient evidence to support this treatment in clinical practice [929].

Platelet Rich Plasma (PRP)

Few studies in humans have evaluated the effect of PRP on penile curvature, plaque size, PDQ and IIEF [930-935]. The effect of PRP in patients with PD remains to be proven and should be considered experimental. An ongoing phase 2b randomized placebo-controlled crossover trial has enrolled 25 patients with a planned target of 80 men with PD: first ongoing data on nine patients in the treatment group vs eight in the placebo group showed no difference in curvature at three months in comparison to baseline [936].

8.2.3.1.3 Topical treatments

Topical verapamil and H-100 Gel

There is insufficient evidence that topical treatments (verapamil and H-100 Gel) applied to the penile shaft, with or without the use of iontophoresis (now known as transdermal electromotive drug administration), result in adequate levels of the active compound within the tunica albuginea [937-940].

8.2.3.1.4 Other treatments

Extracorporeal shockwave treatment

The mechanism of action involved in ESWT for PD is still unclear.

Four RCTs and one meta-analysis [941-945] assessed the efficacy of ESWT for PD. Three were sham-controlled trials while one compared ESWT with the combination of ESWT and PDE5I (tadalafil) [946].

All trials showed positive findings in terms of pain relief, but no effect on penile curvature and plaque size. Inclusion criteria varied widely among studies and further investigation is needed. Therefore, ESWT should not be used as a primary treatment for penile curvature in men with PD. The results are summarised in Table 8.4 online Appendix 5.

Penile traction therapy

In men with PD, potential mechanisms for disease modification with penile traction therapy (PTT) have been proposed, including collagen remodelling via decreased myofibroblast activity and matrix metalloproteinase up-regulation [947, 948].

The stated clinical goals of PTT are to non-surgically reduce curvature, enhance girth, and recover lost length, which are attractive to patients with PD. However, clinical evidence is limited due to the small number of patients included (267 in total), the heterogeneity in the study designs, and the non-standardised inclusion and exclusion criteria which make it impossible to draw any definitive conclusions about this therapy [949-953].

Most of the included patients will need further treatment to ameliorate their curvature for satisfactory sexual intercourse. Moreover, the effect of PTT in patients with calcified plaques, hourglass or hinge deformities which are, theoretically, less likely to respond to PTT has not been systematically studied. In addition, the treatment can result in discomfort and be inconvenient as the device needs to be used for an extended period (2-8 hours daily), but has been shown to be tolerated by highly-motivated patients. There were no reported serious adverse effects, including skin changes, ulcerations, hypo-aesthesia or diminished rigidity [951, 954].
In conclusion, PTT seems to be effective and safe for patients with PD [955], but there is still lack of evidence to give any definitive recommendation in terms of its use as a monotherapy for PD.

Vacuum erection device

Vacuum erection device (VED) therapy results in dilation of cavernous sinuses, decreased retrograde venous blood flow and increased arterial inflow [956]. Intracorporeal molecular markers are affected by VED application, including decreases in hypoxia-inducible factor-1α, TGF-β1, collagenase, and apoptosis, and increases in endothelial nitric oxide synthase (eNOS) and α-smooth muscle actin, given their role in the pathogenesis of PD [957]. Only two retrospective studies assessed the efficacy of VED therapy in mechanically straightening the penile curvature of PD as monotherapy and further studies are needed [958, 959].

Multimodal treatment

There is some evidence suggesting that a combination of different oral agents can be used for the treatment of the acute phase of PD. However, there does not seem to be a consensus on which drugs to combine or the optimum drug dosage; nor has there been a comparison of different drug combinations.

A long-term study assessing the role of multimodal medical therapy (injectable verapamil associated with antioxidants and local diclofenac) demonstrated that treatment was efficacious to treat PD patients. It concluded that combination therapy reduced pain more effectively than verapamil alone, making this specific combination treatment more effective compared to monotherapy [957]. Furthermore, combination protocols including injectable therapies, such as CCH, have been studied in controlled trials. The addition of adjunctive PTT and VED has been described; however, limited data are available regarding their use [960].

Penile traction therapy has been evaluated as an adjunct therapy to intralesional injections with interferon, verapamil, or CCH [901, 961, 962]. These studies have failed to demonstrate significant improvements in penile length or curvature, except for one subset analysis identifying a 0.4 cm length increase among men using the devices for > 3 hours/day [962]. A meta-analysis demonstrated that men who used PTT as an adjunct to surgery or injection therapy for PD had, on average, an increase in stretched penile length (SPL) of 1 cm compared to men who did not use adjunctive PTT. There was no significant change in curvature between the two groups [963].

Data available on the combined treatment of CCH and the use of VED between injection intervals have shown significant mean improvements in curvature (-17º) and penile length (+0.4 cm) after treatment. However, it is not possible to determine the isolated effect of VED because of a lack of control groups [914, 963].

Also, a combination of PDE5I (sildenafil 25 mg twice daily) after CCH treatment (shortened protocol combined with VED) is superior to CCH alone for improving penile curvature and erectile function [964]. Further studies are necessary to externally validate those findings.

8.2.3.1.5 Summary of evidence and recommendations for conservative treatment of Peyronie's disease

Summary of evidence	LE
Conservative treatment for PD is primarily aimed at treating patients in the early stage of the disease in order to relieve symptoms and prevent progression.	3c
There is no convincing evidence supporting oral treatment with acetyl esters of carnitine, vitamin E, potassium para-aminobenzoate (potaba) and pentoxifylline.	3c
Due to adverse effects, treatment with oral tamoxifen is no longer recommended.	3c
Nonsteroidal anti-inflammatory drugs can be used to treat pain in the acute phase.	4
Contradictory evidence is available for intralesional treatment with calcium channel antagonists: verapamil and nicardipine.	4
Intralesional treatment with Collagenase clostridium histolyticum showed significant decreases in penile curvature, plaque diameter and plaque length in men with stable disease.	1b
Intralesional treatment with interferon may improve penile curvature, plaque size, density, and pain.	2b
Intralesional treatment with steroids hase been shown to have adverse effects, including tissue atrophy, thinning of the skin and immunosuppression.	3c
No high-level evidence is available to support treatment with intralesional hyaluronic acid or botulinum toxin.	3c
Intralesional hyaluronic acid may be used to improve pain, penile curvature and IIEF scores.	2b
A combination of oral and intralesional hyaluronic acid treatment improves penile curvature and plaque size.	1b
There is no evidence that topical treatments applied to the penile shaft result in adequate levels of the active compound within the tunica albuginea.	3c
There is no efficacy data for the use of iontophoresis.	3c
Extracorporeal shockwave treatment may be offered to treat penile pain, but it does not improve penile curvature and plaque size.	2b
Treatment with penile traction therapy alone or in combination with injectable therapy as part of a multimodal approach may reduce penile curvature and increase penile length, although the available studies have considerable limitations.	3c

Recommendation	Strength rating
Offer conservative treatment to patients not fit for surgery or when surgery is not acceptable to the patient.	Strong
Fully counsel patients regarding all available treatment options and outcomes before starting any treatment.	Strong
Do not offer oral treatment with vitamin E, potassium para-aminobenzoate (potaba), tamoxifen, pentoxifylline, colchicine and acetyl esters of carnitine to treat Peyronie's disease (PD).	Strong
Use nonsteroidal anti-inflammatory drugs to treat penile pain in the acute phase of PD.	Strong
Use extracorporeal shockwave treatment (ESWT) to treat penile pain in the acute phase of PD.	Weak
Use phosphodiesterase type 5 inhibitors to treat concomitant erectile dysfunction or if the deformity results in difficulty in penetrative intercourse in order to optimise penetration.	Weak
Offer intralesional therapy with interferon alpha-2b to patients with stable curvature dorsal or lateral > 30^{o} seeking a minimal invasive procedure.	Weak
Offer intralesional therapy with Collagenase *Clostridium Histolyticum* to patients with stable PD and dorsal or lateral curvature > 30^{0}, 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 use intralesional platelet-rich plasma or hyaluronic acid, either alone or in combination with oral treatment, to reduce penile curvature, plaque size or pain outside the confines of a clinical trial.	Strong
Do not offer ESWT to improve penile curvature and reduce plaque size.	Strong
Offer penile traction devices and vacuum devices to reduce penile deformity or as part of a multimodal therapy approach, although outcome data is limited.	Weak

8.2.3.2 Surgical treatment

Although conservative treatment for PD may resolve painful erections in most men, only a small percentage experience significant straightening of the penis. The aim of surgery is to correct curvature and allow penetrative intercourse. Surgery is indicated in patients with significant penile deformity and difficulty with intercourse associated with sexual bother. Patients must have a stable disease for three to six months (or more than nine to twelve months after onset of PD) [871, 965, 966]. In addition to this requirement, other situations that may precipitate an indication for surgery, such as failed conservative or medical therapies, extensive penile plaques, or patient preference, when the disease is stable [967, 968].

Before considering reconstructive surgery, it is recommended to document the size and location of penile plaques, the degree of curvature, complex deformities (hinge or hourglass), the penile length and the presence or absence of ED. The potential aims and risks of surgery should be fully discussed with the patient so that he can make an informed decision [966]. Specific issues that should be mentioned during this discussion are: risk of penile shortening; ED, penile numbness; and delayed orgasm, the risk of recurrent curvature, potential for palpation of knots and stitches underneath the skin, potential need for circumcision at the time of surgery, residual curvature and the risk of further penile wasting with shortening procedures [871, 969]. Selection of the most appropriate surgical intervention is based on penile length assessment, curvature severity and erectile function status, including response to pharmacotherapy in cases of ED [871]. Patient expectations from surgery must also be included in the pre-operative assessment. The main objective of surgery is to achieve a “functionally straight” penis, and this must be fully understood by the patient to achieve the best possible satisfaction outcomes after surgery [966, 970].

Three major types of reconstruction may be considered for PD: (i) tunical shortening procedures; (ii) tunical lengthening procedures; and, (iii) penile prosthesis implantation, with or without straightening techniques in the presence of concomitant ED and residual curvature [971, 972].

Penile degloving with associated circumcision (as a means of preventing post-operative phimosis) should be considered the standard approach for all types of procedures, although modifications have been described. Only one study has suggested that circumcision is not always necessary (e.g., in cases where the foreskin is normal pre-operatively) [973]. Non-degloving techniques have been described that have been shown to prevent ischaemia and lymphatic complications after subcoronal circumcision [974, 975].

There are no standardised questionnaires for the evaluation of surgical outcomes. Data from well-designed prospective studies are scarce, with low levels of evidence. Data are mainly based on retrospective single-centre studies, typically non-comparative and non-randomised, or expert opinion [871]. Therefore, surgical outcomes must be treated with caution.

8.2.3.2.1 Tunical shortening procedures

Tunical shortening procedures achieve straightening of the penis by shortening the longer, convex side of the penis. For men with good erectile function, adequate penile length, without complex deformities, such as an hourglass or hinge type narrowing abnormalities, and non-severe curvature, a tunical shortening procedure can be considered an appropriate surgical approach. Numerous different techniques have been described, although they can be classified as excisional, incisional and plication techniques. The Nesbit procedure operation is based on an elliptical excision of tunica albuginea opposite to the point of maximum curvature [977, 978].

The Yachia technique is based on a completely different concept, as it utilises the Heinke-Mikowitz principle for which a longitudinal tunical incision is closed transversely to shorten the convex side of the penis. This technique, initially described by Lemberger in 1984, was popularised by Yachia in 1990, when he reported a series of 10 cases [979-984].

Pure plication techniques are simpler to perform. They are based on single or multiple plications performed without making excisions or incisions on the tunical albuginea, to limit the potential damage to the veno-

occlusive mechanism [874, 985-1001]. Another modification described the '16-dot' technique that consists of the application of two pairs of parallel Essed-Schroeder plications tensioned more or less depending on the degree of curvature [1002-1005]. Results and satisfaction rates are similar to both incision/excision techniques.

In general, using these tunical shortening techniques, complete penile straightening is achieved in > 85% of patients. Recurrence of the curvature and penile hypo-aesthesia is uncommon (~10%) and the risk of post-operative ED is low. Penile shortening is the most commonly reported adverse outcome of these procedures. Shortening of 1-1.5 cm has been reported for 22-69% of patients, which is rarely the cause of post-operative sexual dysfunction and patients may perceive the loss of length as greater than it actually is. It is therefore strongly advisable to measure and document the penile length peri-operatively, both before and after the straightening procedure, whichever technique is used (Table 17).

As mentioned above, there are multiple techniques with small modifications and all of them have been reported in retrospective studies, most of them without appropriate comparison between techniques and therefore the level of evidence is not sufficient to recommend one particular method over another.

Table 17: Results of tunical shortening procedures for PD (data from different, non-comparable studies) [874, 979-1002, 1006-1009]

	Tunical shortening procedures				
	Nesbit	**Modified Nesbit**	**Yachia**	**16-dot / mod16-dot**	**Simple plication**
No. of patients/studies	652 / 4	387 / 5	150 / 6	285 / 5	1068 / 18
Significant penile shortening (%)*†	8.7% (5-39)	3.2% (0-13)	3.5% (0-10)	5.9% (0-6)	8.9% (0-55)
Any penile shortening (%)*	21.8% (9-39)	58.% (23-74)	69% (47-97)	44.6% (40-52)	33.4% (0-90)
Penile straightening (%)*	88.5% (86-100)	97.6% (92-100)	95.5% (93-100)	96.9% (95-100)	94.7% (85-100)
Post-operative *de novo* ED (%)*	6.9% (0-17)	3% (0-13)	9.6% (0-13)	3.8% (0-13)	8.1% (0-38)
Penile hypoesthesia (%)*	11. 8% (2-60)	5.6% (0-31)	1% (0-3)	8.2% (6-13)	9% (0-47)
Overall satisfaction (%)*	83.5% (76-88)	95.4% (87-100)	86.8% (78-100)	94% (86-100)	86.4% (52-100)
Follow-up (months)*	(69-84)	(19-42)	(10-24)	(18-71)	(12-141)

**Data are expressed as weighted average. † Defined as > 30 degrees of curvature. Ranges are in parentheses. ED = Erectile dysfunction.*

8.2.3.2.2 Tunical lengthening procedures

Tunical lengthening procedures are performed on the concave side of the penis after making an incision or partial excision of the plaque, with coverage of the defect with a graft. Although tunical lengthening procedures rarely lead to long-term penile length gain, they aim to minimise penile shortening caused by plication of the tunica albuginea, and correct complex deformities. In practice, tunical lengthening procedures are often combined with penile plication or shortening procedures to correct residual curvature and therefore may also result in penile shortening [1010]. Tunical lengthening surgery is preferable in patients with significant penile shortening, severe curvature and/or complex deformities (hourglass or hinge) but without underlying ED. The definition of severe curvature has been proposed to be > 60°, although no studies have validated this threshold. On the concave side of the penis, at the point of maximum curvature, which usually coincides with the location of the plaque, an incision is made, creating a defect in the albuginea that is covered with a graft. Complete plaque removal or plaque excision may be associated with higher rates of post-operative ED due to venous leak, but partial excision in cases of florid calcification may be permissible [1011, 1012]. Patients who do not have pre-operative ED should be informed of the significant risk of post-operative ED of up to 50% [969].

A large number of different grafts have been used. The ideal graft should be resistant to traction, easy to suture and manipulate, flexible (although not too much, to avoid aneurysmal dilations), readily available, cost-effective, and morbidity should be minimal, especially when using autografts. No graft material meets all of these requirements. Moreover, the studies performed did not compare different types of grafts and biomaterials and were often single-centre retrospective studies so there is not a single graft that can be recommended for

surgeons [1013]. The use of geometric principles introduced by Egydio may help to determine the exact site of the incision, and the shape and size of the defect to be grafted [1014].

Grafts for PD surgery can be classified into four types (Table 18) [1015]:

- Autografts: taken from the individual himself, they include the dermis, vein, temporalis fascia, fascia lata, tunica vaginalis, tunica albuginea and buccal mucosa.
- Allografts: also of human origin but from a deceased donor, including the pericardium, fascia lata and dura mater.
- Xenografts: extracted from different animal species and tissues, including bovine pericardium, porcine small intestinal submucosa, bovine and porcine dermis, and TachoSil® (matrix of equine collagen).
- Synthetic grafts: these include Dacron® and Gore-Tex®.

All the autologous grafts have the inconvenience of possible graft harvesting complications. Dermal grafts are commonly associated with veno-occlusive ED (20%) due to lack of adaptability, so they have not been used in contemporary series [1013, 1016-1027]. Vein grafts have the theoretical advantage of endothelial-to-endothelial contact when grafted to underlying cavernosal tissue. The saphenous vein has been the most commonly used vein graft [1028-1043]. For some extensive albuginea defects, more than one incision may be needed. Tunica albuginea grafts have perfect histological properties but have some limitations: the size that can be harvested, the risk of weakening penile support and making future procedures (penile prosthesis implantation) more complicated [1044-1046]. Tunica vaginalis is easy to harvest and has little tendency to contract due to its low metabolic requirements, although better results can be obtained if a vascular flap is used [1047-1051]. Under the pretext that by placing the submucosal layer on the corpus cavernosum the graft feeds on it and adheres more quickly, the buccal mucosal graft has recently been used with good short-term results [1052-1058].

Cadaveric dura mater is no longer used due to concerns about the possibility of infection [1059, 1060]. Cadaveric pericardium (Tutoplast©) offers good results by coupling excellent tensile strength and multidirectional elasticity/expansion by 30% [950, 1012, 1023, 1061, 1062]. Cadaveric or autologous fascia lata or temporalis fascia offers biological stability and mechanical resistance [1063-1065].

Xenografts have become more popular in recent years. Small intestinal submucosa (SIS), a type I collagen-based xenogenic graft derived from the submucosal layer of the porcine small intestine, has been shown to promote tissue-specific regeneration and angiogenesis, and supports host cell migration, differentiation and growth of endothelial cells, resulting in tissue structurally and functionally similar to the original [1066-1075]. As mentioned above, pericardium (bovine, in this case) has good traction resistance and adaptability, and good host tolerance [1043, 1076-1079]. Grafting by collagen fleece (TachoSil©) in PD has some major advantages such as decreased operating times, easy application and an additional haemostatic effect [1080-1085].

It is generally recommended that synthetic grafts, including polyester (Dacron®) and polytetrafluoroethylene (Gore-Tex®) are avoided, due to increased risks of infection, secondary graft inflammation causing tissue fibrosis, graft contractures, and possibility of allergic reactions [982, 1086-1089].

Post-operative penile rehabilitation to improve surgical outcomes has been suggested with a number of studies describing the use of VED and PTT to prevent penile length loss of up to 1.5 cm [1090]. Daily nocturnal administration of PDE5I enhances nocturnal erections, encourages perfusion of the graft, and may minimise post-operative ED rates [1091]. Massages and stretching of the penis have also been recommended once wound healing is complete.

Table 18: Results of tunical lengthening procedures for PD (data from different, non-comparable studies) [950, 982, 1012, 1016-1085, 1092, 1093]

	Year of publication	No. of patients / studies	Success (%)*	Penile shortening (%)*	*De novo* ED (%)*	Follow-up (mo)*
Autologous grafts						
Dermis	1974-2019	718 / 12	81.2% (60-100)	59.9% (40-75)	20.5% (7-67)	(6-180)
Vein grafts	1995-2019	690 / 17	85.6% (67-100)	32.7% (0-100)	14.8% (0-37)	(12-120)
Tunica albuginea	2000-2012	56 / 3	85.2% (75-90)	16.3% (13-18)	17.8% (0-24)	(6-41)
Tunica vaginalis	1980-2016	76 / 5	86.2% (66-100)	32.2% (0-83)	9.6% (0-41)	(12-60)
Temporalis fascia / Fascia lata	1991-2004	24 / 2	100%	0%	0%	(3-10)
Buccal mucosa	2005-2016	137 / 7	94.1% (88-100)	15.2% (0-80)	5.3% (0-10)	(12-45)
Allografts (cadaveric)						
Pericardium	2001-2011	190 / 5	93.1% (56-100)	23.1% (0-33)	37.8% (30-63)	(6-58)
Fascia lata	2006	14 / 1	78.6%	28.6%	7.1%	31
Dura matter	1988-2002	57 / 2	87.5%	30%	17.4% (15-23)	(42-66)
Xenografts						
Porcine SIS	2007-2018	429 / 10	83.9% (54-91)	19.6% (0-66)	21.9% (7-54)	(9-75)
Bovine pericardium	2002-2020	318 / 6	87.4% (76.5-100)	20.1% (0-79.4)	26.5% (0-50)	(14-67)
Bovine dermis	2016	28 / 1	93%	0%	25%	32
Porcine dermis	2020	19 / 1	73.7%	78.9%	63%	85
TachoSil®	2002-2020	529 / 7	92.6% (83.3-97.5)	13.4% (0-93)	13% (0-21)	(0-63)

**Data are expressed as weighted average. Ranges are in parentheses.*
ED = Erectile dysfunction; SIS = Small intestinal submucosa.

It must be emphasised that there have been no RCTs comparing surgical outcomes in PD. The risk of ED seems to be greater for penile lengthening procedures [871]. Recurrent curvature is likely to be the result of failure to wait until the disease has stabilised before surgery is undertaken, re-activation of the condition following the development of stable disease, or the use of early re-absorbable sutures (e.g., Vicryl) that lose their tensile strength before ensuing fibrosis has resulted in acceptable strength of the repair. Accordingly, it is recommended that only non-absorbable sutures or slowly re-absorbed absorbable sutures (e.g., polydioxanone) should be used. With non-absorbable sutures, the knot should be buried to avoid troublesome irritation of the penile skin, but this issue may be alleviated by the use of slowly re-absorbable sutures (e.g., polydioxanone) [1094]. Penile numbness is a potential risk of any surgical procedure, involving mobilisation of the dorsal neurovascular bundle. This is usually a temporary neuropraxia, due to bruising of the dorsal sensory nerves. Given that the usual deformity is dorsal, the procedure most likely to induce this complication is a lengthening (grafting) procedure, or the association with (albeit rare) ventral curvature [971].

8.2.3.2.3 Penile prosthesis

Penile prosthesis (PP) implantation is typically reserved for the treatment of PD in patients with concomitant ED not responding to conventional medical therapy (PDE5I or intracavernous injections of vasoactive agents) [871]. Although inflatable prostheses (IPPs) have been considered more effective in the general population with ED, some studies support the use of malleable prostheses in these patients with similar satisfaction rates [871, 1095, 1096]. The evidence suggests that there is no real difference between the available IPPs [1097]. Surgeons can and should advise on which type of prosthesis best suits their patients but it is the patient who should ultimately choose the prosthesis to be implanted [1098].

Most patients with mild-to-moderate curvature can expect an excellent outcome simply by cylinder insertion [1041, 1099]. If the intra-operative curvature after placement of the prosthesis is < 30° no further action is indicated, since the prosthesis itself will act as an internal tissue expander to correct the curvature during the subsequent six to nine months. If, the curvature is > 30°, the first-line treatment should be modelling with the prosthesis maximally inflated (manually bent on the opposite side of the curvature for 90 seconds, often accompanied by an audible crack) [1100, 1101]. If, after performing this manoeuvre, a deviation > 30° persists,

subsequent steps to be considered include incision with or without collagen fleece coverage (if the defect is small, it can be left uncovered) or plaque incision and grafting are performed [1102-1107]. However, the defect may be covered if it is larger, and this can be accomplished using grafts commonly used in grafting surgery (described above) which prevent herniation and recurrent deformity and buckling due to the scarring of the defect [1108, 1109]. The risk of complications (infection, malformation, etc.) is not increased compared to that in the general population. However, a small risk of urethral perforation (3%) has been reported in patients with 'modelling' over the inflated prosthesis [1100].

In selected cases of end-stage PD with ED and significant penile shortening, a lengthening procedure, which involves simultaneous PP implantation and penile length restoration, such as the "sliding" technique has been proposed [1110]. However, the "sliding" technique is not recommended due to reported cases of glans necrosis because of the concomitant release of the neurovascular bundle and urethra, new approaches for these patients have been recently described, such as the MoST (Modified Sliding Technique), MUST (Multiple-Slit Technique) or MIT (Multiple-Incision Technique) techniques, but these should only be used by experienced high-volume surgeons and after full patient counselling [1111-1114].

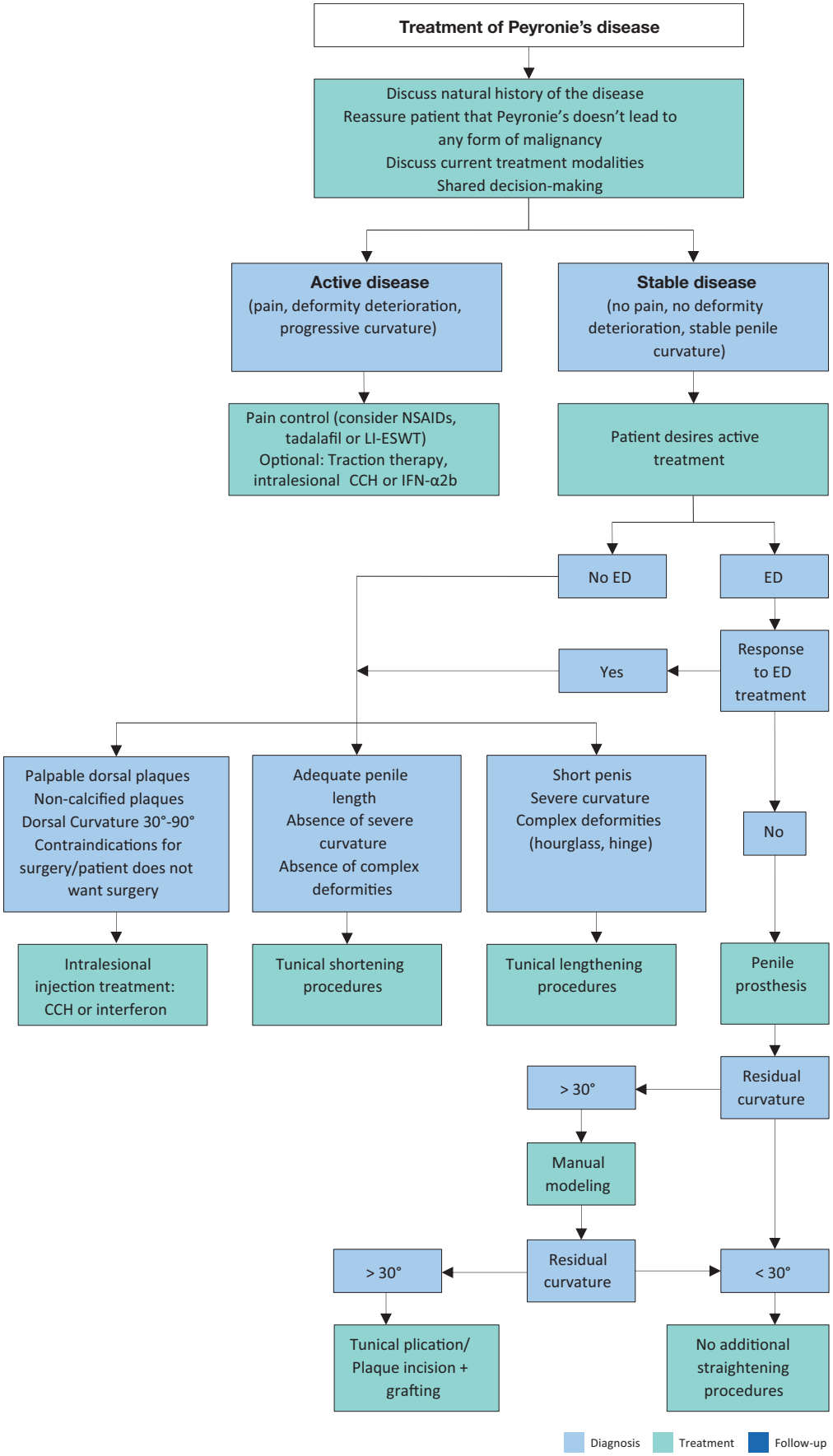
While patient satisfaction after IPP placement in the general population is high, satisfaction rates have been found to be significantly lower in those with PD. Despite this, depression rates decreased after surgery in PD patients (from 19.3%-10.9%) [1115]. The main cause of dissatisfaction after PPI in the general population is shortening; therefore, patients with PD undergoing PP surgery must be counselled that the prostheses are not designed to restore the previous penile length [1115, 1116].

8.2.3.2.4 Summary of evidence and recommendations for surgical treatment of Peyronie's disease

Summary of evidence	**LE**
Surgery for PD should only be offered in patients with stable disease and with functional impairment.	2b
In patients with concomitant PD and ED without response to medical treatment, penile prosthesis implantation with or without additional straightening manoeuvres is the technique of choice.	2a
In other cases, factors such as penile length, rigidity of erection, degree of curvature, presence of complex deformities and patient choice must be taken into account when deciding whether to undertake tunical shortening or lengthening procedures.	3

Recommendation	**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 the deformity.	Strong
Assess penile length, curvature severity, erectile function (including response to pharmacotherapy in case of erectile dysfunction [ED]) and patient expectations prior to surgery.	Strong
Use tunical shortening procedures as the first treatment option for congenital penile curvature and for PD with adequate penile length and rigidity, less severe curvatures and absence of complex deformities (hourglass or 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 (hourglass or hinge). The type of graft used is dependent on the surgeon and patient preference, as no graft has proven superior to its counterparts.	Weak
Do not use the sliding technique 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 straightening procedures (modelling, plication, incision or excision with or without grafting), in PD patients with ED not responding to pharmacotherapy.	Strong

Figure 10: Treatment algorithm for Peyronie's disease



ED = erectile dysfunction; LI-ESWT= low-intensity extracorporeal shockwave treatment; NSAIDs =non-steroidal anti-inflammatory drugs; CCH = Collagenase Clostridium histolyticum; IFN-α2b = Interferon-α2b.

9. PENILE SIZE ABNORMALITIES AND DYSMORPHOPHOBIA

9.1 Definition, epidemiology and classification

9.1.1 ***History***

Throughout history, the size of the penis has symbolised a marker of masculinity [1117] and has created intense debate in societies with different social and cultural implications [1118]. Indeed, along with the capacity for vaginal penetration, the penis is linked to an ancestral sense of men's fertility and sexual performance, making the size of the penis a source of distinguishing male identity [1119, 1120]. Evidence of male supremacy and dominance as represented by phallometric designs can be found across cultures and history and is still currently supported by contemporary media, including the pornographic industry [1121, 1122].

Overall, cosmetic surgery has the potential to restore self-esteem, reduce anxiety, social phobia and depressive mood states regarding body concerns, increasing individuals' well-being and quality of life (QoL) [1123, 1124]. Yet, some candidates for cosmetic surgery may have psychopathological conditions and surgery may result in negative outcomes [1124, 1125].

In the real-life setting, it is interesting to note that 84% of women report being satisfied with their male partners' penile size whereas 55% of the male partners were satisfied with their penile size and 45% of them report that they would like to have a larger penis [1126]. In this context, men with a high level of social-desirability were more likely than others to self-report having a larger penis [1127]. A recent study also demonstrated that reducing the depth of penetration led to a statistically significant 18% reduction of overall sexual pleasure with an average 15% reduction in the length of the penis [1128].

Additionally, the subjective impression of penile size may have a negative effect on sexual functioning and QoL, impacting sexual life in about 10% of men [1129-1131]. This prevalence sharply rises in patients seeking penile augmentation procedures [1132, 1133].

Furthermore, the fact that a subgroup of men does not achieve reasonable levels of satisfaction and emotional adjustment after penile augmentation procedures, underlines that with certain psychopathological conditions men will not benefit from such invasive procedures [1134]. These men may represent a psychologically vulnerable group of individuals in whom penile augmentation procedures will have negative effects and, as such, require clinical and psychological support. Clinicians should possess the skills to anticipate and address such vulnerability through a personalized psychological assessment. Additionally, they should take into account cultural norms to facilitate an understanding of patient expectations [1135].

With the increased use of penile augmentation procedures worldwide, either medical or surgical, it becomes crucial to create evidence-based recommendations to guide clinicians in this challenging and controversial area.

9.1.2 ***Definition***

To date short penis condition represents both a diagnostic and treatment challenge [1136, 1137]. An accurate measurement of the penile shaft is a mandatory step in the assessment of patients complaining of a short penis and defining the norm [1138]. Indeed, a standard tool to address penile measurements and to counsel patients seeking penile augmentation procedures is needed. To date, the standard penile size has yet to be clearly defined. Even though several investigators have attempted to provide objective measurements to define a normal penile size, there is still no consensus on this (Table 19).

Table 19: Summary of papers reporting objective penile measurements

Authors	Year	Patients, n	Age, years	Flaccid length, cm	Stretched length, cm	Erect length, cm	Flaccid circum-ference, cm	Erect circum-ference, cm
Loeb [1139]	1899	50; Caucasian	(17 – 35)	9.41	NA	NA	NA	NA
Ajmani *et al.* [1140]	1985	320; African - Nigeria	(17-23)	8.19 ±0.94	NA	NA	8.83 ±0.02	NA
Schonfeld *et al.* [1141]	1942	54; Caucasian - USA	(20 – 25)	NA	13.02	NA	NA	NA
Kinsey *et al.* [209]	1948	2770; Caucasian	(20 – 59)	9.7	16.74	NA	NA	NA
Bondil *et al.* [1142]	1992	905; Caucasian - France	53.18 ±18.19	10.74 ±1.84	16.74 ±2.29	NA	NA	NA
Richters *et al.* [1143]	1995	156; Caucasian - Australia	NA	NA	NA	15.99	NA	NA
Wessels *et al.* [1144]	1996	80; Caucasian - USA	54 ±14.37	8.85 ±2.38	12.45 ±2.71	12.89 ±2.91	9.71 ±1.71	12.30 ±1.31
Smith *et al.* [1145]	1998	184; Caucasian - Australia	NA	NA	NA	15.71 ±2.31	NA	NA
Bogaert *et al.* [1146]	1999	3417; Caucasian - USA	30.45 ±11.27	9.83 ±1.80	NA	15.60 ±1.88	NA	NA
Ponchietti *et al.* [1147]	2001	3300; Caucasian - Italy	(17 - 19)	9 (5-12)	12.5 (8 - 16.5)	NA	10 ±0.75	NA
Schneider *et al.* [1148]	2001	111; Caucasian - Germany	18.24 ±0.43	8.60 ±1.50	NA	14.48 ±1.99	NA	NA
Spyropoulos *et al.* [1149]	2002	52; Caucasian - Greece	25.9 ±4.4	7.76 ±1.3	12.18 ±1.7	NA	8.68 ±1.12	NA
Awwad *et al.* [1150]	2005	271; Arab - Jordan	44.6 ±16.3	9.3 ±1.9	13.5 ±2.3	NA	8.9 ±1.5	NA
Mehraban *et al.* [1151]	2007	1500; Arab - Iran	29.61 ±5.50	NA	11.58 ±1.45	NA	8.66 ±1.01	NA
Promodu *et al.* [1152]	2007	301; Indian	31.58 ±6.38	8.21 ±1.44	10.88 ±1.42	12.93 ±1.63	9.14 ±1.02	11.49 ±1.04
Aslan *et al.* [1153]	2011	1132; Arab - Turkish	20.3 ±0.9	9.3 ±1.3	13.7 ±1.6	NA	NA	NA
Choi *et al.* [1154]	2011	144; oriental - Korea	57.3 ±16.5	7.7 ±1.7	11.7 ±1.9	NA	NA	NA
Shalaby *et al.* [1155]	2014	2000; African - Egypt	31.6 ± 4.2	NA	13.84 ±1.35	NA	NA	NA
Veale *et al.* [1136]	2014	15521; Caucasian - UK	NA	9.16 ±1.57	13.24 ±1.89	13.12 ±1.66	9.31 ±0.90	11.66 ±1.10
Habous *et al.* [1156]	2015	778; Arab - Saudi Arabia	43.7 (20–82)	NA	NA	14.34 ±1.86	NA	11.50 ±1.74
Hussein *et al.* [1157]	2017	223; Arab - Iraq	41.3 ±15	9.8 ±2.0	12.6 ±1.9	NA	NA	NA
Alves Barboza *et al.* [1158]	2018	Tot 627 - Brazil African 167; Caucasian 283	53.6 ±15 53.8 ±13.8 53.7 ±15.5	NA NA NA	NA 16.5 ±1.7 15.8 ±1.6	NA NA NA	NA NA NA	NA NA NA
Di Mauro *et al.* [1159]	2021	4685; Caucasian - Italy	19 ±6.2	9.47 ±2.69	16.78 ±2.55	NA	9.59 ±3.08	12.03 ±3.82

Nguyen Hoai *et al.* [1160]	2021	14597; Asian - Vietnam	33.1 ±10.7	9.03 (5.10-13.20)	14.67 (8.30-19.90)	NA	8.39 (5.34-11.3)	NA
Takure [1161]	2021	271; African - Nigeria	57.3 ±16.4	10.3 ±2.4	13.7 ±2.5	NA	NA	NA
Sole *et al.* [1162]	2022	800; Caucasian - Argentina	54.2 ±17.6	11.4 ±2	15.2 ±2.2	NA	10.1 ±1.3	NA

Measurements are expressed as median/mean, (IQR)/±SD

The other factor that strongly affects penile measurements is the interobserver variability and the underestimation of the stretched penile length (SPL) when compared to the erect state [1163].

Despite the aforementioned limitations, SPL, defined as the distance between the pubic symphysis and the apex of the glans, represents the most overlapping measurement of the erect penis. Accordingly, a SPL of less than 2.5 standard deviations (SD) below the mean for the male's age and race is considered as micropenis [1164, 1165].

Summary of evidence	**LE**
There is a difference between true micropenis (anatomical-endocrinological)/short penis (complaint)/ buried penis (complaint short penis + obesity) (panel consensus). Small penis anxiety/syndrome refers to a man's excessive anxiety regarding his normal-sized penis.	4
A true micropenis is a congenital condition where the stretched penile length is 2.5 SD cm less than the average length in the population group and is the result of an underlying genetic or endocrine condition.	3
A buried penis is a normal-sized penis where there is a functional and visible loss of penile length due to an underlying pathological condition such as obesity or traumatic loss of length. The penis is covered by prepubic, scrotal or penile subcutaneous tissue or skin.	3
Penile Dysmorphic Disorder is a shorthand concept applied to Body Dysmorphic Disorder cases characterised by a strong focus on a perceived deficiency or flaw in a normal size or shape penis, resulting in mental health impairment and significant damage in important areas of the individual's life.	3

9.1.3 Epidemiology and Classification

The overall incidence of micropenis in the male population is not clearly documented. Epidemiological studies demonstrate that between 0.015% - 0.66% of male newborns have a micropenis [1166, 1167]. There are concerns that the prevalence of this congenital abnormality is increasing due to *in-utero* exposure to endocrine-disrupting chemicals before and during pregnancy [1167]. Despite the limited prevalence of micropenis, there is a major demand for penile augmentation procedures worldwide. This phenomenon can be partially explained by the increased interest in pornography in recent years and the altered perception of a normal penile size [1118, 1168, 1169].

Due to the heterogeneity of clinical situations related to short penis conditions, a classification based on the underlying aetiology is provided below (Table 20).

Table 20: Classification of the clinical conditions underlying a short penis condition or dysmorphophobia in the adult

Group name	**Aetiology**	**Definition**	**Pathogenesis**	**Prevalence, %**
False penile shortness	Acquired	Reduced exposure of the penile shaft in the presence of normal penile size	Adult acquired buried penis	NA
Intrinsic penile shortness	Congenital	Small penis due to an incomplete genital development secondary to a congenital condition	• Hypogonadotropic hypogonadism • Genetic syndromes • Bladder exstrophy–epispadias complex	0.9 - 2.1

Intrinsic penile shortness	Acquired	Shortening/shrinking of the corpora cavernosa due to an acquired pathological process	• Peyronie's Disease • Radical prostatectomy • Radical cystectomy • Radiation therapy • Low flow priapism • Multiple penile operations (e.g., urethral surgery or PP infection) • Penile traumatic event (traumatic or surgical amputation for penile cancer)	NA
Body dysmorphic disorder	Acquired	Perceived defect or flaw in the individual's physical appearance followed by significant distress or impairment in important areas of the individual's life	• Penile Dysmorphic Disorder	1.8 – 9.5

9.1.3.1 False penile shortness - congenital or acquired

Among causes underlying a false penile shortness, the buried penis is the only well-known condition. Historically, a buried penis has been considered a congenital disease affecting children: the so-called "concealed penis" or "webbed penis" [1170, 1171]. Indeed, an abnormal development of the dartos fascia may lead to the entrapment of the penile shaft to the peri-genital tissue leading to this clinical manifestation. On the other hand, a buried penis in the adult is widely recognised as an acquired condition, termed the adult acquired buried penis (AABP) [1172].

The aetiology underlying the development of AABP is deemed to be related to a chronic inflammatory state of the penile dartos which leads to a progressive retraction and scarring of the peri-genital teguments [1173, 1174]. The progressive entrapment of the phallus causes a moist environment which facilitates bacterial and fungal growth causing chronic inflammation [1175]. The ensuing fibrosis results in further entrapment of the penile shaft in the peri-genital tissue [1174, 1175].

Although the exact prevalence of AABP is unknown, its incidence seems to be increasing along with the growing prevalence of obesity, which represents the main risk factor [1176]. Other factors contributing to AABP include aggressive circumcision, following surgical treatment in the obese or penile cancer (PC), or chronic dermatological conditions such as lichen sclerosis (LS) [1177-1179].

The AABP is commonly associated with erectile and voiding dysfunctions, difficulties in maintaining adequate genital hygiene and a poor QoL [1177-1179]. A summary of risk factors for AABP and underlying issues requiring surgery is detailed in Table 21.

Table 21: Summary of studies reporting clinical characteristics of patients with AABP

Study	Year	n	Age, yr	BMI	DM (%)	HT (%)	Smoking habits (%)	History of penile cancer (%)	History of LS (%)	Underlying issues requiring surgery (%)
Ngaage *et al.* [1180]	2021	15	53 ±15.7	37.4 ±4.3	7 (54%)	NR	0	6 (46%)	NR	Urinary or sexual difficulties 9 (60.0%)

Kara *et al.* [1181]	2021	13	22.4 ±4.8	26 ±6.2	7%	7%	NR	0	NR	Cosmetic issues 13 (100%), self-esteem/ psychological well-being 13 (100%), urinary or sexual difficulties 13 (100%)
Zhang *et al.* [1182]	2020	26	33 ±5.7	29 ±5.4	NR	NR	NR	NA	NR	-
Monn *et al.* [1183]	2020	67	54.76 ±12.7	40.4 ±6.7	20 (47.6%)	NR	NR	NA	NR	Urinary difficulties 50 (74.6%), pain 21(31.3%), sexual difficulties 52 (77.6%)
Gao *et al.* [1184]	2020	32	32.5 (26-38)	-	NR	NR	NR	NR	NR	Cosmetic issues 32 (100%)
Erpelding *et al.* [1185]	2019	16	54 (44-62)	47.7 (25.5-53.3)	9 (56%)	NR	4 (25%)	NR	2 (12.5%)	-
Hesse *et al.* [1186]	2019	27	56 ±15	49 ±14	12 (44%)	16 (59%)	NR	NR	NR	Pain 12 (44%), sexual difficulties 8 (30%), difficulty in ambulating 9 (33%)
Zhang *et al.* [1187]	2019	15	33.2 ±4.6	28.9 ±5.3	NR	NR	NR	0	NR	-
Monn *et al.* [1188]	2019	13	43.4 ±15.3	42.0 ±7.3	6 (46.2%)	NR	4 (30.8%)	NR	NR	-
Aube *et al.* [1189]	2019	24	61.5 (54–67)	38.1 (33.6–43.7)	NR	NR	13 (54.2%)	NR	17 (70.8%)	Personal hygiene 19 (79.2%), urinary difficulties 14 (58.3%), sexual difficulties 19 (79.2%)
Cocci *et al.* [1190]	2019	47	51.8 ±18.4	30 ±2.3	16 (34%)	18 (38.29%)	NR	NR	10 (10.63%)	Sexual difficulties 13 (27.66%), urinary difficulties 13 (27.66%), combination of urinary and sexual difficulties 12 (25.54%)
Pariser *et al.* [1191]	2018	64	53 (42-63)	45 (38-53)	32 (50%)	NR	16 (25%)	0	NR	-

Theisen *et al.* [1192]	2018	16	48.5	44.7	9 (56%)	9 (56%)	NR	NR	12 (78%)	-
Fuller *et al.* [1193]	2017	12	-	45.4 ±13.8	NR	NR	NR	NR	NR	-
Voznesensky *et al.* [1194]	2017	14	50 ±10.5	55 ±13.7	NR	NR	NR	NR	NR	-
Hampson *et al.* [1177]	2017	42	-	-	48%	67%	NR	1	33%	Personal hygiene (67%); urinary or sexual difficulties (52%)
Ghanem *et al.* [1195]	2017	10	29.4 ±6.1	26.5 ±3.7	NR	NR	NR	NR	NR	-
Tausch *et al.* [1172]	2016	56	-	39 (22-63)	NR	NR	NR	NR	NR	-
Westerman *et al.* [1196]	2015	15	51 (26-75)	42.6 (29.8-53.9)	8 (53.3%)	NR	NR	0	13 (87%)	Cosmetic issues 11 (100%), urinary difficulties 6 (40%), sexual difficulties 3 (20%)
Rybak *et al.* [1197]	2014	11	54.2 ±44.7	49.2 (42.4-64.5)	NR	NR	NR	0	0	-
Shaeer *et al.* [1198]	2009	64	(22-54)	-	NR	NR	NR	0	0	Cosmetic issues 64 (100%)

Measurements are expressed as median/mean, (IQR)/±SD
BMI = body mass index; DM = diabetes mellitus; HT = hypertension; LS = lichen sclerosis.

The aim of AABP treatment is to restore the functional genital anatomy and to improve QoL [1177, 1178]. So far, different authors have proposed a number of classifications for AABP based upon both clinical presentation and the surgical procedure required [1172, 1191].

9.1.3.2 Intrinsic penile shortness – congenital

This category encompasses the so-called "true micropenis" [1199-1201]. Despite male genital malformations being recognised as the most common birth defects, they represent a rare clinical entity with a prevalence between 0.9% and 2.1% [1202, 1203]. Normal genital development is under the influence of hormonal stimulation during the fetal and pubertal periods [1204]. Several genetic syndromes may cause disturbance of the physiological hormonal axis needed for a normal genital development [1199, 1205]. Micropenis may also exist as an isolated finding without a definitive etiological cause in up to 25% of the cases. The classification of the clinical conditions associated with intrinsic penile shortness in the adult is presented in Table 22.

Table 22: Classification of the clinical conditions underlying intrinsic penile shortness in the adult

Aetiology	Disturbs
Hypogonadotropic hypogonadism	• Genetic diseases • Iatrogenic or traumatic injury to pituitary gland or hypothalamus
Hypergonadotropic Hypogonadism	• Chromosomal alterations (e.g., Klinefelter Syndrome) • Androgen Synthesis Defects • Dysgenetic gonads
Syndromic or Multiple Congenital Anomalies	• Bladder exstrophy–epispadias complex • Hypospadias
Unknown	-

Amongst the pre-existing clinical entities associated with micropenis, the bladder exstrophy–epispadias complex (BEEC) is the most studied [1177, 1178, 1201]. It represents a spectrum of genitourinary malformations ranging in severity from epispadias to bladder exstrophy or exstrophy of the cloaca. It is considered as a rare disease, with a prevalence at birth of 1/10,000 [1199, 1201, 1203, 1206]. Even though surgical reconstruction aims to improve body image, this clinical entity is frequently burdened by psychosocial and psychosexual dysfunctions in the long term [1207-1213]. Additionally, male infertility is frequently associated due to poor sperm quantity or quality and hormonal impairment [1214].

9.1.3.3 Intrinsic penile shortness – acquired

This category includes a series of pathological entities that lead to the shortening of the corpora cavernosa. The mechanism underlying intrinsic penile shortening can be acute, as in the case of penile trauma or surgical amputation due to penile cancer or chronic due to a progressive fibrotic process involving the corpora cavernosa [1215-1217].

Traumatic genital injuries may commonly result from traffic accidents and gunshot wounds [1217]. Rarely, a penile amputation can be the result of circumcision and genital surgical procedures such as hypospadias repair, penile prosthesis implantation or urethroplasty, and may result in a decrease in penile length [1218-1222].

Among chronic causes of penile shortening, Peyronie's disease (PD), treatments for prostate cancer, particularly radical prostatectomy (RP) and radical cystectomy represent the most common [1132, 1215, 1216, 1223-1231].

9.1.3.4 Body dysmorphic disorder

Body dysmorphic disorder (BDD) is a clinical diagnosis defined by the American Psychiatric Association (APA; DSM-5) as the strong distress generated by perceived defect(s) or flaw(s) in the individual's physical appearance. This flaw is not observable to others, or, in case it exists, it appears only slightly [1232]. This condition is followed by significant impairment in important areas of the individual's social or occupational life. Body dysmorphic disorder has been allocated to the Obsessive Compulsive and Related Disorders section [1232]. Muscle dysmorphia is a typology within BDD characterising individuals – usually men – with a strong pre-occupation with their perceived small muscles and body shape. Sometimes, men with BDD/muscle dysmorphia also present with an exaggerated focus on the size or shape of their penis. In those cases, Penile Dysmorphic Disorder (PDD) can be used as a shorthand concept – not listed in APA's DSM-5 coding system. Both BDD and PDD are conceptually different from small penis anxiety (SPA) or small penis syndrome, which refers to a man's excessive anxiety regarding his normal-sized penis. Small penis anxiety is not included under APA's nomenclature but men with SPA may be at risk for BDD [1233]. All these definitions exclude men with true micropenis [1232, 1234, 1235]. Prevalence data shows that 2.2% of men in the USA and 1.8% in Germany suffer from BDD [1232]. Between 3%-16% of patients undergoing cosmetic surgery are expected to present BDD, a higher rate in men (15.3%) than in women (10.9%) [1236].

These psychopathological entities must be differentiated from Gender Dysphoria, i.e., the clinical distress associated with the incongruence between gender identity and the gender assigned at birth; and from Koro, i.e., sudden anxiety about the penis falling back into the abdomen [1232].

*9.1.4 **Summary of evidence and recommendations for classification***

Summary of evidence	**LE**
Male genital malformations represent a rare clinical entity with an overall prevalence between 0.9% and 2.1%.	3
Obesity, lichen sclerosis and penile cancer treatment are risk factors for AABP.	4
Adult acquired buried penis (AABP) is commonly associated with erectile and voiding dysfunctions, difficulties in maintaining adequate genital hygiene and a poor quality of life.	3
Adult acquired buried penis condition can be staged upon both clinical presentation and the surgical procedure required according to available classification systems	3
Bladder exstrophy–epispadias complex (BEEC) is a rare clinical condition frequently associated with male genital malformations, particularly micropenis.	2b
Penile trauma and surgical amputation due to penile cancer are the most common acute causes of intrinsic penile shortening.	3
The most frequent aetiologies leading to a chronic intrinsic penile shortening are PD, treatments for prostate cancer (RP, radiation therapy and androgen-deprivation therapy) and radical cystectomy.	2b

Body dysmorphic disorder (BDD) is a clinical entity associated with a significant distress or impairment in important areas of the individual's life.	2b
Penile Dysmorphic Disorder (PDD) can be used as a shorthand concept to describe BDD patients mainly focused on penile size/shape.	4
Body dysmorphic disorder /PDD can be revealed in patients requiring cosmetic surgery.	3

Recommendations	Strength rating
A detailed genital examination should be considered in all men and particularly in men with BMI > 30, lichen sclerosis or penile cancer history and complaints of urinary/sexual difficulties or poor cosmesis to exclude the presence of an adult acquired buried penis (AABP) condition.	Strong
Use classification systems to classify AABP clinical presentation and surgical management.	Weak
Inquire on the presence of body dysmorphic disorder/penile dysmorphic disorder in patients with normal-sized penis complaining of short penile size.	Strong

9.2 Diagnosis

*9.2.1 **Medical history, physical examination and psychological assessment***

9.2.1.1 Medical History

The first step in the evaluation of short penis is a detailed medical history [1237]. Common causes of penile shortness should be screened and observed (e.g., history of phimosis, priapism, hypospadias/epispadias, penile trauma, penile cancer, prostate cancer, penile pain with or without acquired penile curvature suggestive of PD). A past or present diagnosis of BDD should also be noted.

9.2.1.2 Sexual history

Besides a comprehensive clinical interview with open questions regarding sexual education, development, or previous sexual experiences and fantasies, psychometric tools can be used. These include measurements of sexual functioning (e.g., The International Index of Erectile Function [IIEF]), sexual distress (e.g., The Sexual Distress Scale for men), and sexual satisfaction (e.g., Global Measure of Sexual Satisfaction) [307, 1238, 1239]. The propensities for sexual excitation and sexual inhibition may be further considered, (e.g., Sexual Inhibition/ Sexual Excitation Scales), as well as measurements of relationship satisfaction (e.g., Global Measure of Relationship Satisfaction) [1239, 1240]. Special focus should be put on the assessment of sexual performance expectations (e.g., The Dysfunctional Sexual Beliefs Questionnaire) [1241]. As a complementary assessment, body image perception can be further considered (e.g., The Body-Image Questionnaire).

9.2.1.3 Physical examination and penile size measurements

An accurate physical examination focused on the genital area is essential to the patient's initial assessment. The assessment of penile size and shape is mandatory to plan any subsequent medical or surgical treatment but methods for penile measurements seem to vary amongst surgeons [1138, 1242]. The EAU Guidelines Panel on Sexual and Reproductive Health considers a stretch penile length measurement as the bare minimum. If possible, the Panel also advocates additional measurements in both flaccid and erect state after intracavernosal injection of erectogenic agents, compulsory before any surgical indication. Stretched penile length (SPL) can be measured both dorsally and/or ventrally from the penopubic skin junction-to-glans tip (STT) or dorsally from the pubic bone-to-glans tip (BTT) using either a measuring tape or a Vernier calliper. Overall, the measurement of penile size has not been standardised and to date there is no consensus definition due to high heterogeneity in terms of data assessment and reporting methodologies amongst different studies [1242].

Moreover, penile girth should be noted in every patient. As for girth, both distal (coronal) and mid-shaft measurements should be recorded. Furthermore, both measures of circumference can be compared to the head-to-base ratio. The former can help classify penile shape which can be documented through photography [1243]. Although used as a surrogate, STT underestimates erect penile length by about 20% [876, 1244]. Nonetheless, it is important to note that BTT seems to have a better correlation with erect penile length, especially in overweight and obese men [876].

Table 23: Penile size measurement

Length
State Erect, stretched or flaccid ***Anatomic Landmarks*** Dorsally and/or ventrally from the penopubic skin junction-to-glans tip (STT) Dorsally from the pubic bone-to-glans tip (BTT)
Girth
State Erect or flaccid ***Anatomic Landmarks*** Proximal (penopubic skin junction) Middle shaft Distal (Coronal or subcoronal)
Shape
Head-to-base ratio Standardised photography

9.2.1.4 Psychological assessment

A sub-group of men requesting penile augmentation procedures, usually surgery, present with strong psychological vulnerability, including BDD [1233]. This subgroup of men may be at risk for increasing psychopathology and suicide attempts and will be unlikely to achieve their surgery expectations [1245]. Currently, there is a set of freely available self-reported tools that may be used to screen patients at risk for psychopathology or poor surgical outcomes, including the Body Dysmorphic Disorder Questionnaire and The Cosmetic Procedure Screening Scale for Penile Dysmorphic Disorder, screening for psychopathological cases regarding body and penile dysmorphic disorder [1233, 1246]. Likewise, The Male Genital Self-Image Scale, and the Index of Male Genital Image, measure men's perceptions and satisfaction regarding their genitals [1247, 1248]. In addition, the Beliefs About Penile Size Scale captures beliefs about the size of the penis as well as internal psychological processes [1249]. However, evidence on BDD/PDD, further psychopathological comorbidities, and the differential diagnosis regarding personality disorders, and disorders from the obsessive-compulsive, psychotic, or emotional spectrum, should be performed by an accredited mental health expert. In addition, the subjective penile size perception should be evaluated [1134].

9.2.1.5 Counselling and outcomes assessment - Validated questionnaires

The Augmentation Phalloplasty Patient Selection and Satisfaction Inventory (APPSSI) questionnaire is a 5-item questionnaire proposed for the assessment and counselling about penile augmentation surgical treatment [1250]. The Beliefs about Penis Size (BAPS) is a 10-item questionnaire created for audit and outcome research to assess men's beliefs about penile size [1249]. Both questionnaires have failed to correlate with penile size and lack of objective validation has restricted their use.

Other well-known self-reported psychosexual questionnaires may be considered: the IIEF-15 and the Male Sexual Health Questionnaire (MSHQ) should be administered to record baseline sexual function status and can also be used to assess its changes after treatment; the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) can also be helpful to assess patient and partner's treatment satisfaction [307, 1251, 1252].

9.2.2 ***Imaging***

There is a lack of evidence regarding the use of imaging techniques in the assessment of patients complaining about penile shortness. Although a penile Doppler ultrasound or a penile magnetic resonance imaging may provide additional data regarding the penile anatomy and the extent of penile burying, there is no evidence that this additional information could contribute to the physical examination to justify its routine use in this clinical scenario [1138, 1253-1256].

Summary of evidence	LE
Medical/sexual history taking and physical examination are essential parts of the evaluation of men with a short penis complaint.	4
Among stretched penile measurements dorsal and/or ventrally from the penopubic skin junction-to-glans tip (STT) may underestimate erect penile length.	2b
Among stretched penile measurements dorsally from the pubic bone-to-glans tip (BTT) has a better correlation with erect penile length, especially in overweight and obese men.	2b
Flaccid and erect state measurements to assess penile length may add useful information on penile size.	4
Penile girth assessment may add useful information on penile size and shape.	4
The Body Dysmorphic Disorder Questionnaire, The Cosmetic Procedure Screening Scale for Penile Dysmorphic Disorder, The Male Genital Self-Image Scale and the Index of Male Genital Image are self-reported tools useful to screen patients at risk for psychopathology.	2b
Mental health counselling helps detect men requesting penile augmentation procedures present with strong psychological vulnerability, including BDD/PDD.	2b
Validated questionnaire (e.g., APPSSI, BAPS, IIEF-15, MSHQ, EDITS) help assess baseline sexual function and beliefs about penile size.	4

Recommendations	Strength rating
Take a comprehensive medical and sexual history from every patient presenting complaining of short penile size.	Strong
Use stretched penile measurements (skin junction-to-glans tip or dorsally from the pubic bone-to-glans tip) to define penile length.	Weak
Measure flaccid and erect measurements to assess penile length in detail.	Weak
Measure penile girth in every patient presenting complaining of a short penile size.	Weak
Use validated questionnaires to screen for body dysmorphic disorder (BDD) in cases of a normal-sized penis.	Weak
Use validated questionnaires (e.g., IIEF-15, BAPS) to assess baseline sexual function and beliefs concerning penile size.	Weak
Refer patients with suspected BDD for mental health counselling.	Strong

9.3 Management

*9.3.1 **Non-surgical Treatments***

9.3.1.1 Psychotherapy

Penile augmentation is often motivated by the desire to improve self-perception and self-esteem [1257]. Cosmetic treatments may help increase individuals' well-being and QoL, improving self-esteem and emotional states [1123, 1124, 1138]. Still, psychotherapy is recommended when psychopathological comorbidities are detected, or when aversive relationship dynamics may underly the request for penile augmentation. Addressing patients' and partners' motivations and expectations regarding penile augmentation seems to be a key psychotherapeutic target while no other empirical evidence is described. Similarly, men with BDD and SPA present a significant discrepancy between the perceived and ideal size of the penis, internalising the belief they should have a larger penis [1258]. Cognitive behaviour therapy for BDD could be applied to cases of anxiety regarding penis size, although no clinical trials have been reported [1259]. In all, it is worth noting that psychotherapy should normalise the great variability of genital shape and size [1133]. Managing patient expectations could be a means to improve results and well-being associated with the surgery process.

9.3.1.2 Penile traction therapy

Despite the various surgical techniques, there are also non-invasive methods that are used to enhance penile length, including penile traction therapy (PTT) [1260]. In a pilot phase-II prospective study that evaluated the efficacy and tolerability of a penile-extender device in the treatment of short penis, Gontero *et al.*, used the same traction device for at least 4 hours/day for 6 months and achieved a significant gain in length, of +2.3 and +1.7 cm for the flaccid and stretched penis, respectively (both $p < 0.001$) [1261]. However, the change in the penile girth was not significant. In a further prospective study, these results were confirmed by Nikoobakht *et al.*, who found a significant improvement in the mean length both for the flaccid (8.8 ± 1.2 cm to 10.5 ± 1.2 cm, $P < 0.05$) and the stretched state (11.5 ± 1.0 cm to 13.2 ± 1.4 cm, $p < 0.05$) following 3 months of use of a penile traction device [1262]. At six-month follow-up, compared to baseline, a mean gain of +1.7 ± 0.8, +1.3 ± 0.4, and +1.2 ± 0.4

cm was reported for the flaccid, stretched, and erect penile lengths, respectively ($p < 0.001$, for all). The broad spectrum of available PTT studies is summarised in Table 24.

Overall, PTT seems effective in lengthening the penis both in the flaccid and stretched state with minimal side effects. Yet it is not effective for penile girth enhancement. However, the quality of evidence is poor due to the lack of RCTs, and the availability of only heterogeneous and small PTT cohorts has also been proven effective in the restoration of length or correction of deformities due to several diseases, including PD, or post-RP conditions [955, 1263-1265].

Table 24: Penile traction therapy (PPT)

Author (year)	Year	n	Study design	Device	Treatment protocol	Mean age ± SD	Mean gain in penile dimensions cm (SD)
Nowroozi *et al.* [1266]	2015	54	Prospective	AndroPenis	4-6 hours per day for 6 months	30.1 ± 4.8	Flaccid length: 1.7 ± 0.8 Stretched length: 1.3 ± 0.4 Erected length: 1.2 ± 0.4
Nikoobakht *et al.* [1262]	2011	23	Prospective	Golden Erect	4–6 hours per day during the first 2 weeks and then 9 hours per day until the end of the third month	26.5 ± 8.1	Flaccid length: 1.7 Stretched length: 1.71 Circumference: -0.22 Glans penis circumference: -0.35
Gontero *et al.* [1261]	2008	21	Prospective	Golden Erect	at least 4 h/day for 6 months	45.7 ± 11.1	Flaccid length: 2.3 Stretched length: 1.7 Circumference: NR

NR = not reported.

9.3.1.3 Vacuum erection device

Vacuum erection devises (VED) are generally considered for patients who fail oral ED therapies [413, 1237]. In contrast, data regarding the use of VEDs on penile elongation is scarce. In a study with 27 men whose SPL was < 10 cm, the use of a VED three times a week for 20 minutes on each occasion, for six months, did not result in a significant increase in flaccid or SPL [1267]. On the other hand, the benefits of using a VED following PPI and RP have been demonstrated in the literature [1267-1272].

9.3.1.4 Endocrinological therapies

Testosterone administration has been used for a long time to increase the length of the penis in infant or pre-pubertal boys with micropenis. Topical administration of T or DHT has also been proposed by other authors with reported better outcomes with DHT, especially in poor responders to T or in those with type 2 alpha reductase deficiency [1273, 1274]. Finally, the possible use of the combination of hCG and FSH treatment has also been proposed with positive outcomes [1275, 1276]. Despite the treatment suggested it should be recognised that no face-to-face comparisons are available so far.

9.3.1.5 Summary of evidence and recommendations for the non-surgical management of short penile size

Summary of evidence	LE
Psychotherapy should not be undertaken in the realm of preventing individuals' legitimate choice to improve their lives. Conversely, psychotherapy is recommended when psychopathological comorbidities are detected, or when aversive relationship dynamics may underly the request for penile augmentation.	3
Cognitive behaviour therapy for BDD could be applied to cases of anxiety regarding penis size.	3
Penile traction therapy proved to be an effective treatment to achieve penile lengthening.	3
Vacuum erection devices proved to be an ineffective treatment in achieving penile lengthening.	3
Testosterone therapy, transdermal dihydrotestosterone and recombinant gonadotropins can restore penile size in boys with micropenis or disorders of sex development.	2b
Testosterone therapy does not increase penile size in adult men and in men with late-onset hypogonadism.	3

Recommendations	Strength rating
Consider psychotherapy when psychopathological comorbidities are detected, or when aversive relationship dynamics may underlie the request for penile augmentation.	Strong
Consider the use of penile traction therapy as a conservative treatment to increase penile length.	Weak
Do not use vacuum erection devices to increase penile length.	Weak
Use endocrinological therapies to restore penile size in boys with micropenis or disorders of sex development.	Strong
Do not use testosterone therapy or other hormonal therapies to increase penile size in men after puberty.	Strong

9.3.2 ***Surgical Treatments***

9.3.2.1 *Surgical treatment of adult acquired buried penis*

9.3.2.1.1 Adult acquired buried penis surgical procedures classification

According to the classification proposed by Pariser *et al.* different procedures may range from low complexity (including un-burying of penile shaft, reconstruction of penile shaft with the use of skin flaps or grafts, plastic surgical techniques to reconstruct the scrotum) to high complexity [including surgical removal of the suprapubic fat pad (escutcheonectomy) and operations to skin and subcutaneous fat layers of the abdominal wall (apronectomy] [1191].

The purpose of any surgical approach is to unbury the penile shaft, reconstruct genital teguments and eventually remove peri-genital or excess abdominal tissue in order to reduce the risk of recurrence. The goal is to balance an effective surgical procedure aiming to improve patient QoL, while minimising the incidence of postoperative complications. Lifestyle changes and risk factors modification, particularly weight loss, are widely considered as a proactive approach to minimise AABP surgical complications and should be encouraged before surgical intervention is undertaken. The broad spectrum of surgical interventions described to manage AABP is summarised in Table 25.

Table 25: Surgical interventions to manage adult acquired buried penis [1174]

Study	Year	n	Type of intervention (%)	Classification of intervention* (%)
Ngaage *et al.* [1180]	2021	15	3 (20%) abdominoplasty, 5 (33%) panniculectomy, 11 (73%) monsplasty, 3 (20) shaft reconstruction with scrotal flap, 7 (47%) STSG.	7 category II, 5 category IV, 3 category V
Kara *et al.* [1181]	2021	13	13 (100%) circumcision, penile liberation and STSG.	13 category II
Zhang *et al.* [1182]	2020	26	26 (100%) suprapubic liposuction and a modified Devine's technique.	26 category IV
Monn *et al.* [1183]	2020	67	53 (79.1%) split-thickness skin graft (STSG), 19 (28.4%) ligament fixation, 38 (56.7%) pubic lipectomy, 10 (14.9%) pubic liposuction, 17 (25.4%) abdominal panniculectomy, 16 (23.9%) urethroplasty.	-
Gao *et al.* [1184]	2020	32	32 (100%) suprapubic liposuction, suspensory ligament release and preputioplasty.	32 category IV
Aube *et al.* [1189]	2019	24	17 (70.8%) STSG, 17 (70.8%) penopubic ligament fixation, 17 (70.8%) pubic lipectomy, 9 (37.5%) abdominal panniculectomy, 3 (12.5%) pubic liposuction.	-
Cocci *et al.* [1190]	2019	47	(27.66%) circumcision, (19.14%) scrotoplasty, (4.25%) V-Y plasty of the pre-pubic region, (12.76%) thin STSG, (36.17%) thick STSG, (57.44%) suprapubic fat pad excision, (25.53%) abdominoplasty, (36.17%) division of the suspensory ligament.	-
Erpelding *et al.* [1185]	2019	16	2 (12.5%) penile liberation and STSG, 1 (6.2%) penile liberation, STSG, eschutcheonectomy and urethroplasty, 1 (6.2%) penile liberation, STSG and urethroplasty, 4 (25%) penile liberation, STSG, eschutcheonectomy and urethroplasty, 4 (25%) penile liberation, STSG, eschutcheonectomy and scrotoplasty, 4 (25%) penile liberation, STSG, eschutcheonectomy.	4 category II, 12 category IV

Hesse *et al.* [1186]	2019	27	27 (100%) Penile liberation, STSG, panniculectomy, abdominoplasty and monsplasty.	-
Zhang *et al.* [1187]	2019	15	15 (100%) suprapubic liposuction, penile suspensory ligament release and insertion of folded acellular dermal matrix between corpora cavernosa and pubis symphysis.	15 category IV
Monn *et al.* [1188]	2019	13	6 (46.2%) penile liberation, full thickness graft to the penis using the escutcheon tissue as a graft source, 7 (53.8%) penile liberation, panniculectomy, full thickness graft to the penis using the escutcheon tissue as a graft source.	6 category IV, 7 category V
Pariser *et al.* [1191]	2018	64	3 (5%) penile unburying with local skin flap, 17 (27%) skin graft to the shaft, 7 (11%) scrotal surgery (scrotectomy or scrotoplasty), 33 (52%) escutcheonectomy, 4 (6%) abdominal panniculectomy.	3 category I, 17 category II, 7 category III, 33 category IV, 4 category V
Theisen *et al.* [1192]	2018	16	16 (100%) escutcheonectomy, scrotectomy, and penile STSG.	16 category IV
Fuller *et al.* [1193]	2017	12	12 (100%) escutcheonectomy, scrotoplasty and penile STSG.	12 category IV
Voznesensky *et al.* [1194]	2017	12	11 (92%) debridement of penile skin and STSG to the penis, 12 (100%) escutcheonectomy, 10 (83%) abdominoplasty, 7 (59%) scrotoplasty, 12 (100%) securing the supra-penile dermis to the pubic dermal or periosteal tissue.	12 category IV/V
Hampson *et al.* [1177]	2017	42	42 (100%) limited suprapubic panniculectomy, radical excision of penile shaft skin and reconstruction with STSG and scrotoplasty if needed.	42 category IV
Ghanem *et al.* [1195]	2017	10	10 suprapubic liposuction.	10 category IV
Tausch *et al.* [1172]	2016	56	25 (45%) phalloplasty with or without a scrotal flap (if significant abdominal component panniculectomy to remove the excess suprapubic fat), 12 (21%) penile shaft reconstruction with STSG, 19 (34%) penile shaft reconstruction with STSG following excision of the involved tissues with any necessary adjunctive procedures.	-
Westerman *et al.* [1196]	2015	15	15 (100%) phalloplasty with ventral slit scrotal flap.	15 category II
Rybak *et al.* [1197]	2014	11	11 (100%) penile release, 10 (90.9%) STSG.	1 category I, 10 category II
Shaeer *et al.* [1198]	2009	64	64 (100%) adhesiolysis, suprapubic and lateral lipectomy, anchoring the penoscrotal and penopubic junctions, and skin coverage by a local flap.	64 category IV

The current evidence highlights the efficacy of AABP surgical treatment which has a low incidence of recurrence and satisfactory functional outcomes, as shown in Table 26, yet there is a significant incidence of post-operative complications (up to 3.5% of grade V according to Clavien-Dindo Classification) [1277].

Table 26: Surgical and functional outcomes of adult acquired buried penis repair [1174]

Study	Year	Overall post-operative complications	Recurrence of burying	Sexual outcomes	Urinary outcomes	Cosmetic outcomes
Ngaage *et al.* [1180]	2021	6 (44%)	2 (13%)	Spontaneous erections in 5 (83%)	7 (78%) voiding in standing position	-
Kara *et al.* [1181]	2021	4 (30%)	-	Increase in IIEF & SSS	-	All patients were pleased with the cosmetic outcome

Zhang *et al.* [1182]	2020	21 (80.8%)	-	-	-	Most patients had positive feedback toward their result of the operation, with a mean grade of 4.5+0.7.17 patients (65%) who were very satisfied with the outcome. Six patients (23%) were satisfied with the outcome. Three patients (12%) were neither satisfied nor dissatisfied with the outcome. None of the patients were dissatisfied nor very dissatisfied with the outcome
Monn *et al.* [1183]	2020	24 (57.1%)	-	33 (49.3%) patients with erection post-operatively	-	Satisfied 25 (37.3%); unsatisfied 9 (13.4%); neutral 33 (49.3%)
Gao *et al.* [1184]	2020	-	-	Increase in IIEF	-	-
Aube *et al.* [1189]	2019	15 (62.5%)	-	Good postoperative erection	-	Patient satisfaction in the case of a successful procedure was: 16 patients (76.2%) satisfied with the procedure, 5 patients (23.8%) neutral/not responding and no patients (0%) dissatisfied
Erpelding *et al.* [1185]	2019	3 (18.7%)	-	-	-	-
Hesse *et al.* [1186]	2019	15 (55.5%)	-	-	-	Nearly all patients (96%) reported early satisfaction with the procedure
Zhang *et al.* [1187]	2019	11 (73.3%)	-	No difficulty in sexual intercourse	None of the patients reported difficulty in urination	10 patients (66.7%) were very satisfied with the outcome, 4 patients (26.6%) were satisfied with the outcome, 1 patient (6.7%) was neither satisfied nor dissatisfied with the outcome, and no patient was dissatisfied with the appearance and function
Cocci *et al.* [1190]	2019	7 (14.9%)	-	Increase in IIEF of 3 points, vaginal penetration became possible in 97.87% of patients, erectile function improved in 42.55%, 48.93% needed to take PDE5i to enhance their nocturnal erections, improvement in penile erogenous sensation was recorded in 6.38%	-	-
Monn *et al.* [1188]	2019	5 (38.4%)	-	-	-	All patients reported subjective satisfaction with the cosmesis of their surgical outcome

Pariser *et al.* [1191]	2018	42 (65%)	-	-	-	-
Theisen *et al.* [1192]	2018	2 (10.5%)	1 (5.2%)	Significant improvement in 10 of 13 questions (77%)	Significant improvement in 10 of 12 questions (83%)	
Fuller *et al.* [1193]	2017	0 (0%)	-	-	-	-
Voznesensky *et al.* [1194]	2017	9 (75%)	9 (75%)	Improvement or the same degree of sexual activity (75%).	Improvement in urination (92%)	-
Ghanem *et al.* [1195]	2017	-	-	-	-	3 (30%) of the patients were very satisfied with the result, 5 (50%) patients were satisfied, 1 patient (10%) was neither satisfied nor dissatisfied, and 1 (10%) patient was dissatisfied. No patients were very dissatisfied.
Tausch *et al.* [1172]	2016	-	-	-	-	-

Summary of evidence	**LE**
Various surgical procedures may be considered to restore genital anatomy in adult acquired buried penis (AABP) patients.	3
Adult acquired buried surgery is burdened by a significant incidence of postoperative complications.	3
Lifestyle changes and risk factors modification, particularly weight loss, are widely considered as a proactive approach to minimise AABP surgical complications.	4
Adult acquired buried surgery may provide satisfactory functional outcomes with a low incidence of recurrence.	3

Recommendations	**Strength rating**
Extensively counsel patients on the benefits and complications of adult acquired buried penis (AABP) surgery.	Strong
Initiate lifestyle changes and modification of risk factors, particularly weight loss, to minimise AABP surgical complications and to optimise surgical outcomes.	Strong
Consider surgical treatment to address AABP.	Weak

9.3.2.2 Surgical treatment of congenital intrinsic penile shortness

Current literature reports a wide spectrum of possible surgical interventions aimed to address penile shortness. Nonetheless, the proposed spectrum of surgical interventions starts from less invasive procedures - such as suspensory ligament release (SLR) - to more complex genital reconstruction - such as total phallic reconstruction (TPR) [1278, 1279].

9.3.2.2.1 Suspensory ligament release (SLR)

This technique involves a surgical incision and SLR of the penis which attaches the penis to the pubic bone. The surgical access is via an infrapubic incision and may be combined with an elongating V-Y skin plasty [1279]. Several authors reported outcomes of SLR in the context of a congenital intrinsic penile shortness (Table 27).

Table 27: Suspensory ligament release [1278]

Author (year)	Year	n	Study design	Age, years	Follow-up, months	Stretched penile length gain, cm
Littara *et al.* [1280]	2019	21	Retrospective	38.08 ±1.1	12	1.1
Zhang *et al.* [1187]	2019	15	Retrospective	33.2 ± 4.6	3	4.3 ±1.6
Li *et al.* [1279]	2006	27	Retrospective	NR	16	1.1 ±1.1
Spyropoulos *et al.* [1250]	2005	11	Retrospective	25-25	Not reported	1.6 (1–2.3)

Measurements are expressed as median/mean, (IQR)/±SD.

9.3.2.2.2 Ventral phalloplasty/scrotoplasty

This intervention is based on a ventral shaft skin plasty to move the peno-scrotal angle proximally and increase the exposure of the penile shaft. A longitudinal incision or Z-plasty at the penoscrotal junction, securing the tunica albuginea to the proximal tunica dartos was performed by Xu *et al.* in 41 patients [1281]. The correction was successful in all patients with an improved median length of +2.1 cm in the flaccid state.

9.3.2.2.3 Suprapubic lipoplasty/liposuction/lipectomy

This intervention aims to reduce the thickness of the suprapubic fat pad either with a minimally invasive approach (liposuction) or surgically (lipectomy). The flattening of the suprapubic fat pad aims to increase penile shaft exposure.

Ghanem *et al.*, performed liposuction in ten patients using a 50-cc syringe with a 3- and 6-mm liposuction needle [1195]. The amount of fat removed ranged from 325 to 850 mL with a mean of 495.50 ± 155.39 mL. Three (30%) of the patients were very satisfied with the post-operative result, five (50%) patients were satisfied, one patient (10%) was neither satisfied nor dissatisfied, and one (10%) patient was dissatisfied. No patients were very dissatisfied. Shaeer's monsplasty technique was investigated in 20 patients [1282]. At three months post-operatively, the flaccid visible length was 7.1 ± 2.1cm, with a 57.9% improvement in length, and the erect visible length was 11.8 ± 2.1cm, with a 32% improvement in length. At final follow-up (eighteen months) a 73.1% improvement in satisfaction rate was detected.

9.3.2.2.4 Total phallic reconstruction (TPR)

This represents the most complex genital reconstruction possible, aiming to create a new phallus with a neo-urethra. The operation is reserved for severe penile insufficiency cases (e.g., congenital micropenis, exstrophy-epispadias complex) as the benefit should be balanced over possible complications [1278].

Lumen *et al.*, treated seven male patients (aged 15 to 42 years) with phalloplasty (6 with radial forearm free flap and 1 with anterolateral thigh flap) and implant surgery was offered approximately 1 year after the phallic reconstruction [1283]. There were no complications after surgical formation of the neophallus. Two complications were reported in the early post-operative period. Two patients developed urinary complications (stricture and/or fistula). Patient satisfaction after surgery was high in six cases and moderate in one case. Four patients underwent penile implant surgery and 50% were subsequently removed.

Perovic *et al.*, conducted TPR using musculocutaneous latissimus dorsi (MLD) in twelve patients [1284]. The mean (range) follow-up was 31 (6–74) months, and the penile size was 16 (14–18) cm long and 13 (11–15) cm in circumference. There was no flap loss or partial skin necrosis.

Garaffa *et al.*, reported a series of TPR using the radial artery forearm free flap in 16 patients with bladder/cloacal exstrophy and micropenis-epispadias complex [1285]. In one patient the distal third of the phallus was lost due to acute thrombosis of the arterial anastomosis immediately post-operatively. Almost all (93%) were fully satisfied in terms of cosmesis and size. Urethral stricture and fistula were the most common complications, which developed only at the native neourethral anastomosis. They were successfully managed by revision surgery. Sexual intercourse was achieved in 11 of the 12 patients who underwent PPI.

9.3.2.2.5 Summary of evidence and recommendations for surgical treatment of congenital intrinsic penile shortness

Summary of evidence	LE
Considering the wide spectrum and the complexity of surgical interventions aimed at addressing penile shortness, this surgery should be reserved to high volume centres.	4
Suspensory ligament release, ventral phalloplasty and suprapubic lipoplasty/liposuction/lipectomy provide an objective increase in penile length.	3
Suspensory ligament release, ventral phalloplasty and suprapubic lipoplasty/liposuction/lipectomy are associated with a significant incidence of complications.	3
Total phallic reconstruction provides satisfactory surgical and functional outcomes in men with micropenis.	3

Recommendations	Strength rating
Perform penile augmentation surgery in high-volume centres.	Strong
Use suspensory ligament release (SLR), ventral phalloplasty and suprapubic lipoplasty/ liposuction/lipectomy to address penile lengthening.	Weak
Extensively discuss possible complications related to suspensory ligament release, ventral phalloplasty and suprapubic lipoplasty/liposuction/lipectomy.	Strong
Use total phallic reconstruction to restore genital anatomy in patients affected by congenital micropenis.	Weak

9.3.2.3 Surgical treatment of acquired penile shortness

9.3.2.3.1 Penile prosthesis implantation (PPI)

The literature fails to show a direct relationship between PPI and penile length in men with ED and no concomitant PD. In a study by Deveci *et al.*, SPL was evaluated in men undergoing primary implant surgery due to diabetes or RP [1286]. Either three-piece (Alpha-1, Mentor, USA) and two-piece implants (Ambicor, AMS, Boston Scientific, USA) were used and most patients (72%) reported a subjective decrease in penile length, although no statistically significant difference was demonstrated in measured SPL [1286]. In another study, 45 patients with PD with no deformity or penile curvature < 30° or severe penile fibrosis/scarring were implanted with an AMS 700 LGX [1287]. The mean stretched penile length improved from 13.1 ± 1.2 cm to 13.7 ± 1.1 cm and 14.2 ± 1.2 cm at six and twelve months, respectively. A significant difference was also observed in the length of the stretched flaccid penis between six and twelve months [1287].

Some authors have evaluated the erect penile length following PPI. In a prospective study where patients with PD were excluded, erect penile length was compared from baseline achieved by intracavernosal injection and after PPI inflation. The authors demonstrated that there were 0.83 ± 0.25, 0.75 ± 0.20 and 0.74 ± 0.15 cm decreases in erect penile length six weeks, six months, and one year post-operatively, respectively [1288]. A study where patients with PD were excluded confirmed these results as the median pre-operative pharmacologically induced length (14.25 ± 2 cm) was decreased to median post-prosthesis penile length (13.5 ± 2.13 cm) [1289].

9.3.2.3.2 Penile disassembly

Penile disassembly has been described as a technique for penile lengthening [1290]. It consists of the separation of the penis into its anatomical components and the insertion of autologous cartilage in the space created between the glans cap and the tip of corpora cavernosa. Perovic *et al.*, in a study with 19 patients submitted to penile disassembly and implantation of autologous rib cartilage followed by VED therapy, reported an increase of 3 cm and 3.1 cm in SPL and erect length, respectively [1290]. The results of this surgery are poorly documented and significant complications such as glans necrosis can ensue.

9.3.2.3.3 Lengthening corporal manoeuvres

Penile length restoration with the use of the sliding technique (ST) and concomitant PPI was first described in a small series of three patients in 2012, and further supported by a larger series of 28-patient in a multi-centre study in 2015 [1110, 1114]. Although this technique is only used in cases of end-stage PD with severe shortening of the shaft, 95% of men were satisfied with their increase in length with an average penile lengthening of 3.2 cm (range, 2.5-4 cm). The modified sliding technique (MoST) and multiple slit technique (MuST) are further modifications of the original ST [1111, 1112]. In a series by Egydio *et al.*, 143 patients with

penile shortening and narrowing due to PD amongst other aetiologies underwent MoST or MuST procedures. The mean (range) penile length gain was 3.1 (2-7) cm at a median (range) follow-up of 9.7 (6-18) months [1111].

9.3.2.3.4 Total phallic reconstruction (TPR)

Radial forearm free flap is the most used reconstructive approach for TPR. In a single-centre study, Falcone *et al.*, reported their experience of ten patients who underwent TPR using RAFFF after traumatic penile loss [1291]. In six individuals, the urethral stump was sufficient for primary anastomosis and neourethra formation. The remaining patients had total penile avulsion and were voiding via a perineal urethrostomy. Consequently, a two-stage urethroplasty was necessary. Two patients developed an acute arterial thrombosis of the microsurgical anastomosis, which was successfully treated with emergency exploration. One patient had a neourethral stricture and fistula that required revision. All patients who underwent complete urethral repair were able to void and ejaculate through the phallus. After a median follow-up of 51 months, all patients were satisfied with the acquired size, cosmesis, and sensation. Six patients received a PPI and were able to also engage in penetrative intercourses. However, three patients had revision surgery (two due to infection and one due to mechanical failure) [1291].

9.3.2.3.5 Summary of evidence and recommendations for surgical treatment of acquired penile shortness

Summary of evidence	**LE**
Penile prosthesis implantation is not effective in increasing penile length.	3
The evidence for the use of penile disassembly manoeuvres and the lengthening corporal manoeuvres are limited.	3
Total phallic reconstruction yields to satisfactory outcomes despite the high incidence of post-operative complications.	3

Recommendations	**Strength rating**
Do not recommend penile prosthesis implantation, penile disassembly or lengthening corporal manoeuvres to patients seeking penile lengthening options.	Strong
Use total phallic reconstruction to restore genital anatomy in genetic males with penile inadequacy due to traumatic loss.	Weak

9.3.2.4 Penile girth enhancement

9.3.2.4.1 Penile Girth enhancement history

Nomograms were created for penile girth measurements, including flaccid penis circumference (n = 9407, 9.31 ± 0.90 cm) and erect circumference (n = 381, 11.66 ± 1.10 cm) [1136]. Unlike penile lengthening, there are no precise definitions or indications for penile girth enlargement in the literature or existing international guidelines [1292]. In recent years, men have increasingly approached urologists for penile girth enhancement to increase their self-confidence, to be cosmetically satisfied or to satisfy their partners [1293]. Current reports on penile girth enhancement techniques are from recent years [1293, 1294]. Although these surgical techniques are more and more frequently requested, the level of evidence for their use in clinical practice is low, notwithstanding the ethical considerations of surgery in this vulnerable group of patients.

9.3.2.4.2 Injection therapy

Injectable filling materials can be classified according to their different properties. They can be autologous, biological or synthetic. The fat injection material is obtained from the patient's own tissue (autologous), usually by liposuction (see the following surgical therapy section). Biological fillers can be of human and animal (collagen) or bacterial (Hyaluronic acid) origin. Poly-l-lactic acid (PLA), hydroxyethyl methacrylate, polyalkylimide hydrogel (PAAG), polymethylmethacrylate (PMMA), calcium hydroxyapatite (CHA), silicon and paraffin constitute filler materials of synthetic origin (Table 28) [1295].

Table 28: Origin of injectable filling materials

Autologous	Autologous fat tissue
Biological	Hyaluronic acid
Synthetic	Poly-l-lactic acid, hydroxyethyl methacrylate, polyacrylamide hydrogel, polymethylmethacrylate, calcium hydroxyapatite, silicon, paraffin

9.3.2.4.2.1 Soft tissue fillers (Hyaluronic acid and PMMA)

Hyaluronic acid

Injection of hyaluronic acid (HA) gel is one of the most commonly used injectable fillers in the field of plastic surgery [1237, 1296]. The application of HA for penile girth enhancement has recently gained increasing popularity due to its biocompatibility and infrequent mild temporary side effects. The newly invented cross-linked HA has a more lasting effect over time [1297]. Hyaluronic acid has been used for patients for penile girth enhancement. Studies have reported that an increase of 1.4 to 3.78 cm in penile girth is achieved with HA injection (Table 29). Patient satisfaction is high (78-100%) and no severe side effects have been reported [704, 1298-1301].

Table 29: Published data on evaluation of Hyaluronic acid injection therapy on penile girth enhancement

Author	Year	n	Study design	Age, years	Follow-up, months	Girth gain, cm	Complications, n (%)
Zhang *et al.* [1302]	2022	38	Retrospective	31.2 ± 6.7	12	2.44 ± 1.14	3 (7.9)
Ahn *et al.* [704]	2021	32	Multi-centre RCT	20-65	5-6	2.27± 1.26	2 (6.3)
Quan *et al.* [1303]	2021	230	Retrospective	30.34±5.23	6	1.80 ± 0.83	10 (4.3)
Yang *et al.* [1300]	2020	39	Multi-centre RT	19-65	5-6	2.1 ± 1.0	2 (5.13)
Yang *et al.* [1301]	2020	33	Multi-centre RT	20-66	18	1.41 ± 1.48	3 (9.1)
Yang *et al.* [1298]	2019	36	Multi-centre RT	20-65	11-12	1.69 ± 1.53	1 (2.78)
Kwak *et al.* [1299]	2011	50	Retrospective	42.5 (27-61)	18	3.78 ± 0.35	0 (0)
Summary		N/A	N/A	19-66	5-18	1.40 – 3.78	0-9.1

Measurements are expressed as median/mean, (IQR)/±SD.

Polymethylmethacrylate (PMMA)

Polymethylmethacrylate (PMMA) microspheres have been injected as a wrinkle filler. An average increase in penile circumference of 3.5 cm was reported in two studies using PMMA for penile girth enhancement [1304, 1305]. The authors reported that post-operative swelling and inflammatory reaction resolved within a few days and no pattern of PMMA microspheres migration to neighbouring regions was seen.

Poly-l-lactic acid

Poly-l-lactic acid (PLA) is another widely used soft tissue filler. Poly-l-lactic acid has enhanced effects by stimulating fibroblast proliferation and increasing collagen deposition in tissue. An average increase of 1.2 to 2.4 cm has been reported in the penile girth with PLA injection. No complications other than temporary local pain and swelling were reported in the treated patients [1298, 1306].

9.3.2.4.2.2 Other Fillers (silicone, paraffin)

Foreign body injections are still frequently practised in many countries (especially in East Asia and East Europe), either by the patient himself or by healthcare workers, using various substances such as paraffin, silicone or petroleum jelly (Vaseline), to increase the circumference of the penis [1307]. This results in a chronic granulomatous inflammatory foreign body reaction [1307, 1308]. The result of this practice is a pathological condition called sclerosing lipogranuloma of the penis also referred as paraffinoma or siliconoma according to the substance used [1307]. The resultant inflammatory process ranges from oedema and infection to Fournier's gangrene. Penile reconstructive surgeries may be required when siliconoma and paraffinoma require excision [1307-1313].

9.3.2.4.3 Surgical therapy

9.3.2.4.3.1 Autologous fat injection

This is a surgical technique based on thinning the lower abdomen with liposuction and injecting the harvested fat tissue into the penile shaft [1314-1317]. In retrospective studies, an average increase of 2 to 3.5 cm in penile circumference was reported in patients who underwent autologous fat injection. No statistically significant

decrease was observed in IIEF scores and no serious adverse events, such as penile abscess or deformity requiring reoperation occurred. Post-operative satisfaction survey showed that more than 75% of patients were satisfied (Table 30) [1280, 1314, 1315, 1318].

Table 30: Published data on the evaluation of autologous fat injection on penile girth enhancement

Author (year)	Year	n	Study design	Age (years)	Follow-up (months)	Girth gain (cm)	Complications, n (%)
Littara *et al.* [1280]	2019	334	Retrospective	36	12	2.76	49 (14.67)
Salem *et al.* [1318]	2019	15	Prospective	33 (23-45)	6	2-3.5	N/A
Kang *et al.* [1314]	2012	52	Retrospective	42.1	6	2.18-2.28	1 (1.92)
Panfilov *et al.* [1315]	2006	60	Retrospective	33.8	12	2.65	3 (5)
Summary	N/A	N/A	N/A	33-42.1	6-12	2-3.5	1.92-14.67

Measurements are expressed as median/mean, (IQR)/±SD.

9.3.2.4.3.2 Grafting procedures (albugineal and peri-cavernosal)
Until more rigorous multi-institutional studies reporting on complications and validated outcomes are known, penile girth enhancement procedures using grafts should be considered experimental (Table 31).

In a study of 69 patients using the porcine dermal acellular matrix graft (InteXen; American Medical Systems, Minnetonka, MN, USA) a 3.2 cm increase in flaccid state and 2.4 cm in erect state was reported at one year following surgery. The procedure was performed with an infrapubic incision, and 68 of 69 patients reported significant satisfaction using the Augmentation Phalloplasty Patient Selection and Satisfaction Inventory. Graft fibrosis has been observed in up to 13% of patients, and a mean reduction in penile length of 0.5 cm has been reported in patients with fibrosis [1319].

Techniques using venous grafts for penile girth enhancement have also been described [1320]. Initial results are encouraging, but better designed RCTs are needed.

Dermal fat grafts are free only grafts composed of deepithelialized dermis and subcutaneous fat. An area of approximately 10 x 5 cm is required for graft harvesting. An increase in penile girth of 1.67 to 2.3 cm has been reported in studies with the dermal fat graft technique. Penile oedema up to 27%, painful erection up to 27%, and curvature due to graft fibrosis up to 9% have been reported. Side effects such as penile hypoesthesia, skin necrosis, and infection were not reported [1250, 1321, 1322].

Table 31: Published data on evaluation of grafting techniques on penile girth enhancement

Author (year)	Year	n	Study design	Technique	Age, years	Follow up (months)	Girth gain (cm)	Complications, n (%)
Zhang *et al.* [1324]	2016	30	Retrospective	Dermal graft	23.7 (19-35)	13	1.5	1 (3.3)
Xu *et al.* [1322]	2016	23	Retrospective	SLR + skin advancement + dermal fat graft	23 (18-33)	6	1.67	7 (30.43)
Tealab *et al.* [1325]	2013	18	Retrospective	Acellular collagen matrix graft	24 (19-38)	12	2.3	8 (44.44)
Mertziatis *et al.* [1321]	2013	82	Retrospective	SLR + skin advancement + Dermal fat graft	24	12	2.2	25 (31.64)
Spyropoulos *et al.* [1250]	2005	4	Retrospective	SLR + Dermal fat graft	32	14	2.3	No major complication

Alei *et al.* [1319]	2012	69	Retrospective	Porcine dermal acellular matrix graft	28.2 (19-59)	12	Flaccid: 3.2; Erect: 2.4	19 (27.5)
Austoni *et al.* [1320]	2002	39	Retrospective	Corporal venous graft	24-47	9	Flaccid: no change, Erect: 2.9	1 (2.56)
Summary	N/A	N/A	N/A	N/A	18-68	6-48	0-4.9	0-44.44%

9.3.2.4.3.3 Biodegradable scaffolds

This is a technique based on using fibroblasts (harvested from patients' own scrotum skin and dartos tissue) in tissue cultures and seeding them in microporous biodegradable poly-lacti-co-glycolic acid (PLGA) scaffolds and implanting these scaffolds between Dartos and Buck's fascia. A limited number of studies have reported girth gain of up to 4.02 cm with implantation of biodegradable scaffolds [1326-1328] (Table 32).

Table 32: Published data on the evaluation of implantation of biodegradable scaffolds

Author	Year	n	Study design	Age (years)	Follow up (months)	Girth gain (cm)	Complications, n (%)
Djordjevic *et al.* [1326]	2018	21	Retrospective	28 (22-37)	38 (13-66)	Flaccid: 1.1 ± 0.4; Erect: 1±0.3	2 (9.52)
Jin *et al.* [1327]	2011	69	Multi-centre non-controlled	33±9.14	6	Flaccid: 4.01; Erect: 4.02	6 (8.69)
Perovic *et al.* [1328]	2006	84	Multi-centre prospective non-controlled	28.77±6.61	24.67	Flaccid: 3.35; Erect: 2.47	8 (9.52)
Summary	N/A	N/A	N/A	18-60	6-60	1-4.02	8.69-9.52%

9.3.2.4.3.4 Subcutaneous penile implant (Penuma®)

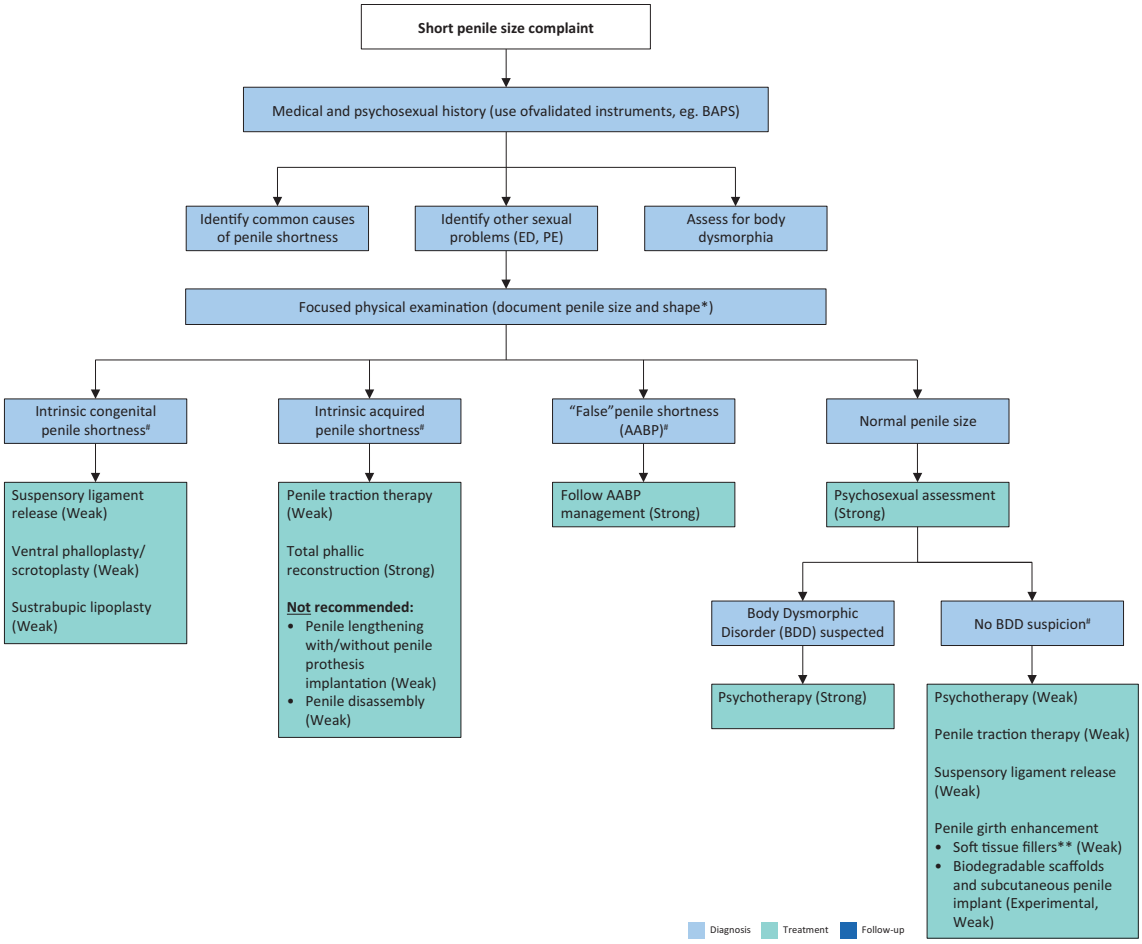
Recently, a silicone penile implant called "Penuma®" (International Medical Devices [Beverly Hills, CA, USA]) has been approved and has shown promising results for penile girth enhancement. Penuma® is a soft silicone subcutaneous implant placed on 3/4 of the penile shaft and fixed to the glans with a polyester mesh [1323]. Studies have reported an average increase in penile circumference of 2 to 5 cm with Penuma® insertion. According to published data complication rates (usually mild and transient, occur in <5%) and the removal rate (1%) of the implant has been reported to be relatively low [1323, 1329].

9.3.2.4.4 Summary of evidence and recommendations for penile girth enhancement

Summary of evidence	LE
Various surgical approaches with specific outcomes and complications have been considered to address penile girth enhancement, with limited benefit.	3
Hyaluronic acid (HA), Poly-l-lactic acid (PLA), hydroxyethyl methacrylate, polyacrylamide hydrogel (PAAG), polymethylmethacrylate (PMMA), calcium hydroxyapatite are used as injectable materials for penile girth enhancement.	3
Patient satisfaction with soft tissue fillers (especially HA, PMMA and PLA) is high (> 78%).	3
No complications other than temporary local pain and swelling were reported in patients treated with soft tissue fillers.	3
Using silicone, paraffin and petroleum jelly (Vaseline) in penile girth enhancement causes a range of complications ranging from oedema up to infection to Fournier's gangrene.	3
Not enough long term data are available on autologous fat injection for penile girth enhancement.	4
Not enough long term data are available on grafting procedures (dermal acellular matrix graft, venous grafts or dermal fat grafts).	4
Grafting procedures are associated with high complication rate and low rate of patient's satisfaction.	3
Not enough long term data are available on biodegradable scaffolds and subcutaneous penile implant (Penuma®) .	4

Recommendations	Strength rating
Counsel patients extensively regarding the risks and benefits of penile girth enhancement techniques.	Strong
Do not use silicone, paraffin and petroleum jelly (Vaseline) to address penile girth enhancement.	Strong
Use hyaluronic acid, soft tissue fillers and autologous fat injection to address penile girth enhancement.	Weak
Do not use hyaluronic acid, soft tissue fillers and autologous fat injection to address penile girth enhancement in men with penile dysmorphic disorder.	Weak
Do not use grafts in penile girth enhancement as they are considered experimental.	Strong
Do not use biodegradable scaffolds and subcutaneous penile implant (Penuma®) to address penile girth enhancement as experimental.	Strong

Figure 11: Management of short penile size



** Penile length should be measured stretched both from the penopubic skin junction-to-glans tip (STT) and from the pubic bone-to-glans tip (BTT).*

 # There is a lack of evidence to recommend one treatment over another.

***Hyaluronic acid (HA), poly-l-lactic acid (PLA), hydroxyethyl methacrylate, polymethylmethacrylate (PMMA), polyacrylamide hydrogel (PAAG) and calcium hydroxyapatite are considered as injectable materials for penile girth enhancement. Although the level of evidence is low, there is more evidence for HA, PLA and PMMA. Do not use silicone, paraffin or Vaseline (Strong evidence against).*

The strength of recommendations is depicted between brackets where appropriate.

9.3.2.5 Functional outcomes: sexual function, sensitivity, impact on quality of life and emotional adjustment

Cosmetic treatments, including surgery, help to restore self-esteem, reduce anxiety, social phobia, and depressive mood states regarding body concerns, and increase individuals' well-being and QoL [1123, 1124]. Therefore, we can expect men with genuine short penis to use available resources to adjust the length or girth of their penis as a mean to improve their sense of identity and fit cultural standards regarding penile size and function. Currently, the results of penile augmentation techniques seem mixed. The utilization of fillers led to enhanced genital self-image and self-esteem, as well as reduced symptoms of PDD. However, no effects were observed in terms of self-confidence or satisfaction with sexual relationship [1257]. Likewise, penile lengthening or girth enhancement surgery seem to result in poor satisfaction, poor erectile function and sensitivity in men with normal penis size [1134]. Despite those negative outcomes, cases of increased satisfaction have been registered [1330]. Male genital self-image has been related to IIEF domains: sexual desire, orgasmic and erectile function, intercourse and overall satisfaction [1247]. Similarly, perceived penis size seems to predict erectile function more than objective size [1130]. In addition, reduced penetrative and receptive oral sex is associated with men's dissatisfaction regarding their penis [1331]. For these reasons, more efforts should be made in order to clarify the impact of penile augmentation treatments on men's and partners' well-being and QoL. As for men with BDD, they have shown reduced erectile and orgasmic function, as well as less intercourse satisfaction as compared with controls, while men with SPA revealed reduced satisfaction. Sexual desire seemed untouched in BDD and SPA cases [1257, 1332].

9.3.2.6 Final remarks

The complaint of "short penis" is variable in presentation and aetiology. Some patients demonstrate anatomical and pathological conditions while others do not. A vast array of treatments for different aetiologies of "short penis," both surgical and non-surgical, have been reviewed. If psychopathological symptoms are detected, the patient must be referred for further medical diagnosis. Treatment for short-penis syndrome requires a multi-disciplinary approach, including medical and ethical considerations, and the majority of reported outcomes are based on a paucity of evidence.

10. PRIAPISM

Priapism is a persistent or prolonged erection in the absence of sexual stimulation that fails to subside. It can be divided into ischaemic, non-ischaemic and stuttering priapism. The guidelines are based on three systematic reviews addressing the medical and surgical management of ischaemic and non-ischaemic priapism and the overall management of priapism related to sickle cell disease [1333-1335].

10.1 Ischaemic (Low-Flow or Veno-Occlusive) Priapism

10.1.1 Epidemiology, aetiology, pathophysiology and Diagnosis

Ischaemic priapism is a persistent erection marked by rigidity of the corpora cavernosa and by little or no cavernous arterial inflow [1336]. Ischaemic priapism is the most common subtype of priapism, accounting for > 95% of all episodes [1336, 1337]. In ischaemic priapism, there are time-dependent metabolic alterations within the corpus cavernosum progressively leading to hypoxia, hypercapnia, glucopenia and acidosis [1338, 1339].

Ischaemic priapism that lasts beyond 4 hours is similar to a compartment syndrome and characterised by the development of ischaemia within the closed space of the corpora cavernosa, which severely compromises the cavernosal circulation. Emergency medical intervention is required to minimise irreversible consequences, such as smooth muscle necrosis, corporal fibrosis and the development of permanent erectile dysfunction (ED) [1340, 1341]. The duration of ischaemic priapism represents the most significant predictor for irreversible consequences, thus including ED. In this context, interventions beyond 48-72 hours of onset may help to relieve the erection and pain, but have little clinical benefit in preventing long-term ED [1342].

No specific pathophysiological causes of ischaemic priapism can be identified in most cases [1336, 1343], although the common aetiological factors include sickle cell disease (SCD), haematological dyscrasias, neoplastic syndromes, and several pharmacological agents (e.g., intracavernosal PGE1 therapy) (Table 33). Ischaemic priapism may occur (0.4-35%) after intracavernosal injection of erectogenic agents [1336, 1340, 1344-1346]. The risk is higher with papaverine-based combinations [1347], while the risk of priapism is < 1% following prostaglandin E1 injection [1348].

Second-generation antipsychotics (33.8%), other medications (11.3%), and alpha-adrenergic antagonists (8.8%) accounted for the greatest percentage of published drug-induced priapism cases [1349]. Isolated cases of priapism have been described in men who have taken PDE5Is [1336]. Data from the FDA Adverse Reporting System Public Dashboard showed that PDE5Is-induced priapism accounted for only 2.9% of drug-induced priapism. However, most of these men also had other risk factors for priapism, and it is unclear whether PDE5Is *per se* can cause ischaemic priapism [1336, 1350]. Since most men who experience priapism following PDE5I treatment have additional risk factors for ischaemic priapism, PDE5Is use is usually not regarded as a risk factor in itself. In terms of haemoglobinopathies, SCD is the most common cause of priapism in childhood, accounting for 63% of cases. It is the primary aetiology in 23% of adult cases [1348].

Mechanisms of SCD-associated priapism may involve derangements of several signalling pathways in the penis [1351]. Contrary to traditional belief, maintenance of physiological testosterone levels does not cause priapism, but rather preserves penile homeostasis and promotes normal erectile function [1352, 1353]. Testosterone deficiency is considered a controversial risk factor: it is prevalent in patients with SCD, but recent evidence indicates that it may not be a risk factor for priapism [1354].

Priapism resulting from metastatic or regional infiltration by tumour is rare and usually reflects an infiltrative process, more often involving the bladder and prostate as the primary cancer sites [1355]. In a large retrospective study including 412 men with ischaemic priapism, eleven (3.5%) had malignant priapism, of which seven cases were a consequence of local invasion while the others were secondary to haematological malignancy [1356]. The conventional therapeutic recommendations for pharmacological treatment are unlikely to be effective and all of these men should have MRI of the penis and be offered supportive care and medical intervention for their primary cancer. In selected cases where palliative treatment options fail to control penile pain, a palliative penectomy can be considered.

Partial priapism, or idiopathic partial segmental thrombosis of the corpus cavemosum, is a rare condition. It is often classified as a subtype of priapism limited to a single crura without ischaemia, but rather a thrombus is present within the corpus cavernosum. Its aetiology is unknown, but bicycle riding, trauma, drug use, sexual intercourse, haematological diseases and α-blocker intake have all been associated with partial segmental thrombosis [1357]. The presence of a congenital web within the corpora is also a risk factor [1358].

Table 33: Aetiological factors for the development of priapism

Idiopathic
-
Haematological dyscrasias, vascular and other disorders
• SCD • thalassemia • leukaemia • multiple myeloma • haemoglobin Olmsted variant • fat emboli during hyperalimentation • haemodialysis • glucose-6-phosphate dehydrogenase deficiency • factor V Leiden mutation • vessel vasculitis • (e.g., Henoch-Schönlein purpura; Behçet's disease; anti-phospholipid antibodies syndrome)
Infections (toxin-mediated)
• scorpion sting • spider bite • rabies
Metabolic disorders
• amyloidosis • Fabry's disease • gout

Neurogenic disorders
• syphilis • spinal cord injury • cauda equina • syndrome • autonomic neuropathy • lumbar disc herniation • spinal stenosis • cerebrovascular accident • brain tumour • spinal anaesthesia
Neoplasms (metastatic or regional infiltration)
• prostate • urethra • testis • bladder • rectal • lung, kidney
Medications
• Vasoactive erectile agents (i.e., papaverine, phentolamine, prostaglandin E1/alprostadil, combination of intracavernous therapies) • α-adrenergic receptor antagonists (i.e., prazosin, terazosin, doxazosin and tamsulosin) • Anti-anxiety agents (hydroxyzine) • Anticoagulants (heparin and warfarin) • Antidepressants and antipsychotics (i.e., trazodone, bupropion, fluoxetine, sertraline, lithium, clozapine, risperidone, olanzapine, chlorpromazine, thioridazine, phenothiazines and methylphenidate) • Antihypertensives (i.e., hydralazine, guanethidine and propranolol) • Hormones (i.e., gonadotropin-releasing hormone and testosterone) • Recreational drugs (i.e., alcohol, marijuana, cocaine [intranasal and topical], and crack, cocaine)

10.1.1.1 Summary of evidence on the epidemiology, aetiology and pathophysiology of ischaemic priapism

Summary of evidence	LE
Ischaemic priapism is the most common type, accounting for more than 95% of all cases.	1b
Ischaemic priapism is identified as idiopathic in most patients, while sickle cell disease is the most common cause in childhood.	1b
Ischaemic priapism occurs relatively often (about 5%) after intracavernous injections of papaverine-based combinations, while it is rare (< 1%) after prostaglandin E1 monotherapy.	2a
Priapism is rare in men who have taken Phosphodiesterase Type 5 Inhibitors, with only sporadic cases reported.	4

10.1.2 ***Diagnostic evaluation***

10.1.2.1 History

Taking a comprehensive history is critical in priapism diagnosis and treatment [1336, 1359]. The medical history must specifically enquire about SCD or any other haematological abnormality [1360, 1361] and a history of pelvic, genital or perineal trauma. The sexual history must include the duration of the erection; the presence and degree of pain; prior drug treatment and recreational drug use; history of priapism and methods of treatment; and erectile function prior to the last priapism episode [1336]. The history can help to determine the underlying priapism subtype (Table 34). Ischaemic priapism is classically associated with progressive penile pain and the erection is rigid. Conversely, non-ischaemic priapism is often painless and the erections often fluctuate in rigidity.

Table 34: Key findings in priapism (adapted from Broderick *et al.* [1336])

	Ischaemic priapism	Non-ischaemic priapism
Corpora cavernosa fully rigid	Typically	Seldom
Penile pain	Typically	Seldom
Abnormal penile blood gas	Typically	Seldom
Haematological abnormalities	Sometimes	Seldom
Recent intracavernosal injection	Sometimes	Sometimes
Perineal trauma	Seldom	Typically

10.1.2.2 Physical examination

In ischaemic priapism, the corpora are fully rigid and tender, but the glans penis is soft. The patient usually complains of severe pain. Pelvic examination may reveal an underlying pelvic or genitourinary malignancy [1356].

10.1.2.3 Laboratory testing

Laboratory testing should include a complete blood count, white blood cell count with blood cell differential, platelet count and coagulation profile to assess anaemia and detect haematological abnormalities [1336, 1359].

Aspiration of blood from the corpora cavernosa is compulsory as an entry level investigation. It usually reveals dark ischaemic blood. Blood gas analysis is essential to differentiate between ischaemic and non-ischaemic priapism (Table 34). Further laboratory testing should be directed by the history, clinical examination and laboratory findings. These may include specific tests (e.g., haemoglobin electrophoresis) for diagnosis of SCD or other haemoglobinopathies.

10.1.2.4 Penile imaging

Colour Doppler US of the penis and perineum is recommended after clinical diagnosis and can differentiate ischaemic from non-ischaemic priapism as an alternative or adjunct to blood gas analysis (Figure 12) [1362-1365]. Colour Doppler US can identify the presence of the fistula as a blush with 100% sensitivity and 73% specificity [1364].

Ultrasound of the penis should be performed before corporal blood aspiration in ischaemic priapism to prevent aberrant blood flow which can mimic a non-ischaemic or reperfusion picture after intervention for low-flow priapism [1366].

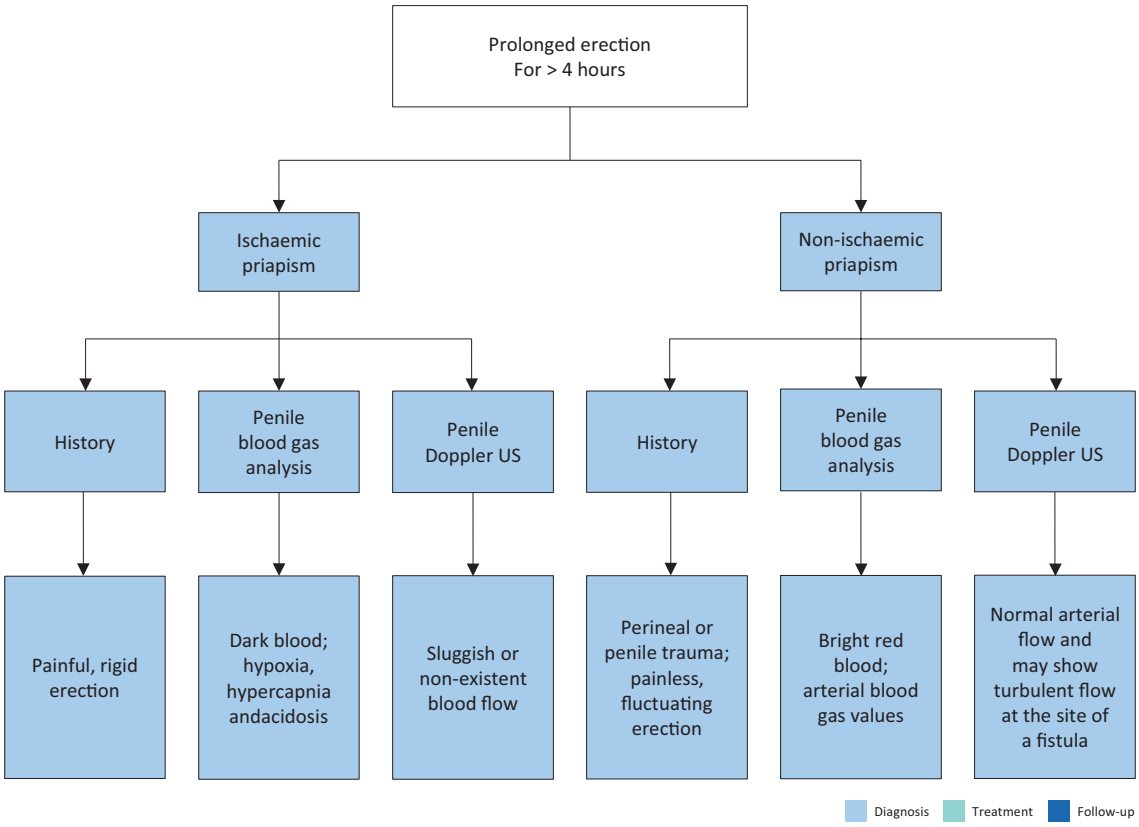
Penile MRI can be used in the diagnostic evaluation of priapism and may be helpful in selected cases of ischaemic priapism to assess the viability of the corpora cavernosa and the presence of penile fibrosis. In cases of refractory priapism or delayed presentation (> 48 hours), smooth muscle viability can be indirectly assessed. In a prospective study of 38 patients with ischaemic priapism, the sensitivity of MRI in predicting non-viable smooth muscle was 100%, when correlated with corpus cavernosum biopsies [1366]. All patients with viable smooth muscle on MRI maintained erectile function on clinical follow-up with the non-viable group being offered early prosthesis.

Table 34: Typical blood gas values (adapted from Broderick *et al.* [1336])

Source	pO_2 (mmHg)	pCO_2 (mmHg)	pH
Normal arterial blood (room air) (similar values are found in arterial priapism)	> 90	< 40	7.40
Normal mixed venous blood (room air)	40	50	7.35
Ischaemic priapism (first corporal aspirate)	< 30	> 60	< 7.25

pCO_2 partial pressure of carbon dioxide; pO_2 partial pressure of oxygen

Figure 12: Differential diagnosis of priapism



10.1.2.5 Summary of evidence and recommendations for the diagnosis of ischaemic priapism

Summary of evidence	LE
Medical history including the assessment of known haematological abnormalities (e.g., SCD), history of pelvic/perineal/genital trauma, prior drug treatment or recreational drug use is essential to identify the possible a etiology and the type of priapism	3
Blood gas analysis performed before blood aspiration from the corpora can differentiate between ischaemic and non-ischaemic priapism. A full blood count and haemoglobinopathy screen could reveal haematological alterations.	3
Penile Colour Doppler US can differentiate from ischaemic and non-ischaemic priapism when performed before corporal blood aspiration.	3
Penile MRI can predict non-viable smooth muscle in patients with ischaemic priapism.	3

Recommendations	Strength rating
Take a comprehensive history to establish the diagnosis which can help to determine the priapism subtype.	Strong
Include a physical examination of the genitalia, perineum and abdomen in the diagnostic evaluation.	Strong
Include a full blood count, white blood cell count with blood cell differential, platelet count and coagulation profile. Directed further laboratory testing should be performed depending upon the history and clinical and laboratory findings. In children with priapism, perform a complete evaluation of all possible causes.	Strong
Perform a haemoglobinopathy screen in patients with low flow priapism who are at high risk of sickle cell disease or thalassemia.	Strong
Analyse the blood gas parameters from blood aspirated from the penis to differentiate between ischaemic and non-ischaemic priapism.	Strong

Perform colour duplex ultrasound of the penis and perineum before aspiration to differentiate between ischaemic and non-ischaemic priapism.	Strong
Use magnetic resonance imaging of the penis in cases of prolonged ischaemic priapism or refractory priapism, as an adjunct to predict smooth muscle viability.	Weak

10.1.3 ***Disease management***

Acute ischaemic priapism is a medical emergency. Urgent intervention is mandatory and should follow a stepwise approach. The aim of any treatment is to restore penile detumescence, without pain, in order to prevent corporal smooth muscle fibrosis and subsequent ED.

10.1.3.1 Medical Management – first-line treatment

First-line medical treatments for ischaemic priapism of more than 4 hours duration are strongly recommended before any surgical treatment. Conversely, first-line treatments initiated beyond 48 hours, while relieving priapism, have little documented benefit in terms of long-term erectile function preservation. This is likely to be the consequence of irreversible smooth muscle hypoxia and damage that begins to be established by approximately 48 hours of the onset of ischaemia [1340-1342]. It has been shown in a series of 50 patients with low-flow priapism who were successfully treated and followed-up for a mean of 66 months, that those with priapism lasting for more than 48 hours had a significant risk of ED [1340].

Historically, several first-line treatments have been described including exercise, ejaculation, ice packs, cold baths, and cold water enemas [1336]. However, there is limited evidence for the benefit of these measures and they may even exacerbate the condition in SCD patients. Success rates for these conservative measures alone have rarely been reported. In a small series, cold water enemas have been reported to induce detumescence in six out of ten cases [1367]. In another study 24.5% of 122 patients achieved detumescence following priapic episodes lasting for more than 6 hours by cooling of the penis and perineum, and walking upstairs [1368].

10.1.3.1.1 Penile anaesthesia/analgesia

Blood aspiration and intracavernous injection of a sympathomimetic agent can be performed without any anaesthesia; however, anaesthesia may be necessary when there is severe penile pain. Whilst anaesthesia may not alleviate the ischaemic pain, cutaneous anaesthesia facilitates subsequent therapies. The treatment options for penile anaesthesia/systemic analgesia include:

- dorsal nerve block;
- circumferential penile block;
- subcutaneous local penile shaft block;
- oral conscious sedation (for paediatric patients).

10.1.3.1.2 Aspiration ± irrigation with 0.9% w/v saline solution

The first intervention for an episode of priapism lasting more than 4 hours consists of corporal blood aspiration to drain the stagnant blood from the corporal bodies, making it possible to relieve the compartment-syndrome-like condition within the corpus cavernosum. Blood aspiration may be performed with intracorporeal access either through the glans or via percutaneous needle access to the lateral aspect of the proximal penile shaft, using a 16 or 18 G angio-catheter or butterfly needle. The needle must penetrate the skin, the subcutaneous tissue and the tunica albuginea to drain blood from the corpus cavernosum .

Some clinicians advocate using two angiocatheters or butterfly needles at the same time to accelerate drainage, as well as aspirating and irrigating simultaneously with a saline solution [1368]. Aspiration should be continued until bright red, oxygenated blood is aspirated.

Several case series have reported outcomes for first-line treatments; however, in most cases, aspiration and irrigation were combined with intracavernosal injection of sympathomimetic agents [1334], thus making it difficult to draw conclude the success rate of aspiration + irrigation
alone [1334]. Overall, case series and retrospective studies reported a success rate ranging from 0 to 100% of cases [1334]. In an RCT, 70 patients with ischaemic priapism lasting more than 6 hours secondary to intracavernosal injection were treated with aspiration plus saline irrigation at different temperatures [1368]. The study reported an 85% success rate with the optimum results achieved using a 10°C saline infusion after blood aspiration.

There is insufficient data to determine whether aspiration followed by saline intracorporeal irrigation is more effective than aspiration alone.

10.1.3.1.3 Aspiration ± irrigation with 0.9% w/v saline solution in combination with intracavernous injection of pharmacological agents.

This combination is currently considered the standard of care for the treatment of ischaemic priapism [1336, 1369, 1370]. Pharmacological agents include sympathomimetic drugs or α-adrenergic agonists. Intracavernous sympathomimetic agents include phenylephrine, etilephrine, ephedrine, epinephrine, norepinephrine and metaraminol with a resolution rate of up to 80% [1336, 1369, 1371-1378]. The use of intracavernous adrenaline injection alone has also been sporadically reported [1379]. It has been reported that the use of a sympathomimetic agent combined with prior intracavernosal aspiration or irrigation had a resolution ranging from 80 to 100% of cases as compared with 58% in those who had a sympathomimetic injection alone [1334, 1370].

The potential treatment-related adverse effects of intracavernous phenylephrine (and other sympathomimetic agents) include headache, dizziness, hypertension, reflex bradycardia, tachycardia and palpitations and sporadic subarachnoid haemorrhage [347]. Monitoring of blood pressure and pulse should be performed during intracavernous administration of sympathomimetic agents. As intracavernous sympathomimetic agents can cause hypertension, the Guidelines Panel is of the opinion that these agents are contraindicated in patients with malignant or poorly controlled hypertension, as there are case reports of significant cardiovascular and neurological complications following the use of these pharmacological agents for priapism [1372, 1380, 1381]. Similarly, data suggest that sympathomimetic agents cause a hypertensive crisis when given with monoamine oxidase inhibitors, hence these medications should not be used together [1382].

10.1.3.1.4 Intracavernosal and oral pharmacological agents

Pharmacological agents for the treatment of priapism are discussed in more detail in the following section. Table 35 summarises dosing and administration of these agents.

- *Phenylephrine*

Phenylephrine is a selective α-1-adrenergic receptor agonist that has been observed in small case series to be effective at producing detumescence in priapism, when given as an intracavernosal injection, with few adverse effects [1377, 1383]. Phenylephrine is the recommended adrenergic agonist drug of choice due to its high selectivity for the α-1-adrenergic receptor, without concomitant β-mediated inotropic and chronotropic cardiac effects [1371, 1375, 1376].

Phenylephrine has potential cardiovascular adverse effects [1336, 1369, 1371, 1372, 1375, 1376] and it is recommended that blood pressure and pulse are monitored every fifteen minutes for one hour after injection. This is particularly important in older men with pre-existing cardiovascular diseases. After injection, the puncture site should be compressed and the corpus cavernosum massaged to facilitate drug distribution.

- *Etilephrine*

Etilephrine is also an adrenergic agonist that directly stimulates both α and β adrenergic receptors [1370]. Most of the literature describing the use of etilephrine for treatment of priapism is related to men with SCD but there are small retrospective case series that have reported its benefits for priapism secondary to iatrogenic causes [1384, 1385]. Etilephrine is the second most widely used sympathomimetic agent [1372].

- *Methylene blue*

Methylene blue is a guanylate cyclase inhibitor, that may be a potential inhibitor of endothelial-mediated cavernous smooth muscle relaxation. Small retrospective case series have reported its successful use for treating short-term pharmacologically-induced priapism [1386, 1387]. Treatment-related adverse effects include a transient burning sensation and blue discolouration of the penis.

- *Adrenaline*

Adrenaline produces both α-adrenergic receptor agonist and β-adrenergic receptor activity. Intracavernosal adrenaline has been used in patients with ischaemic priapism due to an intracavernous injection of vasoactive agents. The limited literature [1379, 1388] suggests that adrenaline can achieve detumescence in short-term priapism, with one small case series reporting a success rate of over 50% after a single injection, with an overall success rate of 95% with repeated injections [1379, 1388].

- *β-2-agonists*

Oral terbutaline is a β-2-agonist with minor β-1 effects and some α-agonist activity; although its mechanism of action is not yet fully understood [1389-1391]. The main use of terbutaline is for prevention of recurrent episodes of prolonged erection. Oral treatment with terbutaline was tested in three placebo-controlled RCTs

[1390-1392] showing a success rate of 30 to 60% in patients with ischemic priapism associated with intracavernous injection of erectogenic agents. Terbutaline should be given cautiously in patients with coronary artery disease, increased intravascular fluid volume, oedema or hypokalaemia [1391]. In a single multi-centre prospective study, another β-2-agonist, salbutamol, has been reported to induce detumescence in 34% of cases of prolonged erection (more than three hours) after intracavernous injection of erectogenic agents [1393]. However, more robust data are needed to recommend oral salbutamol for the treatment of ischaemic priapism.

Table 35: Medical treatment of ischaemic priapism

Drug	Dose/Instructions for use
Phenylephrine	• Intracavernous injection of 200 µg every 3-5 minutes. • Maximum dosage is 1 mg within 1 hour. • Lower doses are recommended in children and patients with severe cardiovascular diseases.
Etilephrine	• Intracavernosal injection at a concentration of 2.5 mg in 1-2 mL normal saline.
Methylene blue	• Intracavernous injection of 50-100 mg, left for 5 minutes. It is then aspirated and the penis is compressed for an additional 5 minutes.
Adrenaline	• Intracavernous injection of 2 mL of 1/100,000 adrenaline solution up to five times over 20 minutes.
Terbutaline	• Oral administration of 5 mg for priapism lasting more than 2.5 hours, after intracavernous injection of vasoactive agents.

10.1.3.1.5 Management of priapism related to sickle cell disease

The results of a systematic review on the overall management of priapism related to SCD found that few studies were conducted exclusively on patients with SCD and studies on mixed populations usually did not report separate data on SCD patients [1335]. Clear and systematic reporting of patient characteristics, interventions and outcomes was lacking, and the length of follow-up, if reported, varied significantly among the studies. Overall, the quality of studies was deemed poor to allow high-quality, evidence-based recommendations to be made.

Urgent intervention is essential and the general approach is similar to that described for other cases of ischaemic priapism and should be co-ordinated with a haematologist [1394-1396].

However, as with other haematological disorders, other therapeutic interventions may also need to be implemented [1394, 1396, 1397]. Specific measures for SCD-related priapism include intravenous hydration and narcotic analgesia while preparing the patient for aspiration and irrigation. Additionally, supplemental oxygen administration and alkalinisation with bicarbonate can be helpful [1395].

Haemoglobin S (HbS) percentage should be measured in all SCD patients with acute priapism. Exchange blood transfusion has also been proposed, with the aim of increasing tissue delivery of oxygen [1398]. The transfused blood should be sickle cell haemoglobin negative and Rh and Kell antigen matched [1399]; however, the evidence is inconclusive as to whether exchange transfusion itself helps to resolve priapism. A systematic review reported that the mean time to detumescence was eleven days with exchange transfusions compared to eight days with conventional treatment. Moreover, there were nine cases of ASPEN syndrome (association of SCD, priapism, exchange transfusion and neurological events) as a consequence of blood transfusion [1400].

A series of ten patients with SCD-related priapism showed that it was safe to perform exchange transfusion [1398]; however, several reports suggest that exchange transfusion may result in serious neurological sequelae [1400]. Therefore, routine use of exchange transfusion is not recommended as a primary treatment intervention in this group unless there is a risk of SCD-related symptoms. However, in patients who failed medical management, transfusion may be required to enable general anaesthesia to be safely administered prior to definitive surgery [1401].

10.1.3.2 Surgical management- second-line treatments

Second-line intervention typically refers to surgical intervention in the form of penile shunt surgery and penile implant insertion for refractory or delayed ischaemic priapism, and should only be considered when other medical management options have failed. There is no evidence detailing the time frames before moving

on to surgery after first-line treatment, although a period of at least 1 hour of first-line treatment without detumescence can be considered prior to moving to surgical intervention.

A number of clinical indicators suggest failure of first-line treatment including continuing corporal rigidity, cavernosal acidosis, anoxia, severe glucopenia, absence of cavernosal artery inflow by penile colour duplex US, and elevated intracorporal pressure [1402].

10.1.3.2.1 Penile shunt surgery

Penile shunt surgery aims to produce an outflow for ischaemic blood from the corpus cavernosum into the corpus spongiosal tissues, thereby allowing restoration of normal circulation within these structures. Accordingly, a shunt creates an opening in the tunica albuginea, with either the glans, corpus spongiosum, or a vein for blood drainage (Table 50) [1336, 1369, 1403].

The type of shunt procedure is chosen according to the surgeon's preference and familiarity with the procedure. It is conventional practice for distal shunt procedures to be tried before considering proximal shunting.

It is important to assess the success of surgery by direct observation of penile rigidity or by repeated testing (e.g., cavernous blood gas testing) [1336, 1369, 1404, 1405]. The use of penile colour US may not give appropriate information because of the hyperaemic (reperfusion) period that follows decompression after the ischaemic state [1406].

The recovery rates of erectile function in men undergoing shunt surgery following prolonged episodes of priapism are low and are directly related to the duration of priapism, pre-operative erectile status and age [1404, 1405, 1407]. If ischaemic priapism resolves within 24 hours of onset, it has been reported that 78-100% of patients regain spontaneous functional erections (with or without PDE5Is use). In contrast, other studies have shown that priapism for more than 36-48 hours appears to result in both structural and functional effects on corporal smooth muscle, with poorer outcomes (ED > 90%) [1404]. In general, shunt procedures undertaken after this period (36-48 hours) may only serve to limit pain without any beneficial effects on erectile function and early penile prosthesis insertion can be considered [1342, 1409].

Procedures for shunting require incision through the tunica albuginea and expose collagen to coagulation factors in the penile blood and thus activate the blood-clotting cascade. Peri-operative anti-coagulation is advocated to facilitate resolution of the priapism. There was an 84% decrease in priapism recurrence in the shunt group that received peri-procedural anti-thrombotic treatment (325 mg acetylsalicylic acid pre-operatively, and 5000 IU intraoperative heparin, 81 mg acetylsalicylic acid and 75 mg clopidogrel post-operatively for 5 days) compared with the group that did not receive peri-procedural anti-thrombotic treatment after failed aspiration [1410].

Four categories of shunt procedures have been reported [1336, 1370, 1403, 1409]. The limited data available does not allow one procedure to be recommended over another. However, distal shunts are less invasive and associated with lower rates of post-operative ED and therefore are recommended as the first surgical intervention of choice (Appendix 6 Table 10.1).

- *Percutaneous distal (corpora-glanular) shunts*

Winter's procedure uses a Trucut biopsy needle to create a fistula between the glans penis and each corpus cavernosum [1336, 1348, 1370, 1406, 1411]. Post-operative sequelae are uncommon [1412]. Winter's shunt is easy to perform, but has been reported as the least successful operation to create a distal shunt [1405]. This is because the diameter of the Trucut needle is only 1.6 mm (14-18 g) and therefore cannot accommodate the increased blood flow from post-ischaemic hyperaemia, resulting in poor drainage, increased intracavernous pressure and consequent premature closure of the shunt [1406].

Ebbehoj's technique involves making multiple tunical incision windows between the glans and each tip of the corpus cavernosum by means of a size 11 blade scalpel passed several times percutaneously [1336, 1370, 1406, 1413, 1414].

T-Shunt involves performing a bilateral procedure using a scalpel with a size 10 blade inserted through the glans just lateral to the urethral meatus until it enters the tip of the corpus cavernosum. The blade is then rotated 90° away (to the lateral side) from the urethral meatus and withdrawn [1336, 1370, 1406, 1415] (LE: 3). If unsuccessful, the procedure is repeated on the opposite side. The T-shunt can be followed by a tunnelling procedure using a size 8/10 Hegar dilator inserted through the glans and into the corpus cavernosum, which

can also be performed using US guidance, mainly to avoid urethral injury [1415]. The entry sites in the glans are sutured following detumescence. Tunnelling with a 7 mm metal sound or 7/8 Hegar dilator is necessary in patients with priapism duration > 48 hours. Tunnelling is a potentially attractive procedure as it combines the features of distal and proximal shunts with proximal drainage of the corpus cavernosum and may ameliorate the profibrotic effect of sludged blood retained in the corpus cavernosum [1407, 1409, 1415].

- *Open distal (corpora-glanular) shunts*

Al-Ghorab's procedure consists of an open bilateral excision of circular cone segments of the distal tunica albuginea via the glans penis, along with subsequent glans closure by running suture with absorbable material. A transverse incision on the glans may compromise arterial blood flow because distal deep dorsal arteries run longitudinally in the glans [1336, 1370, 1406, 1416-1418].

Burnett's technique (Snake manoeuvre) is a modification of the Al-Ghorab corpora-glanular shunt. It involves retrograde insertion of a 7/8 Hegar dilator into the distal end of each corpus cavernosum through the original Al-Ghorab glandular excision. After removal of the dilator from the corpus cavernosum, blood evacuation is facilitated by manual compression of the penis sequentially from a proximal to distal direction. After detumescence, the glans penis is closed as in the Al-Ghorab procedure [1336, 1370, 1406, 1419, 1420]. Reported complications include wound infection, penile skin necrosis and urethrocutaneous fistulae [1420].

- *Open proximal (corpora-spongiosal) shunts*

Quackles's technique uses a trans-scrotal or perineal approach; a proximal open shunt technique creates a communication between the corpus cavernosum and the corpus spongiosum. The most frequent complications include an unwanted urethro-cavernous fistula and urethral stricture or cavernositis [1336, 1370, 1403, 1421]. The risk of urethral injury is less with a perineal approach to the bulb of the corpus spongiosum. Proximal shunts are more invasive and ED rates are documented to be higher [1402].

- *Peno-scrotal decompression*

More recently a proximal decompression technique with the aim to spare the glans with high success rates has been described. The technique is based upon opening of the proximal corpus cavernosum combined with proximal and distal tunnelling using a suction tip [1422]. In a cohort of 25 patients, 12 had undergone previous corpora-glanular shunt surgery. Recurrence was observed in two of 25 patients with unilateral peno-scrotal decompression. In the 15 patients who had follow-up data, 40% had ED. Whilst, representing a promising technique, PSD in cases of refractory priapism may further delay penile prosthesis insertion with detrimental effects on surgical outcomes including penile shortening and prosthetic infection.

- *Vein anastomoses/shunts*

Grayhack's procedure mobilises the saphenous vein below the junction of the femoral vein and anastomoses the vein end-to-side onto the corpus cavernosum. Venous shunts may be complicated by saphenofemoral thrombus formation and by pulmonary embolism [1336, 1370, 1423-1425].

10.1.3.2.2 Immediate penile prosthesis implantation

The studies pertaining to penile implantation surgery are principally retrospective non-randomised case series (Appendix 9 online supplementary evidence). All of the studies described priapism resolution rate, sexual function and surgical adverse events although the follow-up period was variable [1333].

Refractory, therapy-resistant, acute ischaemic priapism or episodes lasting more than 48 hours usually result in complete ED, and possibly significant penile deformity in the long-term. In these cases, immediate penile prosthesis implantation surgery is advocated [1426, 1427, 1429].

Gadolinium-enhanced penile MRI [1366] and cavernosal smooth muscle biopsy have been used to diagnose smooth muscle necrosis (which, if present, would suggest that shunting is likely to fail) and may help in decision-making and patient counselling in cases of refractory or delayed presentation (> 48 hours) that may be considered for immediate penile prosthesis insertion.

Early implantation of a penile prosthesis is associated with lower infection rates (6-7% vs. 19-30%), penile shortening (3% vs. 40%) and revision rates (9% vs. 27%) compared to late insertion. General satisfaction rate for early implantation is higher (96%) than for late implantation (60%) [1342] (Appendix 10 online supplementary evidence). Potential complications that could compromise immediate penile prosthesis implantation include distal erosion and infection [1426, 1428], along with a small rate of revision surgery [1426]. Early surgery also offers the opportunity to maintain penile length and girth and prevent penile curvature due to cavernosal

fibrosis. The prosthesis can be exchanged for an inflatable prosthesis at a later date, which may allow upsizing of the implant cylinders [1430].

The decision on which type of implant to insert is dependent on patient suitability, surgeons' experience, and availability and cost of the equipment. The immediate insertion of a malleable penile prosthesis is recommended to avoid the difficulty and complications of delayed prosthetic surgery in the presence of corporal fibrosis.

There are no randomised trials comparing the efficacy and complication rates of malleable and inflatable penile prostheses. Despite the higher infection rate in priapism patients compared to those with virgin prosthesis, in patients who are well-motivated and counselled prior to the procedure, immediate inflatable penile prosthesis implantation may be undertaken, although in most cases a semi-rigid implant is more suitable as it is easier to implant and reduces operative time and hence the risk of prosthetic infection. A further issue with immediate insertion of an inflatable penile prosthesis is that the patient must begin cycling the device immediately to avoid a fibrous capsule forming and contracting. Early cycling of an inflatable penile prosthesis prevents penile curvature and shortening [1342].

Currently, there are no clear indications for immediately implanting a penile prosthesis in men with acute ischaemic priapism, although this can be considered in men with delayed or refractory priapism [1369].

Relative indications include [1336]:

- Ischaemia that has been present for more than 48 hours.
- Failure of aspiration and sympathomimetic intracavernous injections in delayed priapism (> 48 hours).
- Magnetic resonance imaging or corporal biopsy evidence of corporal smooth muscle necrosis [1336, 1426].
- Failure of a shunting procedure; although, in delayed cases (> 48 hours), implantation might be considered ahead of shunt surgery.
- Refractory priapism in patients who have undergone shunting procedures.

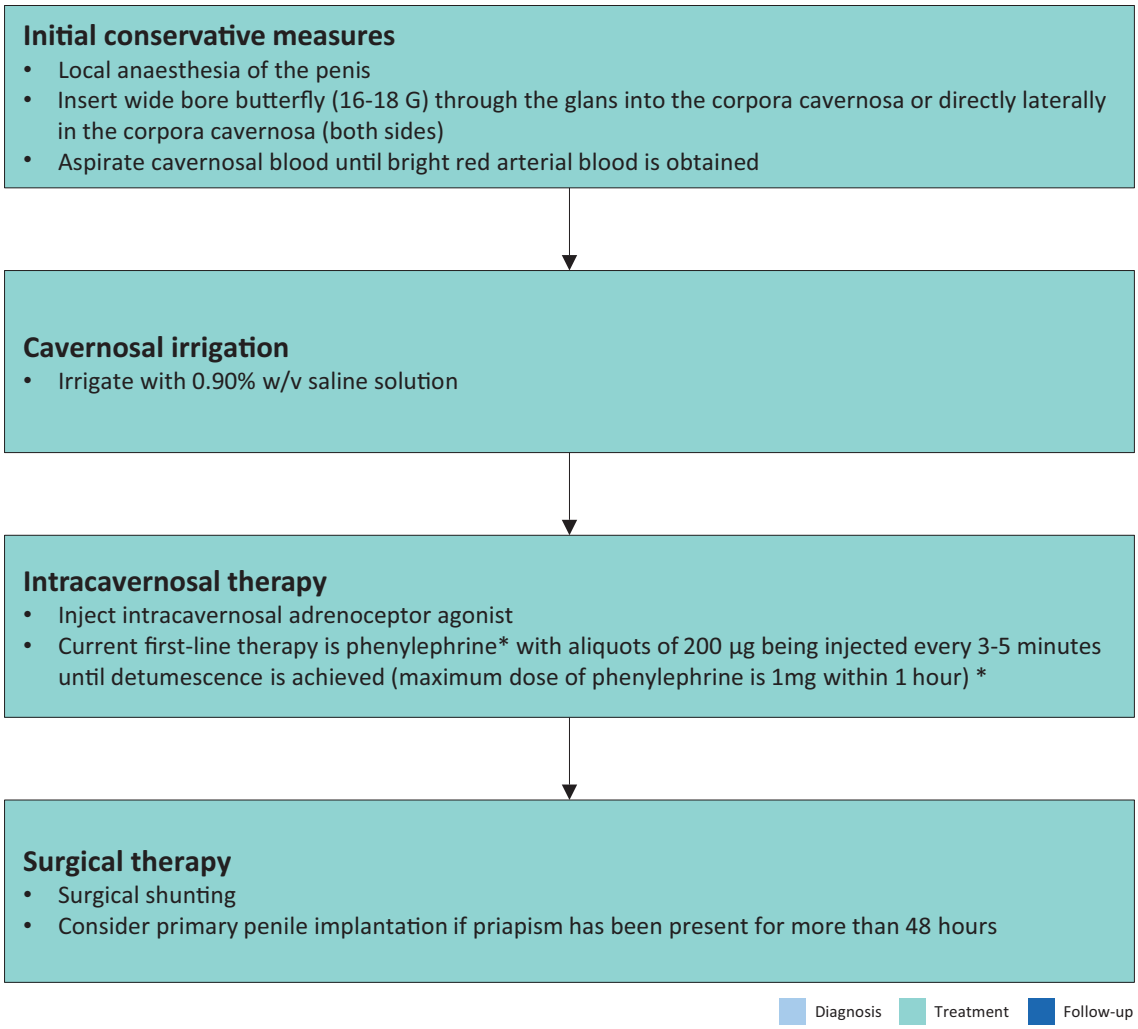
The optimal time for implantation is within the first three weeks from the priapism episode [1342, 1402, 1431]. If shunt surgery has been performed, penile prosthesis implantation can be further delayed in order to allow reduction of oedema, wound healing and risk of prosthetic infection. A vacuum device to avoid fibrosis and penile shortening may be used during this waiting period [1432].

10.1.3.2.3 Surgery for non-acute sequelae after ischaemic priapism

Structural changes may occur after ischaemic priapism including cavernosal tissue necrosis and fibrosis with consequent penile scarring, megalophallic deformities, penile shortening, and occasional penile loss [1403, 1426, 1433, 1434]. Erectile dysfunction is also often observed [1336, 1435]. Unfortunately, these outcomes can still occur despite apparently successful first or second-line treatment in detumescence of the penis.

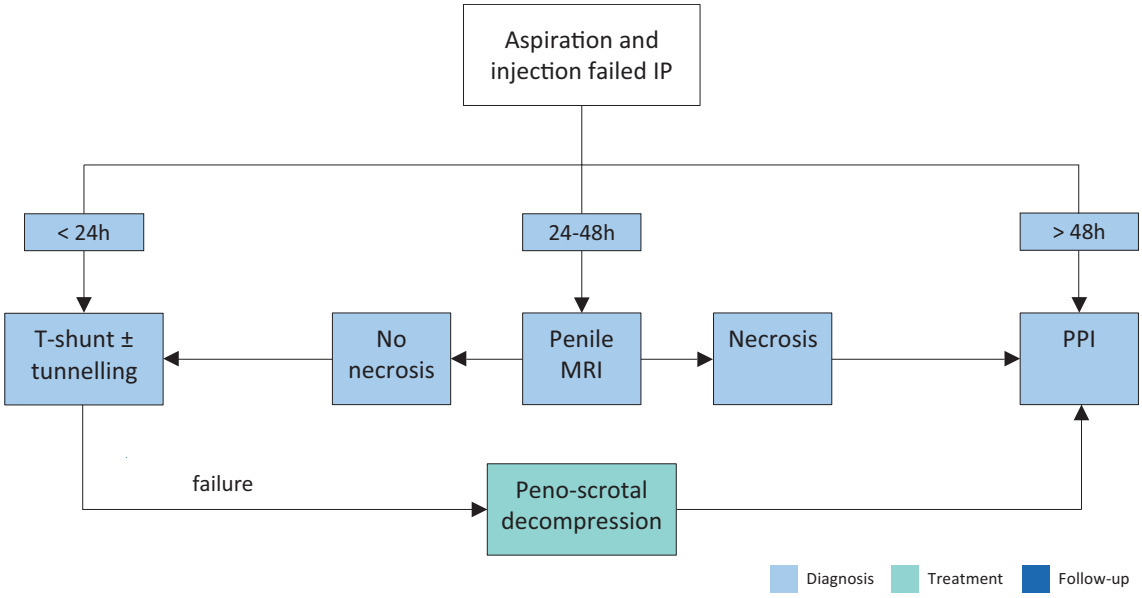
Penile prosthesis implantation is occasionally indicated in SCD patients with severe ED because other therapeutic options, such as PDE5Is and intracavernous injections are avoided as they may provoke a further priapism event [1336, 1369]. In severe corporal fibrosis, narrow-based prosthetic devices are preferable because they are easier to insert and need less dilatation [1426]. After severe priapism that has resulted in penile destruction with complicated deformities or even loss of penile tissue, it may be necessary to make changes to the surgical technique. Multiple corporotomies, corporal excavation, optical corporotomy-Shaeer technique, dilatation with Carrion-Rosello cavernotome, Uramix or Mooreville cavernotome, excision of scar tissue, and use of small-diameter prosthesis, or penile reconstruction using grafts can be utilised, if concomitant prosthesis implantation is considered [1408, 1436].

Figure 13: Management work-up of ischaemic priapism



(*) Dose of phenylephrine should be reduced in children. It can result in significant hypertension and should be used with caution in men with cardiovascular disease. Monitoring of pulse and blood pressure is advisable in all patients during administration and for one hour afterwards. Its use is contraindicated in men with a history of cerebro-vascular disease and significant hypertension.

Figure 14: Surgical management of priapism



MRI = Magnetic resonance imaging; PPI = penile prosthesis implantation; IP = ischaemic priapism.

10.1.4 Summary of evidence and recommendations for treatment of ischaemic priapism

Summary of evidence	LE
Ischaemic priapism is a medical emergency and immediate intervention is mandatory.	2b
Erectile function preservation is directly related to the duration of ischaemic priapism, age and pre-operative erectile status.	2b
Medical treatment is variably effective in case of priapism lasting less than 48 hours.	2b
Aspiration ± irrigation with 0.9% results in over 80% success rate when combined with intracavernous injection of sympathomimetic drugs.	2b
Phenylephrine is the recommended drug due to its favourable safety profile in the cardiovascular system compared to other drugs. Phenylephrine is usually diluted in normal saline with a concentration of 100-500 µg/mL and given in 200 µg doses every three to five minutes directly into the corpus cavernosum. Maximum dosage is 1 mg within one hour. Patient monitoring is highly recommended.	2b
Oral terbutaline has a success rate in up to 60% of cases when priapism is associated with intracavernous injection of erectogenic agents.	1b
Exchange transfusion in patients with priapism associated with SCD may result in serious neurological sequelae.	2b
Shunt procedures are effective to resolve priapism and provide pain relief. No clear recommendation of the superiority of one type of shunt over another can be given. Distal shunts are less invasive and associated with lower rate of erectile dysfunction.	2b
Peri- and post-operative anticoagulant prophylaxis (325 mg acetylsalicylic acid pre-operatively, 5,000 IU heparin intra-operatively and 81 mg acetylsalicylic acid and 75 mg clopidogrel five days post-operatively) may prevent priapism recurrence.	3
Erectile dysfunction is almost inevitable in prolonged cases or ischaemic priapism. Early implantation of penile prosthesis is associated with lower infection rates and complications compared to late implantation.	2b

Recommendations	Strength rating
Start management of ischaemic priapism as early as possible (within four to six hours) and follow a stepwise approach.	Strong
Decompress the corpus cavernosum by penile aspiration and washout until fresh red blood is obtained as first treatment step.	Strong

Replace blood aspiration with intracavernous injection of a sympathomimetic drug as the first step in priapism secondary to intracavernous injections of vasoactive agents.	Strong
Perform intracavernous injection of a sympathomimetic drug in priapism that persists despite aspiration.	Strong
Repeat aspiration and intracavernous injection of a sympathomimetic drug in cases that persist despite prior aspiration and intracavernous injection of a sympathomimetic drug, before considering surgical intervention.	Strong
Treat ischaemic priapism associated with sickle cell disease in the same fashion as idiopathic ischaemic priapism. Do not use exchange transfusion as a primary treatment. Provide other supportive measures (intravenous hydration, oxygen administration with alkalisation with bicarbonate, blood exchange transfusions), but do not delay initial treatment to the penis.	Strong
Proceed to surgical treatment only when blood aspiration and intracavernous injection of sympathomimetic drugs have failed.	Strong
Perform distal shunt surgical procedures first and combine them with tunnelling if necessary.	Weak
Use proximal procedures in cases of distal shunt failure (< 48 hours) or in patients who do not wish to proceed with immediate penile implant insertion.	Weak
Discuss implantation of a penile prosthesis in cases of delayed presentation (> 48 hours) and in cases refractory to injection therapy and distal shunting.	Weak
Delay implantation of a penile prosthesis if a shunt has been performed, to minimise the risk of infection and erosion of the implant.	Strong
Decide on which type of implant to insert based on: • patient suitability; • surgeons' experience; and • availability and cost of equipment. If a malleable penile prosthesis is implanted it can be exchanged later for an inflatable penile implant.	Strong

10.2 Priapism in Special Situations

*10.2.1 **Stuttering (recurrent or intermittent) priapism***

Stuttering priapism, also termed intermittent or recurrent priapism, is a distinct condition that is characterised by repetitive and painful episodes of prolonged erections. Erections are self-limiting with intervening periods of detumescence [1395, 1437]. These are analogous to repeated episodes of ischaemic priapism. In stuttering priapism the duration of the erections is generally shorter than in ischaemic priapism [1370]. The frequency and/or duration of these episodes are variable and a single episode can sometimes progress into prolonged ischaemic priapism.

Robust epidemiological studies of stuttering priapism are lacking [1438, 1439]. However, recurrent priapism episodes are common in men with SCD (42-64%) [1440, 1441] while in adolescents and young men the incidence of priapism is 35%, of whom 72% have a history of stuttering priapism [1438].

The aetiology of stuttering priapism is similar to that of ischaemic priapism. Whilst SCD is the most common cause, idiopathic cases and cases due to a neurological disorder have been reported. Men who have acute ischaemic priapism, especially which has been prolonged (for more than four hours) are at risk of developing stuttering priapism [1435].

Several studies have proposed alternative mechanisms for stuttering priapism including inflammation, cellular adhesion, NO metabolism, vascular reactivity and coagulation [1336, 1352, 1395, 1437, 1442-1445]. Although debated, androgens have also been observed to have an association with priapism [1446]. Therefore, one of the options for the treatment of stuttering priapism is to reduce serum testosterone levels to hypogonadal levels, which then suppresses androgen-associated mechanisms believed to be involved in triggering recurrent priapism.

10.2.1.1 Diagnostic evaluation

History, physical examination, laboratory testing and penile imaging follow the same principals as ischaemic priapism. In stuttering priapism there is a history of recurrent episodes of prolonged erections. These episodes can occur from several daily to isolated incidents every few months, continuously or followed by incident-free periods, of unknown duration, even months and years [1447]. The onset of the priapic episodes usually occurs

during sleep and detumescence does not occur upon waking. These episodes can be painful and may be the reason that the patient first seeks medical attention. Erections are painful and the penis is rigid as in ischaemic priapism, but the duration of events is usually shorter. Between erections the penis is usually normal, but in some cases signs of fibrosis can be found. Rarely, the penis may become enlarged, a condition known as megalo-phallus.

Recommendations for the diagnosis of stuttering priapism are the same as those described in section 10.1.2.5

10.2.1.2 Disease management

The primary goal in the management of patients with stuttering priapism is the prevention of further episodes and limiting the chances of developing a prolonged ischaemic priapism that is refractory to conventional treatment options. In most cases, stuttering priapism can be managed by pharmacological treatment. The management of each acute episode is similar to that for ischaemic priapism; aspiration/irrigation in combination with intracavernous injections of α-adrenergic agonists.

10.2.1.2.1 α-Adrenergic agonists

Studies of oral α-adrenergic agonists have suggested some prophylactic benefit for daily treatment with these agents [1448]. Adverse effects include tachycardia and palpitations. Pseudoephedrine is widely used as an oral decongestant and can be a first-line treatment option for stuttering priapism [1390]. However, its effect on corporal smooth muscle is not fully understood. Etilephrine has been used successfully to prevent stuttering priapism caused by SCD. It is usually taken orally at doses of 5-10 mg daily, with response rates of up to 72% [1449-1451]. In a placebo-controlled RCT comparing medical prophylaxis with etilephrine and ephedrine, there was no difference in efficacy between the two drugs [1451].

10.2.1.2.2 Hormonal manipulations of circulating testosterone

The aim of hormonal manipulation is to down-regulate circulating testosterone levels to suppress the action of androgens on penile erection [1351, 1395, 1452]. This can be achieved by GnRH agonists or antagonists, antiandrogens or oestrogens [1453, 1454]. Potential adverse effects may include hot flushes, gynaecomastia, ED, loss of libido, and asthenia. All approaches have a similar efficacy profile while the potential cardiovascular toxicity of oestrogens limits their clinical use. Alternative endocrine approaches that have been used with some success include 5-α-reductase inhibitors [1455, 1456] and ketoconazole; an anti-fungal agent that reduces adrenal and testicular androgen production [1452, 1457].

The duration of hormonal treatment for effective suppression of recurrent priapism is problematic. It is not possible to draw any conclusions on the dose, duration of treatment and the efficacy. Caution is strongly advised when prescribing hormonal treatments to pre-pubertal boys and adolescents, and specialist advice from paediatric endocrinologists should be sought. Likewise, hormonal agents have a contraceptive effect and interfere with normal sexual maturation and spermatogenesis and affect fertility. Therefore, men who are trying with their partner to conceive should be comprehensively counselled before using hormonal treatment. Moreover, sperm cryopreservation may be considered to mitigate any potential effects of anti-androgen therapy on fertility.

10.2.1.2.3 Digoxin

Digoxin is a cardiac glycoside and positive inotrope that is used to treat congestive heart failure. Digoxin regulates smooth muscle tone through several different pathways leading to penile detumescence [1351, 1395, 1458]. The use of maintenance digoxin doses (0.25-0.5 mg/daily) in idiopathic stuttering priapism reduces the number of hospital visits and improves QoL [1395]. In a small, clinical, double-blind, placebo-controlled study, digoxin decreased sexual desire and excitement with a concomitant reduction in penile rigidity, regardless of any significant change in plasma levels of testosterone, oestrogens and LH [1458]. Adverse effects include decreased libido, anorexia, nausea, vomiting, confusion, blurred vision, headache, gynaecomastia, rash and arrhythmia.

10.2.1.2.4 Terbutaline

Terbutaline has been used to prevent stuttering priapism with detumescence rates of 36% in patients with alprostadil-induced priapism [1390]. The only RCT (n = 68) in patients with pharmacologically-induced priapism, demonstrated detumescence in 42% of the terbutaline-treated group compared to only 15% in the placebo-treated group [1391]. Adverse effects include nervousness, shakiness, drowsiness, palpitations, headache, dizziness, hot flushes, nausea and weakness.

10.2.1.2.5 Gabapentin

Gabapentin has anticonvulsant, antinociceptive and anxiolytic properties and is widely used as an analgesic and anti-epileptic agent. Its proposed mechanism of action is to inhibit voltage-gated calcium channels, which attenuates synaptic transmission [1452], and reduces testosterone and FSH levels [1459]. It is given at a dose of 400 mg, four times daily, up to 2,400 mg daily, until complete penile detumescence occurs, with subsequent maintenance administration of 300 mg/daily [1460]. Adverse effects include anorgasmia and impaired erectile function.

10.2.1.2.6 Baclofen

Baclofen is a gamma-aminobutyric acid (GABA) derivative that acts as a muscle relaxant and anti-muscle spasm agent. It can inhibit penile erection and ejaculation through GABA activity and prevents recurrent reflexogenic erections or prolonged erections from neurological diseases [1351]. Oral baclofen has little efficacy and it is not usually used in stuttering priapism but intrathecal administration is more effective [1395, 1461-1463]. Adverse effects include drowsiness, confusion, dizziness, weakness, fatigue, headache, hypotension and nausea.

10.2.1.2.7 Hydroxyurea

Hydroxyurea blocks the synthesis of deoxyribonucleic acid (DNA) by inhibiting ribonucleotide reductase, which has the effect of arresting cells in the S-phase [1452, 1464]. Hydroxyurea is an established treatment for ameliorating SCD and improving life expectancy [1394, 1465]. For patients with recurrent priapism, there is limited evidence to suggest a prophylactic role of hydroxyurea [1452, 1464, 1466]. Adverse effects include oligo-zoospermia and leg ulcers.

10.2.1.2.8 Phosphodiesterase type 5 inhibitors

Low doses of PDE5Is have a paradoxical effect in alleviating and preventing stuttering priapism; mainly in patients with idiopathic and SCD-associated priapism [1351, 1395, 1443, 1467-1471]. It is important to remember that therapy should be started when the penis is in its flaccid state and not during an acute episode. There is a delay of one week before treatment is effective. There are no reported impairments in male sexual function.

10.2.1.2.9 Intracavernosal injections

Some patients with stuttering priapism, who have started on systemic treatment to prevent recurrence of unwanted erections, may not see therapeutic benefits immediately and temporarily require intracavernous self-injections at home with sympathomimetic agents [1351, 1395]. The most commonly used drugs are phenylephrine and etilephrine [1336, 1370, 1439, 1450].

Tissue plasminogen activator (TPA) is a secreted serine protease that converts the pro-enzyme plasminogen to plasmin, which acts as a fibrinolytic enzyme. Limited clinical data have suggested that a single intracavernous injection of TPA can successfully treat patients with recalcitrant priapism [1452, 1472]. Mild bleeding is the most commonly observed adverse effect.

10.2.1.2.10 Penile prosthesis

Patients with medically refractory stuttering priapism require frequent visits to the emergency department and are always at risk of a major ischaemic episode, which can be mitigated with insertion of a penile prosthesis [1408, 1429, 1473]. Nevertheless, penile prosthesis for preventing stuttering priapism should not be offered before medical treatment and a penile prosthesis should be performed only in carefully selected patients as a last resort [1408]. In patients with permanent ED due to stuttering priapism, medical treatments for ED should be used cautiously because of the risk of inducing an ischaemic episode and a penile prosthesis can be considered [1408, 1474].

10.2.1.3 Summary of evidence and recommendations for treatment of stuttering priapism

Summary of evidence	LE
The primary goal in the management of patients with stuttering priapism is prevention of future episodes, which can generally be achieved pharmacologically.	2b
Hormonal therapy with GnRH agonists or antagonists or antiandrogens is able to reduce the risk of recurrent priapism episodes although it is associated with adverse events (hot flushes, gynaecomastia, ED, loss of libido, asthenia and infertility)	3
Phosphodiesterase type 5 inhibitors have a paradoxical effect in alleviating and preventing stuttering priapism, mainly in patients with idiopathic and sickle cell disease-associated priapism.	3
The evidence with other systemic drugs (digoxin, α-adrenergic agonists, baclofen, gabapentin and terbutaline, hydroxyurea) is limited.	3

Recommendations	Strength rating
Manage each acute episode according to the treatment recommendations for ischaemic priapism (section 10.1.4).	Strong
Use hormonal therapies (mainly gonadotropin-receptor hormone agonists or antagonists) and/or anti-androgens for the prevention of future episodes in patients with frequent relapses. Do not use them before sexual maturation is reached.	Weak
Initiate treatment with phosphodiesterase type 5 inhibitors only when the penis is in its flaccid state.	Weak
Use digoxin, α-adrenergic agonists, baclofen, gabapentin or terbutaline only in patients with frequent and uncontrolled relapses.	Weak
Use intracavernous self-injections of sympathomimetic drugs at home for treatment of acute episodes on an interim basis until ischaemic priapism has been alleviated.	Weak

10.2.1.4 Follow-up

Follow-up for stuttering priapism includes history and clinical examination to assess the efficacy of treatment in preventing or alleviating erectile events as well as assessing erectile function and penile fibrosis.

*10.2.2 **Priapism in children***

The classification of priapism in children is similar to that in adults. In addition to ischaemic, stuttering and non-ischaemic priapism, a fourth type, neonatal priapism is also described [1336]. Priapism in children is considered rare as no data on its prevalence exist. Sickle cell disease is the major cause of priapism in children, followed by leukaemia (10%), trauma (10%), idiopathic causes (19%) and drugs (5%) [1475]. One study showed that 25% of children experienced SCD-related priapism in a pre-pubertal period [1476]. Another study revealed that 90% of men with SCD had their first priapism episode before age 20 years [1441]. Priapism in children should be evaluated and treated in a timely manner, as untreated ischaemic priapism may lead to ED and psychosexual disorders in adulthood [1477]. A multi-disciplinary team approach should be utilised with specialist input from haematologists and paediatric endocrinologists.

10.3 Non-ischaemic (high-flow or arterial) priapism

Non-ischaemic priapism is a persistent erection caused by unregulated cavernous arterial inflow [1336]. According to aetiology, non-ischaemic priapism can be categorised into four types: traumatic, neurogenic, iatrogenic and idiopathic in origin.

*10.3.1 **Epidemiology/aetiology/pathophysiology***

Epidemiological data on non-ischaemic priapism are almost exclusively derived from small case series [1336, 1364, 1478-1480]. Non-ischaemic priapism is significantly less common than the ischaemic type, comprising only 5% of all priapism cases [1336]. The most frequent cause of non-ischaemic priapism is blunt perineal or penile trauma [1481]. The injury results in a laceration in the cavernosal artery or branches, leading to a fistula between the artery and the lacunar spaces of the sinusoidal space [1480]. The resultant increased blood flow results in a persistent and prolonged erection [1482].

There is often a delay between the trauma and the development of the priapism that may be up to two to three weeks [1483]. This is suggested to reflect either spasm or ischaemic necrosis of the injured artery, with the fistula only developing as the spasm resolves or when the ischaemic segment "blows up". The priapism typically occurs after a nocturnal erection or an erection related to sexual activity, resulting in the sudden increase of blood flow and pressure in the cavernous arteries [1484]. The patient typically reports an erection that is not fully rigid and is not associated with pain because the venous drainage is not compromised and the penile tissue does not become ischaemic [1485].

Non-ischaemic priapism can occur after acute spinal cord injury, presumably due to loss of sympathetic input, leading to predominant parasympathetic input and increased arterial flow [1486]. It has also been reported to occur following internal urethrotomy [1487], Nesbit procedure [1488], circumcision [1489], transrectal prostate biopsy [1490], and brachytherapy for prostate cancer [1491]. Some cases have also been described following shunting procedures performed for ischaemic priapism due to a lacerated cavernosal artery (conversion of low-flow to high-flow priapism) [1492-1494]. Although SCD is usually associated with ischaemic priapism, occasional cases of high-flow priapism have been reported; however, the pathophysiological mechanism remains unclear [1495]. Finally, metastatic malignancy to the penis can also rarely cause non-ischaemic priapism [1496, 1497].

*10.3.2 **Diagnostic evaluation***

10.3.2.1 History

A comprehensive history is mandatory in non-ischaemic priapism diagnosis and follows the same principles as described in section 10.1.2.1. Arterial priapism should be suspected when the patient reports a history of pelvic, perineal, or genital trauma; no penile pain (discomfort is possible); and a persistent, not fully rigid erection. The corpus cavernosum can become fully rigid with sexual stimulation, so sexual intercourse is usually not compromised. The onset of post-traumatic non-ischaemic priapism can be delayed by several hours to weeks following the initial injury [1336].

10.3.2.2 Physical examination

In non-ischaemic priapism, the corpora are tumescent but not fully rigid. Abdominal, penile and perineal examination may reveal evidence of trauma [1336]. Neurological examination is indicated if a neurogenic aetiology is suspected.

10.3.2.3 Laboratory testing

Laboratory testing should include a blood count with white blood cell differential and a coagulation profile to assess for anaemia and other haematological abnormalities. Blood aspiration from the corpus cavernosum shows bright red arterial blood in arterial priapism, while blood is dark in ischaemic priapism. Blood gas analysis is essential to differentiate between non-ischaemic and ischaemic priapism. Blood gas values in high-flow priapism show normal arterial blood [1336] (Table 34).

10.3.2.4 Penile imaging

Colour duplex US of the penis and perineum is recommended and can differentiate non-ischaemic from ischaemic priapism [1362-1364]. Ultrasound must be performed without intracavernosal vasoactive drug injection [1498]. In non-ischaemic priapism, US helps to localise the fistula site and appears as a characteristic colour blush and turbulent high-velocity flow on Doppler analysis [1499]. Patients with non-ischaemic priapism have normal to high blood velocities in the cavernous arteries [1365, 1500].

Selective pudendal arteriography can reveal a characteristic blush at the site of injury in arterial priapism [1501, 1502]. However, due to its invasiveness, it should be reserved for the management of non-ischaemic priapism when embolisation is being considered [1336, 1359].

The role of MRI in the diagnostic evaluation of priapism is controversial. Its role in non-ischaemic priapism is limited because the small penile vessels and fistulae cannot be easily demonstrated [1503].

10.3.2.5 Summary of evidence and recommendations for the diagnosis of non-ischaemic priapism

Summary of evidence	LE
Non-ischemic priapism is less common than ischemic and is usually associated with blunt perineal or penile trauma leading to the development of intracavernosal fistula	2b
Medical history and blood gas analysis are able to differentiate between ischemic and non-ischemic priapism	2b
Blood aspiration from the corpora in case of non-ischemic priapism reveal bright red arterial blood with normal arterial gas values	2b
Penile duplex US is able to identify intracavernosal fistula responsible for non-ischemic priapism	2b

Recommendations	Strength rating
Take a comprehensive history to establish the diagnosis, which can help to determine the priapism subtype.	Strong
Include a physical examination of the genitalia, perineum and abdomen in the diagnostic evaluation.	Strong
Include a neurological examination if neurogenic non-ischaemic priapism is suspected.	Strong
Include complete blood count, white blood cell differential, and coagulation profile for laboratory testing.	Strong
Analyse the blood gas parameters from blood aspirated from the penis to differentiate between ischaemic and non-ischaemic priapism.	Strong
Perform colour duplex ultrasound of the penis and perineum to differentiate between ischaemic and non-ischaemic priapism.	Strong
Perform selected pudendal arteriography when embolisation is planned for non-ischaemic priapism.	Strong

10.3.3 ***Disease management***

Although the conventional belief is that the management of non-ischaemic priapism is not an emergency because the corpus cavernosum does not contain ischaemic blood; however, recent data indicate that the duration of non-ischaemic priapism can also impact EF. In a case series consisting of six patients with high-flow priapism after median follow-up of 4.5 (2-12) weeks, all patients reported development of ED or distal penile flaccidity [1430]. The goal of treatment is closure of the fistula. Non-ischaemic priapism can be managed conservatively or by direct perineal compression. Failure of conservative treatment requires selective arterial embolisation [1504]. The optimal time interval between conservative treatment and arterial embolisation is under debate. Definitive management can be performed at the discretion of the treating physician and should be discussed with the patient so that they can understand the risks of treatment [1336, 1359].

10.3.3.1 Conservative management

Conservative management may include applying ice to the perineum or perineal compression, which is typically US-guided. The fistula occasionally closes spontaneously. Even in cases where the fistula remains patent, intercourse is still possible [1364, 1479, 1505, 1506]. Androgen deprivation therapy (e.g., leuprolide injections, bicalutamide and ketoconazole) has been reported in case series to enable closure of the fistula reducing spontaneous and sleep-related erections [1507]. However, sexual dysfunction due to these treatments must be considered. Patients may develop ED or distal penile flaccidity while undergoing conservative treatment [1430].

Blood aspiration is not helpful for the treatment of arterial priapism and the use of α-adrenergic antagonists is not recommended because of potential severe adverse effects (e.g., transfer of the drug into the systemic circulation).

10.3.3.2 Selective arterial embolisation

Selective arterial embolisation can be performed using temporary substances, such as autologous blood clot [1508-1510] and gel foam [1509, 1511], or permanent substances such as microcoils [1509, 1511-1513], ethylene-vinyl alcohol copolymer (PVA), and N-butyl-cyanoacrylate (NBCA) [1514]. It is assumed that temporary embolisation provides a decreased risk of ED, with the disadvantage of higher failure/recurrence rates, as a consequence of artery embolisation using temporary materials. However, there is insufficient evidence to

support this hypothesis. Success rates ranging between 61.7 and 83.3%, and ED rates from 0-33.3% after the first arterial embolization have been reported, suggesting that failure/recurrence may not be significantly higher with temporary embolisation materials, and preservation of erectile function may not be that different between the two modalities either [1484]. Other potential complications of arterial embolisation include penile gangrene, gluteal ischaemia, cavernositis, and perineal abscess [1336, 1515]. Repeated embolisation is a reasonable option for treating non-ischaemic priapism, both in terms of efficacy and safety [1484].

10.3.3.3 Surgical management

Surgical ligation of the fistula is possible through a transcorporeal or inguinoscrotal approach, using intra-operative Doppler US. Surgery is technically challenging and associated with significant risks, particularly of ED [1516]. Surgery is rarely performed and should only be considered when there are contraindications for selective embolisation, if embolisation is unavailable, or repeated embolisations have failed. If the patient desires more definitive treatment and is not sexually active or has pre-existing ED, surgical intervention can be an appropriate option [1484]. Erectile dysfunction rates ranging from 0-50% have been reported following treatment for non-ischaemic priapism, with surgical ligation having the highest reported rates [1484]. Patients can require penile prosthesis implantation for ED in the long-term [1408].

10.3.3.4 Summary of evidence and recommendations for the treatment of non-ischaemic priapism

Summary of evidence	**LE**
Non-ischaemic priapism can cause erectile dysfunction over time and early definitive management should be undertaken.	3
Conservative management applying ice to the perineum or site-specific perineal compression is an option in all cases. The use of androgen deprivation therapy may enable closure of the fistula reducing spontaneous and sleep-related erections.	3
Selective artery embolisation, using temporary or permanent substances, has high success rates. No definitive statement can be made on the best substance for embolisation in terms of sexual function preservation and success rate.	3
Repeated embolisation is a reasonable option for the treatment of non-ischaemic priapism.	2b
Selective surgical ligation of the fistula is associated with high risk of erectile dysfunction.	3

Recommendations	**Strength rating**
Perform definitive management for non-ischaemic priapism at the discretion of the treating physician as it is not a medical emergency.	Weak
Manage non-ischaemic priapism conservatively with the use of site-specific perineal compression as the first step. Consider androgen deprivation therapy only in adults.	Weak
Perform selective arterial embolisation when conservative management has failed.	Strong
Perform the first selective arterial embolisation using temporary material.	Weak
Repeat selective arterial embolisation with temporary or permanent material for recurrent non-ischaemic priapism following selective arterial embolisation.	Weak
Reserve selective surgical ligation of a fistula as a final treatment option when repeated arterial embolisations have failed.	Weak

10.3.3.5 High-flow priapism in children

Non-ischaemic priapism is a rare condition, especially in children. The embarrassment that children may have in speaking about it to their parents can lead to misdiagnosis and underestimating the prevalence of this condition [1517]. The aetiology, clinical presentation, diagnostic and therapeutic principles are comparable with those of arterial priapism in adults. However, some differentiating features should be noted.

Idiopathic non-ischaemic priapism can be found in a significant percentage of children [1518]. Perineal compression with the thumb may be a useful manoeuvre to distinguish ischaemic and non-ischaemic priapism, particularly in children, where it may result in immediate detumescence, followed by the return of the erection with the removal of compression [1484]. Conservative management using ice applied to the perineum or site-specific perineal compression may be successful, particularly in children [1519, 1520]. Although reportedly successful, embolisation in children is technically challenging and requires treatment within a specialist paediatric vascular radiology department [1374, 1521].

10.3.3.6 Follow-up

During conservative management of non-ischaemic priapism, physical examination and colour duplex US can be useful tools to assess treatment efficacy. Close follow-up using colour duplex US and MRI can help detect distal penile fibrosis and be beneficial in clinical decision-making to intervene with embolisation earlier [1430]. Follow-up after selective arterial embolisation should include clinical examination, colour duplex US, and erectile function assessment. If in doubt, repeat arteriography is required. The goals are to determine if the treatment was successful, identify signs of recurrence, and verify any anatomical and functional sequelae [1498].

11. MALE INFERTILITY

11.1 Definition and classification

Infertility is defined by the inability of a sexually active, non-contraceptive couple to achieve spontaneous pregnancy within twelve months [1522]. Primary infertility refers to couples that have never had a child and cannot achieve pregnancy after at least 12 consecutive months having sex without using birth control methods. Secondary infertility refers to infertile couples who have been able to achieve pregnancy at least once before (with the same or different sexual partner).

In 30-40% of cases, no male-associated factor is found to explain the underlying impairment of sperm parameters and historically was referred to as idiopathic male infertility. These men present with no previous history of diseases affecting fertility and have normal findings on physical examination and endocrine, genetic and biochemical laboratory testing, although semen analysis may reveal pathological findings (see Section 11.3.2). It is now believed that idiopathic male infertility may be associated with several previously unidentified pathological factors, which include but are not limited to endocrine disruption as a result of environmental pollution, generation of reactive oxygen species (ROS)/sperm DNA damage, or genetic and epigenetic abnormalities [1523]. Unexplained male infertility is defined as infertility of unknown origin with normal sperm parameters and partner evaluation. Between 20 and 30% of couples will have unexplained infertility.

11.2 Epidemiology/aetiology/pathophysiology/risk factors

*11.2.1 **Introduction***

About 15% of couples do not achieve pregnancy within one year and seek medical treatment for infertility [1524]. One in eight couples encounter problems when attempting to conceive a first child and one in six when attempting to conceive a subsequent child [1525]. In 50% of involuntarily childless couples, a male-infertility-associated factor is found, usually together with abnormal semen parameters [1522]. For this reason, in all infertile couples the male should undergo medical evaluation by a urologist trained in male reproduction.

Male fertility can be impaired as a result of many different conditions (Table 36), thus including [1522]:

- congenital or acquired urogenital abnormalities;
- genetic abnormalities;
- varicocele;
- urogenital tract infections;
- increased scrotal temperature (e.g., as a consequence of varicocele);
- endocrine disturbances;
- immunological factors;
- iatrogenic factors (e.g., previous scrotal surgery);
- malignancy;
- gonadotoxic exposure (e.g., radiotherapy or chemotherapy);

Advanced paternal age has emerged as one of the main risk factors associated with the progressive increase in the prevalence of male factor infertility [1526-1533].

Advanced maternal age must be considered in the management of every infertile couple, and in the subsequent decisions throughout the diagnostic and therapeutic strategy of the male partner [1534, 1535]. This should include the age and ovarian reserve of the female partner, since these parameters might determine decision-making in terms of timing and therapeutic strategies (e.g., assisted reproductive technology [ART] vs. surgical intervention) [1526-1529]. Earlier evaluation is still a matter of debate in couples in with female partners older than 35 years who have not conceived for 6 months as ovarian reserve may fall [1536-1538].

Table 36 summarises the main male-infertility-associated factors.

Table 36: Male infertility causes and associated factors and percentage of distribution in 10,469 patients [1539]

Diagnosis	Unselected patients (n = 12,945)	Azoospermic patients (n = 1,446)
All	100%	11.2%
Infertility of known (possible) cause	42.6%	42.6%
Maldescended testes	8.4	17.2
Varicocele	14.8	10.9
Sperm auto-antibodies	3.9	-
Testicular tumour	1.2	2.8
Others	5.0	1.2
Idiopathic infertility	30.0	13.3
Hypogonadism	10.1	16.4
Klinefelter syndrome (47, XXY)	2.6	13.7
XX male	0.1	0.6
Primary hypogonadism of unknown cause	2.3	0.8
Secondary (hypogonadotropic) hypogonadism	1.6	1.9
Kallmann syndrome	0.3	0.5
Idiopathic hypogonadotropic hypogonadism	0.4	0.4
Residual after pituitary surgery	< 0.1	0.3
Late-onset hypogonadism	2.2	-
Constitutional delay of puberty	1.4	-
Others	0.8	0.8
General/systemic disease	2.2	0.5
Cryopreservation due to malignant disease	7.8	12.5
Testicular tumour	5.0	4.3
Lymphoma	1.5	4.6
Leukaemia	0.7	2.2
Sarcoma	0.6	0.9
Disturbance of erection/ejaculation	2.4	-
Obstruction	2.2	10.3
Vasectomy	0.9	5.3
Cystic fibrosis (congenital bilateral absence of vas deferens)	0.5	3.0
Others	0.8	1.9

11.2.2 Summary of evidence and recommendations on epidemiology and aetiology of male infertility

Summary of evidence	LE
Infertility affects 15% of couples of reproductive age.	3
A male factor infertility can be identified in about 50% of infertile couples.	2a
A pure male factor infertility can be identified in about 20% of infertile couples.	2a
Several risk factors such as genetic factors, urogenital abnormalities, endocrine disorders, malignant diseases and gonadotoxic treatments can cause male infertility.	2a

Recommendations	Strength rating
Perform infertility evaluation in couples who have not conceived after twelve months of regular, unprotected intercourse.	Strong
Investigate both partners simultaneously to categorise the cause of infertility.	Strong
Investigate all men belonging to couples seeking medical help for fertility problems.	Strong

11.3 Diagnostic work-up

Important treatment decisions are based on the results of semen analysis and most studies indicate semen parameters are a surrogate outcome for male fertility. However, a semen analysis *per se* cannot distinguish fertile from infertile men [1540].

The Guidelines panel concludes that a comprehensive andrological examination is always indicated in infertile couples, both if semen analysis shows abnormalities and in men with normal sperm parameters as compared with reference values [1541-1543].

Focused evaluation of male patients should include: a medical and reproductive history; physical examination; semen analysis – with strict adherence to World Health Organization (WHO) reference values for human semen characteristics [1544, 1545], and hormonal evaluation [1546]. Other investigations (e.g., genetic analysis and imaging) may be required depending on the clinical features and semen parameters.

*11.3.1 **Medical/reproductive history and physical examination***

11.3.1.1 Medical and reproductive history

Medical history should evaluate any risk factors and behavioural patterns that could affect male partner's fertility, such as lifestyle, family history (including, testicular cancer), comorbidities (including systemic diseases; e.g., hypertension, diabetes mellitus, obesity, MetS, testicular cancer, etc.), genito-urinary infections (including sexually transmitted infections), history of testicular surgery and exclude any potential known gonadotoxic medication or recreational drugs [1547].

Typical findings from the history of a patient with infertility include:

- cryptorchidism (uni- or bilateral);
- testicular torsion and trauma;
- genitourinary infections;
- exposure to environmental toxins;
- gonadotoxic medications (e.g., anabolic drugs, chemotherapeutic agents, etc.);
- exposure to radiation or cytotoxic agents.

11.3.1.2 Physical examination

A focused physical examination is compulsory in the evaluation of every infertile male, including presence of secondary sexual characteristics. The size, texture and consistency of the testes must be evaluated. In clinical practice, testicular volume is assessed by Prader's orchidometer [1548]; orchidometry may over-estimate testicular volume compared to US assessment [1549]. There are no uniform reference values in terms of Prader's orchidometer-derived testicular volume, due to differences in the populations studied (e.g., geographic area, nourishment, ethnicity and environmental factors) [1548-1550]. The mean Prader's orchidometer-derived testis volume reported in the European general population is 20.0 ± 5.0 mL [1548], whereas in infertile patients it is 18.0 ± 5.0 mL [1548, 1551-1553]. The presence of the vas deferens, fullness of epididymis and presence of a varicocele should be always determined. Likewise, palpable abnormalities of the testis, epididymis, and vas deferens should be evaluated. Other physical alterations, such as abnormalities of the penis (e.g., phimosis, short frenulum, fibrotic nodules, epispadias, hypospadias, etc.), abnormal body hair distribution and gynecomastia, should also be evaluated.

Typical findings from the physical examination of a patient with characteristics suggestive for testicular deficiency include:

- abnormal secondary sexual characteristics;
- abnormal testicular volume and/or consistency;
- testicular masses (potentially suggestive of cancer);
- absence of testes (uni-bilaterally);
- gynaecomastia;
- varicocele.

*11.3.2 **Semen analysis***

The 6th edition the WHO Manual for the Examination and Processing of Human Semen [1545] has been published on July 2021 and comprises of three sections: i) semen examination; ii) sperm preparation and cryopreservation; and, iii) quality assessment and quality control.

Procedures for semen examination are divided:

- Basic examinations, that should be performed by every laboratory, based on standardised procedures and evidence-based techniques.
- Extended analyses, which are performed by choice of the laboratory or by special request from the clinicians.
- Advanced examinations.

Basic examination summary [1544]:

- Assessment of sperm numbers: the laboratory should not stop assessing the number of sperm at low concentrations (2 million/mL), as suggested in the 5th edition, but report lower concentrations, noting that the errors associated with counting a small number of spermatozoa may be high. It is recognised that the total sperm numbers per ejaculate (sperm output) have more diagnostic value than sperm concentration; therefore, semen volume must be measured accurately.
- Assessment of sperm motility: the categorisation of sperm motility has reverted back to fast progressively motile, slow progressively motile, non-progressively motile and immotile (grade a, b, c or d) because presence (or absence) of rapid progressive spermatozoa is recognised to be clinically important.
- Assessment of sperm morphology: the 6th edition has recommended the Tygerberg strict criteria by sperm adapted Papanicolaou staining.
- Assessment of vitality should not be performed in all samples, only if more than 60% of spermatozoa are immotile.

Extended examinations

This chapter contains procedures to detect leukocytes and markers of genital tract inflammation, sperm antibodies, indices of multiple sperm defects, sequence of ejaculation, methods to detect sperm aneuploidy, semen biochemistry and sperm DNA fragmentation.

Reference ranges and reference limits

The lower fifth percentile of the distribution of semen analysis values from approximately 3500 men in 12 countries who have contributed to a natural conception within 12 months of trying does not represent a limit between fertile and infertile men. For a general prediction of live birth *in vivo* as well as *in vitro*, a multiparametric interpretation of the entire men's and partner's reproductive potential are needed. Reference values for semen parameters are represented in Table 37 [1541].

Moreover, more complex testing (e.g., sperm DNA fragmentation) than classic semen analysis may be required in everyday clinical practice, particularly in men belonging to couples with recurrent pregnancy loss from natural conception or ART and in men with unexplained male infertility. Although definitive conclusions cannot be drawn, given the heterogeneity of the studies, increased sperm DNA damage is associated with pregnancy failure [1523, 1554, 1555].

Table 37: Lower reference limits (5th centiles and their 95% CIs) for semen characteristics

Parameter	**2021 Lower reference limit (95% CI)**
Semen volume (mL)	1.4 (1.3-1.5)
Total sperm number (106/ejaculate)	39 (35-40)
Sperm concentration (106/mL)	16 (15-18)
Total motility (PR + NP, %)	42 (40-43)
Progressive motility (PR, %)	30 (29-31)
Vitality (live spermatozoa, %)	54 (50-56)
Sperm morphology (normal forms, %)	4 (3.9-4.0)

Other consensus threshold values	
pH	> 7.2
Peroxidase-positive leukocytes (10^6/mL)	< 1.0
Tests for antibodies on spermatozoa	
MAR test (motile spermatozoa with bound particles, %)	No evidence-based reference values. Each laboratory should define its normal reference ranges by testing a sufficiently large number of fertile men.
Immunobead test (motile spermatozoa with bound beads, %)	No evidence-based reference limits.
Accessory gland function	
Seminal zinc (µmol/ejaculate)	≥ 2.4
Seminal fructose (µmol/ejaculate)	≥ 13
Seminal neutral α-glucosidase (mU/ejaculate)	≥ 20

CIs = confidence intervals; MAR = mixed antiglobulin reaction; NP = non-progressive; PR = progressive (a+b motility).

** Distribution of data from the population is presented with one-sided intervals (extremes of the reference population data). The lower 5th percentile represents the level under which only results from 5% of the men in the reference population were found.*

If semen analysis is normal according to WHO criteria, a single test is sufficient. If the results are abnormal on at least two tests, further andrological investigation is indicated.

None of the individual sperm parameters (e.g., concentration, morphology and motility), are diagnostic *per se* of infertility. According to WHO reference criteria 5th edn., it is important to differentiate between the following [1556]:

- oligozoospermia: < 16 million sperm/mL;
- asthenozoospermia: < 32% progressive motile sperm;
- teratozoospermia: < 4% normal forms.

According to the WHO reference criteria 6th edn., this subdivision is not reported, although the EAU Guidelines panel considers this further segregation still clinically relevant in the everyday clinical practice.

Often, all three anomalies occur simultaneously, which is defined as oligo-astheno-terato-zoospermia (OAT) syndrome. As in azoospermia (namely, the complete absence of spermatozoa in semen), in severe cases of oligozoospermia (spermatozoa < 5 million/mL) [1557], there is an increased incidence of obstruction of the male genital tract and genetic abnormalities. In case of azoospermia, full andrological investigation should be warranted to classify obstructive azoospermia (OA) versus non-obstructive azoospermia (NOA). A recommended method to diagnose absolute azoospermia versus cryptozoospermia is semen centrifugation at 3,000 g for 15 minutes and a thorough microscopic examination by phase contrast optics at ×200 magnification of the pellet. All samples can be stained and re-examined microscopically [1558]. This is to ensure that small quantities of sperm are detected, which may be potentially used for intra-cytoplasmic sperm injection (ICSI); therefore removing the need for surgical intervention.

Advanced examinations

Obsolete tests such as the human oocyte and human zona pellucida binding and the hamster oocyte penetration tests have been completely removed. Research tests include assessment of ROS and oxidative stress, membrane ion channels, acrosome reaction and sperm chromatin structure and stability, computer-assisted sperm analysis (CASA).

Measurement of Oxidative Stress

Oxidative stress is considered to be central in male infertility by affecting sperm quality, function, as well as the integrity of sperm [1559]. Oxidative stress may lead to sperm DNA damage and poorer DNA integrity, which are associated with poor embryo development, miscarriage and infertility [1560, 1561]. Spermatozoa are vulnerable to oxidative stress and have limited capacity to repair damaged DNA. Oxidative stress is generally associated with poor lifestyle (e.g., smoking) and environmental exposure, and therefore antioxidant regimens and lifestyle interventions may reduce the risk of DNA fragmentation and improve sperm quality [1562]. However, these data have not been supported by RCTs. Although ROS can be measured by various assays (e.g., chemiluminescence),

no standardised testing methods for ROS are available and routine measurement of ROS testing should remain experimental until these tests are validated in RCTs [1563].

11.3.3 ***Measurement of sperm DNA Fragmentation Index (DFI)***

Sperm DNA fragmentation, or the accumulation of single- and double-strand DNA breaks occur in sperm, and an increase in the level of sperm DNA fragmentation has been shown to reduce the chances of natural conception [1564]. Although no studies have unequivocally and directly tested the impact of sperm DNA damage on the clinical management of infertile couples, sperm DNA damage is more common in infertile men and has been identified as a major contributor to male infertility, as well as poorer outcomes following ART [1565, 1566], including impaired embryo development [1565], miscarriage, recurrent pregnancy loss [1554, 1555, 1567], and birth defects [1565]. Sperm DNA damage can be increased by several factors including hormonal anomalies, varicocele, chronic infection and lifestyle factors (e.g., smoking) [1566].

Several assays have been described to measure sperm DNA damage. It has been suggested that current methods for assessing sperm DNA integrity still do not reliably predict treatment outcomes from ART and there is controversy whether to recommend them routinely for clinical use [1566, 1568, 1569]. Terminal deoxynucleotidyl transferase mediated deoxyuridine triphosphate nick end labelling (TUNEL) and the alkaline comet test (COMET) directly measure DNA damage. Conversely, sperm chromatin structure assay (SCSA) and sperm chromatic dispersion test (SCD) are indirect tools for DNA fragmentation assessment. The SCSA is still the most widely studied and one of the most commonly used techniques to detect sperm DNA damage [1570, 1571]. In SCSA, the number of cells with DNA damage is indicated by the DNA fragmentation index (DFI) [1572], whereas the proportion of immature sperm with defects in the histone-to-protamine transition is indicated by high DNA stainability [1573]. It is suggested that a threshold DFI of 25% as measured with SCSA, is associated with reduced pregnancy rates via natural conception or intra-uterine insemination (IUI) [1571]. Furthermore, DFI values > 50% on SCSA are associated with poorer outcomes from *in vitro* fertilisation (IVF). More recently, the mean COMET score and scores for proportions of sperm with high or low DNA damage have been shown to be of value in diagnosing male infertility and providing additional discriminatory information for the prediction of both IVF and ICSI live births [1566].

- *Testicular sperm in men with raised SDF in ejaculated sperm*

Testicular sperm is reported to have lower levels of SDF compared to ejaculated sperm [1574]. The use of testicular sperm for ICSI is associated with possibly improved outcomes compared with ejaculated sperm in men with high sperm DNA fragmentation [1574, 1575]. Men with unexplained infertility with raised DNA fragmentation may be considered for TESE after failure of ART, although they should be counselled that live-birth rates are under reported in the literature and patients must weigh up the risks of performing an invasive procedure in a potentially normozoospermic or unexplained condition. The advantages of the use of testicular sperm in men with cryptozoospermia have not yet been confirmed in large scale randomised studies [1576]. A recent meta-analysis has suggested that TESE-ICSI may improve the outcomes from ART but there is significant heterogeneity of data and the authors suggest that RCTs are needed to validate the use of TESE in men with raised SDF [1577].

In terms of a practical approach, urologists may offer the use of testicular sperm in patients with high SDF. However, patients should be counselled regarding the low levels of evidence for this (i.e., non-randomised studies). Furthermore, testicular sperm should only be used in this setting once the common causes of oxidative stress have been excluded, including varicoceles, modifications of dietary/lifestyle factors and treatment of accessory gland infections.

11.3.4 ***Hormonal determinations***

In men with testicular deficiency, hypergonadotropic hypogonadism (also called primary hypogonadism) is usually present, with high levels of FSH and LH and, with or without low levels of testosterone. Generally, the levels of FSH negatively correlate with the number of spermatogonia [1578]. When spermatogonia are absent or markedly diminished, FSH level is usually elevated; when the number of spermatogonia is normal, but maturation arrest exists at the spermatocyte or spermatid level, FSH level is usually within the normal range [1578]. However, for patients undergoing TESE, FSH levels do not accurately predict the presence of spermatogenesis, as men with maturation arrest on histology can have both normal FSH and testicular volume [1579, 1580]. Furthermore, men with NOA and high levels of FSH may still harbour focal areas of spermatogenesis at the time of TESE or microdissection TESE (mTESE) [1580, 1581]. Despite current findings need to be confirmed, growing data suggest that lower preoperative serum anti-Müllerian hormone (AMH) levels are associated with higher likelihood of positive sperm retrieval outcomes in men undergoing mTESE [1582, 1583].

11.3.5 ***Genetic testing***

All urologists working in andrology must have an understanding of the genetic abnormalities most commonly associated with infertility, so that they can provide correct advice to couples seeking fertility treatment. Current routine clinical practice in genetic testing is based on the screening of genomic DNA from peripheral blood samples. However, screening of chromosomal anomalies in spermatozoa (sperm aneuploidy) and preimplantation genetic testing (PGT) are also feasible and indicated in selected cases (e.g., recurrent miscarriage) [1584-1590].

11.3.5.1 Chromosomal abnormalities

Chromosomal abnormalities can be numerical (e.g., trisomy) or structural (e.g., inversions or translocations). In a survey of pooled data from 11 publications, including 9,766 infertile men, the incidence of chromosomal abnormalities was 5.8% [1591]. Of these, sex chromosome abnormalities accounted for 4.2% and autosomal abnormalities for 1.5%. In comparison, the incidence of abnormalities was 0.38% in pooled data from three series, with a total of 94,465 new-born male infants, of whom 131 (0.14%) had sex chromosomal abnormalities and 232 (0.25%) autosomal abnormalities [1591]. The frequency of chromosomal abnormalities increases as testicular deficiency becomes more severe. Patients with sperm count < 5 million/mL already show a 10-fold higher incidence (4%) of mainly autosomal structural abnormalities compared to the general population [1592, 1593]. Men with NOA are at highest risk, especially for sex chromosomal anomalies (e.g., Klinefelter syndrome) [1594, 1595].

Based on the frequencies of chromosomal aberrations in patients with different sperm concentration, karyotype analysis is currently indicated in men with azoospermia or oligozoospermia (spermatozoa < 10 million/mL) [1593]. Notwithstanding, the clinical value of spermatozoa < 10 million/mL remains a valid threshold until further studies, evaluating the cost-effectiveness, in which costs of adverse events due to chromosomal abnormalities (e.g., miscarriages and children with congenital anomalies) are performed [1596].

11.3.5.1.1 Sex chromosome abnormalities (Klinefelter syndrome and variants [47,XXY; 46,XY/47, XX mosaicism])

Klinefelter syndrome is the most common sex chromosomal abnormality [1597]. Adult men with Klinefelter syndrome usually have small firm testes along with features of primary hypogonadism. The phenotype is the final result of a combination between genetic, hormonal and age-related factors [12]. The phenotype varies from that of a normally virilised male to one with the stigmata of androgen deficiency. In most cases infertility and reduced testicular volume are the only clinical features that can be detected. Leydig cell function is also commonly impaired in men with Klinefelter syndrome and thus testosterone deficiency is more frequently observed than in the general population [1598], although rarely observed during the peri-pubertal period, which usually occurs in a normal manner [12, 1599]. Rarely, more pronounced signs and symptoms of hypogonadism can be present, along with congenital abnormalities including heart and renal problems [1600].

The presence of germ cells and sperm production are variable in men with Klinefelter syndrome and are more frequently observed in mosaicism, 46,XY/47,XXY. In patients with azoospermia, TESE or mTESE are therapeutic options as spermatozoa can be recovered in up to 50% of cases [1601, 1602]. Although the data are not unique [1602], there is growing evidence that TESE or mTESE yields higher sperm recovery rates when performed at a younger age [1594, 1603].

Since Klinefelter syndrome is associated with several general health problems, appropriate medical follow-up is therefore advised [13, 1604, 1605]. Testosterone therapy may be considered if testosterone levels are in the hypogonadal range when fertility issues have been addressed [15]. Moreover, men with Klinefelter syndrome are at higher risk of metabolic and cardiovascular diseases (CVD), including venous thromboembolism (VTE) and diabetes, particularly when starting testosterone therapy [1606]. In addition, a higher risk of haematological malignancies has been reported in men with Klinefelter syndrome [13].

Testicular sperm extraction in peri-pubertal or pre-pubertal boys with Klinefelter syndrome aiming at cryopreservation of testicular spermatogonial stem cells is still considered experimental and should only be performed within a research setting [1607]. The same applies to sperm retrieval in older boys who have not considered their fertility potential [1608].

11.3.5.1.2 Autosomal abnormalities

Genetic counselling should be offered to all couples seeking fertility treatment (including IVF/ICSI) when the male partner has an autosomal karyotype abnormality. The most common autosomal karyotype abnormalities are Robertsonian translocations, reciprocal translocations, paracentric inversions, and marker chromosomes. It is important to look for these structural chromosomal anomalies because there is an increased associated risk of aneuploidy or unbalanced chromosomal complements in the foetus. When IVF/ICSI is carried out for men with translocations, PGD or amniocentesis should be performed [1609, 1610].

11.3.5.2 Cystic fibrosis gene mutations

Cystic fibrosis (CF) is an autosomal-recessive disorder [1611]. It is the most common genetic disease of Caucasians; 4% are carriers of gene mutations involving the CF transmembrane conductance regulator (CFTR) gene located on chromosome 7p. It encodes a membrane protein that functions as an ion channel and influences the formation of the ejaculatory duct, seminal vesicle, vas deferens and distal two-thirds of the epididymis. Approximately 2,000 CFTR mutations have been identified and any CFTR alteration may lead to congenital bilateral absence of the vas deferens (CBAVD). However, only those with homozygous mutations exhibit CF disease [1612]. Congenital bilateral absence of the vas deferens is a rare reason of male factor infertility, which is found 1% of infertile men and in up to 6% of men with obstructive azoospermia [1613]. Clinical diagnosis of absent vasa is easy to miss and all men with azoospermia should be carefully examined to exclude CBAVD, particularly those semen volume < 1.0 mL and acidic pH < 7.0 [1614-1616]. In patients with CBAVD-only or CF, epididymal sperm aspiration (micro or percutaneous; MESA and PESA respectively), TESA, or TESE in combination with ICSI, can be used to achieve pregnancy. However, higher sperm quality, easier sperm retrieval and better ICSI outcomes are associated with CBAVD-only patients as compared with CF patients [1612].

The most frequently found mutations are F508, R117H and W1282X (according to their traditional definitions), but their frequency and the presence of other mutations largely depend on the ethnicity of the patient [1617, 1618]. Given the functional relevance of a DNA variant (the 5T allele) in a non-coding region of CFTR [1619], it is now considered a mild CFTR mutation rather than a polymorphism and it should be analysed in each CBAVD patient. Men with CBAVD often have mild clinical stigmata of CF (e.g., history of chest infections). When a man has CBAVD, it is important to test his partner for CF mutations. If the female partner is found to be a carrier of CFTR mutations, the couple must consider carefully whether to proceed with ICSI, as the risk of having a child with CF or CBAVD will be 50%, depending on the type of mutations carried by the parents. If the female partner is negative for known mutations, the risk of being a carrier of unknown mutations is ~0.4% [1620].

11.3.5.2.1 Unilateral or bilateral absence/abnormality of the vas and renal anomalies

Congenital unilateral absence of the vas deferens (CUAVD) is usually associated with ipsilateral absence of the kidney and probably has a different genetic causation [1621]. Cystic fibrosis transmembrane conductance regulator gene mutation screening is indicated in men with unilateral absence of the vas deferens with normal kidneys. The prevalence of renal anomalies is rare for patients who have CBAVD and CFTR mutations [1622]. Abdominal US should be undertaken both in unilateral and bilateral absence of vas deferens without CFTR mutations. Findings may range from CUAVD with ipsilateral absence of the kidney, to bilateral vessel and renal abnormalities, such as pelvic kidney [1623].

11.3.5.3 Y microdeletions – partial and complete

Microdeletions on the Y-chromosome are termed AZFa, AZFb and AZFc deletions [1624]. Clinically relevant deletions remove partially, or in most cases completely, one or more of the AZF regions, and are the most frequent molecular genetic cause of severe oligozoospermia and azoospermia [1625]. In each AZF region, there are several spermatogenesis candidate genes [1626].

11.3.5.3.1 Clinical implications of Y microdeletions

The clinical significance of Yq microdeletions can be summarised as follows:

- They are not found in normozoospermic men, proving there is a clear cut cause-and-effect relationship between Y-deletions and spermatogenic failure [1627].
- The highest frequency of Y-deletions is found in azoospermic men (8-12%), followed by oligozoospermic (3-7%) men [1628, 1629].
- Deletions are extremely rare with a sperm concentration > 5 million/mL (~0.7%) [1630].
- AZFc deletions are most common (65-70%), followed by Y-deletions of the AZFb and AZFb+c or AZFa+b+c regions (25-30%). AZFa region deletions are rare (5%) [1631].

- Complete deletion of the AZFa region is associated with severe testicular phenotype (Sertoli cell only syndrome [SCOS]), while complete deletions of the AZFb region is associated with spermatogenic arrest. Complete deletions that include the AZFa and AZFb regions are of poor prognostic significance for retrieving sperm with TESE. Therefore, TESE should not be attempted in these patients [1632, 1633].
- Deletions of the AZFc region causes a variable phenotype ranging from azoospermia to oligozoospermia.
- Testicular sperm can be found in 50-75% of men with AZFc microdeletions [1632-1634].
- Men with AZFc microdeletions who are oligo-azoospermic or in whom sperm is found at the time of TESE must be counselled that any male offspring will inherit the deletion.
- Classical (complete) AZF deletions do not confer a risk for cryptorchidism or testicular cancer [1630, 1635].

The specificity and genotype/phenotype correlation reported above means that Y-deletion analysis has both a diagnostic and prognostic value for testicular sperm retrieval [1635].

11.3.5.3.1.1 Testing for Y microdeletion

Historically, indications for AZF deletion screening are based on sperm count and include azoospermia and severe oligozoospermia (spermatozoa count < 5 million/mL). A meta-analysis assessing the prevalence of microdeletions on the Y chromosome in oligo-zoospermic men in 37 European and North American studies (n = 12,492 oligo-zoospermic men) showed that the majority of microdeletions occurred in men with sperm concentrations ≤ 1 million sperm/mL, with < 1% identified in men with > 1 million sperm/mL [1630]. In this context, while an absolute threshold for clinical testing cannot be universally given, patients may be offered testing if sperm counts are < 5 million sperm/mL, but must be tested if ≤1 million sperm/mL.

With the contribution of the European Academy of Andrology (EAA) guidelines and the European Molecular Genetics Quality Network external quality control programme (http://www.emqn.org/emqn/), Yq testing has become more reliable in different routine genetic laboratories. The EAA guidelines provide a set of primers capable of detecting > 95% of clinically relevant deletions [1636].

*11.3.6 **Imaging in infertile men***

In addition to physical examination, a scrotal US may be helpful in: (i) measuring testicular volume; (ii) assessing testicular anatomy and structure in terms of US patterns, thus detecting signs of testicular dysgenesis often related to impaired spermatogenesis (e.g., non-homogeneous testicular architecture and microcalcifications) and testicular tumours; and, (iii) finding indirect signs of obstruction (e.g., dilatation of rete testis, enlarged epididymis with cystic lesions, or absent vas deferens) [1549]. In clinical practice, Prader's orchidometer-derived testicular volume is considered a reliable surrogate of US-measured testicular volume, easier to perform and cost-effective [1548]. Nevertheless, scrotal US has a relevant role in testicular volume assessment when Prader's orchidometer is unreliable (e.g., large hydrocele, inguinal testis, epididymal enlargement/fibrosis, thickened scrotal skin; small testis, where the epididymis is large in comparison to the total testicular volume [1548, 1549]). Ultrasound patterns of testicular inhomogeneity [1637, 1638] is usually associated with ageing, although it has also been reported in association with testicular atrophy and fibrosis [1549]. A diagnostic testicular biopsy is not recommended when testicular inhomogeneity is detected [1637, 1638].

11.3.6.1 Scrotal US

Scrotal US is widely used in everyday clinical practice in patients with oligo-zoospermia or azoospermia, as infertility has been found to be an additional risk factor for testicular cancer [1639, 1640]. It can be used in the diagnosis of several diseases causing infertility including obstructive azoospermia (see section 11.4), testicular neoplasms and varicocele.

11.3.6.1.1 Testicular neoplasms

In one study, men with infertility had an increased risk of testicular cancer (hazard ratio [HR] 3.3). When infertility was refined according to individual semen parameters, oligozoospermic men had an increased risk of cancer compared with fertile control subjects (HR 11.9) [1641]. In a recent systematic review infertile men with testicular microcalcification (TM) were found to have a ~18-fold higher prevalence of testicular cancer [1642]. The utility of US as a routine screening tool in men with infertility to detect testicular cancer remains a matter of debate [1639, 1640].

Indeed, these testicular lesions are difficult to characterise as being benign or malignant based only upon US criteria, including size, vascularity and echogenicity.

A dichotomous cut-off of certainty in terms of lesion size that may definitely distinguish benign from malignant testicular masses is currently not available. A systematic review and meta-analysis was carried out by the Testicular Cancer and the Sexual and reproductive health EAU Guidelines panels to to define which scrotal US or magnetic resonance imaging (MRI) characteristics can predict benign or malignant disease in pre- or post-pubertal males with indeterminate testicular masses [1643]. Benign and malignant masses were classified using the reported reference test: i.e., histopathology, or 12 months progression-free radiological surveillance. A total of 32 studies were identified, including 1692 masses of which 28 studies and 1550 masses reported scrotal US features, four studies and 142 masses reported MRI features. Meta-analysis of different scrotal US (B-mode) values in post-pubertal men demonstrated that a size of ≤0.5 cm had a significantly lower OR of malignancy compared to masses of >0.5 cm ($p < 0.001$). Comparison of masses of 0.6-1.0 cm and masses of > 1.5 cm also demonstrated a significantly lower OR of malignancy ($p = 0.04$). There was no significant difference between masses of 0.6-1.0 and 1.1-1.5 cm. Scrotal US in post-pubertal men also had a significantly lower OR of malignancy for heterogenous masses compared to homogenous masses ($p = 0.04$), hyperechogenic vs. hypoechogenic masses ($p < 0.01$), normal vs. increased enhancement ($p < 0.01$), and peripheral vs. central vascularity ($P < 0.01$), respectively. There were limited data on pre-pubertal SUS, pre-pubertal MRI and post-pubertal MRI [1643].

Small hypoechoic/hyperechoic areas may be diagnosed as intra-testicular cysts, focal Leydig cell hyperplasia, fibrosis and focal testicular inhomogeneity after previous pathological conditions. Hence, they require careful periodic US assessment and follow-up, especially if additional risk factors for malignancy are present (i.e., infertility, bilateral TM, history of cryptorchidism, testicular atrophy, inhomogeneous parenchyma, history of testicular tumour, history of/contralateral tumour) [1549].

In the case of interval growth of a lesion and/or the presence of additional risk factors for malignancy, testicular biopsy/surgery may be considered, although the evidence for adopting such a management policy is limited. In 145 men referred for azoospermia who underwent US before testicular biopsy, 49 (34%) had a focal US abnormality; a hypoechoic lesion was found in 20 patients (14%), hyperechoic lesions were seen in 10 patients (7%); and, a heterogeneous appearance of the testicular parenchyma was seen in 19 patients (13%). Of 18 evaluable patients, 11 had lesions < 5 mm; all of which were confirmed to be benign. All other patients with hyperechoic or heterogeneous areas on US with subsequent tissue diagnoses were found to have benign lesions. The authors concluded that men with severe infertility who have incidental testicular lesions, negative tumour markers and lesions < 5 mm may be observed with serial scrotal US examinations and enlarging lesions or those of greater dimension can be considered for histological biopsy [1644].

Other studies have suggested that if a testicular lesion is hyperechoic and non-vascular on colour Doppler US and associated with negative tumour markers, the likelihood of malignancy is low and consideration can be given to regular testicular surveillance, as an alternative to radical surgery. In contrast, hypoechoic and vascular lesions are more likely to be malignant [1645-1649]. However, most lesions cannot be characterised by US (indeterminate), and histology remains the only certain diagnostic tool. A multidisciplinary team discussion (MDT), including invasive diagnostic modalities, should therefore be considered in these patients.

The role of US-guided intra-operative frozen section analysis in the diagnosis of testicular cancer in indeterminate lesions can be considered, and several authors have proposed its value in the intra-operative diagnosis of indeterminate testicular lesions [1650]. Although the default treatment after patient counselling and MDT discussion may be radical orchidectomy, an US-guided biopsy with intra-operative frozen section analysis may be offered as an alternative to radical orchidectomy and potentially obviate the need for removal of the testis in a patient seeking fertility treatment. In men with azoospermia a concurrent TESE with sperm banking can also be performed at the time of surgical intervention.

11.3.6.1.2 Varicocele

At present, the clinical management of varicocele is still mainly based on physical examination; nevertheless, scrotal colour Doppler US is useful in assessing venous reflux and diameter, when palpation is unreliable and/or in detecting recurrence/persistence after surgery [1549]. Definitive evidence of reflux and venous diameter may be utilised in the decision to treat (see Section 11.4.3.1 and 11.4.3.2).

11.3.6.1.3 Other

Scrotal US is able to detect changes in the proximal part of the seminal tract due to obstruction. Especially for CBAVD patients, scrotal US is a favourable option to detect the abnormal appearance of the epididymis. Given that, three types of epididymal findings are described in CBAVD patients: tubular ectasia (honeycomb appearance), meshwork pattern, and complete or partial absence of the epididymis [1651, 1652].

11.3.6.2 Transrectal US

For patients with a low seminal volume, acidic pH and severe oligozoospermia or azoospermia, in whom obstruction is suspected, scrotal and transrectal US are of clinical value in detecting CBAVD and presence or absence of the epididymis and/or seminal vesicles (SV) (e.g., abnormalities/agenesis). Likewise, transrectal US (TRUS) has an important role in assessing obstructive azoospermia (OA) secondary to CBAVD or anomalies related to the obstruction of the ejaculatory ducts, such as ejaculatory duct cysts, seminal vesicle dilatation or hypoplasia/atrophy, although retrograde ejaculation should be excluded as a differential diagnosis [1549, 1653].

*11.3.7 **Summary of evidence and recommendations for the diagnostic work-up of male infertility***

Summary of evidence	**LE**
Semen analysis alone cannot distinguish fertile from infertile men.	2a
Diagnosis of male infertility is associated with an increased risk of death and comorbidities.	2a
Male infertility evaluation should include a medical, reproductive and family history, assessment of lifestyle and behavioural risk factors, physical examination, semen analysis and hormonal evaluation.	2a
Genetic analysis and imaging may be required depending on the clinical features and semen parameters.	2a
Testicular volume can be measured with a Prader orchidometer or using testicular ultrasound.	2a
Semen analyses is described in the latest edition of the WHO Manual for the Examination and Processing of Human Semen. Abnormal semen characteristics are expressed as below the 5th percentiles of a reference population of 3500 men who contributed to a natural conception within 12 months.	3
Oxidative stress has a detrimental impact on sperm quality but there is a lack of validated assays to measure ROS and oxidative stress in the evereday clinical practice.	2b
High sperm DNA fragmentation index (SDF) is associated with reduced pregnancy rates via natural conception or intra-uterine insemination, poor assisted reproductive techniques (ART) outcomes, recurrent pregnancy loss and unexplained infertility.	2a
A possible advantage of the use of testicular sperm for ICSI in patients with high SDF in ejaculated sperm has not been confirmed in large scale RCTs.	3
Gonadotropins and total testosterone measurement are useful to diagnose testicular deficiency and to classify the type of hypogonadism.	2a
Follicle-stimulating hormone values have been negatively associated with sperm count.	2a
Chromosomal abnormalities are frequently found in men with severe oligozoospermia (spermatozoa <5 million/mL) or azoospermia.	2a
Klinefelter syndrome is associated with non-obstructive azoospermia, hypogonadism and general health problems, including metabolic, cardiovascular and oncologic diseases.	2a
Cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations may be associated with congenital bilateral absence of the vas deferens CBAVD and obstructive azoospermia.	2a
The prevalence of renal anomalies is rare for patients with unilateral and bilateral absence of the vas deferens and CFTR mutations.	2a
The highest frequency of Y-microdeletions is found in azoospermic men followed by oligospermic men but is extremely rare with a sperm concentration > 5 million/mL.	2a
Complete deletions that include the AZFa and AZFb regions are of poor prognostic significance for retrieving sperm with surgery.	2a
Testicular sperm can be found in 50-75% of men with AZFc microdeletions.	2a
Male offspring of men with AZF microdeletions will inherit the deletion.	2a
Genetic abnormalities found during the diagnostic work-up might impact on the psychological and overall health of the couple and the offspring.	2a
Scrotal ultrasound is used to measure testicular volume, assess testicular anatomy including detecting signs of obstruction and testicular dysgenesis.	2a
Infertile men have a higher risk of testicular cancer compared to fertile controls.	2a
An essential approach for infertile men with US-detected indeterminate testicular lesion is a multidisciplinary discussion with focus on the size of the lesion, echogenicity, vascularity and previous patient's history (e.g., cryptorchidism, previous history of germ cell tumour [GCT]).	2a

Scrotal ultrasound is useful in assessing venous reflux and diameter of the spermatic vein, mostly when palpation is unreliable or in detecting recurrence/persistence after surgery	2a
In patients with a low seminal volume, acidic pH and either severe oligozoospermia or azoospermia in the absence of CBAVD, transrectal ultrasound should be used to detect complete or partial ejaculatory duct obstruction	2b

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., assisted reproductive technology (ART) versus surgical intervention).	Strong
Examine all men seeking medical help for fertility problems, including men with abnormal semen parameters.	Strong
Take a complete medical reproductive and family history, assessment of lifestyle and behaviour risk factors, physical examinationand semen analysis	Strong
Counsel infertile men or men with abnormal semen parameters on the associated health risks.	Weak
Assess testicular volume with a Prader's orchidometer or testicular ultrasound (US).	Weak
Perform semen analyses according to the latest edition of the WHO Manual for the Examination and Processing of Human Semen. Perform at least two consecutive semen analyses if the baseline analysis was abnormal.	Strong
Do not routinely use reactive oxygen species (ROS) testing in the diagnosis and management of the male partner of an infertile couple.	Weak
Perform sperm DNA fragmentation (SDF) testing in the assessment of couples with recurrent pregnancy loss from natural conception and failure of ART or men with unexplained infertility.	Strong
Consider the use of testicular sperm for ICSI in patients with high SDF in ejaculated sperm as experimental	Weak
Perform a hormonal evaluation including serum total testosterone and Follicle Stimulating Hormone/Luteinising Hormone at least in all cases of oligozoospermia and azoospermia.	Strong
Offer standard karyotype analysis and genetic counselling to all men with azoospermia and oligozoospermia (spermatozoa < 5 million/mL) for diagnostic purposes.	Strong
Provide long-term endocrine follow-up and appropriate medical treatment to men with Klinefelter syndrome.	Strong
Perform Y-chromosome microdeletion testing in men with sperm concentrations of ≤ 1 million sperm/mL. Considerit in men with sperm concentrations of < 5 million sperm/mL.	Strong
Inform men with Yq microdeletion and their partners who wish to proceed with intra-cytoplasmic sperm injection (ICSI) that microdeletions will be passed to sons.	Strong
Do not perform testicular sperm extraction in patients with complete deletions that include the AZFa and AZFb regions.	Strong
Test men with structural abnormalities of the vas deferens (unilateral or bilateral absence with no renal anomalies) and their partners for cystic fibrosis transmembrane conductance regulator gene mutations.	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
Perform scrotal US in patients with infertility, as there is a higher risk of testis cancer.	Weak
Discuss invasive diagnostic modalities (e.g., US-guided testicular biopsy with frozen section versus radical orchidectomy versus surveillance) in infertile men with US-detected indeterminate testicular lesions, especially if additional risk factors for malignancy are present in a multidisciplinary team setting.	Weak
Perform transrectal US if a partial or complete distal obstruction is suspected.	Strong

11.4 Special Conditions and Relevant Clinical Entities

*11.4.1 **Cryptorchidism***

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 [1654]. Approximately 30% of undescended testes are non-

palpable and may be located within the abdominal cavity. These guidelines will only deal with management of cryptorchidism in adults.

11.4.1.1 Classification

The classification of cryptorchidism is based on the duration of the condition and the anatomical position of the testes. If the undescended testis has been identified from birth then it is termed congenital while diagnosis of acquired cryptorchidism refers to men in whom testes were situated within the scrotum. Cryptorchidism is categorised as bilateral or unilateral and the location of the testes (inguinal, intra-abdominal or ectopic).

Studies have shown that treatment of congenital and acquired cryptorchidism results in similar hormonal profiles, semen analysis and testicular volumes [1655, 1656]. However, testicular volume and hormonal function are reduced in adults treated for congenital bilateral cryptorchidism compared to unilateral cryptorchidism [1657].

11.4.1.1.1 etiology and pathophysiology

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, including exposure to endocrine disrupting chemicals. Besides cryptorchidism, TDS includes hypospadias, reduced fertility, increased risk of malignancy, and Leydig/Sertoli cell dysfunction [1658]. Cryptorchidism has also been linked with maternal gestational smoking [1659] and premature birth [1660].

11.4.1.1.2 Pathophysiological effects in maldescended testes

11.4.1.1.2.1 Degeneration of germ cells

The degeneration of germ cells in maldescended testes is apparent even after the first year of life and varies, depending on the position of the testes [1661]. During the second year, the number of germ cells declines further. Treatment between the age of six to 18 months is therefore recommended to conserve spermatogonial stem cells, safe guard future spermatogenesis and hormone production, as well as to decrease the risk for tumours [1662]. Surgical treatment is the most effective. Meta-analyses on the use of medical treatment with GnRH and hCG have demonstrated poor success rates [1663, 1664]. It has been reported that hCG treatment may be harmful to future spermatogenesis [1665]. The EAU Guidelines on Paediatric Urology do not recommend endocrine treatment to achieve testicular descent on a routine basis, but endocrine treatment with GnRH analogues in boys with bilateral undescended testis is recommended [1666].

There is increasing evidence to suggest that in unilateral undescended testis, the contralateral normal descended testis may also have structural abnormalities, including smaller volume, softer consistency and reduced markers of future fertility potential (spermatogonia/tubule ratio and dark spermatogonia) [1655, 1667]. This implies that unilateral cryptorchidism may affect the contralateral testis and patients and parents should be counselled appropriately.

11.4.1.1.2.2 Relationship with fertility

Semen parameters are often impaired in men with a history of cryptorchidism [1668]. Early surgical treatment may have a positive effect on subsequent fertility [1669]. In men with a history of unilateral cryptorchidism, paternity is almost equal (89.7%) to that in men without cryptorchidism (93.7%). Outcome studies for untreated bilateral undescended testes revealed that 100% are oligospermic and 75% azoospermic men. Among those successfully treated for bilateral undescended testes, 75% still remain oligospermic and 42% azoospermic [1670]. It is also important to screen for hypogonadism, as this is a potential long-term sequelae of cryptorchidism and could contribute to impaired fertility and potential problems such as testosterone deficiency and MetS [1671].

11.4.1.1.2.3 Germ cell tumours

As a component of TDS, cryptorchidism is a risk factor for testicular cancer and is associated with testicular microcalcifications and intratubular germ cell neoplasia *in situ* (GCNIS), formerly known as carcinoma *in situ* (CIS) of the testes. In 5-10% of testicular cancers, there is a history of cryptorchidism [1672]. The risk of a germ cell tumour is 3.6-7.4 times higher than in the general population and 2-6% of men with a history of cryptorchidism will develop a testicular tumour [1654]. Orchidopexy performed before the onset of puberty has been reported to decrease the risk of testicular cancer [1673]. However, there is evidence to suggest that even men who undergo early orchidopexy still harbour a higher risk of testicular cancer than men without cryptorchidism [1674]. Therefore, all men with a history of cryptorchidism should be warned that they are at increased risk of developing testicular cancer and should perform regular testicular self-examination [1675].

11.4.1.2 Disease management

11.4.1.2.1 Hormonal treatment

Human chorionic gonadotropin or GnRH is not recommended for the treatment of cryptorchidism in adulthood.

11.4.1.2.2 Surgical treatment

In adolescence, removal of an intra-abdominal testis (with a normal contralateral testis) can be recommended, because of the risk of malignancy [1676]. In adults, with a palpable undescended testis and a normal functioning contralateral testis (i.e., biochemically eugonadal), an orchidectomy may be offered as there is evidence that the undescended testis confers a higher risk of GCNIS and future development of a GCT [1677] and regular testicular self-examination is not an option in these patients. In patients with unilateral undescended testis and impaired testicular function on the contralateral testis as demonstrated by biochemical hypogonadism and/or impaired sperm production (infertility), an orchidopexy may be offered to preserve androgen production and fertility. However, based on Panel consensus multiple biopsies of the unilateral undescended testis are recommended at the time of orchidopexy to exclude intra-testicular GCNIS as a prognostic indicator of future development of GCT. As indicated above, the correction of bilateral cryptorchidism, even in adulthood, can lead to sperm production in previously azoospermic men and therefore may be considered in these patients or in patients who place a high value on fertility preservation [1678]. Vascular damage is the most severe complication of orchidopexy and can cause testicular atrophy in 1-2% of cases. In men with non-palpable testes, the post-operative atrophy rate was 12% in cases with long vascular pedicles that enabled scrotal positioning. Post-operative atrophy in staged orchidopexy has been reported in up to 40% of patients [1679]. At the time of orchidectomy in the treatment of GCT, biopsy of the contralateral testis should be offered to patients at high risk for GCNIS (i.e., history of cryptorchidism, < 12 mL testicular volume, poor spermatogenesis [1680]).

11.4.1.3 Summary of evidence recommendations for cryptorchidism

Summary of evidence	**LE**
Cryptorchidism is multifactorial in origin and can be caused by genetic factors and endocrine disruption early in pregnancy.	2a
Cryptorchidism is often associated with testicular dysgenesis and is a risk factor for infertility and GCTs and patients should be counselled appropriately.	2b
Paternity in men with corrected unilateral cryptorchidism is almost equal to men without cryptorchidism.	1b
Bilateral cryptorchidism significantly reduces the likelihood of paternity and patients should be counselled appropriately.	1b

Recommendations	**Strength rating**
Do not use hormonal treatment for cryptorchidism in post-pubertal men.	Strong
Perform simultaneous testicular biopsy, for the detection of intratubular germ cell neoplasia *in situ* (formerly carcinoma *in situ*), if undescended testes are corrected in adulthood.	Strong
Offer adult men with unilateral undescended testis and normal hormonal function/spermatogenesis orchidectomy.	Strong
Offer adult men with unilateral or bilateral undescended testis with biochemical hypogonadism and or spermatogenic failure (i.e., infertility) unilateral or bilateral orchidopexy, if technically feasible.	Weak

11.4.2 ***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 [1681]. The lifetime risk of TGCT varies among ethnic groups and countries. The highest annual incidence of TGCT occurs in Caucasians, and varies from 10/100,000 (e.g., in Denmark and Norway) to 2/100,000 (e.g., in Finland and the Baltic countries). Generally, seminomas and non-seminomas are preceded by GCNIS, and untreated GCNIS eventually progresses to invasive cancer [1682-1684]. There has been a general decline in male reproductive health and an increase in testicular cancer in western countries [1685, 1686]. In almost all countries with reliable cancer registries, the incidence of testicular cancer has increased [1635, 1687]. This has been postulated to be related to TDS, which is a developmental disorder of the testes caused by environmental and/or genetic influences in pregnancy. Endocrine disrupting chemicals have also been associated with sexual dysfunction [1688] and abnormal semen parameters [1689]. These

cancers arise from premalignant gonocytes or GCNIS [1690]. Testicular microcalcification, seen on US, can be associated with TGCT and GCNIS of the testes [1642, 1691, 1692].

11.4.2.1 Testicular germ cell cancer and reproductive function

All men with cancer must be offered sperm cryopreservation prior to the therapeutic use of gonadotoxic agents or ablative surgery that may impair spermatogenesis or ejaculation (i.e., chemotherapy, radiotherapy or retroperitoneal surgery) [1693, 1694].

Men with TGCT have decreased semen quality, even before cancer treatment. Azoospermia has been observed in 24% of men with TGCT [1695] and oligospermia in 50% [1696]. Given that the average ten-year survival rate for testicular cancer is 98% and it is the most common cancer in men of reproductive potential, it is mandatory to include counselling regarding fertility preservation prior to any gonadotoxic treatment [1696, 1697]. All patients should be offered ejaculated semen preservation as the most cost-effective strategy for fertility preservation, or sperm extracted surgically (e.g., c/mTESE). Indeed, treatment for TGCT, including orchidectomy because of the risk of a non-functioning remaining testicle, may have a negative impact on reproductive function [1695]. If shown to be azoospermic or severely oligozoospermic, it is recommended that men should undergo sperm cryopreservation prior to orchidectomy to allow an opportunity to perform a concomitant TESE and prior to further potential gonadotoxic/ablative surgery [1696]. The surgical principles in onco-TESE do not differ from the technique of TESE for men with infertility (e.g., NOA) [1698, 1699]. In this context, it is recommended to organise cryopreservation care delivery networks that enables referral to a urologist adept in TESE.

Rates of under-utilisation of semen analysis and sperm cryopreservation have been reported to be high; resulting in the failure to identify azoospermic or severely oligozoospermic patients at diagnosis who may benefit from advanced fertility-preserving procedures such as oncoTESE. The argument that performing cryopreservation prior to orchidectomy may delay subsequent treatment is not supported by contemporary clinical practice, indeed adverse impact on survival has not been investigated. In this context, orchidectomy should not be unduly delayed if there are no facilities for cryopreservation or there is a potential delay in treatment.

Since chemotherapy and RT are teratogenic, contraception must be used during treatment and for at least six months after completion [1700]. Both chemotherapy and RT can impair fertility. Long-term infertility is rare after RT and dose-cumulative-dependent with chemotherapy. Treatment of TGCT can result in additional impairment of semen quality [1701] and increased sperm aneuploidy up to two years following gonadotoxic therapy [1702]. Spermatogenesis usually recovers one to four years after chemotherapy [74]. Chemotherapy is also associated with DNA damage and an increased SDF rate [1703]. However, sperm aneuploidy levels often decline to pre-treatment levels 18-24 months after treatment [1702]. Several studies reviewing the offspring of cancer survivors have not shown a significant increased risk of genetic abnormalities in the context of previous chemotherapy and radiotherapy [1704].

In addition to spermatogenic failure, patients with TGCT have Leydig cell dysfunction, even in the contralateral testis [1705]. The measurement of pre-treatment levels of testosterone, SHBG, LH and oestradiol may help to stratify those patients at increased risk of hypogonadism and provide a baseline for post-treatment hypogonadism. The risk of hypogonadism may be increased in men treated for TGCT. Likewise, the risk of hypogonadism is increased in the survivors of testicular cancer and serum testosterone levels should be evaluated during the management of these patients [1706]. However, this risk is greatest at 6-12 months post-treatment and suggests that there may be some improvement in Leydig cell function after treatment. Therefore, it is reasonable to delay initiation of testosterone therapy, until the patient shows continuous signs or symptoms of testosterone deficiency [1682]. The risk of low libido and erectile dysfunction is also increased in TGCT patients [1707]. Patients treated for TGCT are also at increased risk of CVD [1703]. Therefore, patients may require a multi-disciplinary therapy approach and, in this context, survivorship programmes incorporating a holistic view of patients considering psychological, medical and social needs could be beneficial. In patients who place a high value on fertility potential, the use of testosterone therapy in men with symptoms suggestive for TDS needs to be balanced with worsening spermatogenesis. In these patients consideration can be given to the use of selective oestrogen receptor modulators (SERMs; e.g., clomiphene) or gonadotrophin analogues (e.g., hCG), although these are off-label treatments in this particular clinical setting.

11.4.2.2 Testicular microcalcification (TM)

Microcalcification inside the testicular parenchyma can be found in 0.6-9% of men referred for testicular US [1708, 1709]. Although the true incidence of TM in the general population is unknown, it is most probably rare. Ultrasound findings of TM have been seen in men with TGCT, cryptorchidism, infertility, testicular torsion

and atrophy, Klinefelter syndrome, hypogonadism, Disorders of Sex Development and varicocele [1659]. The incidence reported seems to be higher with high-frequency US machines [1710]. The relationship between TM and infertility is unclear, but may relate to testicular dysgenesis, with degenerate cells being sloughed inside an obstructed seminiferous tubule and failure of the Sertoli cells to phagocytose the debris. Subsequently, calcification with hydroxyapatite occurs. Testicular microcalcification is found in testes at risk of malignant development, with a reported incidence of TM in men with TGCT of 6-46% [1711-1713]. A systematic review and meta-analysis of case-control studies indicated that the presence of TM is associated with a ~18-fold higher odds ratio for testicular cancer in infertile men (pooled OR: 18.11, 95% CI: 8.09, 40.55; $p < 0.0001$) [1642].

Testicular microcalcification should therefore be considered pre-malignant in this setting and patients counselled accordingly. Testicular biopsies from men with TM have found a higher prevalence of GCNIS, especially in those with bilateral microcalcifications [1714]. However, TM can also occur in benign testicular conditions and the microcalcification itself is not malignant. Therefore, the association of TM and TGCT is controversial and the challenge is to identify those men at risk of harbouring GCNIS and future risk of TGCT. Further investigation of the association between TM and GCNIS requires testicular biopsies in large series of men without signs of TGCT with or without risk factors for TGCT. However, clinicians and patients should be reassured that testicular cancer does not develop in most men with asymptomatic TM [1692]. Men potentially at high-risk of harbouring or developing GCNIS include those with infertility, atrophic testes, undescended testes, history of TGCT, and contralateral TM and it has been suggested that men with these risk factors could be offered testicular biopsy [1686, 1691]. Patients with a history of TGCT and TM in the contralateral testis and sub-fertile patients have been demonstrated to have an increased risk of GCNIS [1692], while there are only a few studies showing a further increase in GCNIS with TM in the context of cryptorchidism [1686, 1709, 1715]. A useful algorithm has been proposed [1686] to stratifying those patients at increased risk of GCNIS who may benefit from testicular biopsy. However, when undertaking a biopsy in this setting, the full risks and complications of adopting this strategy must be explained to the patient.

Decastro *et al.,* [1716] suggested that testicular cancer would not develop in most men with TM (98.4%) during a five-year follow-up. As such, an extensive screening programme would only benefit men at significant risk. In this context it would be prudent to advise patients with TM and risk factors for testicular cancer to at least undergo regular testicular examination. It has been suggested that these patients could also be offered annual physical examination by a urologist and US follow-up, although follow-up protocols may be difficult to implement in this invariably young cohort of patients [1659]. As testicular atrophy and infertility have an association with testicular cancer, some authors recommend biopsy or follow-up US if TM is seen [1686]. However, most patients who are azoospermic will be undergoing therapeutic biopsy (i.e., with the specific purpose of sperm retrieval) and therefore a definitive diagnosis can be made and there is a lack of evidence demonstrating a higher prevalence of testicular cancer in patients with both TM and testicular atrophy. In patients with incidental TM, the risk of GCNIS is low and a logical approach is to instruct patients to perform regular testicular self-examination.

11.4.2.3 Summary of evidence and recommendations for germ cell malignancy and testicular microcalcification

Summary of evidence	**LE**
Testicular germ cell tumour (TGCT) affects approximately 1% of sub-fertile men.	2b
Men with TGCT frequently have impaired sperm parameters at diagnosis.	2a
Semen analysis and sperm cryopreservation before orchidectomy allows the identification of TGCT patients with azoospermia, who may benefit from concomitant surgical sperm retrieval (i.e., onco-TESE).	2b
Treatment of TGCT can result in decreased sperm quality, sperm aneuploidy, increased sperm DNA fragmentation (SDF), hypogonadism, sexual dysfunction and cardiovascular diseases.	2a
Testicular microcalcifications (TM) can be found in men with benign conditions (e.g., cryptorchidism, infertility, testicular torsion and atrophy, Klinefelter syndrome, hypogonadism, DSD, varicocele) and (pre)malignant (GCNIS) or malignant conditions (TGCT).	2a
Testicular microcalcifications are associated with a higher risk of testicular cancer in infertile men.	1a
Men potentially at risk for harbouring or developing GCNIS include those with bilateral TM, infertility, atrophic testes, undescended testes, history of TGCT, and contralateral TM.	2a
Since TGCT will not develop in most men with TM, an extensive screening programme or invasive testicular biopsy is not indicated without additional risk factors.	2b

Recommendations	Strength rating
Advise men with testicular microcalcification (TM) to perform self-examination even without additional risk factors, as this may result in early detection of a 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
Offer testicular biopsy to infertile men with TM, who belong to one of the following higher risk groups: spermatogenic failure (infertility), bilateral TM, atrophic testes (< 12 mL), history of undescended testes and TGCT.	Weak
Perform inguinal surgical exploration with testicular biopsy or offer orchidectomy after multi-disciplinary team meeting and discussion with the patient, if there are suspicious findings on physical examination or US in patients with TM with associated lesions.	Strong
Manage men treated for TGCT in a multi-disciplinary team setting with a dedicated late-effects clinic and survivorship program, since they are at increased risk of developing hypogonadism, sexual dysfunction and cardiovascular risk.	Strong
Perform sperm cryopreservation prior to planned orchidectomy or before additional neoadjuvant or adjuvant oncological therapies.	Strong
Offer onco-testicular sperm extraction (onco-TESE) at the time of radical orchidectomy in men with testicular cancer and azoospermia or severe abnormalities in their semen parameters.	Strong

*11.4.3 **Varicocele***

Varicocele is a common congenital abnormality, that may be associated with the following andrological conditions:

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

11.4.3.1 Classification

The following classification of varicocele [1522] is useful in clinical practice:

- Subclinical: not palpable or visible at rest or during Valsalva manoeuvre, but can be shown by special tests (Doppler US).
- Grade 1: palpable during Valsalva manoeuvre.
- Grade 2: palpable at rest.
- Grade 3: visible and palpable at rest.

11.4.3.2 Diagnostic evaluation

The diagnosis of varicocele is made by physical examination and Scrotal Doppler US is indicated if physical examination is inconclusive or semen analysis remains unsatisfactory after varicocele repair to identify persistent and recurrent varicocele [1522, 1717]. A maximum venous diameter of > 3 mm in the upright position and during the Valsalva manoeuvre and venous reflux with a duration > 2 seconds correlate with the presence of a clinically significant varicocele [1718, 1719]. To calculate testicular volume Lambert's formula (V=L x W x H x 0.71) should be used, as it correlates well with testicular function in patients with infertility and/or varicocele [1720]. Patients with isolated, clinical right varicocele should be examined further for abdominal, retroperitoneal and congenital pathology and anomalies.

11.4.3.3 Basic considerations

11.4.3.3.1 Varicocele and fertility

Varicocele is present in almost 15% of the normal male population, in 25% of men with abnormal semen analysis and in 35-40% of men presenting with infertility [1522, 1721-1723]. The incidence of varicocele among men with primary infertility is estimated at 35–44%, whereas the incidence in men with secondary infertility is 45–81% [1522, 1722, 1723]. Worsening semen parameters are associated with a higher grade of varicocele and age [1722, 1724].

The exact association between reduced male fertility and varicocele is unknown. Increased scrotal temperature, hypoxia and reflux of toxic metabolites can cause testicular dysfunction and infertility due to increased overall survival and DNA damage [1723].

The exact association between reduced male fertility and varicocele is unknown. Increased scrotal temperature, hypoxia and reflux of toxic metabolites can cause testicular dysfunction and infertility due to increased [1721, 1723].

11.4.3.3.2 Varicocelectomy

Varicocele repair has been a subject of debate for several decades. A meta-analysis of RCTs and observational studies in men with only clinical varicoceles has shown that surgical varicocelectomy significantly improves semen parameters in men with abnormal semen parameters, including men with NOA with hypo-spermatogenesis or late maturation (spermatid) arrest on testicular pathology [1721, 1725-1728]. A meta-analysis showed that improvements in semen parameters are usually observed after surgical correction in men with abnormal semen parameters [1729]. Varicocelectomy can also reverse sperm DNA damage and improve OS levels [1721, 1723]. Pain resolution after varicocelectomy occurs in 48-90% of patients [1730]. A systematic review has shown greater improvement in higher-grade varicoceles and this should be taken into account during patient counselling [1731].

In RCTs, varicocele repair in men with a subclinical varicocele was ineffective at increasing the chances of spontaneous pregnancy [1732]. Also, in randomised studies that included mainly men with normal semen parameters no benefit was found to favour treatment over observation. This was also reported in a systematic review and meta-analysis including prospective randomised and non-randomised studies [1733]. In studies including patients with abnormal semen parameters pregnancy rates (OR 1.29, 95% CI 1.00–1.65, p = 0.04) and total sperm count (mean difference: 12.34 million/ml, 95% CI 3.49–21.18, p = 0.006) were significantly improved by varicocele treatment compared with observation. A benefit for varicocele treatment was not found for sperm progressive motility and normal sperm morphology [1733]. When pre- versus post-treatment values were considered in the varicocele treatment arm only a benefit in terms of sperm count, progressive motility, and normal morphology was found [1733]. Another systematic review and meta-analysis evaluated the change in conventional semen parameters after varicocele repair (n=1,426) compared to untreated controls (n=996) [1734]. Significantly improved post-operative semen parameters where reported in treated patients compared to controls with regards to sperm concentration (SMD 1.73; 95% CI 1.12 to 2.34; p<0.001), total sperm count (SMD 1.89; 95% CI 0.56 to 3.22; p < 0.05), progressive sperm motility (SMD 3.30; 95% CI 2.16 to 4.43; p < 0.01), total sperm motility (SMD 0.88; 95% CI 0.03 to 1.73; p=0.04) and normal sperm morphology (SMD 1.67; 95% CI 0.87 to 2.47; p < 0.05) [1734].

A Cochrane review from 2012 concluded that there is evidence to suggest that treatment of a varicocele in men from couples with otherwise unexplained subfertility may improve a couple's chance of spontaneous pregnancy [1735]. Similarly, a Cochrane review from 2021 including 5,384 participants showed that varicocele treatment may improve pregnancy rates compared to delayed or no treatment (RR 1.55, 95% CI 1.06 to 2.26) [1736]. Two meta-analyses of RCTs comparing treatment to observation in men with a clinical varicocele, oligozoospermia and otherwise unexplained infertility, favoured treatment, with a combined OR of 2.39-4.15 (95% CI: 1.56-3.66) and (95% CI: 2.31-7.45), respectively [1728, 1735]. Average time to improvement in semen parameters is up to two spermatogenic cycles [1737, 1738] with spontaneous pregnancy occurring between six and twelve months after varicocelectomy [1739, 1740]. A further meta-analysis has reported that varicocelectomy may improve outcomes following ART in oligozoospermic men with an OR of 1.69 (95% CI: 0.95-3.02) [1741].

11.4.3.3.3 Prophylactic varicocelectomy

In adolescents with a varicocele, there is a significant risk of over-treatment because most adolescents with a varicocele have no problem achieving pregnancy later in life [1742]. Prophylactic treatment is only advised in case of documented testicular growth deterioration confirmed by serial clinical or Doppler US examinations and/or abnormal semen analysis [1743, 1744].

Varicocelectomy and NOA

Several non-randomised studies have suggested that varicocelectomy may lead to sperm appearing in the ejaculate in men with azoospermia. In one such study, microsurgical varicocelectomy in men with NOA led to sperm in the ejaculate post-operatively with an increase in ensuing natural or assisted pregnancies [1745]. Meta-analyses have further corroborated these findings; 468 patients diagnosed with NOA and varicocele underwent surgical varicocele repair or percutaneous embolisation. In patients who underwent varicocelectomy, SRRs increased compared to those without varicocele repair (OR: 2.65; 95% CI: 1.69-4.14; p < 0.001). In 43.9%

of the patients (range: 20.8%-55.0%), sperm were found in post-operative ejaculate. These findings indicate that varicocelectomy in patients with NOA and clinical varicocele is associated with improved SRR, that sperm retrieval may be avoided when sperm reappear in the ejaculate following varicocelectomy. However, the quality of evidence available is low and the risks and benefits of varicocele repair must be discussed fully with the patient with NOA and a clinically significant varicocele prior to embarking upon treatment intervention [1726]. The current understanding of the underlying genetic defects of NOA must be taken into account when interpreting contemporary literature.

Varicocelectomy and hypogonadism
Evidence also suggests that men with clinical varicoceles who are hypogonadal may benefit from varicocele intervention. One meta-analysis studied the efficacy of varicocele intervention by comparing the pre-operative and post-operative serum testosterone of 712 men. The combined analysis of seven studies demonstrated that the mean post-operative serum testosterone improved by 34.3 ng/dL (95% CI: 22.57-46.04, $p < 0.00001$, $I^2 = 0\%$) compared with their pre-operative levels. An analysis of surgery vs. untreated control results showed that mean testosterone among hypoganadal patients increased by 105.65 ng/dL (95% CI: 77.99-133.32 ng/dL), favouring varicocelectomy [1746]. However, results must be treated with caution and adequate cost-benefit analysis must be undertaken to determine the risks and benefits of surgical intervention over testosterone therapy in this setting. Although, varicocelectomy may be offered to hypogonadal men with clinically significant varicoceles, patients must be advised that the full benefits of treatment in this setting must be further evaluated with prospective RCTs.

11.4.3.3.4 Varicocelectomy for assisted reproductive technology and raised SDF
Varicocelectomy can improve sperm DNA integrity [1742, 1747]. A systematic review and meta-analysis analysed data from 1,070 infertile men with clinical varicocele and showed that varicocelectomy was associated with reduced post-operative SDF rates (weighted mean difference 7.23%; 95% CI: 8.86 to 5.59) [1748]. Improvement of DNA integrity was independent from the assay used (SCSA vs. TUNEL vs. SCD) and the surgical technique performed. The estimated weighted mean difference was greater in studies with pre-operative mean fragmentation index ≥ 20% than that in studies with SDF < 20%, suggesting that varicocelectomy might be more beneficial in men with elevated baseline SDF values [1748]. The magnitude of the effect size increased as a function of preoperative SDF levels (coefficient: 0.23; 95%CI: 0.07 to 0.39).

There is now increasing evidence that varicocele treatment may improve DNA fragmentation and outcomes from ART [1741, 1742]. As a consequence, more recently it has been suggested that the indications for varicocele intervention should be expanded to include men with raised DNA fragmentation. If a patient has failed ART (e.g., failure of implantation, embryogenesis or recurrent pregnancy loss) there is an argument that if DNA damage is raised, consideration could be given to varicocele intervention after extensive counselling [1749], and exclusion of other causes of raised SDF [1742, 1750].The dilemma remains as to whether varicocele treatment is indicated in men with raised SDF and normal semen parameters. This decision would need a full and open discussion with the infertile couple, taking into consideration the female partners ovarian reserve and the surgical risks and potential delays in ART associated with varicocele intervention.

In a meta-analysis of non-azoospermic infertile men with clinical varicocele by Estevez *et al.*, four retrospective studies were included of men undergoing ICSI, and included 870 cycles (438 subjected to ICSI with prior varicocelectomy, and 432 without prior varicocelectomy). There was a significant increase in the clinical pregnancy rates (OR 1.59, 95% CI: 1.19-2.12, I2 = 25%) and live birth rates (OR 2.17, 95% CI: 1.55-3.06, I2 = 0%) in the varicocelectomy group compared to the group subjected to ICSI without previous varicocelectomy [1726]. A further study evaluated the effects of varicocele repair and its impact on pregnancy and live birth rates in infertile couples undergoing ART in male partners with oligo-azoospermia or azoospermia and a varicocele [1741]. In 1,241 patients, a meta-analysis demonstrated that varicocelectomy improved live birth rates for the oligospermic (OR = 1.699) men and combined oligo-azoospermic/azoospermic groups (OR = 1.761). Pregnancy rates were higher in the azoospermic group (OR = 2.336) and combined oligo-azoospermic/azoospermic groups (OR 1.760). Live birth rates were higher for patients undergoing IUI after intervention (OR 8.360).

11.4.3.4 Disease management
Several treatments are available for varicocele (Table 38).

Impact on pregnancy rate and semen parameters
Current evidence indicates that microsurgical varicocelectomy is the most effective among the different varicocelectomy techniques [1742, 1751]. A Cochrane review reported that microsurgical subinguinal varicocelectomy probably improves pregnancy rates slightly more compared to other surgical treatments (RR

1.18, 95% CI 1.02 to 1.36) [1736]. A subgroup analysis from a systematic review of prospective randomised and non-randomised studies reported that surgical approach (including all possible surgical techniques) significantly improved pregnancy rates and sperm concentration as compared with controls, while the same was not demonstrated for radiological treatment [1733]. However, the most recent Cochrane review showed inconclusive results about the effect of surgical vs. radiological treatment on pregnancy rates and varicocele recurrence [1736]. There are no large prospective RCTs comparing the efficacy of the various interventions for varicocele.

Complications

Microsurgical repair results in fewer complications and lower recurrence rates compared to the other techniques [1736, 1752, 1753]; however, this procedure, requires microsurgical training. The various other techniques are still considered viable options, although recurrences and hydrocele formation appear to be higher [1753].

Radiological techniques (sclerotherapy and embolisation) are minimally invasive approaches for varicocele treatment. Although higher recurrence rates have been reported compared to microscopic varicocelectomy [1754], a meta-analysis showed that the incidence of varicocele recurrence was similar after surgical ligation and sclero-embolisation [1754]. In terms of complications, a meta-analysis of twelve studies comparing 738 cases of surgical ligation vs. 647 cases of sclero-embolisation, showed that overall complications rate did not differ significantly between the groups (OR 1.48; 95% CI 0.86–2.57, p = 0.16) [1754]. The incidence of post-operative hydrocele is significantly higher after surgical ligation than sclero-embolisation, but radiological techniques are associated with higher incidence of post-operative orchiepidydimitys [1754].

Robot-assisted varicocelectomy has a similar success rate compared to the microscopic varicocelectomy technique, although larger prospective randomised studies are needed to establish the most effective method [1755-1757].

Table 38: Recurrence and complication rates associated with treatments for varicocele

Treatment	Recurrence/ Persistence %	Overall complications	Specific Complications
Antegrade sclerotherapy [1757, 1758]	5-9	Hydrocele (5.5%), haematoma, infection, scrotal pain, testicular atrophy, epididymitis	Technical failure 1-9%, left-flank erythema
Retrograde sclerotherapy [1759, 1760]	6-9.8	Hydrocele (3.3%) wound infection, scrotal pain	Technical failure 6-7.5%, adverse reaction to contrast medium, flank pain, persistent thrombophlebitis, venous perforation
Retrograde embolization [1759, 1761]	3-11	Hydrocele (10%) haematoma, wound infection	Technical failure 7-27%, pain due to thrombophlebitis, radiological complications (e.g., reaction to contrast media), misplacement or migration of coils (to femoral vein or right atrium), retroperitoneal haemorrhage, fibrosis, ureteric obstruction, venous perforation
Open operation			
Scrotal operation	-	Testicular atrophy, arterial damage with risk of devascularisation and testicular gangrene, scrotal haematoma, post-operative hydrocele	
Inguinal approach [1762, 1763]	2.6-13	Hydrocele (7.3%), testicular atrophy, epididymo-orchitis, wound complications	Post-operative pain due to incision of external oblique fascia, genitofemoral nerve damage
Open retroperitoneal high ligation [1751, 1764]	15-29	Hydrocele (5-10%), testicular atrophy, scrotal oedema	External spermatic vein ligation failure

Microsurgical inguinal or Subinguinal [1752, 1762, 1765, 1766]	0.4	Hydrocele (0.44%), scrotal haematoma	
Laparoscopy [1724, 1751, 1752, 1767, 1768]	3-6	Hydrocele (7-43%) epididymitis, wound infection, testicular atrophy due to injury of testicular artery, bleeding	External spermatic vein ligation failure, intestinal, vascular and nerve damage; pulmonary embolism; pneumo-scrotum; peritonitis; post-operative pain in right shoulder (due to diaphragmatic stretching during pneumo-peritoneum)

11.4.3.5 Summary of evidence and recommendations for varicocele

Summary of evidence	**LE**
The presence of varicocele in some men is associated with progressive testicular damage from adolescence onwards and a consequent potential reduction in fertility.	2a
Although the treatment of varicocele in adolescents may be effective, there is a significant risk of over-treatment as the majority of boys with a varicocele will have no fertility problems later in life.	3
Varicocele repair may be effective in men with abnormal semen parameters, a clinical varicocele and otherwise unexplained male factor infertility.	1a
Varicocele repair may improve pregnancy rates and sperm concentration in adult infertile men with abnormal semen analyses, while benefits in sperm motility and normal morphology are less clear.	1a
Although there are no prospective randomised studies evaluating this, meta-analyses have suggested that varicocele repair is associated with sperm appearing in the ejaculate of men with non-obstructive azoospermia.	2
Microscopic approach (inguinal/subinguinal) may have lower recurrence and complications rates than non-microscopic approaches (retroperitoneal and laparoscopic), although no RCTs are available yet.	2a
Varicocele is associated with raised sperm DNA fragmentation (SDF) and intervention has been shown to reduce SDF and may improve the outcomes from ART.	2a

Recommendations	**Strength rating**
In adolescents offer surgery for varicocele associated with a persistent small testis (size difference of > 2 mL or 20%), which should be confirmed on two subsequent visits performed six months apart.	Strong
Do not treat varicocele in infertile men who have normal semen analysis and in men with a sub-clinical varicocele.	Strong
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 of assisted reproductive techniques, including recurrent pregnancy loss, failure of embryogenesis and implantation.	Weak

*11.4.4 **Male accessory gland infections and infertility***

11.4.4.1 Introduction

Infection of the male urogenital tract is a potentially curable cause of male infertility [1769-1771]. The WHO considers urethritis, prostatitis, orchitis and epididymitis to be male accessory gland infections (MAGIs) [1769]. The effect of symptomatic or asymptomatic infections on sperm quality is contradictory [1772]. A systematic review of the relationship between sexually transmitted infections, such as those caused by *Chlamydia trachomatis,* genital mycoplasmas, *Neisseria gonorrhoeae, Trichomonas vaginalis* and viruses, and infertility was unable to draw a strong association between sexually transmitted infections and male infertility due to the limited quality of reported data [1773].

11.4.4.2 Diagnostic evaluation

11.4.4.2.1 Semen analysis

Semen analysis (see Section 11.3.2) clarifies whether the prostate is involved as part of a generalised MAGI and provides information regarding sperm quality.

11.4.4.2.2 Microbiological findings

After exclusion of UTI (including urethritis), > 10^6 peroxidase-positive white blood-cells (WBCs) per millilitre of ejaculate indicate an inflammatory process. Semen culture or polymerase chain reaction (PCR) analysis should be performed for common urinary tract pathogens in all suspected cases of genitourinary tract infections. A concentration of > 10^3 CFU/mL urinary tract pathogens in the ejaculate is indicative of significant bacteriospermia [1774]. The sampling should be delivered the same day to the laboratory because the sampling time can influence the rate of positive micro-organisms in semen and the frequency of isolation of different strains [1775]. The ideal diagnostic test for isolating C. trachomatis in semen has not yet been established [1776], but the most accurate method is PCR [1777-1779].

Historical data show that *Ureaplasma urealyticum* is pathogenic only in high concentrations (> 10^3 CFU/mL ejaculate). Fewer than 10% of samples analysed for *Ureaplasma* exceeded this concentration [1780]. Normal colonisation of the urethra hampers the significance of mycoplasma-associated urogenital infections, using samples such as the ejaculate [1781].

A meta-analysis indicated that Ureaplasma parvum and *Mycoplasma genitalium* were not associated with male infertility, but a significant relationship existed between U. urealyticum (OR: 3.03 95% CI: 1.02–8.99) and *Mycoplasma hominis* (OR: 2.8; 95% CI: 0.93– 3.64) [1782]. For these reasons, the treatment is not always recommended.

The prevalence of human papilloma virus (HPV) in the semen ranges from 2 to 31% in the general population and is higher in men with unexplained infertility (10-35.7%) [1783, 1784]. Systematic reviews have reported an association between male infertility, poorer pregnancy outcomes and semen HPV positivity [1785-1787]. However, data still needs to be prospectively validated to clearly define the clinical impact of HPV infection in semen. Additionally, seminal presence of Herpes Simplex virus (HSV)-2 in infertile men may be associated with lower sperm quality compared to that in HSV-negative infertile men [1772]. However, it is unclear if anti-viral therapy improves fertility rates in these men.

11.4.4.2.3 White blood cells

The clinical significance of an increased concentration of leukocytes in the ejaculate is controversial [1788]. Although leukocytospermia is a sign of inflammation, it is not necessarily associated with bacterial or viral infections, and therefore cannot be considered a reliable indicator [1789]. According to the WHO classification, leukocytospermia is defined as > 10^6 WBCs/mL. Only two studies have analysed alterations of WBCs in the ejaculate of patients with proven prostatitis [1790, 1791]. Both studies found more leukocytes in men with prostatitis compared to those without inflammation (CPPS, type NIH 3b). Furthermore, leukocytospermia should be further confirmed by performing a peroxidase test on the semen. There is currently no evidence that treatment of leukocytospermia alone without evidence of infective organisms improves conception rates [1792].

11.4.4.2.4 Sperm quality

The deleterious effects of chronic prostatitis (CP/CPPS) on sperm density, motility and morphology have been demonstrated in a recent systematic review based on case-controlled studies [1793]. Both *C. trachomatis* and *Ureoplasma spp.* can cause decreased sperm density, motility, altered morphology and increased DNA damage. Data from a retrospective cross-sectional study showed that *U. urealyticum* was the most frequent single pathogen in semen of asymptomatic infertile men; a positive semen culture was both univariably ($p < 0.001$) and multi-variably ($p = 0.04$) associated with lower sperm concentration [1794]. Human papilloma virus is associated with changes in semen density, sperm motility and sperm DNA damage [1783, 1784]. *Mycoplasma spp.* can cause decreased motility and development of antisperm antibodies [1772].

11.4.4.2.5 Seminal plasma alterations

Seminal plasma elastase is a biochemical indicator of polymorphonuclear lymphocyte activity in the ejaculate [1771, 1795, 1796]. Various cytokines are involved in inflammation and can influence sperm function. Several studies have investigated the association between interleukin (IL) concentration, leukocytes, and sperm function through different pathways, but no correlations have been found [1797-1799]. The prostate is the main site of origin of IL-6 and IL-8 in the seminal plasma. Cytokines, especially IL-6, play an important role in the male

accessory gland inflammatory process [1800]. However, elevated cytokine levels do not depend on the number of leukocytes in expressed prostatic secretion [1801].

11.4.4.2.6 Glandular secretory dysfunction

The secretory function of the prostate gland can be evaluated by measuring seminal plasma pH, citric acid, or γ-glutamine transpeptidase levels, although these parameters are not evaluated anymore in numerous laboratories; the seminal plasma concentrations of these factors are usually altered during infection and inflammation. However, they are not recommended as diagnostic markers for MAGIs [1802].

11.4.4.2.7 Reactive oxygen species

Reactive oxygen species may be increased in infertile patients with asymptomatic *C. trachomatis* and *M. hominis* infection, with subsequent decrease in ROS upon antibiotic treatment. However, ROS levels in infertile patients with asymptomatic *C. trachomatis* and *M. hominis* in the semen are low, making it difficult to draw any firm conclusions [1803]. Chronic urogenital infections are also associated with increased leukocyte numbers [1804]. However, their biological significance in prostatitis remains unclear [1771].

11.4.4.2.8 Disease management

Only antibiotic therapy of chronic bacterial prostatitis (NIH II according to the classification) has provided symptomatic relief, eradication of micro-organisms, and a decrease in cellular and humoral inflammatory parameters in urogenital secretions. Although antibiotics might improve sperm quality [1805], there is no evidence that treatment of CP/CPPS increases the probability of natural conception [1771, 1806].

Asymptomatic presence of *C. trachomatis* and *M. hominis* in the semen can be correlated with impaired sperm quality, which recovers after antibiotic treatment. However further research is required to confirm these findings [1803].

11.4.4.3 Epididymitis

Inflammation of the epididymis causes unilateral pain and swelling, usually with acute onset. Among sexually active men aged < 35 years, epididymitis is most often caused by *C. trachomatis* or *N. gonorrhoea* [1807, 1808]. Sexually transmitted epididymitis is usually accompanied by urethritis. Non-sexually transmitted epididymitis is associated with UTIs and occurs more often in men aged > 35 years [1809].

11.4.4.3.1 Diagnostic evaluation

11.4.4.3.1.1 Ejaculate analysis

Ejaculate analysis according to WHO Laboratory Manual for the Examination and Processing of Human Semen (6th edn) criteria, may indicate persistent inflammatory activity. Transient reductions in sperm counts and progressive sperm motility can be observed [1807, 1810, 1811]. Semen culture might help to identify pathogenic micro-organisms. Development of stenosis of the epididymal ducts, reduction of sperm count, and azoospermia are more important potential sequelae to consider in the follow-up of bilateral epididymitis (see Section 11.3.2).

11.4.4.3.1.2 Disease management

Treatment of epididymitis results in:

- microbiological cure of infection;
- improvement of clinical signs and symptoms;
- prevention of potential testicular damage;
- prevention of transmission;
- decrease of potential complications (e.g., infertility or chronic pain).

Patients with epididymitis known or suspected to be caused by *N. gonorrhoeae* or *C. trachomatis* must be told to also refer their sexual partners for evaluation and treatment [1812].

11.4.4.4 Summary of evidence and recommendation for male accessory gland infections

Summary of evidence	**LE**
Male accessory gland infections are not clearly associated with impaired natural conception.	3
Antibiotic treatment often only eradicates micro-organisms; it has no positive effect on inflammatory alterations and cannot reverse functional deficits and anatomical abnormalities.	2a

Although antibiotic treatment for MAGIs may result in improvement in sperm quality, it does not enhance the probability of conception.	2a
Data are insufficient to conclude whether antibiotics and antioxidants for the treatment of infertile men with leukocytospermia improve fertility outcomes.	3

Recommendations	Strength rating
Treating male accessory gland infections may improve sperm quality, although it does not necessarily improve the probability of increasing conception.	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

11.5 Non-Invasive Male Infertility Management

11.5.1 ***Empirical treatments***

11.5.1.1 Life-style

Environmental and lifestyle factors may contribute to male infertility acting additively on a susceptible genetic background [81, 1640]. Hence, lifestyle improvement can have a positive effect on sperm parameters.
This includes:

- Weight loss: non-controlled studies have suggested that weight loss can result in improved sperm parameters [81, 1813, 1814]. However, data derived from RCTs are more conflicting. A meta-analysis of 28 cohort studies and 1,022 patients, documented that bariatric surgery did not improve sperm quality and function in morbidly obese men [1815]. Data on ART outcomes are lacking. Furthermore weight loss can improve obesity-related secondary hypogonadism, which may result in better outcomes in couples seeking medical care for infertility [1813, 1815].
- Physical activity: a meta-analysis has documented that moderate-intensity (20–40 metabolic equivalents [METs]/week) or even high-intensity (40–80 METs-h/week) recreational physical activity can result in better semen parameters [1816]. Moreover, physical activity might improve hormonal profile [1813].
- Smoking: data derived from a large meta-analysis of 20 studies with 5,865 participants showed a negative association between smoking and sperm parameters [1817].

Alcohol consumption: Data derived from a recent meta-analysis including 15 cross-sectional studies and 16,395 men suggested that moderate alcohol does not adversely affect semen parameters, whereas high alcohol intake can have a detrimental effect on male fertility [1818] heavy chronic alcohol consumption (defined as > 2 drinks/ day [1819]) can reduce testosterone levels [1819].

11.5.1.2 Antioxidant treatment

Oxidative stress is considered to be of the most important contributing factors in the pathogenesis of idiopathic infertility. Reactive oxygen species, the final products of OS, can impair sperm function acting at several levels, including plasma membrane lipid peroxidation, which can affect sperm motility, the acrosome reaction and chromatin maturation leading to increased SDF [1820]. Accordingly, seminal levels of ROS have been negatively associated with ART outcomes [1821]. Despite this, evidence for the role of antioxidant therapy in male infertility is still conflicting. A Cochrane systematic review and meta-analysis including 34 RCTs and 2,876 couples using various antioxidant compounds, it was concluded that antioxidant therapy had a positive impact on live-birth and pregnancy rates in sub-fertile couples undergoing ART cycles [1822]. Similar results were also reported in a meta-analysis including 61 studies with 6,264 infertile men, aged 18-65 years [1823]. However, the quality of the reported studies is poor. The Males, Antioxidants, and Infertility (MOXI) trial found that antioxidants did not improve semen parameters or DNA integrity compared to placebo among infertile men with male factor infertility. Moreover, cumulative live-birth rate did not differ at 6 months between the antioxidant and placebo groups (15% vs. 24%) [1824]. No clear conclusions were possible regarding the specific antioxidants to use or and/or therapeutic regimes for improving sperm parameters and pregnancy rate [1823].

11.5.1.3 Selective oestrogen receptor modulators

Selective oestrogen receptor modulators (SERMs) block oestrogen receptors at the level of the hypothalamus, which results in stimulation of GnRH secretion, leading to an increase in pituitary gonadotropin release and stimulation of spermatogenesis [1825]. Meta-analysed data derived from eleven RCTs showed that SERMs significantly increased pregnancy rate, sperm and hormonal parameters [1826]. Similar results were confirmed in the latest updated meta-analysis of sixteen studies [1825]. However, previous SR failed to find any association between SERMs and pregnancy rate [1827]. It should be recognised that the quality of the papers considered was low and only a few studies were placebo-controlled. In conclusion, although some positive results relating

to the use of SERMs in men with idiopathic infertility have been reported, no conclusive recommendations can be drawn due to poor quality of the available evidence. Furthermore, complications from the use of SERMs were under-reported.

11.5.1.4 Aromatase inhibitors

Aromatase, a cytochrome p450 enzyme, is present in the testes, prostate, brain, bone, and adipose tissue of men; it converts testosterone and androstenedione to oestradiol and oestrone, respectively. Oestradiol negatively feeds back on the hypothalamus and pituitary to reduce gonadotropic secretions, ultimately affecting spermatogenesis. In this context, aromatase inhibitors (AIs) may decrease oestrogen production by reversibly inhibiting cytochrome p450 isoenzymes 2A6 and 2C19 of the aromatase enzyme complex inhibiting the negative feedback of oestrogen on the hypothalamus resulting in stronger GnRH pulses that stimulate the pituitary to increase production of FSH [1828-1831]. Aromatase activity has been associated with male infertility characterised by testicular dysfunction with low serum testosterone and/or testosterone to oestradiol ratio. In this context, AIs have been reported to increase endogenous testosterone production and improve spermatogenesis in the setting of infertility as an off-label option for treatment [1832]. Either steroidal (testolactone) and non-steroidal (anastrozole and letrozole) AIs significantly improve hormonal and semen parameters in infertile men, with a safe tolerability profile, although prospective RCTs are necessary to better define the efficacy of these medications in this clinical setting [1830, 1832].

*11.5.2 **Summary of evidence and recommendation for Non-Invasive Male Infertility Management***

Summary of evidence	**LE**
In infertile men life style factors including obesity, low physical activity, smoking and high alcohol intake are associated with decreased sperm quality.	2a
In men with idiopathic oligo-astheno-teratozoospermia, life-style changes including weight loss and increased physical activity, smoking cessation and alcohol intake reduction may improve sperm quality and the chances of conception.	2a
No conclusive data are available regarding the beneficial treatment with antioxidants in men with idiopathic infertility, although they may improve semen parameters.	1b
No conclusive data are available regarding the use of selective oestrogen receptor modulators (SERMs) in men with idiopathic infertility.	1b
No conclusive data are available regarding the use of steroidal (testolactone) or nonsteroidal (anastrozole and letrozole) aromatase inhibitors in men with idiopathic infertility.	1b

Recommendations	**Strength rating**
Inform infertile men about the detrimental effects of obesity, low physical activity, smoking and high alcohol intake on sperm quality and testosterone levels. Therefore, advise infertile men to improve life style factors to improve their chances of conception.	Strong
Do not routinely treat patients with idiopathic infertility with antioxidants, selective oestrogen receptor modulators (SERMs) or aromatase inhibitors (Ais).	Weak

*11.5.3 **Hormonal therapy***

11.5.3.1 Secondary hypogonadism

(A brief discussion on Pre-Pubertal-Onset can be found in Appendix 12, online supplementary evidence).

Post-Pubertal Onset: Human Chorionic Gonadotrophin (hCG) alone is usually required first to stimulate spermatogenesis. A starting dose of 250 IU hCG twice weekly is suggested, and if normal testosterone levels are reached, hCG doses may be increased up to 2,000 IU twice weekly. Again, semen analysis should be performed every three months to assess response, unless conception has taken place. If there is a failure of stimulation of spermatogenesis, then FSH can be added (75 IU three times per week, increasing to 150 IU three times per week if indicated). Similarly, combination therapy with FSH and hCG can be administered from the beginning of treatment, promoting better outcomes in men with HH [121]. No difference in outcomes were observed when urinary-derived, highly purified FSH was compared to recombinant FSH [121].

Greater baseline testicular volume is a good prognostic indicator for response to gonadotrophin treatment while previous testosterone therapy can have a negative impact on gonadotropin treatment outcomes in men with hypogonadotropic hypogonadism [1833]. However, this observation has been subsequently refuted by a

meta-analysis that did not confirm a real negative role of testosterone therapy in terms of future fertility in this specific setting [121].

11.5.3.1.1 Secondary hypogonadism due to hyperprolactinemia

In the presence of hyperprolactinaemia, causing suppression of gonadotrophins resulting in sub-fertility the treatment independent of aetiology (including a pituitary adenoma) is dopamine agonist therapy or withdrawal of the drug that causes the condition. Dopamine agonists used include bromocriptine, cabergoline and quinagolide.

11.5.3.2 Primary Hypogonadism

There is no substantial evidence that gonadotrophin therapy has any beneficial effect in the presence of classical testicular failure. Likewise, there are no data to support the use of other hormonal treatments (including SERMs or AIs) in the case of primary hypogonadism to improve spermatogenesis [82, 1834].

11.5.3.3 Idiopathic Male Factor Infertility

There is some evidence that FSH treatment increases sperm parameters in idiopathic oligozoospermic men with FSH levels within the normal range (generally 1.5 – 8 mIU/mL)[1835]. It has also been reported that FSH may improve SDF rates as well as ameliorating AMH and inhibin levels [1836-1839]. High-dose FSH therapy is more effective in achieving a testicular response than lower doses are [1840]. A Cochrane review including six RCTs with 456 participants, different treatment protocols and follow-up periods concluded that FSH treatment resulted in higher live-birth and pregnancy rates compared with placebo or no treatment. However, no significant difference among groups was observed when ICSI or IUI were considered [1841]. In a meta-analysis including 15 trials with > 1,200 patients, similar findings after FSH treatment were observed in terms of both spontaneous pregnancies and pregnancies after ART [1842]. A further study showed that in azoospermic men undergoing TESE-ICSI there were improved SRRs and higher pregnancy and fertilisation rates in men treated with FSH compared to untreated men [1843]. In men with NOA, combination hCG/FSH therapy was shown to increase SRR in only one study [1844]. Human chorionic gonadotrophin alone prior to TESE in NOA has not been found to have any benefit on SRRs [1845]. Overall the evidence for the use of hormone therapy prior to SSR is limited and treatment should be confined to clinical trials and not used routinely in clinical practice.

11.5.3.4 Anabolic Steroid Abuse

Oligospermia or azoospermia as a result of anabolic abuse should be treated initially by withdrawal of the anabolic steroid. There is no common indication for treating this disorder; the management is based on case reports and clinical experience. Usually, adequate sperm numbers and quality will improve over a six to twelve-month period from cessation. If after this interval the condition persists, then hCG without or in combination with FSH as an alternative to clomiphene can be used to stimulate spermatogenesis [1846].

11.5.3.5 Summary of evidence and recommendations for treatment of male infertility with hormonal therapy

Summary of evidence	**LE**
Follicle stimulating hormone (FSH) promotes spermatogenesis and testicular growth during puberty. Human chorionic gonadotropin (hCG) acts like luteinizing hormone (LH) and is used to stimulate intratesticular testosterone production and spermatogenesis in men with hypopituitarism after puberty.	2b
Prepubertal secondary hypogonadism requires the association of FSH and hCG or pulsatile GnRH, even if its use is limited by the difficult administration.	1b
Secondary hypogonadism in adults can be effectively treated with subcutaneous hCG and FSH.	2b
The use of GnRH therapy is more expensive and does not offer any advantages compared to gonadotropins for the treatment of hypogonadotropic hypogonadism.	3
In postpubertal forms of secondary hypogonadism, sequential use of hCG and FSH or their combination from the beginning are options.	1b
Testicular volume is one of the main predictors of response to gonadotropin therapy in men with hypogonadotropic hypogonadism.	2a
Dopamine agonists are used to treat hyperprolactinaemia.	2a
FSH therapy (any formulation) has been associated with improvement in sperm quality and increased spontaneous and assisted pregnancy rates in idiopathic infertile males.	2a
No conclusive recommendations can be given on the use of high-dose FSH in men with idiopathic infertility and prior (m)TESE and therefore cannot be routinely advocated.	2a
Testosterone therapy is contraindicated in infertile men.	1a

Recommendations	Strength rating
Induce spermatogenesis in men with congenital or acquired hypogonadotropic hypogonadism who wish to conceive by effective drug therapy (hCG; human menopausal gonadotropins; recombinant FSH; highly purified FSH).	Strong
Use FSH treatment in men with idiopathic oligozoospermia and FSH values within the normal range, to ameliorate spermatogenesis outcomes.	Weak
Do not treat idiopathic infertility with high dose FSH.	Weak
Do not start hormonal stimulation prior TESE in men with non-obstructive azoospermia (NOA) outside clinical trials.	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
Offer dopamine agonist therapy in men with hyperprolactinemia to improve sperm quality.	Weak
Withdraw anabolic steroids in infertile men for six to twelve months month before considering treatment with selective oestrogen receptor modulators (SERMS) or gonadotrophin therapy to induce spermatogenesis.	Weak

11.6 Invasive Male Infertility Management

*11.6.1 **Obstructive azoospermia***

Obstructive azoospermia (OA) is the absence of spermatozoa in the sediment of a centrifuged sample of ejaculate due to obstruction [1769]. OA occurs in 20-40% of men with azoospermia [1847, 1848] and it is characterised by normal FSH values, testes of normal size and epididymal enlargement [1849]. The most common causes of OA are reported in Table 39.

Table 39: Causes of obstruction of the genitourinary system

Intratesticular (15%)
Epididymis (30-67%)
Infection (acute/chronic epididymitis)
Trauma
Post-surgical iatrogenic obstruction (i.e., MESA, hydrocelectomy or other scrotal surgery)
Congenital epididymal obstruction (usually manifests as congenital bilateral absence of the vas deferens [CBAVD])
Other congenital forms of epididymal obstruction (Young's syndrome)
Vas deferens
Vasectomy
Vasotomy/vasography (with improper technique)
Post-surgical iatrogenic obstruction (i.e., scrotal surgery or herniorraphy)
Congenital unilateral (CUAVD) or bilateral absence of the vas deferens (CBAVD)
Ejaculatory ducts
Cysts (Mullerian utricular, prostatic or seminal vesicular)
Infection (acute/chronic epididymitis)
Traumatic
Postsurgical iatrogenic obstruction
Functional obstruction
Idiopathic/acquired local neurogenic dysfunction

11.6.1.1 Diagnostic evaluation

Clinical history-taking should follow the investigation and diagnostic evaluation of infertile men (See Section 11.3). Risk factors for obstruction include prior surgery, iatrogenic injury during inguinal herniorrhaphy, orchidopexy or hydrocelectomy.

11.6.1.1.1 Clinical examination

Clinical examination should follow the guidelines for the diagnostic evaluation of infertile men. Obstructive azoospermia is indicated by at least one testis with a volume > 15 mL, although a smaller volume may be found in some patients with:

- obstructive azoospermia and concomitant partial testicular failure;
- enlarged and dilated epididymis;
- nodules in the epididymis or vas deferens;
- absence or partial atresia of the vas deferens.

When semen volume is low, or absent a search must be made for spermatozoa in urine after ejaculation. Absence of spermatozoa and immature germ cells in the semen pellet suggest complete seminal duct obstruction.

11.6.1.1.2 Hormone levels

Hormones including FSH and inhibin-B should be normal, but do not exclude other causes of testicular azoospermia (e.g., NOA). Although inhibin-B concentration is a good index of Sertoli cell integrity reflecting closely the state of spermatogenesis, its diagnostic value is no better than that of FSH and its use in clinical practice has not been widely advocated [1850].

11.6.1.1.3 Genetic testing

Cystic fibrose transmembrane conductance regulator gene testing should be performed in any patient with unilateral or bilateral absence of the vas deferens or seminal vesicle agenesis [1851].

11.6.1.1.4 Testicular biopsy

Testis biopsies (including fine needle aspiration [FNA]) without performing simultaneously a therapeutic sperm retrieval are not recommended, as this will require a subsequent invasive procedure. Furthermore, even patients with extremes of spermatogenic failure (e.g., Sertoli Cell Only syndrome [SCOS]) may harbour focal areas of spermatogenesis [1852, 1853].

11.6.1.2 Disease management

11.6.1.2.1 Sperm retrieval

Intratesticular obstruction

Only TESE allows sperm retrieval in these patients and is therefore recommended.

Epididymal obstruction

Microsurgical epididymal sperm aspiration (MESA) or percutaneous epididymal sperm aspiration (PESA) [1854] is indicated in men with CBAVD. Testicular sperm extraction and percutaneous techniques, such as testicular sperm aspiration (TESA), are also options [1855]. The source of sperm used for ICSI in cases of OA and the aetiology of the obstruction do not affect the outcome in terms of fertilisation, pregnancy, or miscarriage rates [1856]. Usually, one MESA procedure provides sufficient material for a number of ICSI cycles [1857] and it produces high pregnancy and fertilisation rates [1858]. Overall, pregnancy outcomes from ICSI in men with OA are comparable between epididymal and testicular sperm and also between fresh and frozen–thawed epididymal sperm [1859]. However, these results are from studies of low evidence [1575].

In patients with OA due to acquired epididymal obstruction and with a female partner with good ovarian reserve, microsurgical epididymovasostomy (EV) is recommended [1860]. Epididymovasostomy can be performed with different techniques such as end-to-site and intussusception [1861]. Anatomical recanalisation following surgery may require 3-18 months. A systematic review indicated that the time to patency in EV varies between 2.8 to 6.6 months. Reports of late failure are heterogeneous and vary between 1 and 50% [1862]. Before microsurgery, and in all cases in which recanalisation is impossible, epididymal spermatozoa should be aspirated intra-operatively by MESA and cryopreserved to be used for subsequent ICSI procedures [1863]. Patency rates range between 65% and 85% and cumulative pregnancy rates between 21% and 44% [1864, 1865]. Recanalisation success rates may be adversely affected by pre-operative and intra-operative findings. Robot-assisted EV has similar success rates but larger studies are needed [1866].

Vas deferens obstruction after vasectomy

Vas deferens obstruction after vasectomy requires microsurgical vasectomy reversal. The mean post-procedural patency and pregnancy rates weighted by sample size were 90-97% and 52-73%, respectively [1864, 1865]. The average time to patency is 1.7-4.3 months and late failures are uncommon (0-12%) [1862]. Robot-assisted vasovasostomy has similar success rates, and larger studies, including cost-benefit analysis, are needed to establish its benefits over standard microsurgical procedures [1866].

The absence of spermatozoa in the intra-operative vas deferens fluid suggests the presence of a secondary epididymal obstruction, especially if the seminal fluid of the proximal vas deferens has a thick "toothpaste" appearance; in this case microsurgical EV may be indicated [1867-1869]. Simultaneous sperm retrieval may be performed for future cryopreservation and use for ICSI; likewise, patients should be counselled appropriately.

Vas deferens obstruction at the inguinal level

It is usually impossible to correct large bilateral vas deferens defects, resulting from involuntary excision of the vasa deferentia during hernia surgery in early childhood or previous orchidopexy. In these cases, TESE/MESA/PESA or proximal vas deferens sperm aspiration [1870] can be used for cryopreservation for future ICSI.

Ejaculatory duct obstruction

The treatment of ejaculatory duct obstruction (EDO) depends on its aetiology. Transurethral resection of the ejaculatory ducts (TURED) can be used in post-inflammatory obstruction and cystic obstruction [1863, 1871]. Resection may remove part of the verumontanum. In cases of obstruction due to a midline intraprostatic cyst, incision, unroofing or aspiration of the cyst is required [1863, 1871].

Pregnancy rates after TURED are 20-25% [1696, 1871, 1872]. Complications following TURED include epididymitis, UTI, gross haematuria, haematospermia, azoospermia (in cases with partial distal ejaculatory duct obstruction) and urine reflux into the ejaculatory ducts and seminal vesicles [1871].

Alternative therapies for EDO include, seminal vesiculoscopy to remove debris or calculi and balloon dilation and laser incision for calcification on TRUS [1873]. The alternatives to TURED are MESA, PESA, TESE, proximal vas deferens sperm aspiration and seminal vesicle-ultrasonically guided aspiration.

11.6.1.3 Summary of evidence and recommendations for obstructive azoospermia

Summary of evidence	LE
Obstructive lesions of the seminal tract are frequent in azoospermic or severely oligozoospermic patients, usually with normal-sized testes and normal reproductive hormones.	3

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 and 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

11.6.2 ***Non-obstructive azoospermia***

Non-obstructive azoospermia (NOA) is defined as the absence of sperm at the semen analysis after centrifugation, with usually a normal ejaculate volume. This finding should be confirmed at least at two consecutives semen analyses [1558]. 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.

11.6.2.1 Investigation of non-obstructive azoospermia

Clinical history-taking and clinical examination should follow the investigation and diagnostic evaluation of infertile men (See Section 11.3). Non-obstructive azoospermia can be the first sign of pituitary or germ cell tumours of the testis [1874-1876]. Patients with NOA have been shown to be at increased risk of long-term chronic non-communicable diseases (e.g., cardio-metabolic diseases, cancer) and mortality [1877-1882]. Therefore, investigation of infertile men provides an opportunity for long-term risk stratification for other comorbid conditions [1883]. A complete hormonal investigation and scrotal US are important in the diagnostic work-up of NOA men [1884, 1885].

Concomitant hypogonadism, has been found in about 30% of patients with NOA [288, 1884, 1885]. Biochemical evaluation should be performed to differentiate the types of hypogonadism (i.e., hypogonadotropic hypogonadism vs. hypergonadotropic vs. compensated hypogonadism) as this will determine different therapeutic strategies to treat the hypogonadal male [1886].

Testicular volume is usually low in NOA patients and scrotal US may show signs of testicular dysgenesis (e.g., non-homogeneous testicular architecture and/or microcalcifications) and testicular tumours. Testicular volume may be a predictor of spermatogenic function [1549] and is usually, but not invariably, low in patients with NOA. Some authors have advocated that testicular perfusion detected at US Doppler assessment can predict surgical sperm retrieval at TESE and guide testicular biopsies [1887]; however, to date, data are inconsistent to support a routine role of testicular Doppler evaluation before TESE in order to predict sperm retrieval outcome.

As discussed (see Section 11.3), patients should undergo karyotype analysis [1805, 1806], along with a screening of Y-chromosome micro-deletions [1630, 1888]. In patients with clinical suspicion of CBAVD assessment of mutations in the gene coding for CFTR is also to be recommended [1617, 1618]. Genetic counselling for eventual transmissible and health-relevant genetic conditions should be provided to couples.

11.6.2.2 Surgery for non-obstructive azoospermia

Surgical treatment for NOA is mostly aimed at retrieval of vital sperm directly from the testes (either uni- or bilaterally). This treatment is normally part of ART protocols, including IVF cycles via ICSI. Testicular biopsy before TESE is not recommended.

11.6.2.3 Indications and techniques of sperm retrieval

Spermatogenesis within the testes may be focal, which means that spermatozoa can usually be found in small and isolated foci. With a wide variability among cohorts and techniques, positive SRRs have been reported in up to 50% of patients with NOA [1889, 1890]. Numerous predictive factors for positive SSR have been investigated (see below), although no definitive factors have been demonstrated to predict SSR [1890].

- Histology: The presence of hypospermatogenesis at testicular biopsy showed good accuracy in predicting positive sperm retrieval after TESE compared with maturation arrest pattern or SCOS [1891-1893].
- Hormonal levels: FSH, LH, inhibin B and AMH have been variably correlated with sperm retrieval outcomes, but data from retrospective series are controversial [1582, 1843, 1894-1898].
- Testicular volume has been inconsistently found to be a predictor of positive SSR [1843, 1891, 1897].

In case of complete AZFa and AZFb microdeletions, the likelihood of sperm retrieval is almost zero and therefore TESE procedures are contraindicated [1635]. Conversely, patients with Klinefelter syndrome [1602] and a history of undescended testes have been shown to have higher chance of finding sperm at surgery [1602, 1897, 1899].

Fine needle aspiration mapping

Fine needle aspiration (FNA) mapping technique has been proposed as a prognostic procedure aimed to select patients with NOA for TESE and ICSI [1900]. The retrieved tissue is sent for cytological and histological evaluation to provide information on the presence of mature sperm and on testicular histological pattern. FNA mapping may provide information on the sites with the higher probability of retrieving sperm, thus serving as a guide for further sperm retrieval surgery in the context of ART procedures (e.g., ICSI). A positive FNA requires a secondary therapeutic surgical approach, which may increase the risk of testicular damage, and without appropriate cost-benefit analysis, is not justifiable. No studies have evaluated the salvage rate of mTESE in men who have undergone FNA mapping. Therefore, FNA mapping is not recommended as a primary therapeutic intervention in men with NOA until further RCTs are undertaken.

Testicular sperm aspiration

Testicular sperm aspiration (TESA) is a minimally invasive, office-based, procedure in which testicular tissue is retrieved with a biopsy needle under local anaesthesia. Reported SRRs with TESA range from 11 to 60% according to patient profile and surgical techniques [1901-1904]. Complications after TESA are uncommon and mainly include minor bleeding with scrotal haematoma and post-operative pain [1904]. To date no RCTs have compared SRRs from TESA, cTESE and mTESE. A meta-analysis including data from case-control studies, reported that TESE was two times (95% CI: 1.8-2.2) more likely to result in successful SSR as compared with TESA [1890]. Given the low success rates compared with TESE, TESA is no longer recommended in men with NOA.

Conventional and microTESE

Conventional TESE requires a scrotal incision and open biopsy of the testes [1905]. Reported SRRs in single-arm studies are about 50% [1889]. Observational studies have demonstrated that multiple biopsies yield a higher chance of sperm retrieval [1889, 1906]. Conventional TESE has been associated with a higher rate of complications compared with other techniques [1889]. A total of 51.7% of patients have been found with

intratesticular haematoma at scrotal US 3 months after surgery, with testicular fibrosis observed in up to 30% of patients at six-months' assessment [1907].

Micro TESE is performed with an operative optical microscope to inspect seminiferous tubules at a magnification of 20-25x and it allows to find and extract those tubules which were larger, dilated and opaque as these were more likely to harbour sperm [1905]. The rationale of this technique is to increase the probability of retrieving sperm with a lower amount of tissue sampled and a subsequent lower risk of complications. Lower rates of complications have been observed with mTESE compared to cTESE, both in terms of haematoma and fibrosis [1908]. Both procedures have shown a recovery of baseline testosterone levels after long-term follow-up [1909, 1910]. Therefore, it would be reasonable to provide long-term endocrinological follow-up after TESE (any type) to detect hypogonadism.

A meta-analysis that pooled data analysis of case-control studies comparing cTESE with mTESE showed a lower unadjusted SRR of 35% (95% CI: 30-40) for cTESE and 52% for mTESE [1890]. A meta-analysis comparing cTESE and mTESE in patients with NOA showed a mean SRR of 47% (95% CI: 45;49%). No differences were observed when mTESE was compared with cTESE (46 [range 43-49] % for cTESE vs. 46 [range 42-49] % for mTESE, respectively) [1899]. Meta-regression analysis demonstrated that the SRR per cycle was independent of age and hormonal parameters at enrolment. However, the SRR increased as a function of testicular volume. Retrieved sperms resulted in a live-birth rate of up to 28% per ICSI cycle [1912]. The difference in surgical sperm retrieval outcomes between the two meta-analyses may be explained by the data studied [1890] only one analysed case control studies whilst Corona *et al.*, [1912] also included the single randomised controlled trial), but it is important to note that all the studies comparing cTESE and mTESE have shown that the latter is superior in retrieving sperm.

In this context, studies showed a higher chance of sperm retrieval with mTESE only for patients with a histological diagnosis of SCOS [1908]. In such cases, results ranged from 22.5 to 41% and from 6.3 to 29% for mTESE vs. cTESE, respectively [1908]. Conversely, no difference between the two techniques has been found when comparing patients with a histology suggestive of maturation arrest [1908]. A single study showed a small advantage of mTESE when hypospermatogenesis was found [1910].

In a study assessing the role of salvage mTESE after a previously failed cTESE or TESA, sperm were successfully retrieved in 46.5% of cases [1857]. In studies reporting SSR by micro-TESE for men who had failed percutaneous testicular sperm aspiration or non-microsurgical testicular sperm extraction, the SRR was 39.1% (range 18.4-57.1%) [1911, 1912]. Similarly, a variable SRR has been reported for salvage mTESE after a previously failed mTESE (ranging from 18.4% to 42.8%) [1913, 1914].

A recent meta-analysis investigated the risk of hypogonadism after TESE due to testicular atrophy [1915]; patients with NOA experienced a mean 2.7 nmol/L decrease in total testosterone 6 months after cTESE, which recovered to baseline within 18-26 months. Lower rates of complications have been observed with mTESE compared to cTESE, both in terms of haematoma and fibrosis [1908]. Both procedures have shown a recovery of baseline testosterone levels after long-term follow-up [1909, 1910].

The main limitation to contemporary literature is the paucity of randomised controlled studies comparing cTESE and mTESE. Although no difference in SSR was observed between cTESE/mTESE techniques in patients with NOA in the latest and most comprehensive meta-analysis [1899], it is important to note that in all the individual trials comparing cTESE and mTESE the latter was superior in retrieving sperm. Furthermore, the current data suggests that mTESE has less complications than cTESE and therefore the consensus opinion of the guidelines panel is that mTESE is the optimum approach for surgical sperm retrieval procedures. However, this is based on low-quality evidence and larger RCTs comparing SSR, risks and costs between the two techniques are urgently needed.

Hormonal therapy prior to surgical sperm retrieval approaches

Stimulating spermatogenesis by optimising intratesticular testosterone (ITT) has been proposed to increase the chance of SSR in men with NOA. Similarly, increasing FSH serum levels could stimulate spermatogenesis. To this aim, several treatment options are available, thus including hCG and/or FSH [1838, 1916, 1917] or SERMs [1918], but a standardized protocol is lacking.

No RCT has shown a benefit of hormonal treatment to enhance the chances of sperm retrieval among patients with idiopathic NOA [1919]. A meta-analysis has suggested that hormone stimulation prior to TESE might improve SRR in eugonadal but not in hypergonadotropic hypogonadal patients [1920]; however, the included studies had moderate or severe risk of bias and randomised studies are needed to confirm these findings.

Hormonal therapy has also been proposed to increase the chance of sperm retrieval at salvage surgery after previously failed cTESE or mTESE. . Only small retrospective studies with conflicting results have been conducted [1838, 1920-1922]. The histological finding of hypo-spermatogenesis emerged as a predictor of sperm retrieval at salvage surgery after hormonal treatment [1922]. Patients should be counselled that the evidence for the role of hormone stimulation prior to sperm retrieval surgery in men with idiopathic NOA is limited [1923]. Currently, it is not recommended in routine practice.

11.6.2.4 Recommendations for Non-Obstructive Azoospermia

Summary of evidence	**LE**
Patients with NOA are at increased risk of long term cardio-metabolic diseases, cancer and mortality.	3
Hypogonadism is present in about one third of men with non-obstructive azoospermia (NOA), before surgical for sperm retrieval.	3
Surgery for sperm retrieval is mandatory in NOA men before ART.	1b
Fine needle aspiration (FNA) and testicular sperm aspiration (TESA) have lower sperm retrieval rates compared to TESE in patients with NOA.	1b
FNA requires a secondary therapeutic surgical approach, which may increase the risk of testicular damage, and without appropriate cost-benefit analysis it is not justifiable.	2a
No definitive predictors of positive sperm retrieval before TESE have been identified.	1b
Microdissection TESE has been associated with higher rates of sperm retrieval and lower complications than conventional TESE.	2a
No conclusive data are available regarding the benefit of use of medical therapy before TESE (e.g., recombinant follicle-stimulating hormone [rFSH]; highly purified FSH; human chorionic gonadotrophin; aromatase inhibitors or selective oestrogen receptor modulators [SERMs]) in patients with NOA.	2a

Recommendations	**Strength rating**
Confirm a diagnosis of non-obstructive azoospermia (NOA) in two consecutive semen analyses, when no sperm are found after centrifugation.	Strong
Perform a comprehensive assessment, including detailed medical history, hormonal profile, genetic tests and scrotal ultrasound to investigate the underlying aetiology and associated co-morbidity in patients with NOA.	Strong
Genetic counselling is mandatory in couples with genetic abnormalities prior to any assisted reproductive technology.	Strong
Perform surgery for sperm retrieval in men who are candidates for assisted reproductive technology (i.e., ICSI).	Strong
Do not perform surgery for sperm retrieval in patients with complete AZFa and AZFb microdeletions, since the chance of sperm retrieval is zero.	Strong
Do not perform fine needle aspiration mapping (FNA) and testicular sperm aspiration (TESA) in patients with NOA.	Strong
Do not perform FNA mapping as a prognostic procedure prior to definitive testicular sperm extraction (any type) in patients with NOA in routine clinical practice.	Weak
Use microdissection TESE as the treatment of choice to retrieve sperm in patients with NOA.	Weak
Do not consider pre-operative biochemical and clinical variables as sufficient and reliable predictors of sperm retrieval outcome at surgery in patients with NOA.	Weak
Do not routinely use medical therapy, e.g. hormonal stimulation iin men with NOA and hypergonadotrophic hypogonadism before TESE (any type) to improve sperm recovery.	Weak

11.7 Assisted Reproductive Technologies

Assisted reproductive technology consists of procedures that involve the *in vitro* handling of both human oocytes and sperm, or of embryos, with the objective of establishing pregnancy. A limited summary of ARTs including a discussion on safety can be found in Appendix 13 online supplementary evidence.

11.8 Psychosocial aspects in men's infertility

Male infertility impacts men's psychological well-being resulting in emotional distress and challenges men's sense of identity. Is worth noting that a failed treatment often results in a prolonged grief response, requiring post-treatment psychological support [1924]. The mental health expert is thus regarded as part of the infertility intervention team, acting in all intervention stages, using strategies that may range from psycho-education techniques to more comprehensive psycho-therapeutic approaches [1925]. Furthermore, there should be a deeper focus on preventive policies; It has been recognised that men, such as women, want to become parents. Yet, they have very limited knowledge on infertility related risk factors, including a lack of awareness on the age-related decline in fertility, and tend to overestimate the chance of spontaneous conception [1926, 1927].

12. LATE EFFECTS, SURVIVORSHIP AND MEN'S HEALTH

The EAU Guidelines Panel of Sexual and Reproductive Health have extensively reviewed the literature to provide guidance on: (i) late effects of urological diseases (both occurring during childhood and adulthood) on male sexual and reproductive health; (ii) late and long-term effects of cancers on male sexual and reproductive health; and, (iii) future directions to support personalised medicine strategies for promotion and raising the awareness of male sexual and reproductive health overall.

A systematic literature search for original English-language publications and review articles published up to December 2019 and a further search up to December 2020 were performed using both Pubmed and Google, yielding only a limited number of papers addressing the role of health care professionals in supporting male patients who have suffered from cancers in terms of sexual and reproductive health, or the concept of Men's Health programmes.

Despite considerable public health initiatives over the past few decades, the Panel has observed that there is still a significant gender gap between male and female in life expectancy [1928]. The main contributors to male mortality in Europe are non-communicable diseases (namely CVDs), cancer, diabetes and respiratory disease) and injuries [1679], as highlighted in a recent WHO report disproving the prevailing misconception that the higher rate of premature mortality among men is a natural phenomenon [1928, 1929]. The recent pandemic situation linked with SARS-CoV-2 infection associated diseased (COVID-19) further demonstrates how the development of strategies dedicated to male health is of fundamental importance [1930].

The WHO report also addresses male sexual and reproductive health which is considered under-reported, linking in particular male infertility, as a proxy for overall health, to serious diseases in men [1878, 1879, 1931-1934]. These data suggest that health care policies should redirect their focus to preventive strategies and in particular pay attention to follow-up of men with sexual and reproductive complaints [1881, 1935]. [1935]. Considering that infertile men seem to be at greater risk of death, simply because of their inability to become fathers, is unacceptable [1882]. The Panel aims to develop a concept of a more streamlined and holistic approach to men's health.

For these guidelines, the Panel aimed to challenge clinicians to look beyond the pathology of disorders alone and consider the potential associations with other health disorders. Men with varicoceles have a higher incidence of heart disease and higher risk of diabetes and hyperlipidaemia following diagnosis [1935]. A diagnosis of infertility may have a profound psychological impact on men (and their partners), potentially resulting in anxiety, enduring sadness, anger, and a sense of personal inadequacy and "unmet masculinity" [1936]. A combination of factors, personality, sociocultural background, and specific treatments/professional support, will determine how men cope with this diagnosis [1925].

The most common cancer among European men (excluding non-melanoma skin cancer) is PCa [1937]. Due to new therapeutic approaches, survival rates have improved significantly [1938] and as men live longer, health-

related quality of life and related sexual well-being will become increasingly important [288]. Regardless of the type of treatment used [1692], sexual dysfunction and distress are common post-treatment complications [289, 1939-1941].

Furthermore, little is known about the relevance of fertility and fertility-preservation strategies in cancer survivors [1942-1946]. In PCa, it has been documented that the psychological consequences persist, even after complete remission or cure and erectile function is restored [1947]. In addition, special attention must be given to gay and bisexual men with PCa; these men present specific sexual concerns steaming from heteronormativity standards that have a negative impact in health care quality [1948]. Therefore urologists dealing with sexual and reproductive health are primed to act as a vanguard for cancer survivorship programmes.

Finally, the relationship between ED and heart disease has been firmly established for well over two decades [1949-1955]. Cadiovascular disease is the leading cause of both male mortality and premature mortality [1956-1959]. Studies indicate that all major risk factors for CVD, including hypertension, smoking and elevated cholesterol are more prevalent in men than women [1960-1966]. Given that ED is an established early sign of atherosclerotic disease and predicts cardiovascular events as an independent factor [1951], it provides urologists with the unique opportunity for CVD screening and health modification and optimise CVD risk factors, while treating men's primary complaint (e.g., ED). Currently, both the EAU and AUA guidelines recommend screening for CVD risk factors in men with ED and late onset hypogonadism [1967-1969] (see Sections 3.5.5 and 5.2).

There is clearly a need to prospectively collect data addressing all aspects of male health, including CVD screening protocols and assess the impact of primary and secondary preventive strategies. The EAU Sexual and Reproductive Health Guidelines Panel aims to promote and develop a long-term strategy to raise men's health at a global level.

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14. CONFLICT OF INTEREST

All members of the EAU Sexual and Reproductive Health Guidelines Panel have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of conflict of interest. This information is publicly accessible through the European Association of Urology website http://www.uroweb.org/guidelines/. This document was developed with the financial support of the European Association of Urology. No external sources of funding and support have been involved. The EAU is a non-profit organisation and funding is limited to administrative assistance and travel and meeting expenses. No honoraria or other reimbursements have been provided.

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