

EAU Guidelines on Sexual and Reproductive Health

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TABLE OF CONTENTS

PAGE

1.	INTRODUCTION	9
1.1	Aims and Objectives	9
1.2	Panel composition	9
1.3	Available Publications	9
1.4	Publication History	9
2.	METHODOLOGY	9
2.1	Methods	9
2.2	Review	10
2.3	Future goals	10
3.	MALE HYPOGONADISM	10
3.1	Epidemiology and prevalence of male hypogonadism	10
3.1.1	Body Composition and Metabolic Profile	10
3.1.2	Metabolic Syndrome/Type 2 Diabetes	11
3.2	Physiology of testosterone production	11
3.2.1	Circulation and transport of testosterone	12
3.2.2	Androgen receptor (AR)	13
3.3	Role of testosterone in male sexual and reproductive health	13
3.3.1	Sexual development and maturation	13
3.3.2	Sexual function	13
3.4	Classification and causes of male hypogonadism	14
3.5	Late-onset hypogonadism	16
3.5.1	Diagnostic evaluation	16
3.5.2	History taking	19
3.5.3	Physical examination	19
3.5.4	Summary of evidence and recommendations for the diagnostic evaluation of LOH	19
3.5.5	Recommendations for screening men with LOH	20
3.6	Treatment of LOH	20
3.6.1	Indications and contraindications for treatment of LOH	20
3.6.2	Testosterone therapy outcomes	21
3.6.2.1	Sexual dysfunction	21
3.6.2.2	Body composition and metabolic profile	21
3.6.2.3	Mood and cognition	21
3.6.2.4	Bone	22
3.6.2.5	Vitality and physical strength	22
3.6.2.6	Summary of evidence and recommendations for testosterone therapy outcome	22
3.6.3	Choice of treatment	23
3.6.3.1	Lifestyle factors	23
3.6.3.2	Medical preparations	23
3.6.3.2.1	Oral formulations	23
3.6.3.2.2	Parenteral formulations	24
3.6.3.2.3	Transdermal testosterone preparations	24
3.6.3.2.4	Transmucosal formulations	24
3.6.3.2.4.1	Transbuccal Testosterone preparations	24
3.6.3.2.4.2	Transnasal testosterone preparations	24
3.6.3.2.5	Subdermal depots	24
3.6.3.2.6	Anti-oestrogens	24
3.6.3.2.7	Gonadotropins	25
3.6.3.3	Summary of evidence and recommendations for LOH choice of treatment	27
3.7	Safety and follow up in hypogonadism management	27
3.7.1	Hypogonadism and fertility issues	27
3.7.2	Male breast cancer	27
3.7.3	Lower urinary tract symptoms/benign prostatic hyperplasia	27
3.7.4	Prostate cancer (PCa)	28
3.7.5	Cardiovascular Disease	28

3.7.5.1	Cardiac Failure	29
3.7.6	Erythrocytosis	29
3.7.7	Obstructive Sleep Apnoea	30
3.7.8	Follow up	30
3.7.9	Summary of evidence and recommendations on risk factors in testosterone treatment	31
4.	EPIDEMIOLOGY AND PREVALENCE OF SEXUAL DYSFUNCTION AND DISORDERS OF MALE REPRODUCTIVE HEALTH	32
4.1	Erectile dysfunction	32
4.2	Premature ejaculation	32
4.3	Other ejaculatory disorders	33
4.3.1	Delayed ejaculation	33
4.3.2	Anejaculation and Anorgasmia	33
4.3.3	Retrograde ejaculation	33
4.3.4	Painful ejaculation	34
4.3.5	Haemospermia	34
4.4	Low sexual desire	34
5.	MANAGEMENT OF ERECTILE DYSFUNCTION	43
5.1	Definition and classification	43
5.2	Risk factors	43
5.3	Pathophysiology	44
5.3.1	Pelvic surgery and prostate cancer treatment	45
5.3.2	Summary of evidence on the epidemiology/aetiology/pathophysiology of ED	47
5.4	Diagnostic evaluation (Basic Work-up)	47
5.4.1	Medical and sexual history	47
5.4.2	Physical examination	47
5.4.3	Laboratory testing	48
5.4.4	Cardiovascular system and sexual activity: the patient at risk	48
5.4.4.1	Low-risk category	50
5.4.4.2	Intermediate- or indeterminate-risk category	50
5.4.4.3	High-risk category	50
5.5	Diagnostic Evaluation (Advanced Work-Up)	51
5.5.1	Nocturnal penile tumescence and rigidity test	51
5.5.2	Intracavernous injection test	51
5.5.3	Dynamic duplex ultrasound of the penis	51
5.5.4	Arteriography and dynamic infusion cavernosometry or cavernosography	51
5.5.5	Psychiatric and psychosocial assessment	51
5.5.6	Recommendations for the diagnostic evaluation of ED	53
5.6	Treatment of Erectile Dysfunction	53
5.6.1	Patient education - consultation and referrals	53
5.6.2	Treatment options	53
5.6.2.1	Oral pharmacotherapy	55
5.6.2.2	Topical/Intraurethral Alprostadil	59
5.6.2.3	Shockwave therapy	59
5.6.2.4	Psychosexual counselling and therapy	60
5.6.2.5	Hormonal treatment	60
5.6.2.6	Vacuum erection devices	60
5.6.2.7	Intracavernous injections therapy	60
5.6.2.7.1	Alprostadil	60
5.6.2.8	Combination therapy	61
5.6.2.8.1	Erectile dysfunction after radical prostatectomy	62
5.6.2.9	Vascular surgery	63
5.6.2.9.1	Surgery for post-traumatic arteriogenic ED	63
5.6.2.9.2	Venous ligation surgery	63
5.6.2.9.3	Penile prostheses	64
5.6.2.9.4	Penile prostheses Implantation: complications	64
5.6.2.9.4.1	Conclusions penile prostheses implantation	65

5.6.3	Recommendations for the treatment of ED	66
5.6.4	Follow-up	66
6.	DISORDERS OF EJACULATION	66
6.1	Introduction	66
6.2	Premature ejaculation	67
6.2.1	Epidemiology	67
6.2.2	Pathophysiology and risk factors	67
6.2.3	Impact of premature ejaculation on quality of life	67
6.2.4	Classification	68
6.2.5	Diagnostic evaluation	68
6.2.5.1	Intravaginal ejaculatory latency time	69
6.2.5.2	Premature ejaculation assessment questionnaires	69
6.2.5.3	Physical examination and investigations	69
6.2.5.4	Recommendations for the diagnostic evaluation of PE	70
6.2.6	Disease management	70
6.2.6.1	Psychological aspects and intervention	71
6.2.6.1.1	Recommendation for the assessment and treatment (psychosexual approach) of PE	72
6.2.6.2	Pharmacotherapy	72
6.2.6.2.1	Dapoxetine	72
6.2.6.2.2	Off-label use of antidepressants: SSRIs and clomipramine	73
6.2.6.2.3	Topical anaesthetic agents	73
6.2.6.2.3.1	Lidocaine-prilocaine cream	74
6.2.6.2.3.2	Lidocaine-prilocaine spray	74
6.2.6.2.4	Tramadol	74
6.2.6.2.5	Phosphodiesterase type 5 inhibitors	74
6.2.6.2.6	Other drugs	75
6.2.7	Summary of evidence on the epidemiology/aetiology/pathophysiology of PE	75
6.2.8	Recommendations for the treatment of PE	75
6.3	Retarded or Delayed Ejaculation	76
6.3.1	Definition and classification	76
6.3.2	Pathophysiology and risk factors	76
6.3.3	Investigation and treatment	76
6.3.3.1	Psychological aspects and intervention	77
6.3.3.2	Pharmacotherapy	77
6.4	Anejaculation	77
6.4.1	Definition and classification	77
6.4.2	Pathophysiology and risk factors	77
6.4.3	Investigation and treatment	77
6.5	Painful Ejaculation	78
6.5.1	Definition and classification	78
6.5.2	Pathophysiology and risk factors	78
6.5.3	Investigation and treatment	78
6.5.3.1	Surgical intervention	78
6.6	Retrograde ejaculation	78
6.6.1	Definition and classification	78
6.6.2	Pathophysiology and risk factors	78
6.6.3	Disease management	79
6.6.3.1	Pharmacological	79
6.6.3.2	Management of infertility	79
6.7	Anorgasmia	80
6.7.1	Definition and classification	80
6.7.2	Pathophysiology and risk factors	80
6.7.3	Disease management	80
6.7.3.1	Psychological/behavioural strategies	80
6.7.3.2	Pharmacotherapy	80
6.7.3.3	Management of infertility	81
6.8	Haemospermia	81

6.8.1	Definition and classification	81
6.8.2	Pathophysiology and risk factors	81
6.8.3	Investigations	81
6.8.4	Disease management	82
6.9	Recommendations for the management of recurrent haemospermia	83
7.	LOW SEXUAL DESIRE AND MALE HYPOACTIVE SEXUAL DESIRE DISORDER	84
7.1	Definition and classification	84
7.2	Pathophysiology and risk factors	84
7.2.1	Psychological aspects	84
7.2.2	Biological aspects	84
7.2.3	Risk factors	85
7.3	Diagnostic work-up	85
7.3.1	Assessment questionnaires	85
7.3.2	Physical examination and investigations	85
7.4	Disease management	85
7.4.1	Psychological intervention	85
7.4.2	Pharmacotherapy	86
7.5	Recommendations for the treatment of low sexual desire	86
8.	PENILE CURVATURE	87
8.1	Congenital penile curvature	87
8.1.1	Epidemiology/aetiology/pathophysiology	87
8.1.2	Diagnostic evaluation	87
8.1.3	Disease management	87
8.1.4	Summary of evidence for congenital penile curvature	87
8.1.5	Recommendation for the treatment congenital penile curvature	87
8.2	Peyronie's Disease	87
8.2.1	Epidemiology/aetiology/pathophysiology	87
8.2.1.1	Epidemiology	87
8.2.1.2	Aetiology	87
8.2.1.3	Risk factors	89
8.2.1.4	Pathophysiology	89
8.2.1.5	Summary of evidence on epidemiology/aetiology/pathophysiology of Peyronie's disease	90
8.2.2	Diagnostic evaluation	90
8.2.2.1	Summary of evidence for the diagnosis of Peyronie's disease	91
8.2.2.2	Recommendations for the diagnosis of Peyronie's disease	91
8.2.3	Disease management	91
8.2.3.1	Conservative treatment	91
8.2.3.1.1	Oral treatment	92
8.2.3.1.2	Intralesional treatment	92
8.2.3.1.3	Topical treatments	94
8.2.3.1.4	Multimodal treatment	97
8.2.3.1.5	Summary of evidence for conservative treatment of Peyronie's disease	97
8.2.3.1.6	Recommendations for non-operative treatment of Peyronie's disease	98
8.2.3.2	Surgical treatment	98
8.2.3.2.1	Tunica shortening procedures	99
8.2.3.2.2	Tunica lengthening procedures	100
8.2.3.2.3	Penile prosthesis	102
8.2.3.2.4	Summary of evidence for non-operative treatment of Peyronie's disease	103
8.2.3.2.5	Recommendations for the surgical treatment of penile curvature	104
8.2.3.3	Treatment algorithm	104

9.	MALE INFERTILITY	106
9.1	Definition and classification	106
9.2	Epidemiology/aetiology/pathophysiology/risk factors	106
9.2.1	Introduction	106
9.2.2	Recommendations on epidemiology and aetiology	107
9.3	Diagnostic work-up	107
9.3.1	Medical/reproductive history and physical examination	107
9.3.1.1	Medical and reproductive history	107
9.3.1.2	Physical examination	107
9.3.2	Semen analysis	108
9.3.3	Measurement of sperm DNA Fragmentation Index (DFI)	109
9.3.4	Hormonal determinations	109
9.3.5	Genetic testing	109
9.3.5.1	Chromosomal abnormalities	110
9.3.5.1.1	Sex chromosome abnormalities (Klinefelter syndrome and variants [47,XXY; 46,XY/47, XXY mosaicism])	110
9.3.5.1.2	Autosomal abnormalities	111
9.3.5.2	Cystic fibrosis gene mutations	111
9.3.5.2.1	Unilateral or bilateral absence/abnormality of the vas and renal anomalies	111
9.3.5.3	Y microdeletions - partial and complete	111
9.3.5.3.1	Clinical implications of Y microdeletions	112
9.3.5.3.1.1	Testing for Y microdeletions	112
9.3.5.3.1.2	Genetic counselling for AZF deletions	112
9.3.5.3.1.3	Y-chromosome: 'gr/gr' deletion	113
9.3.5.3.1.4	Autosomal defects with severe phenotypic abnormalities and infertility	113
9.3.5.4	Sperm chromosomal abnormalities	113
9.3.5.5	Measurement of Oxidative Stress	113
9.3.5.6	Outcomes from ART and long-term health implications to the male and offspring	113
9.3.6	Imaging in the infertile male	114
9.3.6.1	Testicular neoplasms	114
9.3.6.2	Varicocele	115
9.3.6.3	Transrectal US	115
9.3.7	Recommendations for the diagnostic work-up of male infertility	116
9.4	Special Conditions and Relevant Clinical Entities	116
9.4.1	Cryptorchidism	116
9.4.1.1	Classification	117
9.4.1.1.1	Aetiology and pathophysiology	117
9.4.1.1.2	Pathophysiological effects in maldescended testes	117
9.4.1.1.2.1	Degeneration of germ cells	117
9.4.1.1.2.2	Relationship with fertility	117
9.4.1.1.2.3	Germ cell tumours	117
9.4.1.2	Disease management	118
9.4.1.2.1	Hormonal treatment	118
9.4.1.2.2	Surgical treatment	118
9.4.1.3	Summary of evidence recommendations for cryptorchidism	118
9.4.2	Germ cell malignancy and male infertility	118
9.4.2.1	Testicular germ cell cancer and reproductive function	119
9.4.2.2	Testicular microcalcification	120
9.4.2.3	Recommendations for germ cell malignancy and testicular microcalcification	121
9.4.3	Varicocele	121
9.4.3.1	Classification	121
9.4.3.2	Diagnostic evaluation	121
9.4.3.3	Basic considerations	121
9.4.3.3.1	Varicocele and fertility	121
9.4.3.3.2	Varicocelectomy	122
9.4.3.3.3	Prophylactic varicocelectomy	122

	9.4.3.3.4	Varicocelectomy for assisted reproductive technology (ART) and for raised DNA fragmentation	122
	9.4.3.4	Disease management	123
	9.4.3.5	Summary of evidence and recommendations for varicocele	125
9.4.4		Male accessory gland infections and infertility	125
	9.4.4.1	Introduction	125
	9.4.4.2	Diagnostic evaluation	125
	9.4.4.2.1	Semen analysis	125
	9.4.4.2.2	Microbiological findings	125
	9.4.4.2.3	White blood cells	126
	9.4.4.2.4	Sperm quality	126
	9.4.4.2.5	Seminal plasma alterations	126
	9.4.4.2.6	Glandular secretory dysfunction	126
	9.4.4.2.7	Reactive oxygen species	126
	9.4.4.2.8	Disease management	126
	9.4.4.3	Epididymitis	127
	9.4.4.3.1	Diagnostic evaluation	127
	9.4.4.3.1.1	Ejaculate analysis	127
	9.4.4.3.1.2	Disease management	127
	9.4.4.4	Summary of evidence and recommendation for male accessory gland infections	127
9.5		Non-Invasive Male Infertility Management	128
	9.5.1	Idiopathic male infertility and OATS	128
	9.5.2	Empirical treatments	128
	9.5.2.1	Life-style	128
	9.5.2.1.1	Weight loss	128
	9.5.2.1.2	Physical activity	128
	9.5.2.1.3	Smoking	128
	9.5.2.1.4	Alcohol consumption	128
	9.5.2.2	Antioxidant treatment	128
	9.5.2.3	Selective oestrogen receptor modulators (SERMs)	129
	9.5.2.4	Aromatase inhibitors	129
	9.5.3	Hormonal therapy	129
	9.5.3.1	Gonadotrophins	129
	9.5.3.2	Secondary Hypogonadism	130
	9.5.3.3	Primary Hypogonadism	131
	9.5.3.4	Idiopathic Male Factor Infertility	131
	9.5.3.5	Anabolic Steroid Abuse	131
	9.5.3.6	Recommendations for treatment of male infertility with hormonal therapy	131
9.6		Invasive Male Infertility Management	131
	9.6.1	Obstructive azoospermia	131
	9.6.1.1	Classification of obstructive azoospermia	132
	9.6.1.1.1	Intratesticular obstruction	132
	9.6.1.1.2	Epididymal obstruction	132
	9.6.1.1.3	Vas deferens obstruction	132
	9.6.1.1.4	Ejaculatory duct obstruction	132
	9.6.1.1.4.1	Functional obstruction of the distal seminal ducts	132
	9.6.1.2	Diagnostic evaluation	133
	9.6.1.2.1	Clinical history	133
	9.6.1.2.2	Clinical examination	133
	9.6.1.2.3	Semen analysis	133
	9.6.1.2.4	Hormone levels	133
	9.6.1.2.5	Genetic Testing	133
	9.6.1.2.6	Testicular biopsy	133
	9.6.1.3	Disease management	133
	9.6.1.3.1	Intratesticular obstruction	133
	9.6.1.3.2	Epididymal obstruction	133
	9.6.1.3.3	Vas deferens obstruction after vasectomy	134

	9.6.1.3.4	Vas deferens obstruction at the inguinal level	134
	9.6.1.3.5	Ejaculatory duct obstruction	134
	9.6.1.4	Summary of evidence and recommendations for obstructive azoospermia	134
9.6.2		Non-obstructive azoospermia	135
	9.6.2.1	Investigation of Non-obstructive azoospermia	135
	9.6.2.2	Surgery for non-obstructive azoospermia	135
	9.6.2.3	Indications and techniques of sperm retrieval	135
	9.6.2.4	Recommendations for Non Obstructive Azoospermia	138
9.7		Assisted Reproductive Technologies	139
	9.7.1	Types	139
	9.7.1.1	Intra-uterine insemination (IUI)	139
	9.7.1.2	In vitro fertilisation IVF	139
	9.7.1.3	Intracytoplasmic sperm injection	140
	9.7.1.4	Intra-cytoplasmic morphologically selected sperm injection (IMSI)	141
	9.7.1.5	PICSI technique: a selection based on membrane maturity of sperm	142
	9.7.1.6	Magnetic-activated cell sorting (MACS)	142
	9.7.2	Safety	142
10.		LATE EFFECTS, SURVIVORSHIP AND MEN'S HEALTH	143
11.		REFERENCES	144
12.		CONFLICT OF INTEREST	232
13.		CITATION INFORMATION	232

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 males. 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 - also 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 multidisciplinary 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/sexualandreproductivehealth/>.

1.3 Available Publications

Alongside the full text version, a quick reference document (Pocket Guidelines) is available in print and as an app for iOS and android devices. These are abridged versions which may require consultation together with the full text version. All documents can be viewed through the EAU website:

<http://www.uroweb.org/guideline/sexualandreproductivehealth/>.

1.4 Publication History

This document is a new Guideline which includes a comprehensive update of the 2018 versions of Male Sexual Dysfunction, Male Infertility and Male Hypogonadism, along with a number of new topics. Additional sections will be added in the coming year to address priapism and male contraception and vasectomy which were addressed in the 2018 versions.

2. METHODOLOGY

2.1 Methods

For the 2020 Sexual and Reproductive Health Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature. A broad and comprehensive literature search, covering all sections of the Guidelines was performed. Databases searched included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between 2013 and 2018 and restricted to English language publications. Detailed search strategies are available online:

<http://www.uroweb.org/guideline/sexualandreproductivehealth/>.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [1, 2]. Each strength rating form addresses a number of key elements namely:

1. the overall quality of the evidence which exists for the recommendation, references used in this text are graded according to a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence [3];
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 of patient values and preferences on the intervention;
6. the certainty of those patient values and preferences.

These key elements are the basis which panels use to define the strength rating of each recommendation. The strength of each recommendation is represented by the words 'strong' or 'weak' [4]. 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 nature and variability of patient values and preferences.

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 the above address.

2.2 Review

Sections of the Sexual and Reproductive Health Guidelines were peer reviewed prior to publication. This is an ongoing process which will continue as the Guidelines is further refined in the coming year.

2.3 Future goals

The results of ongoing and new systematic reviews will be included in the 2021 update of the Sexual and Reproductive Health Guidelines. Systematic reviews planned for 2020 are:

- What is the effectiveness of non-surgical therapies in the treatment of ischaemic priapism in patients with sickle cell disease?
- What is the effectiveness of non-surgical therapies in the management of priapism in patients without sickle cell disease?

3. MALE HYPOGONADISM

3.1 Epidemiology and prevalence of male hypogonadism

Definition: Male hypogonadism is a disorder associated with decreased functional activity of the testes, with decreased production of androgens and/or impaired sperm production [5]. This is caused by poor testicular function or as a result of inadequate stimulation of the testes by the hypothalamic-pituitary axis. Several congenital or acquired disorders causing impaired action of androgens are also described [5]. Hypogonadism may adversely affect multiple organ functions and quality of life (QoL) [6]. Late-onset hypogonadism (LOH) is a clinical condition in the aging male, which, by definition, must comprise both persistent specific symptoms and biochemical evidence of testosterone deficiency [5, 7]. It is a condition 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 over 40 years of age.

Male hypogonadism has also been called *Testosterone Deficiency*; the Panel has agreed to use the term *Male Hypogonadism*, which may better reflect and explain the underlying pathophysiology. Likewise, the Panel has further agreed to continue with the terminology *testosterone therapy* to indicate a therapy with testosterone. The present guidelines will specifically address the management of adult male hypogonadism also called LOH. Some insights related to congenital or pre-pubertal hypogonadism are also provided and summarised where applicable.

The prevalence of hypogonadism increases with age and the major causes are central obesity, co-morbidities (e.g., diabetes) and overall poor health [8]. In healthy aging men there is only a small gradual decline in testosterone; up to the age of 80 years, age accounts for a relatively low percentage of hypogonadism [8]. In men aged between 40-79 years the incidence of symptomatic hypogonadism varies between 2.1-5.7% [9-11]. The incidence of hypogonadism has been reported to be 12.3 and 11.7 cases per 1,000 people per year [9, 12].

There is a high prevalence of hypogonadism within specific populations, including patients with type 2 diabetes (T2DM), metabolic syndrome (MetS), obesity, cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), renal disease and cancer [11]. Low testosterone levels are common in men with T2DM [13] and a high prevalence of hypogonadism (42%) has been reported in T2DM patients [14].

Klinefelter's syndrome, a trisomy associated with a 47,XXY karyotype, is the most prevalent genetic cause of primary hypogonadism (hypergonadotropic hypogonadism), with a global prevalence of 1/500-1,000 live male births [15-17]. However, less than 50% of individuals with Klinefelter syndrome are diagnosed in life [18].

3.1.1 Body Composition and Metabolic Profile

Low testosterone levels are common in men with obesity. Male hypogonadism is associated with a greater percentage of fat mass and a lesser lean mass compared to men with adequate testosterone levels [19]. Much evidence has documented that low testosterone is strongly associated with an increased visceral adiposity, but it also leads to deposition of lipids in the liver and muscle and is associated with atherosclerosis [19]. *In vitro* studies suggest that hypogonadism impairs glucose and triglyceride uptake into subcutaneous fat depots [19]. This enhances the uptake of glucose and triglycerides into ectopic fat depots as described above.

Testosterone therapy has been associated with a reduced percentage of body fat and an increase of lean body mass [20]. Data from a registry study has suggested that over a period of eight years, testosterone therapy with long-acting intramuscular testosterone undecanoate was associated with a substantial but gradual loss of weight along with a reduction in waist circumference [21]. Testosterone also reduces liver fat content and muscle fat stores [19].

3.1.2 **Metabolic Syndrome/Type 2 Diabetes**

Metabolic Syndrome (MetS) is characterised by a number of specific components, including increased waist circumference, dyslipidaemia, hypertension, and impaired glucose tolerance. Hypogonadism is associated with central obesity, hyperglycaemia, insulin resistance and dyslipidaemia (low HDL-cholesterol, raised total and LDL-cholesterol and triglycerides), hypertension and a predisposition to T2DM, which are all components of MetS [22].

A number of randomised controlled trials (RCTs) have shown that testosterone therapy might improve insulin resistance, hyperglycaemia and lower cholesterol and LDL-cholesterol [23-27]. Evidence suggests that testosterone therapy in hypogonadal T2DM improves glycaemic control in some RCTs and registry trials; however, there is no conclusive evidence from RCTs and meta-analyses studies [24, 28, 29]. Recently, a registry study reported that testosterone therapy is associated in time with remission of T2DM [28]. HDL-cholesterol may decrease, remain unchanged or increase with testosterone therapy. Testosterone therapy in men with MetS and low testosterone has also been shown to reduce mortality compared to untreated men [30, 31] although no conclusive evidence is available.

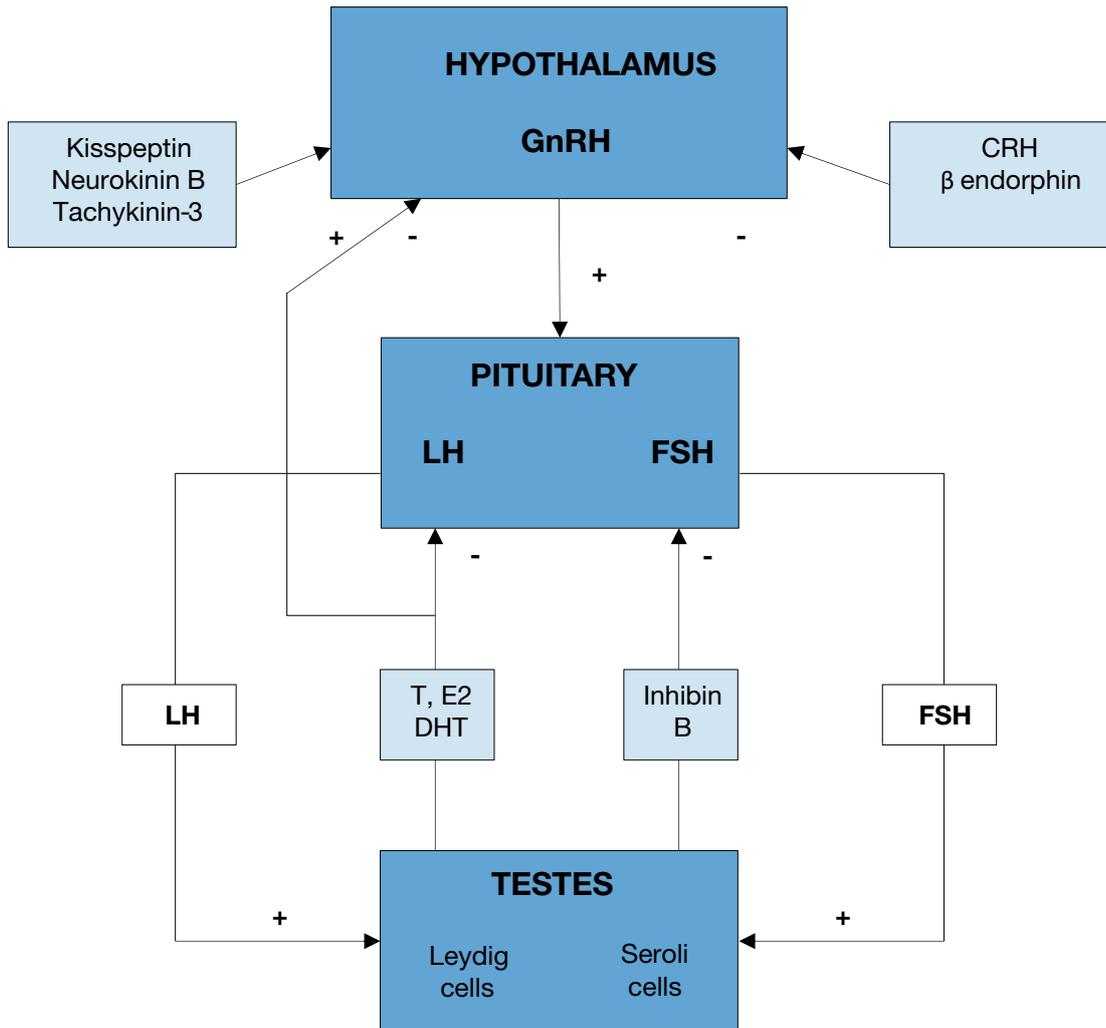
Erectile dysfunction (ED) is common in men with MetS and T2DM (up to 70% of patients). The causes of ED are multifactorial and 30% of men with ED have co-existing testosterone deficiency. Some evidence has suggested that for patients with T2DM this has been demonstrated only to be the case in men with clearly reduced testosterone levels (< 8mmol/L [2.31 ng/mL]) [32]. From a pathophysiological point of view, it has been reported that this is because ED is predominantly due to vascular and neuropathic disease, therefore not likely to be the case in those men who do not have an established vascular disease. Therefore, men presenting with ED should be screened for MetS. Likewise, patients with ED and diabetes may be offered testosterone measurement.

Randomised placebo-controlled trials of testosterone therapy in T2DM have demonstrated improved sexual desire and satisfaction, but not erectile function [24, 32]. The presence of multi-comorbidities in this group of patients may confound the response to testosterone alone.

3.2 **Physiology of testosterone production**

The pituitary gland regulates testis activity, through the secretion of luteinising hormone (LH), which regulates testosterone production in Leydig cells and follicle-stimulating hormone (FSH), which mainly controls sperm production in seminiferous tubules [33, 34]. The production and secretion of gonadotropins is stimulated by hypothalamic gonadotropin releasing hormone (GnRH) and inhibited by a negative feedback mediated by the central action of sex steroids and inhibin B (Figure 1) [33, 34]. Gonadotropin releasing hormone is secreted in a pulsatile manner and negatively controlled by the activity of other hypothalamic neurons, including corticotrophin releasing hormone (CRH) and β endorphin neurons [33, 34]. Conversely, kisspeptin-1 (Kiss-1) neurons, neurokinin-B or tachykinin-3 are involved in GnRH stimulation. Finally, leptin is also involved in the activation of Kiss-1 signaling [35]. About 25 mg of testosterone is present in the normal testes, and, on average, 5-10 mg of testosterone are secreted daily [33, 34]. The testis also produces lesser amounts of other androgens such as androstenedione and dehydroepiandrosterone (DHT). In addition, a small amount of extra-gonadal testosterone is derived from circulating weak adrenal androgen precursor dehydroepiandrosterone (DHEA), although its specific contribution to daily testosterone production is limited in men [36, 37]. In physiological terms, DHT formation accounts for about 6-8% of testosterone metabolism, and the ratio of plasma testosterone/DHT is approximately 1:20 [33, 34]. Finally, testosterone and its precursor, Δ 4 androstenedione, can be aromatised through P450 aromatase to other bioactive metabolites, such as oestrone (E1) and 17- β -estradiol (E2), with a daily production of about 45 μ g [33, 34]. Furthermore, Leydig cells, can also directly produce and release into the bloodstream a small amount of oestrogens, with a daily production rate of about 5-10 μ g (up to 20% of circulating oestrogens) [38].

Figure 1: Physiology of testosterone production



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

3.2.1 Circulation and transport of testosterone

In normal men 60% to 70% of circulating testosterone is bound to the high affinity sex hormone-binding globulin (SHBG), a protein produced by the liver, which prevents its bound testosterone sub-fraction from biological action. The remaining circulating testosterone binds lower affinity, high-capacity binding protein sites, (albumin, α-1 acid glycoprotein and corticosteroid binding protein), and only 1%-2% of testosterone remains non-protein bound [39]. There is a general agreement that testosterone bound to lower affinity proteins can easily dissociate in the capillary bed of many organs accounting for so-called ‘bioavailable’ testosterone [39]. It is important to recognise that several clinical conditions and aging itself can modify SHBG levels, thus altering circulating total testosterone levels (Table 1). Therefore, if not recognised, these factors could lead to an incorrect estimation of male androgen status. Therefore, when indicated (see Table 1) SHBG should be tested and free testosterone calculated.

Table 1: Main factors associated with an increase or reduction of SHBG circulating levels

SHBG increase	Drugs: anticonvulsant, oestrogens, thyroid hormone Hyperthyroidism Hepatic disease Aging Smoking AIDS/HIV
SHBG decrease	Drugs: GH, glucocorticoids, testosterone, anabolic androgenic steroids Hypothyroidism Obesity Acromegaly [40] Cushing Disease Insulin resistance (MetS/T2DM) <ul style="list-style-type: none"> o non-alcoholic fatty liver disease (NAFLD), Nephrotic syndrome

3.2.2 **Androgen receptor (AR)**

Testosterone and DHT exert their biological action through the activation of a specific nuclear receptor. The AR gene is localised on the X chromosome (Xq11-12), encoded in eight exons [41]. Exon 1 includes two polymorphic trinucleotide repeat segments encoding polyglutamine (CAG) and polyglycine (GGN) tracts in the N-terminal transactivation domain of its protein. It has been established that the activity of the AR is inversely associated with the length of the CAG repeat chains [41]. However, the specific role of AR CAG repeat number in relation to hypogonadal symptoms or to clinical management of testosterone deficiency remains unclear [42, 43]. It has been shown in an RCT that a higher CAG repeat number is positively associated with a change in fasting insulin, triglyceride and diastolic blood pressure, demonstrating the more sensitive the receptor the greater the benefit [44].

3.3 **Role of testosterone in male sexual and reproductive health**

3.3.1 **Sexual development and maturation**

Testosterone production in the foetal testis starts between the eighth and ninth week of gestation after the expression of the SRY (Sex-determining Region Y) gene, which regulates the organisation of the undifferentiated gonadal ridge into the testis [45]. During the first trimester, the testes drive the virilisation of internal and external genitalia through placental human chorionic gonadotropin (hCG) stimulated androgen secretion by Leydig cells. During foetal life, testosterone mainly controls the differentiation of internal genitalia and testis descent (regression of gubernaculum testis), whereas DHT is mainly involved in the development of the external male genitalia [46]. During puberty, the reactivation of the hypothalamus-pituitary-gonadal (HPG) axis allows the development of secondary sexual characteristics, spermatogenesis maturation and, along with the contribution of other hormonal axes, the completion of the adolescent growth spurt [5, 47]. Clinical models of aromatase deficiency and oestrogen receptor insensitivity have demonstrated that testosterone conversion to estradiol is essential for epiphyseal closure and growth arrest [48].

3.3.2 **Sexual function**

Testosterone is involved in the regulation of all steps of the male sexual response. Sexual thoughts and motivations are universally accepted as the most testosterone-dependent aspects of male sexual behaviour [20]. The European Male Aging Study (EMAS), a population-based survey including more than 3,400 subjects aged 40-80 years from eight European countries, showed that sexual symptoms and, in particular, sexual desire impairment, ED and a decreased frequency of morning erections were the most specific symptoms associated with age-dependent decline of testosterone [10]. Similar findings were reported in subjects consulting for sexual dysfunctions [49]. Accordingly, several brain areas, including the amygdala, medial preoptic area, paraventricular nucleus of the hypothalamus, and peri-aqueductal grey matter express the AR [49, 50]. Both experimental and clinical studies have documented that testosterone plays a crucial role in regulating penile function. In particular, testosterone controls the structural integrity necessary for penile erection as well as several enzymatic activities within the corpora cavernosa, including a positive action on nitric oxide (NO) formation and a negative influence on the activity of the Ras homolog gene family member A/Rho-associated kinase (RhoA/ROCK) pathways [49, 51]. Testosterone is also involved in penile adrenergic response and cavernous smooth muscle cell turnover [49, 51]. Finally, although some authors have suggested a positive role of testosterone in regulating penile phosphodiesterase 5 (PDE5) expression and activity, other evidence showed a prevalent inhibiting role of oestrogens on this pathway [49, 52].

More limited evidence documented a possible role of testosterone in regulating ejaculatory process acting either at central and peripheral level. Androgen receptors are expressed in several central spinal and super-spinal areas involved in the control of ejaculatory reflex [53]. In addition, the male genital tract expresses NO-PDE5 as well as RhoA/ROCK pathways, which are modulated by testosterone [53].

3.4 Classification and causes of male hypogonadism

Male hypogonadism can be classified according to the origin of the underlying problem into primary, if a consequence of testicular dysfunction, or secondary if due to a pituitary or hypothalamic dysfunction (Table 2).

Primary hypogonadism is also called hypergonadotropic hypogonadism (HH), since the pituitary tries compensating the dysfunctional testis by increasing central stimulation. Conversely, in secondary hypogonadism the testis is inadequately stimulated by gonadotropins resulting in a HH, usually with inappropriately normal or reduced gonadotropin levels [5, 34]. A compensated or subclinical form of hypogonadism, characterised by normal testosterone serum levels and elevated LH production, has also been reported [54]; the clinical significance of the latter condition is unclear [54, 55]. Finally, hypogonadism can also result from a group of several conditions leading to a reduced sensitivity/insensitivity to testosterone and its metabolites (Table 2) [5, 34]. This classification, based on the aetiology of hypogonadism, allows the clinician to adequately select appropriate treatment. In patients with secondary hypogonadism, both fertility and testosterone normalisation can be theoretically achieved with an adequate treatment, whereas in primary hypogonadism only testosterone therapy can be considered, which will impair fertility due to suppression of the hypothalamic pituitary axis (HPG) (Table 2) [5, 34].

In 2017, Grossmann and Matsumoto suggested a new classification of adult male hypogonadism, distinguishing functional versus organic hypogonadism [56]. Accordingly, organic hypogonadism is characterised by any proven pathology affecting the HPG axis and should be treated with the conventional medications (i.e., gonadotropins or TRT); conversely, functional hypogonadism is based on the absence of any recognised organic alterations in the HPG axis and should be treated, first by resolving or improving the associated comorbidities. These Guidelines refer to the validated international classification of adult male hypogonadism.

Table 2: Classification of male hypogonadism

PRIMARY HYPOGONADISM (hypergonadotropic hypogonadism)	
Congenital or developmental disorders	
<i>Common causes</i>	<i>Uncommon causes</i>
Klinefelter syndrome	<ul style="list-style-type: none"> - Rare chromosomal abnormalities - XX male syndrome - 47 XYY syndrome - 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	
<i>Drug-induced</i>	<i>Localised problems</i>
<ul style="list-style-type: none"> - Chemotherapy agents <ul style="list-style-type: none"> • Alkylating agents - Methotrexate <ul style="list-style-type: none"> • Testosterone synthesis inhibitors • Ketoconazole • Aminoglutethimide • Mitotane • Metyrapone 	<ul style="list-style-type: none"> - Bilateral surgical castration or trauma - Testicular irradiation - Orchitis (including mumps orchitis) - Autoimmune testicular failure - Testicular Torsion - Alcohol/Cirrhosis <ul style="list-style-type: none"> • Environmental Toxins

Systemic diseases/conditions with hypothalamus/pituitary impact	
<ul style="list-style-type: none"> - Chronic systemic diseases* - Chronic organ failure* - Glucocorticoid excess (Cushing syndrome)* - Aging* - HIV 	<ul style="list-style-type: none"> - Malignancies <ul style="list-style-type: none"> - Lymphoma - Testis cancer - Spinal cord injury - Vasculitis - Infiltrative diseases (amyloidosis; leukaemia)
SECONDARY HYPOGONADISM (hypogonadotropic hypogonadism)	
Congenital or developmental disorders	
<i>Common causes</i>	<i>Uncommon causes</i>
<ul style="list-style-type: none"> - Hemochromatosis* 	<ul style="list-style-type: none"> - Combined hormone pituitary deficiency - Idiopathic hypogonadotropic hypogonadism (IHH) with variants: <ul style="list-style-type: none"> - Normosmic IHH - Kallmann syndrome - Isolated LH β gene mutations - Prader-Willi Syndrome
Acquired disorders	
<i>Drug-induced</i>	<i>Localised problems</i>
<ul style="list-style-type: none"> - Oestrogens - Testosterone or androgenic anabolic steroids - Progestogens (including cyproterone acetate) - Hyperprolactinaemia-induced drugs - Opiates <ul style="list-style-type: none"> - GnRH agonist or antagonist - Glucocorticoids 	<ul style="list-style-type: none"> - Traumatic brain injury - Pituitary neoplasm (micro/macro adenomas) - Hypothalamus tumours - Pituitary stalk diseases - Iatrogenic <ul style="list-style-type: none"> - Surgical hypophisectomy - Pituitary or cranial irradiation - Inflammatory and infectious diseases <ul style="list-style-type: none"> - Lymphocytic hypophysitis - Pituitary infections - Granulomatous lesions - Sarcoidosis - Wegener's granulomatosis - Other granulomatosis - Encephalitis - Langerhans' histiocytosis - Hyperprolactinaemia as a consequence of localised problems (hypothalamus-pituitary mass)
Systemic diseases/conditions impacting the hypothalamus/pituitary	
<ul style="list-style-type: none"> - Chronic systemic diseases* <ul style="list-style-type: none"> - Metabolic diseases - HIV infection - Chronic organ failure - Chronic Inflammatory Arthritis - Glucocorticoid excess (Cushing syndrome)* - Eating disorders* - Endurance exercise - Acute and critical illness - Aging* 	<ul style="list-style-type: none"> - Spinal cord injury - Transfusion-related iron overload (β-thalassemia)

ANDROGEN RESISTANCE/DECREASED TESTOSTERONE BIOACTIVITY	
Congenital or developmental disorders	
<ul style="list-style-type: none"> - Aromatase deficiency - Kennedy diseases (spinal and bulbar muscular atrophy)and other extensions of CAG repeats - Partial or complete androgen insensitivity - 5α reductase type II (5αR) deficiency 	
Acquired disorders	
<i>Drug-induced</i>	<i>Localised problems</i>
<ul style="list-style-type: none"> - Drug-induced AR blockage <ul style="list-style-type: none"> - Steroidal antiandrogen <ul style="list-style-type: none"> - Cyproterone acetate - Spironolactone - Non-steroidal antiandrogen <ul style="list-style-type: none"> - Flutamide - Bicalutamide - Nilutamide - Drug-induced 5α reductase (5αR) activity blockade <ul style="list-style-type: none"> - Finasteride - Dutasteride - Drug-induced ER blockade <ul style="list-style-type: none"> - Clomiphene - Tamoxifen - Raloxifene - Drug-induced aromatase activity blockade <ul style="list-style-type: none"> - Letrozole - Anastrozole - Exemestane - Increased Sex Hormone Binding Protein (SHBG) 	<ul style="list-style-type: none"> - Celiac disease

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

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

3.5 Late-onset hypogonadism

Testosterone production declines as a function of age. The EMAS study reported a 0.4% per annum (log hormone-age) decrease in total testosterone and a 1.3% per annum decline in free testosterone (FT) [8]. Late onset hypogonadism is the term frequently used to describe this phenomenon and the detection of hypogonadism in adulthood, in particular. Evidence has documented that a number of associated diseases and chronic co-morbidities 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. By combining the data from three different waves of the Massachusetts Male Aging Study (MMAS), a population-based, observational study including 1,709 men aged 40-70 years, Mohr *et al.* [57] showed that associated comorbidities and obesity significantly decreased, whereas smoking tended to increase total, free and bio-available testosterone concentrations. Similarly, data derived from the EMAS study confirm these findings [8, 55]. Based upon these data and other evidence, the concept of *functional and organic hypogonadism* has been recently introduced [56]. The diagnosis of functional hypogonadism is based on the exclusion of a classical (organic) aetiology. The main causes of functional hypogonadism are obesity, co-morbidities and aging with the first two of these accounting for the majority of this definition. Inflammatory cytokines released in states of chronic inflammation, and adipocytokines and estradiol in obesity, can suppress the HPG axis. The role of aging up to the age of 80 years seems relatively small [56]. 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 [56].

3.5.1 Diagnostic evaluation

The phenotype of the hypogonadal patient appears independent of the aetiology causing the problem, but is more often affected by the age of onset of hypogonadism. When androgen deficiency is complete and develops during the foetal life, symptoms can be dramatic, spanning from an almost complete female phenotype (complete androgen insensitivity or enzymatic defects blocking androgen synthesis) to various

defects in virilisation and ambiguous genitalia (micropenis, hypospadias, cryptorchidism) [5, 34]. Delay in puberty with an overall eunuchoidal phenotype (scant body hair, high-pitched voice, small testis, penis and prostate) is typical of defects manifesting in the pre- or peri-pubertal period due to milder central (isolated HH) or peripheral defects (such as in Klinefelter syndrome) [5, 34]. When hypogonadism occurs in adulthood, especially in the case of functional hypogonadism, symptoms can be often relatively mild, difficult to recognise and frequently confused with the aging process [5, 34] or with the comorbid chronic conditions. Several non-specific clinical features such as fatigue, weakness, and decreased energy, as well as sexual impairment may be clinical manifestations. The EMAS study showed that a triad of sexual symptoms, including low libido, reduced spontaneous erections and ED, are typically associated with a decrease in testosterone serum levels [10]. Conversely, psychological and physical symptoms were less informative [10].

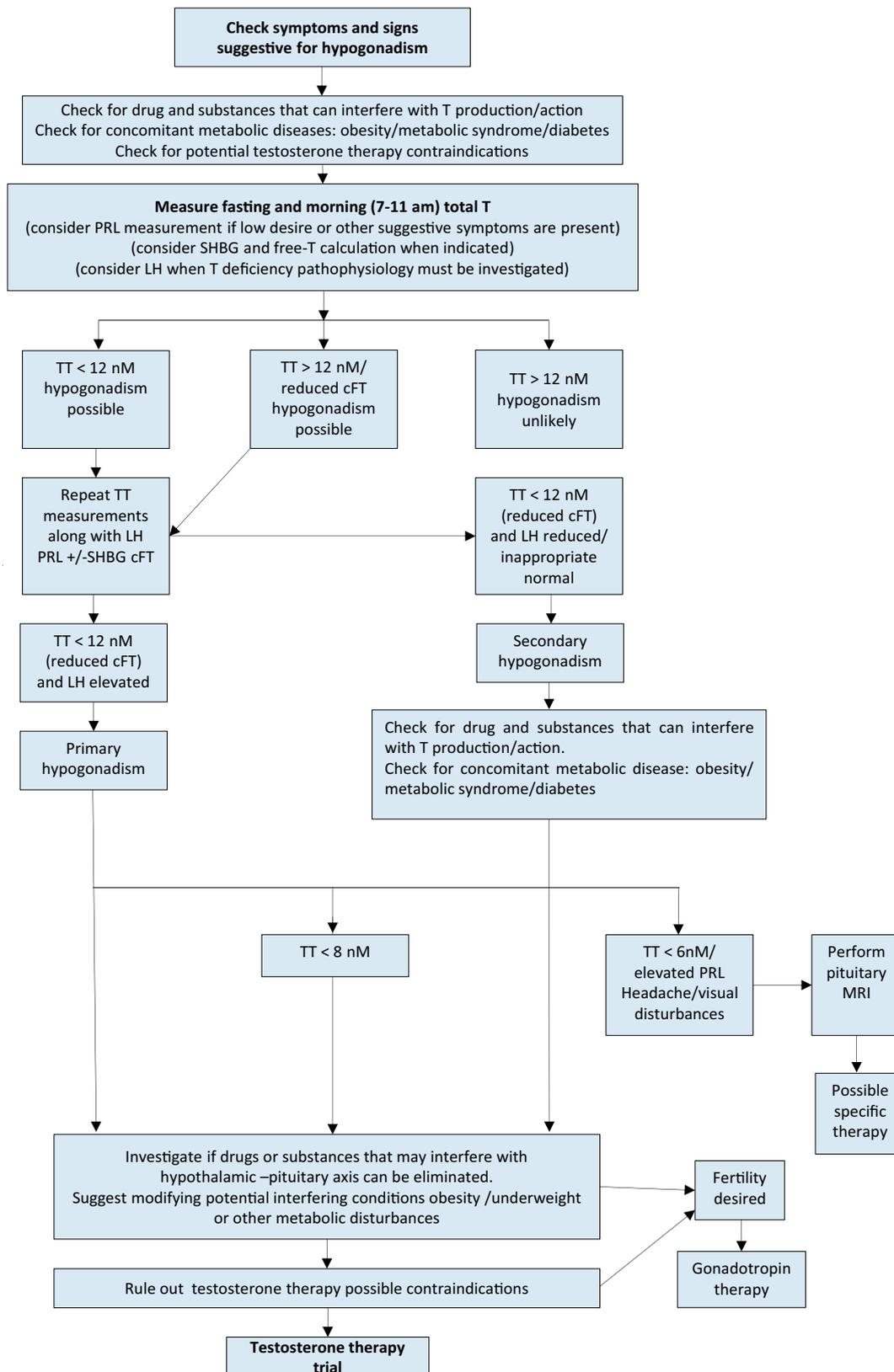
The mainstay of a LOH diagnosis includes the presence of signs and symptoms consistent with hypogonadism, coupled with biochemical evidence of low morning serum total testosterone levels on two or more occasions, measured with a reliable assay. Testosterone levels show a circadian variation, which persist in aging men [58, 59]. Likewise, testosterone levels are potentially influenced by food intake [60]; hence, serum total testosterone should be measured in fasting conditions and in the morning (between 7.00 and 11.00 hours). Moreover, a confirmatory measurement should always be undertaken in the case of a primary pathological value.

Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) represents the standard and 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 [61]. Conversely, 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 [39]. Liquid chromatography-tandem mass spectrometry remains the standard method for fT determination. Alternatively, fT can be derived from specific mathematical calculations taking into account serum SHBG and albumin levels [62] (<http://www.issam.ch/freetesto.htm>).

Data derived from available meta-analyses have documented that testosterone therapy is ineffective when baseline levels are above 12 nmol/L (3.5 ng/mL). Positive outcomes are documented when testosterone levels are below 12 nmol/L, being higher in symptomatic patients with more severe forms of hypogonadism ($T < 8$ nmol/L). Hence, 12 nmol/L should be considered as a possible cut-off to start with testosterone therapy in the presence of hypogonadal symptoms [21, 63]. As reported above, in the presence of clinical conditions which may potentially interfere with SHBG levels, the evaluation of fT should be considered in order to better estimate of androgen levels (Figure 2). Unfortunately, despite its potential clinical value [64], no validated thresholds for fT are available from clinical studies and this represents an area of uncertainty; however, some data indicate that fT levels below 225 pmol/L (< 6.5 ng/dl) are associated with hypogonadal symptoms [10, 49, 65, 66].

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 forms (Figure 2). Due to its negative influence on libido, PRL can be also be considered as first-line screening in patients with reduced sexual desire. In addition, pituitary magnetic resonance imaging (MRI) scanning, as well as other pituitary hormone evaluation, is required in the presence of specific symptoms such as visual disturbances, headache [67, 68] or when hyperprolactinaemia is confirmed. In addition, limited evidence suggests performing pituitary MRI also in the case of severe hypogonadism (< 6 nmol/L; 1.75 ng/mL) with inadequate gonadotropin levels (Figure 2) [67, 68].

Figure 2: Diagnostic evaluation of Late-Onset Hypogonadism



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

History taking

Specific symptoms associated with LOH are shown in Table 3. Past history of surgical intervention for cryptorchidism or hypospadias must be taken into account as possible signs of congenital defects. Likewise, chronic and systemic comorbid conditions must be comprehensively investigated in every patient. Possible use of drugs potentially interfering with the HPG axis should be ruled out (Table 2). Acute illnesses are associated with the development of functional hypogonadism and the determination of serum total testosterone levels should be avoided in these conditions. Several self-reported questionnaires or structural interviews have been developed for the 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 relatively poor and they should not be used for a systematic screening of hypogonadal men [69].

Table 3: Specific symptoms associated with LOH

	Sexual symptoms	Physical symptoms	Psychological symptoms
More specific	<ul style="list-style-type: none">- Reduced libido- Erectile dysfunction- Decreased spontaneous/morning erections	<ul style="list-style-type: none">- Decreased vigorous activity- Difficulty walking >1 km- Decreased bending	<ul style="list-style-type: none">- Low mood/mood deflection- Decreased motivation- Fatigue
Less specific	<ul style="list-style-type: none">- Reduced frequency of sexual intercourse- Reduced frequency of masturbation- Delayed ejaculation	<ul style="list-style-type: none">- Hot flushes- Decreased energy- Decreased physical strength/function/activity	<ul style="list-style-type: none">- Concentration or mnemonic difficulties- Sleep disturbances

3.5.2 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 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. < 1.00) can be useful to identify a eunochoid 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 the suspicion of hypogonadism [70].

3.5.3 Summary of evidence and recommendations for the diagnostic evaluation of LOH

Summary of evidence
Sexual symptoms are the most specific symptoms associated with LOH.
The diagnosis of LOH should be based on specific signs and symptoms of androgen deficiency, together with consistently low serum testosterone levels.
Functional hypogonadism is a consequence of comorbidities/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.

Recommendations	Strength rating
Check for concomitant diseases, drugs and substances that can interfere with testosterone production/action.	Strong
Total testosterone must be measured in the morning (7.00 and 11.00 hours) and in the fasting state, with a reliable method.	Strong
Repeat total testosterone on at least two separate occasions when below 12 nmol/L and before starting testosterone therapy.	Strong
12 nmol/L total testosterone (3.5 ng/mL) represents a reliable threshold to diagnose late onset hypogonadism (LOH).	Strong
Consider sex hormone-binding globulin and free-testosterone calculation when indicated.	Strong
Calculated free-testosterone < 225 pmol/L has been suggested as a possible cut off for diagnosis of LOH.	Weak
Analyse luteinising hormone and follicle-stimulating hormone serum levels to differentiate between primary hypogonadism and secondary hypogonadism forms.	Strong
Consider prolactin (PRL) measurement if low desire (or other suggestive signs/symptoms) and low or low-normal testosterone is present.	Strong
Perform pituitary magnetic resonance imaging (MRI) in secondary hypogonadism, with elevated PRL or specific symptoms of a pituitary mass and/or presence of other anterior pituitary hormone deficiencies.	Strong
Perform pituitary MRI in secondary severe hypogonadism (total testosterone < 6 nmol/L).	Weak

3.5.4 **Recommendations for screening men with LOH**

Recommendations	Strength rating
Screen for late onset hypogonadism (including in T2DM) only in symptomatic men.	Strong
Do not use structured interviews and self-reported questionnaires for systematic screening for LOH as they have low specificity.	Strong

3.6 **Treatment of LOH**

3.6.1 **Indications and contraindications for treatment of LOH**

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). Acute cardiovascular events as well as uncontrolled or poorly controlled congestive heart failure and severe low urinary tract symptoms (International Prostate Symptom Score (IPSS) score > 19) represent other relative contraindications, as there is not sufficient information on the long-term effects of testosterone therapy in these patients [66]. In addition, a positive familial history for venous thromboembolism requires further analyses in order to exclude a condition of undiagnosed thrombophilia-hypofibrinolysis [71]. These patients need to be carefully counselled prior to testosterone therapy initiation. A haematocrit (HCT) level higher than 54% should require testosterone therapy withdrawal, reduction in dose, change of formulation and venesection depending on the clinical situation in order to avoid any potential cardio-vascular complications. Lower levels of baseline HTC (48-50%) should be carefully evaluated before testosterone therapy initiation, in order to avoid pathological increases during treatment, especially in high-risk men such as those with chronic obstructive pulmonary disease (COPD) or Obstructive Sleep Apnea Syndrome (OSAS). Accordingly, the Framingham Heart Study showed that HTC > 48% represented a condition associated with an increased risk of coronary artery disease (CAD) and mortality and was associated with cardio-vascular disorders [72]. Finally, testosterone therapy suppresses gonadotropins and endogenous testosterone secretion as well as spermatogenesis. Hence, testosterone therapy is contraindicated in individuals who desire fertility [73]. Secondary hypogonadism is characterised by low or inappropriately normal gonadotropin levels; therefore, the rationale is to substitute the gonadotropin deficiency with FSH and LH analogues, if fertility is desired [74].

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 \geq 54% Uncontrolled or poorly controlled congestive heart failure
Relative contraindication	IPSS score $>$ 19 Baseline haematocrit 48-50% Familial history for venous thromboembolism

3.6.2 Testosterone therapy outcomes

3.6.2.1 Sexual dysfunction

Sexual concerns are the main symptoms of the hypogonadal patient [5, 10, 75, 76]. 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 for treating sexual dysfunction in eugonadal men [51, 63, 77, 78]. The beneficial effects on sexual function seems to be more related to testosterone level normalisation rather than the specific testosterone formulations used [78, 79].

A recent meta-analysis of only placebo controlled RCTs using the International Index of Erectile Function (IIEF) [80] as a possible tool for outcome evaluation, 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 a better improvement than patients with milder hypogonadism (i.e., total testosterone $<$ 12 nmol/L). Similar results were observed for sexual desire; however, the presence of metabolic comorbidities (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 [63]. Other sexual function parameters, such as intercourse, orgasm and overall satisfaction, were all improved compared with placebo [63]. Men with comorbidities such as diabetes 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 [5, 78]. However, the specific beneficial effect derived from the combined use of testosterone therapy and PDE5Is is not completely clear [51]. Similarly, information related to the combined use of testosterone therapy with other ED pharmacotherapies is lacking [5, 78].

The Sexual Function Trial of the Testosterone Trials (one of the largest placebo-controlled trials on testosterone therapy) documented consistent improvements in ten of twelve measures of sexual activities in older (\geq 65 years old) hypogonadal men particularly in frequency of intercourse, masturbation and nocturnal erections (as measured by PDQ-Q4) [81]. 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 [82]. Furthermore, a study of 220 men with MetS with or without T2DM also found that sexual function did improve in those men who reported sexual problems with improvement in IIEF scores with specific increases in libido and sexual satisfaction [24].

3.6.2.2 Body composition and metabolic profile

Late onset hypogonadism is associated with a greater percentage fat mass and a lesser lean mass compared to testosterone replete men [83]. The major effect of low testosterone is to increase visceral adiposity but also leads to deposition of lipids in the liver and muscle and is associated with atherosclerosis [19]. As detailed above, a number of published data has suggested that testosterone therapy reduces percentage body fat and increases lean mass [84]. Moreover, testosterone therapy also has been also found to decrease waist circumference, body weight and BMI, with these effects more predominant after twelve months of treatment [84-86]. However, it should be recognised that these results 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 [21].

3.6.2.3 Mood and cognition

Several observational studies have documented a relationship between depressive symptoms, reduced QoL and hypogonadism [87, 88]. However, the specific relationship between hypogonadism and the incidence of

depression is still unclear [88]. 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 [81]. However, the final effect was small in magnitude. In line with this data, the largest meta-analysis of available studies, including 1,890 hypogonadal (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 [89]. The BLAST study of testosterone therapy in T2DM reported that those men with depression were less likely to respond in regard to symptoms of sexual dysfunction compared to men without depression [29].

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 [79, 90].

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 in order to assess possible improvement of several aspects of cognitive function. However, the final results failed to demonstrate any beneficial effect of testosterone therapy in improving cognitive function [81].

3.6.2.4 *Bone*

Evidence suggests that bone mineralisation requires circulating sex steroids within the normal range [91]. 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 [91]. Two independent meta-analyses showed a positive effect of testosterone therapy on bone mass density (BMD), with the highest effect at the lumbar level [92, 93]. Similarly, data derived from TTrials confirmed that testosterone therapy increased BMD in hypogonadal aging men, particularly at the lumbar level [81]. However, available data is insufficient to determine the effect of testosterone therapy alone on the risk of bone fractures [91]. In addition, the use of testosterone therapy as an adjunct to anti-resorptive treatment in hypogonadal patients at high risk of fractures is not established. Therefore, anti-resorptive therapy alone must be the first-choice treatment in hypogonadal men at high risk for bone fractures. The combination of anti-reabsorptive treatment with testosterone therapy should be offered only in conjunction with hypogonadal related symptoms.

3.6.2.5 *Vitality and physical strength*

The role of testosterone in stimulating muscle growth and strength is well-established. Accordingly, androgenic-anabolic steroids (AAS) have been using as performance-enhancing agents for increasing physical performance in several competitive sport [94]. To this aim, testosterone therapy in hypogonadal men has been showed to both increase muscle mass and to reduce fat mass, with limited effects on final weight [21]. Despite this evidence, the role of testosterone therapy in older men with mobility limitations remains unclear. Findings from the National Health and Nutrition Examination Survey 1999-2004 [95] were 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 distance walked in six minutes increased > 50 m or the absolute increase in the distance walked by the 387 subjects enrolled in the physical function trial [81]. However, when the whole population of the TTrials was considered, a significant, although modest, positive effect on these two parameters was reported [81]. Similar data were derived from the Vitality Trial [81].

3.6.2.6 *Summary of evidence and recommendations for testosterone therapy outcome*

Summary of evidence
Testosterone therapy can improve milder forms of ED and libido in hypogonadal men.
Testosterone therapy can improve other sexual symptoms, including intercourse frequency, orgasm and overall satisfaction.
Testosterone therapy can similarly increase lean mass, and reduce fat mass, and improves insulin resistance.
Testosterone therapy may improve weight, waist circumference and lipid profile, but findings are not unique.
Testosterone therapy can improve milder depressive symptoms in hypogonadal men.
Testosterone therapy can improve bone mineral density, but information related to fracture risk is lacking.

Recommendations	Strength rating
The use of testosterone therapy T in eugonadal men is not indicated.	Strong
Use testosterone therapy as first-line treatment in symptomatic hypogonadal patients with milder ED.	Strong
Use the combination of phosphodiesterase type 5 inhibitors and testosterone therapy in more severe forms of ED as it may result in better outcomes.	Weak
Use conventional medical therapies for treating severe depressive symptoms and osteoporosis.	Strong
Do not use testosterone therapy to improve body composition, reduce weight and benefit cardio-metabolic profile.	Weak
Do not use testosterone therapy for improving cognition vitality and physical strength in aging men.	Strong

3.6.3 **Choice of treatment**

3.6.3.1 *Lifestyle factors*

As reported above, functional hypogonadism is frequently associated with obesity and metabolic disorders [96]. 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 is able to revert obesity-associated secondary hypogonadism by increasing total testosterone and fT, reducing oestrogens and restoring normal gonadotropin circulating levels [97]. This was confirmed in a recent updated meta-analysis showing that the increase in testosterone was significantly associated with weight reduction [98]. Similar results can be obtained through physical activity, which is associated with the duration of scheduled exercise and weight loss obtained [98]. However, it should be recognised that the increase in testosterone levels observed after a low calorie diet and physical activity is rather modest (1-2 nmol) [97, 98]. In addition, it should be recognised that from 60% to 86% of weight lost is regained after three years and 75% to 121% after five years [99]. A greater testosterone increase can be achieved through bariatric surgery, which results in an average increase of about 10 nmol/L depending on the degree of weight loss [98]. Lifestyle changes represent a relevant and essential part of the management of obesity; however, some evidence suggests that when compared to lifestyle modifications alone, in obese men, testosterone therapy-treated men benefited most from symptomatic relief of their symptoms associated with testosterone deficiency whereas those not treated did not [74]. Accordingly limited evidence suggests that the combination of life-style interventions and testosterone therapy in symptomatic hypogonadal men might result in better outcomes [83]. In particular, a large placebo-controlled RCT aimed to determine whether testosterone treatment combined with lifestyle intervention or lifestyle intervention alone might reduce T2DM incidence and improve glucose tolerance at two years is ongoing [100]. The results of this RCT will better clarify this point.

3.6.3.2 *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 formulations availability and patient needs and expectations [101].

3.6.3.2.1 *Oral formulations*

The esterification of testosterone with a long-chain fatty acid (testosterone undecanoate; TU) enables testosterone to be absorbed by the intestine through the lymphatic system, by-passing liver metabolism. This formulation has been available in oleic acid since the 1970s, and it has been recently reformulated in a mixture of castor oil and propylene glycol laureate (TU caps), to allow the drug to be maintained at room temperature without any degradation of the product [102]. The main limitation is related to the poor bioavailability, which is strongly dependent on the dietary fat content [102]. Recently, the US Food and Drug Administration (FDA) approved a new formulation of oral TU incorporating a liquid-filled hard capsule drug delivery system and containing a higher amount (225 mg) of the compound, which improves oral availability (<https://www.fda.gov/media/110187/download>). In an open label study of approximately four months duration (NCT02722278), 145 (87%) of 166 hypogonadal men enrolled who received the TU caps formulation had mean total testosterone concentration within the normal eugonadal range at the end of treatment (<https://www.fda.gov/media/110187/download>). However, the TU caps compound is not available in Europe.

Mesterolone is a 5 α -DHT derivate available for oral administration. Along with DHT, it cannot be converted to oestrogens and can be used for a limited period and specific indications, such as the presence of painful gynecomastia. However, the lack of a full spectrum of testosterone bioactivity strongly limits its long-term use [102].

3.6.3.2.2 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 mg, every two to three days), thus representing a major limitation for its use [102]. 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 - Sustanon®) which allows some benefit of a smoother 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, often reported as unpleasant by patients and potentially resulting in side effects, such as polycythemia [102, 103]. A longer lasting TU injectable formulation is widely available [102]; this formulation has been demonstrated to have a very good safety/benefit profile allowing the maintenance of normal stable testosterone levels with a dosing regimen 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 >12nmol/L and less than 18nmol/L at that time point [102, 104].

3.6.3.2.3 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 [102]. In addition, the introduction of specific devices and skin enhancers has resulted in better skin penetration of the drugs, thus reducing potential side effects. Adverse local skin side effects are limited when compared to testosterone patches, but they potentially allow transference of testosterone during close contact with the skin's 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) [102]. Moreover, in order 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% [102]. 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 [102]. This testosterone formulation is not available in Europe. Testosterone levels should be monitored to optimise the testosterone dose. Blood collection is best taken between 2-4 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 site of the venepuncture 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 2-3 days. Similar to what reported for mesterolone, DHT is not aromatised but can be useful for treating particular conditions, such as gynecomastia and micropallus [102].

3.6.3.2.4 Transmucosal formulations

3.6.3.2.4.1 Transbuccal Testosterone preparations

A testosterone buccal system is still available in several countries. It consists on 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 edema, blistering and gingivitis [102].

3.6.3.2.4.2 Transnasal testosterone preparations

A gel for intranasal administration is available in some countries, including the USA and Canada. It requires administration two or three times a day using a specific metered-dose pump. The application is rapid, non-invasive, convenient, and avoids secondary transference observed with other topical products [102].

3.6.3.2.5 Subdermal depots

The implantation of testosterone pellets, available in the USA, UK and Australia, represents the longest available testosterone formulation lasting from four to seven months. However, the procedure is invasive and may be unattractive to patients [102].

3.6.3.2.6 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. Essentially, 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 [98]. 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 HPG [96]. 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 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 [102]. 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 thromboembolic disease [102]. In this context patients should be warned of the potential increased risk of venous thromboembolic disorders although data is lacking. Long-term use of these agents can lead to reduced bone density and the development of osteoporosis potentially increasing fracture risk.

3.6.3.2.7 Gonadotropins

Considering the aforementioned limitations regarding the use of anti-oestrogens, gonadotropin therapy should be considered the standard treatment in men with secondary hypogonadism who desire paternity (Table 5) [102]. The treatment is based on the use of human chorionic gonadotropin (hCG), purified from the urine of pregnant women. The most expensive recombinant hCG (rhCG) and LH (rhLH) formulations do not offer clinical advantages [102]. According to a meta-analysis of the available evidence, the use of hCG should be administered with FSH as the combined therapy results in better outcomes. Similar to hCG, the use of recombinant FSH (rFSH) does not seem not to offer any advantages compared to urinary-derived preparations [105]. More details on the use of gonadotropins is provided in section 9.

Table 5: Available preparations for hypogonadism treatment

Formulation	Chemical structure	T 1/2	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 in men	NA	
Luteotropic hormone (LH)					
Recombinant	Human recombinant LH	NA	No data in men	NA	
Follicle-stimulating hormone (FSH)					
Extractive	FSH purified from the urine of pregnant women	NA	75-150 IU 3 times/week	High cost	Multiple weekly administration
Recombinant	Human recombinant FSH	NA	75-150 IU 3 times/week	High cost	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 of meal fat content - Has to be taken with meals
Mesterolone	1 α -methyl-4, 5 α -dihydro-testosterone	12 hours	50-100 mg 2-3 times daily	- Oral convenience - Modifiable dosage - Useful in gynecomastia	- 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 side-effects	- Fluctuations in circulating testosterone levels - Multiple injections - Relative risk of polycythemia
Testosterone cypionathe	17- α -hydroxylester	8 days	200 mg every 2-3 weeks	- Low cost - Short-acting preparation allowing drug withdrawal in case of side-effects	- Fluctuations in circulating testosterone levels - Multiple injections - Relative risk of polycythemia
Testosterone propionate	17- α -hydroxylester	20 hours	100 mg every 2 days	- Low cost - Very short-acting preparation allowing drug withdrawal in case of side-effects	- Fluctuations in circulating testosterone levels - Multiple injections - Relative risk of polycythemia
Testosterone ester mixture Propionate (30mg) Phenylpropionate (60 mg) Isocaproate (60 mg) Decanoate (100 mg)	4-androsten-3-one-17 beta-hydroxy-androst-4-en-3-one	4-5 days	250 mg every 3 weeks	- Low cost - Short-acting preparation allowing drug withdrawal in case of side-effects	- Fluctuations in circulating testosterone levels - Multiple injections - Relative risk of polycythemia
Testosterone undecanoate in castor oil	17- α -hydroxylester	34 days	1000 mg every 10-14 weeks *750 mg every 10 weeks	- Steady-state testosterone level without fluctuation - Long-lasting - Less frequent administration	- Pain at injection site - Long-acting preparation not allowing rapid drug withdrawal in case of side-effects
Surgical implants	Native testosterone	--	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	Steady-state testosterone level without fluctuation	- Possible transfer during intimate contact - Daily administration
Underarm testosterone (testosterone solution 2%)	Native testosterone	NA	60-120 mg/day	Steady-state testosterone level without fluctuation	- Possible transfer during intimate contact - Daily administration
Dihydro-testosterone gel 2.5%	Native dihydro-testosterone	NA	34-70 mg/day	- Steady-state testosterone level without fluctuation - Useful in gynecomastia	- 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	Steady-state testosterone level without fluctuation	- Nasal irritation - Multiple daily administration

NA = not applicable.

3.6.3.3 Summary of evidence and recommendations for LOH choice of treatment

Summary of evidence
Weight loss obtained through a low calorie diet and physical activity result in a small improvement in testosterone levels.
Testosterone gels and long-acting injectable TU represent testosterone preparations with the best safety profile.
Gonadotropin treatment can be used to restore fertility in men with secondary hypogonadism.

NA = not applicable.

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

3.7 Safety and follow up in hypogonadism management

3.7.1 Hypogonadism and fertility issues

The aim of the pharmacological management of hypogonadism is to increase testosterone levels. The first choice is to administer exogenous testosterone. However, while exogenous testosterone provides benefits to the clinical symptoms of hypogonadism, it also inhibits gonadotropin secretion by the pituitary gland, resulting in impaired spermatogenesis and sperm cell maturation [106]. Therefore testosterone therapy is contraindicated in hypogonadal men seeking fertility treatment [73]. When secondary hypogonadism is present, gonadotropin therapy can maintain normal testosterone levels and restore sperm production [5].

3.7.2 Male breast cancer

In vitro and *in vivo* studies have clearly documented that breast cancer growth is significantly influenced by testosterone and/or by its conversion to E2 through different mechanisms and pathways [107]. Accordingly, the use of SERMs still represents an important therapeutic option in the management of this cancer [107]. 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.

3.7.3 Lower urinary tract symptoms/benign prostatic hyperplasia

Based on the assumption that prostate growth is dependent on the presence of androgens, historically testosterone therapy has raised some concerns regarding the possibility of aggravating lower urinary tract symptoms (LUTS) in patients affected by benign prostatic hyperplasia (BPH) [70, 108]. However, pre-clinical and clinical data has indicated that low rather than higher androgen levels may decrease bladder capacity, alter tissue histology and decrease the ratio of smooth muscle to connective tissue, impairing urinary dynamics [70, 108].

A trial of 60 patients undergoing testosterone therapy for six months showed no significant differences in post-voidal residual urine and prostate volume, while storage symptoms as measured by the IPSS significantly improved, despite an increase in PSA level. A larger pre-treatment prostate volume was a predictive factor of improvement in LUTS [109]. A long-term study of 428 men undergoing testosterone therapy for eight years demonstrated significant improvements in IPSS score, no changes in Q_{max} and residual urine volume, but also a significant increase in prostate volume [110]. Similarly data from the Registry of Hypogonadism in Men (RHYME), including 999 subjects with a follow-up of three years, did not document any difference in prostate-specific antigen (PSA) levels, total IPSS score in men undergoing testosterone therapy, compared to those untreated [111]. Similar results were reported in an Italian registry (SIAMO-NOI), collecting data from 432 hypogonadal men from fifteen centres [112]. Accordingly, available meta-analyses did not find significant changes in LUTS compared to placebo [113-119]. On the basis of the most recent literature, there are no grounds to discourage testosterone therapy in hypogonadal patients with BPH/LUTS; instead there is evidence of limited benefit from androgen administration. The only concern is related to patients with severe LUTS (IPSS score >19), as these patients are usually excluded from RCTs, therefore limiting the long-term safety data of testosterone therapy in these subjects [70].

3.7.4 **Prostate cancer (PCa)**

A considerable number of observational studies have failed to demonstrate any association between circulating higher testosterone levels and PCa [120]. On the other hand, analytical studies aimed at investigating the relationship between low levels of testosterone and the 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 disease [120]. This peculiar pattern was also reported in previous trials such as the Health Professionals Follow-up Study, the PCPT and by the Reduction by Dutasteride of Prostate Cancer Events (REDUCE), with varying magnitudes of significance [121].

The most recent 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 an increased risk of PCa. However, a one-year follow-up may be considered too short a time to draw conclusions on PCa occurrence. Furthermore, the analysis was also restricted to studies with longer than one-year follow-up, but no significant changes in PSA levels nor increased risk of PCa were found [114]. Furthermore, at five-year median follow-up in three independent registry studies with more than 1,000 patients undergoing testosterone therapy, PCa occurrence remained at all times well below the reported incidence rate in the general population [122]. Similar results were reported by a more recent large observational study including 10,311 men treated with testosterone therapy and 28,029 controls with a median follow-up of 5.3 years [123]. In addition, the same study, also showed that the risk of PCa was decreased for those subjects in the highest tertile of testosterone therapy cumulative dose exposure compared with controls [123].

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 length, small sample sizes, lack of control arms, heterogeneity in study population and treatment regimen, etc.) [124]. More recently, a meta-analysis derived from thirteen studies including 608 patients, of which 109 had a history of high-risk PCa, with a follow-up ranging from one to 189.3 months [125] suggested that testosterone therapy did not increase the risk of biochemical recurrence, but the available evidence is very poor, limiting data interpretation [125]. Similar considerations can be derived from another meta-analysis including a larger number of studies ($n=21$) [126]. It is important to recognise that the vast majority of studies analysed, included low-risk patients with Gleason score < 8 [125].

In conclusion, recent literature does not support an increased risk of PCa in hypogonadal men undergoing testosterone therapy. On the other hand, while it is obviously necessary to avoid testosterone administration in men with advanced PCa, insufficient long-term prospective data on the safety of androgen administration in PCa survivors [126], without disease recurrence should prompt caution in choosing to treat symptomatic hypogonadal men in this setting. Specifically, patients should be fully counselled that the long-term effects of testosterone therapy in this setting are still unknown and requires further investigation. If the presence of an occult PCa is not detected before initiation of testosterone therapy, treatment may unmask the cancer detected by an early rise in PSA over six to nine months of therapy. 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 adequately discussed with the patients and limited to low-risk subjects.

3.7.5 **Cardiovascular Disease**

Evidence suggests that hypogonadal men have an increased risk of CVD [127, 128]. Whether or not LOH is a cause or consequence of atherosclerosis has not been clearly determined. Late-onset hypogonadism

is associated with CV risk factors which include central obesity, insulin resistance and hyperglycaemia, dyslipidaemia (elevated total cholesterol, LDL-cholesterol, triglycerides and low HDL-cholesterol), pro-thrombotic tendency and a chronic inflammatory state [129]. Atherosclerosis itself is a chronic inflammatory disease, which releases pro-inflammatory cytokines into the circulation which are known to suppress testosterone release from the HPG axis. Evidence from RCTs using testosterone therapy in men with MetS and/or T2DM have demonstrated some benefit in CV risk including a reduction in central adiposity, insulin resistance, total and LDL-cholesterol and suppression of circulating cytokines [14, 23-25, 29, 129]. However, due to the equivocal nature of these studies, testosterone therapy cannot be recommended for indications outside the specific symptoms.

Published data show that LOH is associated with an increase in all-cause and CVD-related mortality [12, 130-133]. These studies are supported by a meta-analysis which concluded that hypogonadism is a risk factor for cardiovascular mortality [134] and morbidity [118]. Importantly, men with low testosterone when compared to eugonadal men with angiographically proven coronary disease have twice the risk of earlier death [128]. 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 the combined data from the lower three quartiles [130]. Androgen deprivation therapy for PCa is linked to an increased risk of CV events and sudden death [135]. Conversely, two long-term epidemiological studies reported reduced cardiovascular events in men with high normal serum testosterone levels [136, 137]. Erectile dysfunction is independently associated with CVD and may be the first clinical presentation of a male with atherosclerosis.

The knowledge that men with hypogonadism and/or ED may have underlying CVD should prompt an individual assessment of their CV risk profile. Individual risk factors (e.g. lifestyle, diet, exercise, smoking, hypertension, diabetes, dyslipidaemia) should be assessed and treated in men with pre-existing CVD and in patients treated with androgen deprivation therapy. Cardiovascular risk reduction can be managed by primary care clinicians, but they should be appropriately counseled by clinicians active in prescribing testosterone therapy [75]. If appropriate, they could be referred to cardiologist for risk stratification and treatment of co-existent comorbidities.

There are no RCTs that provide a clear answer, on whether testosterone therapy affects cardiovascular outcomes. The Trial (n=790) a study in older men [138], the TIMES2 (n=220) [24] and the BLAST studies in men with MetS and T2DM and the pre-frail and frail study in elderly men - all of one-year duration - did not reveal any increase in Major Adverse Cardiovascular Events (MACE) [24, 27, 138, 139]. In this context, MACE is defined as the composite of cardiovascular death, non-fatal acute myocardial infarction, acute coronary syndromes, stroke and cardiac failure. Randomised controlled trials between three and twelve months in men with known heart disease treated with testosterone have not found an increase in MACE events but did report improvement in cardiac ischaemia, angina and functional exercise capacity [140-142]. The European Medicines Agency (EMA) has stated '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 who lack the hormone (a condition known as hypogonadism). 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 medicines.' [143].

As a whole, as for MACE, current available data from interventional studies suggest that there is no increased risk with testosterone therapy with up to three-years of therapy [144-147]. The weight of the currently available published evidence has reported that testosterone therapy in men with diagnosed hypogonadism has neutral or beneficial actions on MACE in patients where the testosterone levels have been normalised. However, these findings could be considered sufficiently reliable for a three-year course of testosterone therapy, after which no available study may exclude further or long-term CV events [148, 149].

3.7.5.1 *Cardiac Failure*

Testosterone treatment is contraindicated in men with severe chronic cardiac failure because fluid retention may lead to an exacerbation of the condition. Some studies including one of twelve month's duration have shown that men with moderate chronic cardiac failure may benefit from low doses of testosterone, which achieve mid-normal range testosterone levels [141, 150, 151]. 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. An interesting observation is that untreated hypogonadism increased the re-admission and mortality rate in men with heart failure [152].

3.7.6 **Erythrocytosis**

An elevated haematocrit is the most common side effect of testosterone therapy. Stimulation of erythropoiesis is a normal biological action, which 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 mode of formulation from topical to parenteral administration and if there is the development of a 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 on health. If the haematocrit exceeds 54% there is a testosterone independent, but weak associated rise in CV events and mortality [72, 153-155]. Any relationship is complex as these studies were based on subjects with any cause of secondary polycythaemia, which included smoking and respiratory diseases. There have been no specific studies including men with only testosterone-induced erythrocytosis.

Three large studies have not shown any evidence that testosterone therapy is associated with an increased risk of venous thromboembolism [156, 157]. However, one study showed that an increased risk was observed peaking at six months after initiation of testosterone therapy, then declining over the subsequent period [158]. No study reported whether or not there was monitoring of the haematocrit, testosterone and/or E2 levels. High endogenous testosterone or E2 levels have not been associated with a greater risk of venous thromboembolism [159]. In one study venous thromboembolism was reported in 42 cases and 40 of these had a diagnosis of an underlying disorder of thrombophilia (including Factor V Leiden deficiency, prothrombin mutations, homocysteinuria) [160]. In an RCT of testosterone therapy in men with chronic stable angina there was no adverse effects on coagulation, by assessment of tissue plasminogen activator or plasminogen activator inhibitor-1 enzyme activity or fibrinogen levels [161]. A meta-analysis of RCTs of testosterone therapy reported that cases of venous thromboembolism were frequently related to underlying undiagnosed thrombophilia-hypofibrinolysis disorders [71].

With testosterone therapy an elevated haematocrit is more likely to occur if the baseline level is toward the upper limit of normal prior to initiation of therapy. Added risks for a raised haematocrit on testosterone therapy include factors, such as smoking or respiratory conditions at baseline. Higher haematocrit values are more common on parenteral rather than topical formulations. 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 the haematocrit over treatment.

An elevated haematocrit in the absence of any co-morbidities or acute cardiovascular 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) and repeated if necessary, with usually no need to stop the testosterone therapy.

3.7.7 **Obstructive Sleep Apnoea**

There is also no evidence that testosterone therapy can result in the onset or worsening of sleep apnoea. It has been demonstrated that combined therapy with Continuous Positive Airway Pressure (CPAP) with the addition of testosterone gel was more effective than CPAP alone in the treatment of obstructive sleep apnoea [162]. 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 [163].

3.7.8 **Follow up**

Testosterone replacement therapy in hypogonadal men has proven to be effective in alleviating symptoms and signs in a specific time-dependent manner. The TTrial clearly showed that testosterone therapy may result in improvement of sexual symptoms as early as three months after testosterone therapy initiation [81]. Similar results have been derived from available meta-analyses [51, 71]. 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). Table 6 summarises the clinical and biochemical parameters that should be monitored during testosterone therapy.

Trials 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 [81]). This approach resulted in a good benefit/risk ratio. Accordingly, a similar approach could be considered during follow-up. The correct timing for testosterone levels evaluation can vary according to the type of testosterone preparation used (Table 5). Testosterone is involved in the regulation of

erythropoiesis [103] and prostate growth [70], 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 very low. Similarly, the risk of dying for PCa in men older than 70 years has not been considered high enough to warrant monitoring in the general population [164]. Hence, the screening for PCa through the determination of PSA and DRE in men younger than 40 older than 70 years during testosterone therapy should be discussed with the patients.

Baseline and, at least, annually glyco-metabolic profile evaluation may be a reasonable consideration, particularly in the management of functional hypogonadism. Moreover, since testosterone therapy may be beneficial for hypogonadal men with low or moderate fracture risk [91], dual energy X-ray absorptiometry (DEXA) bone scan may be also considered at baseline and 18-24 months following testosterone therapy, particularly in those subjects with more severe hypogonadism [91].

Digital rectal examination may detect prostate abnormalities, which can be present even in men with normal PSA values. Hence DRE is mandatory in all men at baseline and during testosterone therapy justify. The decision to stop testosterone therapy or to perform 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% over testosterone therapy requires testosterone therapy withdrawal and phlebotomy in order to avoid potential side effects including venous-thromboembolism and CV events especially in high-risk subjects. In patients with lower risk the situation can be alternatively managed by reducing testosterone dose and by switching formulation along with venesection. A positive family history of venous-thromboembolism should be carefully investigated and the patient counselled in regard to testosterone therapy in order to avoid/prevent a condition of thrombophilia-hypofibrinolysis [71]. Finally, caution should be used in men with pre-existing CVD or at higher risk of CVD

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

Parameters	1 st year of treatment	After the first year of treatment			
	Baseline	3 months	6/12 months	Annually	18-24 months
Clinical					
Symptoms	X	X	X	X	
Body Mass Index					
Waist circumference	X	X	X	X	
Digital rectal examination	X	X	X	X	
Blood pressure	X	X	X	X	
Biochemistry					
PSA (ng/ml)	X	X	X	X	
Haematocrit (%)	X	X	X	X	
Testosterone	X	X	X	X	
Lipid and glycemc profile	X		X	X	
Instrumental					
DEXA	X				X

3.7.9 Summary of evidence and recommendations on risk factors in testosterone treatment

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

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 benefits and lack of sufficient safety data on long-term follow-up.	Weak
Restrict treatment to patients with a low risk for recurrent PCa (i.e., Gleason score < 8; pathological stage T1-2; pre-operative PSA < 10 ng/mL) and should start after at least one year follow-up with a PSA level < 0.01 ng/mL.	Weak
Safety data on the use of testosterone therapy in men treated for breast cancer are unknown.	Strong
Assess for cardiovascular risk factors before commencing testosterone therapy.	Strong
Assess men with known cardiovascular disease (CVD) for cardiovascular symptoms before testosterone therapy and with close clinical assessment and evaluation during treatment.	Strong
Treat men with hypogonadism and pre-existing CVD, venous-thromboembolism or chronic cardiac failure, who require testosterone therapy with caution, by careful clinical monitoring and regular measurement of haematocrit (not exceeding 54%) and testosterone levels.	Weak
Exclude a family history of venous-thromboembolism before commencing testosterone therapy.	Strong
Monitor testosterone, haematocrit at three, six and twelve months after testosterone therapy initiation, and thereafter annually. A haematocrit more than 54% should require testosterone therapy withdrawal and phlebotomy. Reintroduce testosterone therapy at a lower dose once the haematocrit has normalised and consider switching to topical testosterone preparations.	Strong

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 [165]. Among others, the Massachusetts Male Aging Study (MMAS) [166] 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% [167]. The incidence rate of ED (new cases per 1,000 men annually) was 26 in the long-term data from the MMAS study [168] and 19.2 (mean follow-up of 4.2 years) in a Dutch study [169]. In a cross-sectional real-life study among men seeking first medical help for new-onset ED, one in four patients was younger than 40 years, with almost 50% of the young men complaining of severe ED [170]. Differences between these studies can be explained by differences in methodology, in the ages, and socio-economic and cultural status of the populations studied. The prevalence rates of ED studies are reported in Table 7.

4.2 Premature ejaculation

As evidenced by the highly discrepant prevalence rates reported in Table 8 [171], the method of recruitment for study participation, method of data collection and operational criteria can all greatly affect reported prevalence rates of premature ejaculation (PE). The major problem in assessing the prevalence of PE is the lack of a universally recognised definition at the time the surveys were conducted [172]. Vague definitions without specific operational criteria, different manners of sampling, and non-standardised data acquisition have led to tremendous heterogeneity in estimated prevalence [172-176]. The highest prevalence rate of 31% (men aged 18-59 years) was found by the National Health and Social Life Survey (NHSLs) study, which determines adult sexual behavior in the United States [177]. Prevalence rates were 30% (18-29 years), 32% (30-39 years), 28% (40-49 years) and 55% (50-59 years). It is, however, unlikely that the PE prevalence is as high as 20-30% based on the relatively low number of men who present seeking 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 [178]. Two separate observational, cross-sectional surveys from different continents found the overall prevalence of the complaint of PE to be

19.8 and 25.80%, respectively [179, 180]. Further stratifying these complaints into the classifications defined by Waldinger *et al.* [181], lifelong PE was seen at rates of 2.3 and 3.18%, while the rates of acquired PE were 3.9 and 4.48%, variable PE were 8.5 and 11.38% and subjective PE were 5.1 and 6.4% [179, 180]. Both studies showed that men with acquired PE were more likely to seek treatment compared to men with lifelong PE. Treatment seeking behaviour may contribute to errors in the previously reported rates of PE, as it is possible that men with lifelong PE come to terms with their problem and not seek treatment. The additional psychological burden of a new change in ejaculatory latency in acquired PE on the other hand may prompt more frequent treatment seeking behaviours [182]. Thus, it is likely that a disparity between the incidence of the various PE sub-types in the general community and in men actively seeking treatment for PE exists [183, 184]. This disparity could be a further barrier to understanding the true incidence of each sub-type of PE. An approximately 5% prevalence of acquired PE and lifelong PE in general populations is consistent with epidemiological data indicating that around 5% of the population have an ejaculation latency of less than two minutes [185].

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 [186]. However, several well-designed epidemiologic studies revealed that its prevalence is around 3% among sexually active men [177, 187]. According to data from the NHSLs, 7.78% of a national probability sample of 1,246 men between the ages of 18 and 59 years reported "inability achieving climax or ejaculation" [177]. In a similar study where a 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 the inability to reach orgasm. In an international survey of sexual problems among 13,618 men aged 40-80 years from 29 countries, 1.1 to 2.8% of men reported that they frequently experience the inability to reach orgasm [188]. Another study conducted in the United States, where a national probability sample of 1,455 men aged 57 to 85 years was recruited, 20% of men reported the inability to climax and 73% of them reported that they were bothered by this problem. [189]. Considering the findings of these epidemiologic studies and their clinical experiences, some urologists and sex therapists postulated that the prevalence of DE may be higher among older men [190-192]. Similar to the general population, the prevalence of men with the complaint of DE is also small among patients who seek treatment for their sexual problems. An Indian study that evaluated the data on 1,000 consecutive patients with sexual disorders who attended a psychosexual clinic demonstrated that the prevalence of DE was 0.6% and it was observed more frequently in elderly diabetics [193]. Nazareth *et al.* [194] evaluated the prevalence of International Classification of Diseases 10th edition (ICD-10) diagnosed sexual dysfunctions among 447 men attending 13 general practices in London, and the authors found that 2.5% of the men reported inhibited orgasm during intercourse.

4.3.2 Anejaculation and Anorgasmia

Establishing the exact prevalence of anejaculation and anorgasmia is very 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 [177].

According to Kinsey *et al.* [195], 0.14% of the general population have anejaculation. The most common causes of anejaculation were reported as 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 [196].

4.3.3 Retrograde ejaculation

Similar to anejaculation, it is very difficult to estimate the true incidence of retrograde ejaculation (RE). Although RE is generally reported in 0.3% to 2% of patients attending fertility clinics [197], diabetes may increase these rates by leading 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 [198]. In 54 diabetic patients with sexual dysfunction, RE was observed with a 6% incidence [199]. In a more recent controlled trial, RE was observed in 34.6% of diabetic men [200]. 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. In a study that investigated the effect of prostatectomy on QoL it was found that of 5,276 men after TURP, 68% reported postsurgical RE [201]. However, with the development of less invasive techniques, the incidence of RE decreases following the surgical treatment of LUTS [202, 203].

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 and 10% in the general population [204-206]; however, it may increase to 30-75% among men who suffer from chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) [207-211]. It should be noted that the design of the majority of these papers is not scientifically sound and the condition is 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 are difficult to elucidate due to a number of factors including its covert presentation, usually self-limiting nature and patient embarrassment. The symptom represents approximately 1-1.5 % of all urological referrals and occurs in all age groups with a mean age of 37 years [212, 213]. In a PCa screening study of 26,126 men, ~ 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 [214].

4.4 Low sexual desire

The global prevalence of low sexual desire in men ranged from 3-28% [188, 215, 216]. Overall, low solitary versus low dyadic sexual desire, have been reported in 68% and 14% of men, respectively [217]. Also, low sexual desire has been observed as a common complaint in gay men, with its prevalence ranging from 19% to 57% [218, 219]. Despite its relationship with age, low sexual desire has been reported even among young men (i.e., 18-29 years old), with prevalence rates ranging from 6% to 19% [177, 220, 221].

Table 7: The prevalence rates of erectile dysfunction [165]

Date	Authors	Population	Response rate	Age (years)	Measurement technique	Principal findings	Correlates
1993	Solstad <i>et al.</i> [222, 223]	439 men; random population sample (Denmark)	81%	51	Interview and self-administered questionnaire	Overall, 4% of men had ED as assessed by questionnaire Interviews identified a higher frequency of sexual dysfunction	Not reported
1994	Feldman <i>et al.</i> [166] *MMAS	1,290 men; random population sample (United States)	40%	40-70	Self-administered questionnaire	Overall, 52% of men had ED 17.2% of men had minimal ED 25.2% of men had moderate ED 9.6% of men had complete ED	Age
1995	Panser <i>et al.</i> [224]	2,155 men; random population sample (United States)	55%	40-79	Self-administered questionnaire	1% ED in men aged 40-49 years 6% ED in men aged 50-59 years 22% ED in men aged 60-69 years 44% ED in men aged 70-79 years	
1996	Helgason <i>et al.</i> [225]	319 men; random population sample (Sweden)	73%	50-80	Self-administered questionnaire	3% ED in men aged 50-59 years 24% ED in men aged 60-69 years 49% ED in men aged 70-80 years	Age, Prostate cancer, Diabetes, Myocardial infarction, Diuretic use, Warfarin use, H2 receptor blocker use

1996	MacFarlane <i>et al.</i> [226]	1,734 men; random population sample (France)	86%	50-80	Self-administered questionnaire	20% ED in men aged 50-59 years 33% ED in men aged 60-69 years 38% ED in men aged 70-80 years	Age
1996	Fugl-Meyer [215]	1,288 men; random population sample men (Sweden)	52%	18-74	Structured interview	Overall, 5% of men had ED 3% ED in men aged 18-24 years 2% ED in men aged 25-34 years 2% ED in men aged 35-49 years 7% ED in men aged 50-65 years 24% ED in men aged 66-74 years	Age
1999	Laumann <i>et al.</i> [177] *NHSLS	1,244 men; random population sample (United States)	70%	18-59	Structured interview	Overall, 10% of men had ED (moderate plus severe) 7% ED in men aged 18-29 years 9% ED in men aged 30-39 years 11% ED in men aged 40-49 years 18% ED in men aged 50-59 years	Age, Race, Emotional stress, Urinary symptoms, Poor health, Low income
1999	Pinnock <i>et al.</i> [227]	427 men; random population sample (Australia)	69.8%	> 40	Self-administered questionnaire	6% ED in men aged 40-49 years 12% ED in men aged 50-59 years 41% ED in men aged 60-69 years 63% ED in men aged 70-79 years 81% ED in men aged 80+ years	Age, Hypercholesterolemia,
2000	Braun <i>et al.</i> [167] (COLOGNE Study)	8,000 men	56%	30-80	The self-administered questionnaire by mail (Cologne ED Questionnaire)	The prevalence of ED was 19.2%	Age, Hypertension, Diabetes, Pelvic surgery, LUTS
2001	Moreira <i>et al.</i> [228]	1,170 men; attending public places (heavy bias toward younger men) (Brazil)	91%	>18	Self-administered questionnaire	Overall, 14.7% of men had ED (moderate plus severe); 9.4% ED in men aged 18-39 years 15.5% ED in men aged 40-49 years 22.1% ED in men aged 50-59 years 37% ED in men aged 60-69 years 39.6% ED in men aged >70 years	Age, Education, Racial origin, Diabetes, Hypertension, Depression

2001	Meuleman <i>et al.</i> [229]	1,233 men; random population sample (the Netherlands)	70%	40-79	Self-administered questionnaire	Overall, 13% of men had ED 6% ED in men aged 40-49 years 9% ED in men aged 50-59 years 22% ED in men aged 60-69 years 38% ED in men aged 70-79 years	Age
2001	Blanker <i>et al.</i> [205, 230]	1,688 men; random population sample (the Netherlands)	50%	50-75	Self-administered questionnaire	3% ED in men aged 50-54 years 5% ED in men aged 55-59 years 11% ED in men aged 60-64 years 19% ED in men aged 65-69 years 26% ED in men aged 70-78 years	Age, Smoking, Obesity, LUTS, COPD, Treatment for CV disease
2001	Martin-Morales <i>et al.</i> [231]	2,476 men; random population sample (Spain)	75%	25-70	Self-administered questionnaire and single question	Overall, 12.1% of men had ED (single question) and 18.9% for questionnaire According to single question: 3.9% ED in men aged 25-39 years 6.3% ED in men aged 40-49 years 15.9% ED in men aged 50-59 years 32.2% ED in men aged 60-70 years IIEF identified more mild ED, and single question identified more moderate and severe ED	Age, Hypertension, Diabetes, Cardiac disease, Pulmonary disease, Circulatory disease, Rheumatic disease, High cholesterol, Prostatic disease, Allergy, Medication "for nerves", Sleeping tablets, Heavy smoking, Alcohol abuse
2002	Moreira <i>et al.</i> [232]	602 men; random population sample (Brazil)	92%	40-70	Interview	Overall, 14.4% of men had ED (moderate or severe) 9.9% ED in men aged 40-49 years 11.8% ED in men aged 50-59 years 31.7% ED in men aged 60-69 years	Age, Marital status, Diabetes, Depression, IPSS, Decreased physical activity

2002	Moreira <i>et al.</i> [233]	342 men; random population sample (Brazil)	47.6%	40-70	Self-administered questionnaire	Overall, 12.0% of men had ED (moderate or severe) 3.5% ED in men aged 40-49 years 16.7% ED in men aged 50-59 years 39.6% ED in men aged 60-69 years	Age, Diabetes, Hypertension, Heavy smoking
2002	Morillo <i>et al.</i> [234]	1,963 men; random population sample (Columbia, Venezuela and Ecuador)	82%	> 40	Standardised questionnaire	Overall, 19.8% of men had ED (moderate or severe)	Age, Diabetes, Hypertension, BPH
2003	Richters <i>et al.</i> [235]	8,517 men; random population sample (Australia)	69.4%	16-59		Overall, 9.5% of men had ED 4.3% ED in men aged 16-19 years 4.5% ED in men aged 20-29 years 5.1% ED in men aged 30-39 years 12.5% ED in men aged 40-49 years 19.2% ED in men aged 50-59 years	Age
2003	Rosen <i>et al.</i> [236]	12,815 men; random population sample (multinational: United States, United Kingdom, France, Germany, the Netherlands, Italy, Spain)	36.8%	50-80	Self-administered questionnaire (IIEF and DAN-PSS)	According to DAN-PSS: Overall, 48.9% of men had ED 30.8% ED in men aged 50-59 years 55.1% ED in men aged 60-69 years 76% ED in men aged 70-80 years	Age, LUTS, Diabetes, Hypertension, Cardiac disease, Hyperlipidemia, Tobacco use
2004	Rosen <i>et al.</i> [237] *MALES	27,839 men random population sample (multinational: United States, United Kingdom, Germany, France, Italy, Spain, Mexico, and Brazil)	US: 45%; UK: 48%; Germany: 45%; France: 48%; Italy: 53%; Spain: 50%; Mexico: 55% and Brazil: 51%.	20-75	Random digit dialing and interviewed via computer-assisted telephone interviewing. A standardised questionnaire	The overall prevalence of ED in the MALES sample was 16%	Age, High blood pressure, Heart trouble or angina, High cholesterol, Diabetes, Depression or anxiety

2004	Shiri <i>et al.</i> [238]	2,198 men; stratified birth cohort (Finland)	70%	50,60, and 70 at first survey 55, 65, and 75 at second survey	Self-administered questionnaire at two separate time points, 5 years apart	48% of men had minimal ED 15.2% of men had moderate ED 13.2% of men had complete ED	Age, Diabetes, Hypertension, Heart disease, Cerebrovascular disease, Smoking
2005	Laumann <i>et al.</i> [188] *GSSAB	13,750 men; random population sample (world)	19%	40-80	Telephone survey (random dialed digit)	Overall: In Northern Europe, 13.3% had ED In Southern Europe, 12.9% had ED In non-European West, 20.6% had ED In Central/South America, 13.7% had ED In Middle East, 14.1% had ED In East Asia, 13.3% had ED In Southeast Asia, 28.1% had ED	Age
2005	Moreira <i>et al.</i> [239]	750 men; random population sample (Spain)	23%	40-80	Telephone survey (random digit dialing)	Overall, 12.7% had ED	Age
2005	Moreira <i>et al.</i> [240]	750 men; random population sample (Germany)	17.4%	40-80	Telephone survey (random digit dialing)	Overall, 7.9% had ED	Age
2005	Moreira Junior <i>et al.</i> [241]	471 men; random population sample (Brazil)	18%	40-80	Telephone survey (random digit dialing)	Overall, 13.1% of men had ED	Age, Depression
2006	Brock <i>et al.</i> [242]	500 men; random population sample (Canada)	9.7%	40-80	Telephone survey (random digit dialing)	Overall, 16% of men had ED	Age, Depression, Diabetes
2007	De Almeida Claro <i>et al.</i> [243]	2,000 men; random population study (Brazil)	Not reported	>20	Standardised interview with self-reported questionnaire (IIEF)	Overall, 1.7% of men had ED 0.2% ED in men aged 20-30 years 0.22% ED in men aged 31-40 years 1.0% ED in men aged 41-50 years 2.8% ED in men aged 51-60 years 7.0% ED in men aged > 61 years	Age

2007	Ahn <i>et al.</i> [244]	1,570 men; geographically stratified random population study	Not reported	40-79	Self-administered questionnaire (IIEF-5)	Overall, 13.4% had self-reported ED ED prevalence as defined by IIEF-5 score less than 17 was 32.4% According to single question: 4.2% ED in men aged 40-49 years 13.0% ED in men aged 50-59 years 30.1% ED in men aged 60-69 years 41.1% ED in men aged 70-79 years	Age, Single status, Low income, Diabetes, Hypertension, Hyperlipidemia, Heart disease, Musculoskeletal disorders, Alcohol, Depression, Coffee intake
2008	Moreira <i>et al.</i> [245]	750 men; random population sample (Australia)	16.9%	40-80	Telephone survey (random digit dialing)	Overall, 32% of men had ED	Age
2008	Chew <i>et al.</i> [246]	1,580 men; random population sample (Australia)	37.3%	>20	Postal survey Self-administered questionnaire (IIEF-5)	15.7% ED in men aged 20-29 years 8.7% ED in men aged 30-39 years 12.9% ED in men aged 40-49 years 31.6% ED in men aged 50-59 years 52.4% ED in men aged 60-69 years 69.4% ED in men aged 70-79 years 68.2% ED in men aged > 80 years	Age, Marital status
2008	Teles <i>et al.</i> [247]	3,067 men; random population sample (Portugal)	81.3%	40-69	Self-administered questionnaire, including IIEF	Overall, 48.1% of men had ED 29% ED in men aged 40-49 years 50% ED in men aged 50-59 years 74% ED in men aged 60-69 years	Age, Diabetes, Cardiac insufficiency, Psychiatric illness
2008	Moreira <i>et al.</i> [248]	750 men; random population sample (United Kingdom)	17%	40-80	Telephone survey (random digit dialing)	Overall, 17.8% of men had ED	Age
2009	Laumann <i>et al.</i> [249]	742 men; random population sample (United States)	9%	40-80	Telephone survey (random digit dialing)	Overall, 22.5% of men had ED	Age, Depression
2009	Buvat <i>et al.</i> [250]	750 men; random population sample (France)	23.8%	40-80	Telephone survey (random digit dialing)	Overall, 15% of men had ED	Age

2010	Corona <i>et al.</i> [251]	3,369 men; random population study (Europe: Italy, Belgium, United Kingdom, Spain, Poland, Hungary, Estonia)	40%	40-80	Self-administered questionnaire	Overall, 30% of men had ED 6% ED in men aged 40-49 years 19% ED in men aged 50-59 years 38% ED in men aged 60-69 years 64% ED in men 70 and over	Age, Depression, LUTS, Cardiovascular disease, Diabetes, Obesity
2016	Oyelade <i>et al.</i> [252]	241 men; random sampling cross-sectional population based survey (Nigeria)	99%	30-80	Self-administered questionnaire (IIEF-5)	The general prevalence of ED in this study was 58.9%	Age, Hypertension, Use of anti-hypertensive drugs, Diabetes mellitus, Heart disease
2017	Cayan <i>et al.</i> [253]	2,760 men; random population study (Turkey)	Non-reported	≥ 40	Self-administered questionnaire (IIEF-5)	The prevalence of ED was calculated as 33% among all males of ≥ 40 years of age. ED prevalence rates were 17% for 40-49 years, 35.5% for 50-59 years, 68.8% for 60-69 years, and 82.9% for ≥ 70 years	Age, Diabetes, Hypertension, Atherosclerosis, Dyslipidemia, LUTS, Educational status, Monthly income
2017	Quilter <i>et al.</i> [254]	Randomly selected age-stratified population-based sample of 2,000 men (New Zealand)	30%	40-70	Self-reported erectile function (IIEF-5) and a single-question self-assessment tool.	Prevalence of ED was 42% (22% mild, 10% mild to moderate, 6% moderate, and 4% severe)	Age, Anxiety or depression

* Four baseline study estimating the prevalence of Erectile Dysfunction:

MMAS = the Massachusetts Male Aging Study; NHLS = the National Health of Social Life Survey; MALES = the multi-national men's attitudes to life events and sexuality; GSSAB = Global Study of Sexual Attitudes and Behaviours.

BPH = Benign Prostate Hyperplasia; COPD = Chronic Obstructive Pulmonary Disease;

ED = Erectile Dysfunction; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; LUTS = Lower urinary tract symptoms.

Table 8: The prevalence rates of premature ejaculation [171]

Date	Authors	Method of Data Collection	Method of Recruitment	Operational Criteria	Prevalence Rate	Number of Men
1998	Dunn <i>et al.</i> [255]	Mail	General practice registers - random stratification	Having difficulty with ejaculating prematurely	14% (past 3 mo)	617
					31% (lifetime)	618
1999	Laumann <i>et al.</i> (NHSLs) [177]	Interview	NA	Climaxing/ ejaculating too rapidly during the past 12 months	31%	1,410
2002	Fugl-Meyer and Fugl-Meyer [256]	Interview	Population register	NA	9%	1,475
2004	Rowland <i>et al.</i> [257]	Mailed questionnaire	Internet panel	DSM IV	16.3%	1,158
2004	Nolazco <i>et al.</i> [258]	Interview	Invitation to outpatient clinic	Ejaculating fast or prematurely	28.3%	2,456
2005	Laumann <i>et al.</i> [188]	Telephone-personal interview/Mailed questionnaires	Random (systematic) sampling	Reaching climax too quickly during the past 12 months	23.75% (4.26% frequently)	13,618
2005	Basile Fasolo <i>et al.</i> [259]	Clinician-based	Invitation to outpatient clinic	DSM IV	21.2%	12,558
2005	Stulhofer <i>et al.</i> [260]	Interview	Stratified sampling	Often ejaculating in less than 2 minutes	9.5%	601
2007	Porst <i>et al.</i> (PEPA) [178]	Web-based survey Self-report	Internet panel	Control over ejaculation, Distress	22.7%	12,133
2008	Shindel <i>et al.</i> [261]	Questionnaire	Male partners of infertile couples under evaluation	Self-report premature ejaculation	50%	73
2009	Brock <i>et al.</i> [262]	telephone interview	Web-based survey	DSM III	16%	3,816
				Control	26%	
				Distress	27%	
2010	Traeen and Stigum [221]	Mailed questionnaire + internet	Web interview + Randomisation		27%	11,746+1,671
2010	Son <i>et al.</i> [263]	Questionnaire	Internet panel (younger than 60)	DSM IV	18.3%	600
2010	Amidu <i>et al.</i> [264]	Questionnaire	NA	NA	64.7%	255
2010	Liang <i>et al.</i> [265]	NA	NA	ISSM	15.3%	1,127
2010	Park <i>et al.</i> [266]	Mailed questionnaire	Stratified sampling	Suffering from PE	27.5%	2,037
2010	Vakalopoulos <i>et al.</i> [267]	One-on-one survey	Population based cohort	EED	58.43%	522
				ISSM Lifelong PE	17.7%	
2010	Hirshfeld <i>et al.</i> [218]	Web-based survey	Online advertisement in the United States and Canada	Climaxing/ ejaculating too rapidly during the past 12 months	34%	7,001
2011	Christensen <i>et al.</i> [268]	Interview + questionnaire	Population register (random)	NA	7%	5,552
2011	Serefoglu <i>et al.</i> [179]	Interview	Stratified sampling	Complaining about ejaculating prematurely	20.0%	2,593

2011	Son <i>et al.</i> [269]	Questionnaire	Internet panel	Estimated IELT \leq 5 mins, inability to control ejaculation, distress	10.5%	334
2011	Tang and Khoo [270]	Interview	Primary care setting	PEDT \geq 9	40.6%	207
2012	Mialon <i>et al.</i> [271]	Mailed questionnaire	Convenience sampling (18-25 years old)	Control over ejaculation Distress	11.4%	2,507
2012	Shaeer and Shaeer [272]	Web-based survey	Online advertisement in Arabic countries	Ejaculate before the person wishes to ejaculate at least sometimes	83.7%	804
2012	Shindel <i>et al.</i> [273]	Web-based survey	Online advertisement targeted to MSM + distribution of invitation to organisations catering to MSM	PEDT \geq 9	8-12%	1,769
2012	McMahon <i>et al.</i> [274]	Computer assisted interviewing, online, or in-person self-completed	NA	PEDT \geq 11 Self-Reported (always/nearly-always)	16% 13%	4,997
2012	Lotti <i>et al.</i> [275]	Interview	Men seeking medical care for infertility	PEDT \geq 9	15.6%	244
2013	Zhang <i>et al.</i> [276]	Interview	Random stratified sample of married men aged 30-60	Self-reported premature ejaculation	4.7%	728
2013	Lee <i>et al.</i> [277]	Interview	Stratified random sampling	PEDT \geq 11 Self-Reported IELT < 1 min	11.3% 19.5% 3%	2,081 1,035
2013	Gao <i>et al.</i> [180]	Interview	Random stratified sample of monogamous heterosexual men in China	Self-reported premature ejaculation	25.8%	3,016
2013	Hwang <i>et al.</i> [278]	Survey of married couples	Married heterosexual couples in Korea	Estimated IELT < 2 minutes PEDT > 11	21.7% 12.1%	290
2013	Vansintejan <i>et al.</i> [279]	Web Based survey	Online and flyer advertisements to Belgian men who have sex with men (Only HIV+ men in this study)	IPE score < 50% of total possible	4%	72
2013	Shaeer <i>et al.</i> [280]	Web Based survey	Targeting English-speaking males above the age of 18, living most of their lives in the USA, regardless of personal interests and web browsing preferences	ISSM definition [175] PEDT Unfiltered self-reported Filtered self-reported	6.3% 49.6% 77.6% 14.4%	1133

2016	Karabakan [281]	Interview (heavy bias toward younger men)	Targeting police academy students aged 24-30 who applied for routine urological examination	PEDT > 10	9.2%	1000
2017	Gao <i>et al.</i> [282]	Field survey with face-to-face interviews	Comprising men aged 20-68 years in five cities in the Anhui province	Self-estimated IELT	Lifelong PE 10.98% Acquired PE 21.39%	1239

DMS = Diagnostic and Statistical Manual of Mental Disorders; NA = not applicable; ISSM = International Society for Sexual Medicine; PEDT = Premature Ejaculation Diagnostic Tool; IELT = intravaginal ejaculatory latency time; IPE = Index of Premature Ejaculation; mo = months.

5. MANAGEMENT OF ERECTILE DYSFUNCTION

5.1 Definition and classification

Penile erection is a complex physiological process, which involves integration of both neural and vascular events, along with an adequate endocrine milieu. It involves arterial dilation, trabecular smooth muscle relaxation and activation of the corporeal veno-occlusive mechanism [283]. Erectile dysfunction is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance [284]. Erectile dysfunction may affect psychosocial health and have a significant impact on the QoL of patients and their partner's [166, 285-287].

There is increasing evidence that the presence of ED increases the risk of future CV events including MI, cerebrovascular events, and all-cause mortality, with a trend towards an increased risk of cardiovascular mortality [288]. Therefore, ED can be an early manifestation of coronary artery and peripheral vascular disease and should not be regarded only as a QoL issue, but also as a potential warning sign of CVD [289-291]. A cost analysis showed that screening men presenting with ED for CVD represents a cost-effective intervention for secondary prevention of both CVD and ED, resulting in substantial cost savings relative to identification of CVD at the time of presentation [292].

Erectile dysfunction is commonly classified into three groups based on aetiology. These include 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 unmodifiable and modifiable common risk factors including age, diabetes mellitus, dyslipidaemia, hypertension, CVD, BMI/obesity, MetS, hyperhomocysteinemia, lack of exercise, and smoking (a positive dose-response association between quantity and duration of smoking has been demonstrated) [286, 290, 293-300]. Furthermore, an association between ED status and pharmacotherapeutic agents for CVD (e.g., thiazide diuretics and β -blockers, except nebivolol, exert detrimental effects on erectile function, whereas newer drugs i.e., angiotensin-converting enzyme (ACE)-inhibitors, angiotensin-receptor-blockers and calcium-channel-blockers have neutral or even beneficial effects) [290, 301, 302], atrial fibrillation [303], hyperthyroidism [20], vitamin D deficiency [304, 305], hyperuricemia [306], and depression [307] have also been reported as risk factors. Available data do not confirm a clear association between ED and hypothyroidism and hyperprolactinaemia [20].

A number of studies have shown that lifestyle modification [308], including physical activity [309], weight loss [310] and pharmacotherapy [302, 311, 312] for CVD risk factors may be of help in improving sexual function in men with ED. Meta-analytic data reveals a positive effect of lipid-lowering therapy with statins on erectile function [313, 314]. However, it should be emphasised that further controlled prospective studies are necessary to determine the effects of exercise or other lifestyle changes in the prevention and treatment of ED [308].

Further epidemiological data have also highlighted other potential risk factors associated with ED including sleep disorders [315], obstructive sleep apnoea [316], psoriasis [317-319], gouty arthritis [320] and ankylosing spondylitis [321], non-alcoholic fatty liver disease [322], other chronic liver disorders [323], chronic periodontitis [324], open-angle glaucoma [325], inflammatory bowel disease [326], chronic fatigue syndrome [327] and allergic rhinitis [328].

Erectile dysfunction is also frequently associated with other urological conditions and procedures (Table 9). Epidemiological studies have also demonstrated consistent evidence for an association between LUTS/BPH and sexual dysfunction, regardless of age, other comorbidities and lifestyle factors [329]. The Multinational Survey on the Aging Male study, performed in the USA, France, Germany, Italy, Netherlands, Spain, and the UK, systematically investigated the relationship between LUTS and sexual dysfunction in over 12,000 men aged 50-80 years. In the 83% of men who were reported to be sexually active, the overall prevalence of LUTS was 90%, with the overall prevalence of ED 49%, with a reported complete absence of erections in 10% of patients. Moreover, the overall prevalence of ejaculatory disorders was 46% [236]. Regardless of the technique used, surgery for BPH-LUTS had no significant impact on erectile function. In fact, even an improvement was found depending on the degree of improvement of urinary symptoms [330, 331]. An association between ED and CP/CPPS [332], and bladder pain syndrome/interstitial cystitis has been confirmed, mostly in younger men [333]. Furthermore, a relevant interplay and association between ED and PE has also been demonstrated (section 6.2) [334]. An increased risk of ED is reported following transrectal ultrasound (TRUS)-guided prostate biopsy [335] and after open urethroplasty, especially for correction of posterior strictures [336].

Table 9: Urological conditions associated with ED

Urological Condition	Association with ED
LUTS/BPH [329]	Depending on the severity of LUTS and patients' age/population characteristics: Odds ratio (OR) of ED among men with LUTS/BPH ranges from 1.52 to 28.7 and prevalence ranges from 58% to 80%
Surgery for BPH/LUTS (TUR-P, laser, open, laparoscopic, etc.) [330]	Overall, absence of significant variations in terms of erectile function scores after surgery
Chronic Prostatitis/Chronic Pelvic Pain Syndrome [332]	Prevalence of ED among patients with CP/CPPS 29% [24%-33%, 95%CI], Range: 11% - 56% among studies
Bladder Pain Syndrome/Interstitial Cystitis [333]	OR of BPS/IC among patients with ED. Overall: OR (adjusted) = 1.75 [1.12 - 2.71, 95%CI] Age ≥ 60: OR (adjusted) = 1.07 [0.41 - 2.81, 95%CI] Age 40-59: OR (adjusted) = 1.44 [1.02 - 2.12, 95%CI] Age 18-39: OR (adjusted) = 10.40 [2.93 - 36.94, 95%CI]
Premature Ejaculation [334]	OR of ED among patients with PE = 3.68 [2.61 - 5.68, 95%CI]
Urethroplasty surgery for posterior urethral strictures [336]	OR of ED after posterior urethroplasty = 2.51 [1.82 - 3.45, 95%CI]

5.3 Pathophysiology

The pathophysiology of ED may be vasculogenic, neurogenic, anatomical, hormonal, drug-induced and/or psychogenic (Table 10) [283]. In most cases, numerous pathophysiology pathways can co-exist and may all negatively impact on erectile function.

The proposed ED etiological and pathophysiological division should not be considered prescriptive. In most cases, ED is associated with more than one pathophysiological factor and very often, if not always, will have a psychological component. Likewise, organic components can negatively impact on erectile function with different pathophysiological effects. Therefore, Table 10 must be considered for diagnostic classifications only (along with associated risk factors for each subcategory).

Table 10: Pathophysiology of ED

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, 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;
Hypogonadism (any type)
Hyperthyroidism
Hyper- and hypocortisolism (Cushing's disease, etc.)
Panhypopituitarism and multiple endocrine disorders
Mixed pathophysiology pathways
Chronic systemic diseases (e.g., diabetes mellitus, hypertension, metabolic syndrome, chronic renal failure, chronic liver disorders, hyperhomocysteinemia, hyperuricemia, etc.)
Psoriasis; gouty arthritis; ankylosing spondylitis; non-alcoholic fatty liver; 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, etc.)
Drug-induced
Antihypertensives (i.e., thiazidediuretics, beta-blockers)*
Antidepressants (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, etc.)
Psychogenic
Generalised type (e.g., lack of arousability and disorders of sexual intimacy)
Situational type (e.g., partner-related, performance-related issues or due to distress)
Trauma
Penile fracture
Pelvic fractures

GnRH = gonadotropin-releasing hormone; 5-ARIs = 5 α -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. [337].

5.3.1 Pelvic surgery and prostate cancer treatment

Pelvic surgery, especially for oncological disease (e.g., radical prostatectomy (RP) [338] or radical cystectomy [339] and colorectal surgery [340]), may have a negative impact on erectile function and overall sexual health. The most relevant causal factor is a lesion (any) occurring to the neurovascular bundles that control the complex mechanism of the cavernous erectile response, whose preservation (either partial or complete) during surgery eventually configures the so-called nerve-sparing (NS) approach. Thereof, surgery resulting in damage of the neurovascular bundles, will result in ED, although NS approaches have been adopted over the last a few decades. This approach is applicable to all types of surgery that are potentially harmful to erectile function, although to date, only the surgical treatment of PCa has enough scientific evidence supporting its potential pathophysiological association with ED [341-343]. However, even non-surgical treatments of PCa (i.e., radiotherapy; brachytherapy) can be associated with an impairment of erectile function. The concept of an active surveillance (AS) strategy for the treatment of PCa was developed to avoid over-treatment of non-significant localised low-risk diseases, while limiting potential functional side-effects (including ED). However, it is interesting that data suggest that even AS may have a detrimental impact on erectile function (and sexual well-being as a whole) [344-346].

To date the most robust data on patient-reported outcome measures (PROMS) including erectile function, comparing treatments for clinically localised PCa come from the Prostate Testing for Cancer and Treatment (ProtecT) trial where 1,643 patients were randomised to active treatment (either RP or RT) and active monitoring (AM) and were followed-up for six years [347]. Sexual function, including erectile function, and the effect of sexual function on QoL outcomes were assessed with the Expanded Prostate Cancer Index Composite with 26 items (EPIC-26) instrument [348, 349]. At baseline, 67% of men reported erections firm enough for sexual intercourses this fell to 52% in the AM group, 22% in the RT group, and to 12% in the RP group, at six-month assessment. Interestingly, the worst trend over time was recorded in the RP group (with 21% erections firm enough for intercourse after three years versus 17% after six years). In the RT group, the percentage of men reporting erections firm enough for intercourse increased between six and twelve months, with a subsequent further decrease to 27% at six-year assessment. The percentage declined over time on a yearly basis in the AM group, with 41% of men reporting erections firm enough for intercourse at three-year and 30% at six-year evaluation [347].

Radical prostatectomy (either open, laparoscopic or robot-assisted) is a widely performed procedure with a curative intent for patients presenting with clinically localised intermediate- or high-risk PCa and a life expectancy of more than ten years based on health status and comorbidities [350, 351]. This procedure may lead to treatment-specific sequelae affecting health-related QoL. Men undergoing RP (any technique) should be adequately informed before the operation that there is a significant risk of sexual changes other than ED, including decreased libido, changes in orgasm, anejaculation, Peyronie's-like disease, and changes in penile length [343]. These outcomes have become increasingly important with the more frequent diagnosis of PCa in both younger and older men [352-354]. Overall, research has shown that 25-75% of men experience post-RP ED [355], even though these findings suffer from methodological flaws, in particular, the heterogeneity of reporting and assessment of ED in the studies [341, 356]. Conversely, the rate of unassisted post-operative erectile function recovery is in the range of between 20 and 25% in most studies; these rates do not appear to have substantially improved or changed over the past seventeen years, despite the growing attention to post-surgical rehabilitation protocols and the refinement of surgical techniques [356-358].

Overall, patient age, baseline erectile function and surgical volume, with the consequent ability to preserve the neurovascular bundles, seem to be the main factors in promoting the highest rates of post-operative potency [342, 353, 355, 359]. Patients being considered for nerve-sparing RP (NSRP) should ideally be potent pre-operatively [352, 353]. Overall, the recovery time following surgery is of major clinical importance in terms of post-operative recovery of erectile function. Available data confirms that post-operative erectile function recovery can occur up to 48 months after RP [360]. Likewise, it has been suggested that post-operative therapy (any type) should be commenced as close as possible to the surgical procedure [352, 355], although evidence suggests that the number of patients reporting return of spontaneous erectile function has not actually increased.

In terms of the effects of surgical interventions (e.g., robot-assisted RP [RARP] versus other types of surgery), the data is still conflicting. An early systematic review showed a significant advantage in favour of RARP in comparison with open retropubic RP in terms of twelve-month potency rates [361], without significant differences between laparoscopic RP and RARP. Some recent reports confirm that the probability of erectile function recovery is about twice as high for RARP compared with open RP [362]. More recently, a prospective, controlled, non-randomised trial of patients undergoing RP in fourteen Swedish centres comparing RARP versus open retropubic RP, showed a small improvement with respect to erectile function after RARP [363]. Conversely, a randomised controlled phase 3 study of men assigned to open RP or RARP showed that the two techniques yielded similar functional outcomes at twelve weeks [364]. As a whole, more controlled prospective well-designed studies, with longer term follow-up, are necessary to determine if RARP is superior to open RP in terms of post-operative ED rates [365]. Furthermore, to overcome the problem of heterogeneity in the assessment of erectile function, for which there is variability in terms of the PROMS used (IIEF, IIEF-5, EPIC 26, Sexual Health Inventory for Men, etc.) to measure potency or erectile function; the criteria used to define restoration of erectile function should be re-evaluated utilising objective and validated thresholds (e.g., normalisation of scores or return to baseline erectile function) [341].

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 is 34% at 1 year and 57% at 5.5 years, respectively [366, 367]. Similar findings have been reported for stereotactic radiotherapy with 26-55% of previously sexually functioning patients reporting ED at 60 months [368].

Recently other modalities have emerged as potential therapeutic options in patients with clinically-localised PCa, including whole gland and focal (lesion-targeted) treatments, in order to ablate tumours selectively whilst limiting sexual toxicity by sparing the neurovascular bundles. These include high-intensity focused US (HIFU), cryotherapeutic ablation of the prostate (cryotherapy), focal paclitaxel-based vascular-targeted photodynamic therapy, and focal radiation therapy (RT) by brachytherapy or CyberKnife®. Overall, all these approaches have been shown to have a less negative impact on erectile function, although all these approaches lack robust mid- and long-term oncological outcomes and prospective randomised controlled studies are needed to compare functional and oncological outcomes between the treatment modalities [369, 370].

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 [371]. It is important to establish a relaxed atmosphere during history-taking; this will make it easier to ask questions about erectile function and other aspects of the patient's sexual history; and to explain the diagnosis and therapeutic approach to the patient and their partner. Figure 3 lists the minimal diagnostic evaluation (basic work-up) in patients with ED.

The sexual history must include information about previous and current sexual relationships, current emotional status, onset and duration of the erectile problem, and previous consultations and treatments. The sexual health status of the partner(s) (when available) can also be useful. A detailed description should be made of the rigidity and duration of both sexually-stimulated and morning erections and of problems with sexual desire, arousal, ejaculation, and orgasm [372, 373]. Validated psychometric questionnaires, such as the IIEF [80] or its short version the SHIM [80], help to assess the different sexual function domains (i.e. sexual desire, erectile function, orgasmic function, intercourse, and overall satisfaction), as well as the potential impact of a specific treatment modality. Similarly, structured interview have been demonstrated to allow the identification and quantification of the different underlining factors impacting upon erectile function [374].

Psychometric analyses also support the use of the Erectile Hardness Score for the assessment of penile rigidity in practice and in clinical trials research [375]. In cases of depressive mood, clinicians may use the Beck Depressive Inventory [376], which is one of the most recognised self-reported measures in the field, takes approximately ten minutes to complete, and assigns the patient to a specific level of depression (varying from "normal mood" to "extreme depression").

Patients should always be screened for symptoms of possible hypogonadism (testosterone deficiency), including decreased energy, libido, and fatigue; potential cognitive impairment may be also observed in association with hypogonadism (see sections 3.5 and 3.6), as well as for LUTS. In this regard, although LUTS/BPH in itself does not represent a contraindication to treat a patient for LOH, screening for LUTS severity is clinically relevant [7].

5.4.2 **Physical examination**

Every patient must be given a physical examination focused on the genitourinary, endocrine, vascular and neurological systems [377, 378]. A physical examination may reveal unsuspected diagnoses, such as Peyronie's disease, pre-malignant or malignant genital lesions, prostatic enlargement or irregularity/nodularity, or signs and symptoms suggestive for hypogonadism (i.e., small testes, alterations in secondary sexual characteristics etc.).

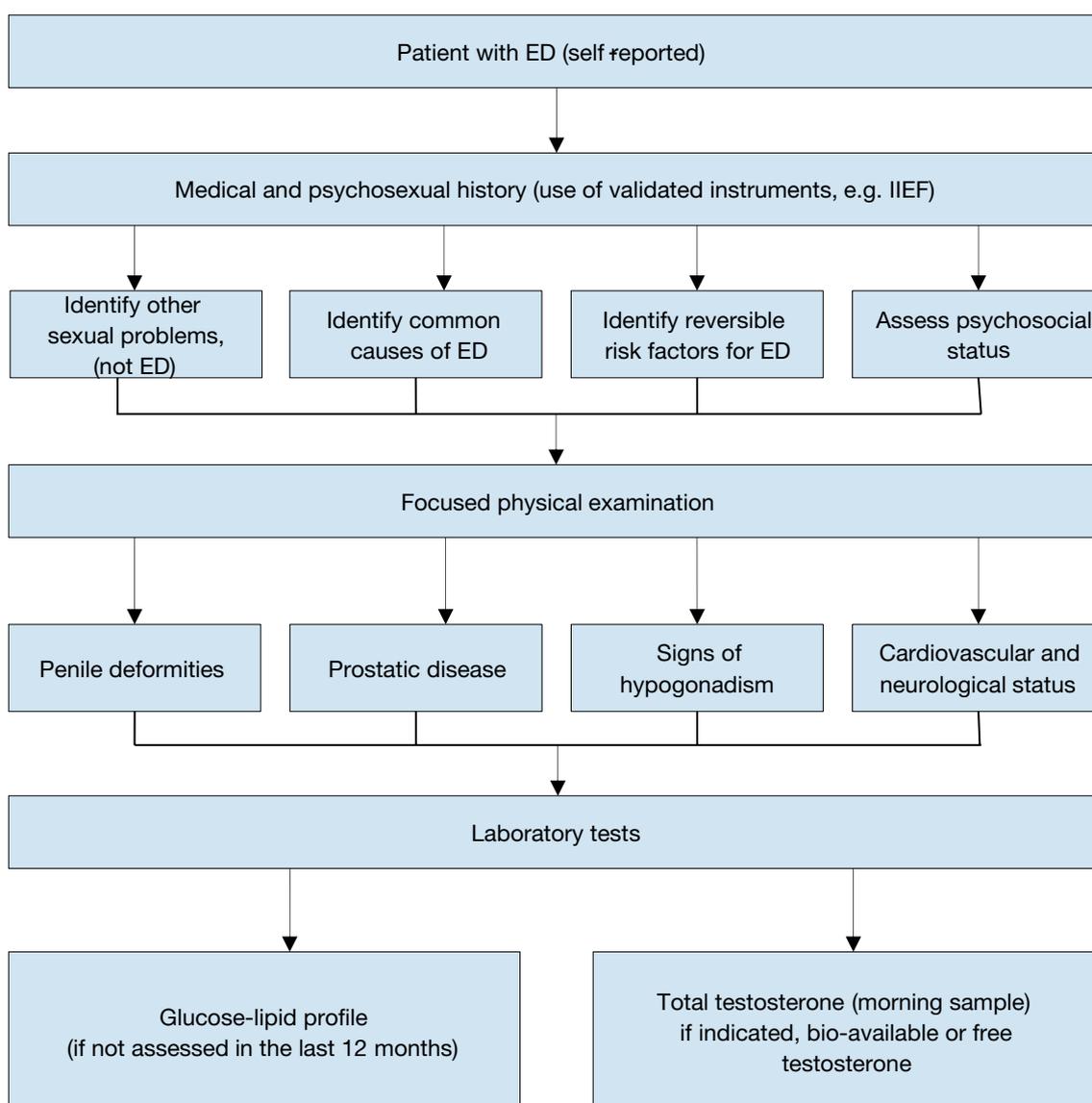
Overall, assessing previous or concomitant penile abnormalities (e.g. hypospadias, congenital curvature, or Peyronie's disease with preserved rigidity) during the medical history and the physical examination is mandatory.

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

5.4.3 Laboratory testing

Laboratory testing must be tailored to the patient's complaints and risk factors. Patients should undergo a fasting blood glucose or HbA1c and lipid profile if they have not been assessed in the previous twelve months. Hormonal tests should include an early morning total testosterone in a fasting state. The bio-available or calculated-free testosterone values may be sometimes needed to corroborate total testosterone measurements. However, the threshold of testosterone required to maintain an erection is low and ED is usually a symptom of more severe cases of hypogonadism (see sections 3.5 and 3.6) [20, 51, 294, 379, 380]. Additional laboratory tests may be considered in selected patients with specific signs and associated symptoms (e.g., PSA [381]; prolactin, and LH [382]). 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 [378].

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



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. Epidemiological surveys have emphasised the association between cardiovascular/metabolic risk factors and sexual dysfunction in both men and women [383]. Overall, ED can improve the sensitivity of screening for asymptomatic CVD in men with

diabetes [384, 385]. Erectile dysfunction significantly increases the risk of CVD, coronary heart disease and stroke. All of these cause mortality and the increase is probably independent of conventional cardiovascular risk factors [289, 290, 386, 387]. 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 [388].

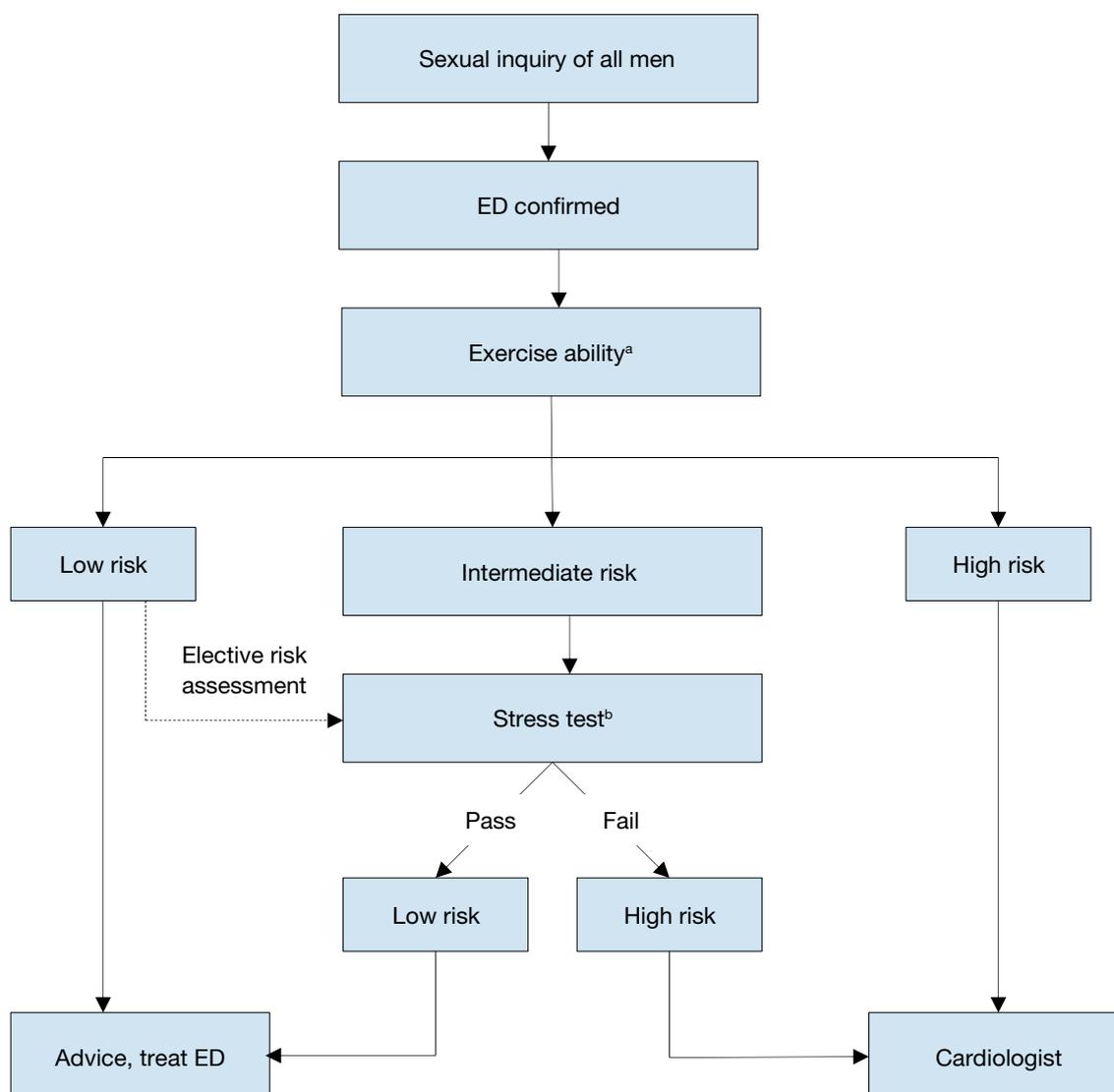
The EAU Guidelines for diagnosing and treating men with ED have been adapted from previously published recommendations from the Princeton Consensus conferences on sexual dysfunction and cardiac risk [389]. The Princeton Consensus (Expert Panel) Conference is dedicated to optimising sexual function and preserving cardiovascular health [389-391]. Accordingly, patients with ED can be stratified into three cardiovascular risk categories (Table 11), which can be used as the basis for a treatment algorithm for initiating or resuming sexual activity (Figure 3). It is also possible for the clinician to estimate the risk of sexual activity in most patients from their level of exercise tolerance, which can be determined when taking the patient's history [312].

Table 11: Cardiac risk stratification (based on 2nd and 3rd Princeton Consensus) [389, 391]

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 4: Treatment algorithm for determining level of sexual activity according to cardiac risk in ED (based on 3rd Princeton Consensus) [389]



^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 four minutes of the Bruce treadmill protocol.

5.4.4.1 Low-risk category

The low-risk category includes patients who do not have any significant cardiac risk associated with sexual activity. Low-risk is typically implied by the ability to perform exercise of modest intensity, which is defined as, ≥ 6 metabolic equivalents of energy expenditure in the resting state without symptoms. According to current knowledge of the exercise demand or emotional stress associated with sexual activity, low-risk patients do not need cardiac testing or evaluation before the initiation or resumption of sexual activity or therapy for sexual dysfunction.

5.4.4.2 Intermediate- or indeterminate-risk category

The intermediate- or indeterminate-risk category consists of patients with an uncertain cardiac condition or patients whose risk profile requires testing or evaluation before the resumption of sexual activity. Based upon the results of testing, these patients may be moved to either the high- or low-risk group. A cardiology consultation may be needed in some patients to help the primary physician determine the safety of sexual activity.

5.4.4.3 High-risk category

High-risk patients have a cardiac condition that is sufficiently severe and/or unstable for sexual activity to carry a significant risk. Most high-risk patients have moderate-to-severe symptomatic heart disease. 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, or a decision made by the cardiologist and/or internist that it is safe to resume sexual activity.

5.5 Diagnostic Evaluation (advanced work-up)

Most patients with ED can be managed based on the basis of medical and sexual history; conversely, some patients may need specific diagnostic tests (Tables 12 and 13).

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 erection(s). 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 ten or more minutes [392]. Nocturnal penile tumescence and rigidity monitoring is an attractive 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 [393].

5.5.2 Intracavernous injection test

The intracavernous injection test gives limited information about the vascular status. A positive test is a rigid erectile response (unable to bend the penis) that appears within ten minutes after the intracavernous injection and lasts for 30 minutes [394]. Overall, the test 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 specifically aimed to study the haemodynamic pathophysiology of erectile function. Therefore in clinical practice it is usually applied in those conditions where a potential vasculogenic aetiology of ED (e.g., diabetes mellitus; renal transplantation; multiple concomitant CV risk factors and/or overt peripheral vascular disease; poor responders to oral therapy, etc.) is suspected. A peak systolic blood flow > 30 cm/s, an end-diastolic velocity of < 3 cm/s and a resistance index > 0.8 are generally considered normal [395, 396]. Recent data have suggested that duplex scanning as a haemodynamic study may be better at tailoring therapy for ED, such as for low-intensity shock wave (LI-SWT) treatment and for diagnosing vasculogenic ED [397]. 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 [398]. Recent studies have advocated the use of computerised tomography (CT) angiography as a diagnostic procedure prior to penile artery angioplasty for patients with ED and isolated penile artery stenosis [399]. Nowadays, dynamic infusion cavernosometry or cavernosography are infrequently used diagnostics tools aimed at diagnosing venogenic ED.

5.5.5 Psychiatric and psychosocial assessment

Whenever clinically indicated, patients with psychiatric disorders should be referred to a psychiatrist. In younger patients (< 40 years) with long-term primary ED [170], psychiatric assessment may be helpful before any clinical assessment is carried out.

Mental health issues are frequently comorbid with ED; 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) [307, 400]. Relationship factors, including lack of satisfaction with the partner, poor sexual relationships, length of the relationship, or feeling emotionally disconnected with the partner during sex, have been related to erectile difficulties and dysfunction [400-402]. On the other hand, feeling emotionally supported, and motivated toward intimacy are protective factors in men with ED [403]. Additionally, the cognitive factors underpinning organic and non-organic ED must also be assessed. Cognitive factors include men's dysfunctional thinking styles and expectations about sexuality and sexual performance. These expectations result from the sexuality norms and stereotypes, shared by a given culture. Expectations emphasising high sexual performance in men, result in sexual performance anxiety, acting as a maintenance factor of ED [404]. Unrealistic expectations about male sexual performance may further align with internal causal attributions regarding the loss of erection (i.e., men attribute the loss of erection to themselves [sense of personal inadequacy]), thereby worsening ED [405]. Likewise, poor self-esteem and cognitive distraction from erotic cues, are expected to negatively impact ED [406, 407].

Psychosexual assessment in ED cases include a clinical interview considering all the previous topics; clinicians are expected to collect information on the individual’s psychopathology symptoms, life stressors, relationship dynamics, cognitive style, and cognitive distraction sources [406]. Also, self-reported measures are frequently used within the psychological context. These may include measurement scales such as the Brief Symptom Inventory [408] for measuring psychopathology symptoms, the Sexual Dysfunctional Beliefs Questionnaire [409] or the Sexual Modes Questionnaire [410] for measuring dysfunctional cognitive styles in men.

Figure 5: Psychiatric and psychosocial assessment

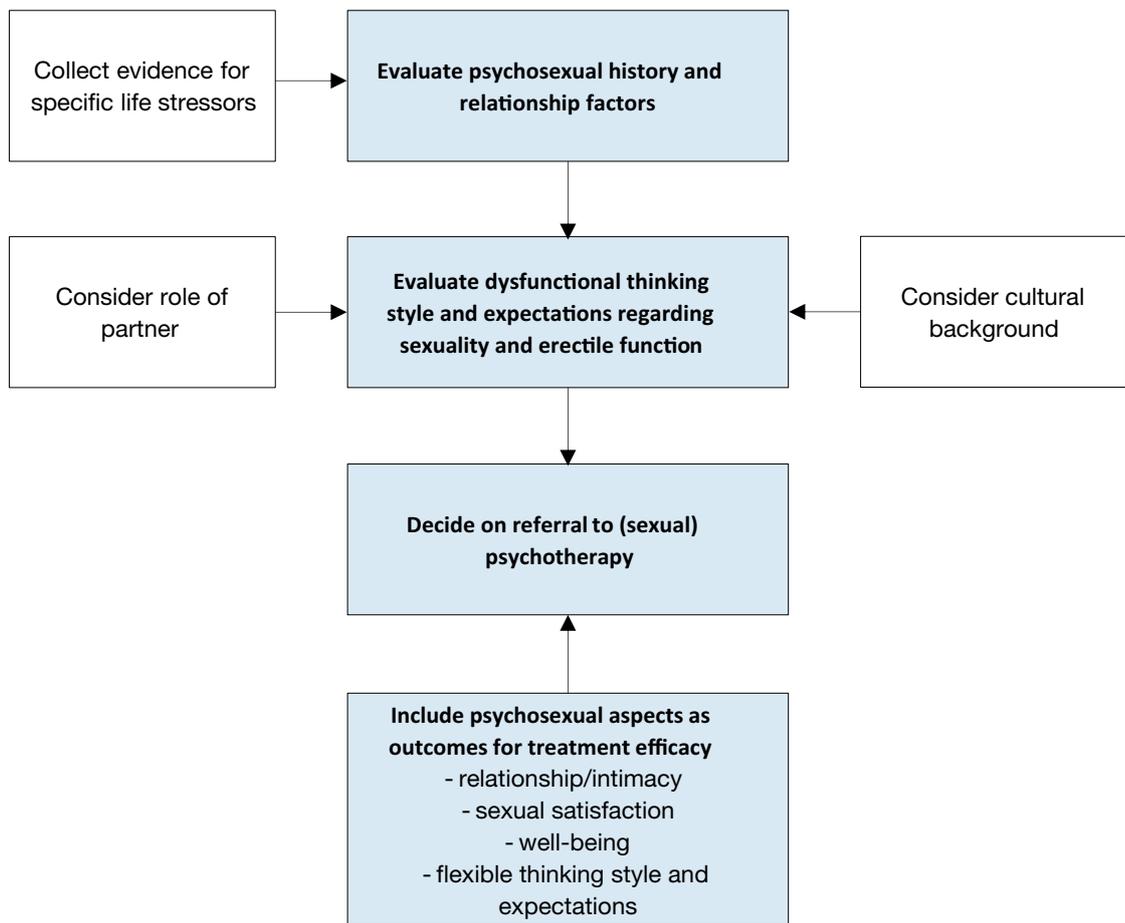


Table 12: Indications for specific diagnostic tests for ED

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 which might require surgical correction (e.g., Peyronie’s disease, congenital penile curvature).
Patients with complex psychiatric or psychosexual disorders.
Patients with complex endocrine disorders.
Specific tests may be indicated at the request of the patient or their partner.
Medico-legal reasons (e.g., implantation of penile prosthesis to document end stage ED, sexual abuse).

Table 13: 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 psychodiagnostic evaluation

5.5.6 Recommendations for the diagnostic evaluation of ED

Recommendations	Strength rating
Take a comprehensive medical and sexual history in every patient presenting for erectile dysfunction (ED). Consider psychosexual development, including life stressors, cultural aspects, and cognitive/thinking style of the patient regarding their sexual performance.	Strong
Use a validated questionnaire related to ED to assess all sexual function domains (e.g., International Index of Erectile Function) and the effect of a specific treatment modality.	Strong
Include a focused physical examination in the initial assessment of men with ED to identify underlying medical conditions and comorbid genital disorders that may be associated with ED.	Strong
Assess routine laboratory tests, including glucose and lipid profile and total testosterone, to identify and treat any reversible risk factors and lifestyle factors that can be modified.	Strong
Include specific diagnostic tests in the initial evaluation of ED in the presence of the conditions presented in Table 11.	Strong

5.6 Treatment of erectile dysfunction

5.6.1 Patient education - consultation and referrals

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 he can understand. This first level approach was shown to favour sexual satisfaction in ED men [411]. Accordingly, consultation with the patient should include firstly a discussion of the expectations and needs of both the patient and their sexual partner. It should also review both the patient and partner's understanding of ED and the results of diagnostic tests, and provide a rationale for the selection of treatment options [412]. Patient and partner education is an essential part of ED management [412, 413], and may prevent misleading information that may be at the core of dysfunctional psychological processes underpinning ED.

5.6.2 Treatment options

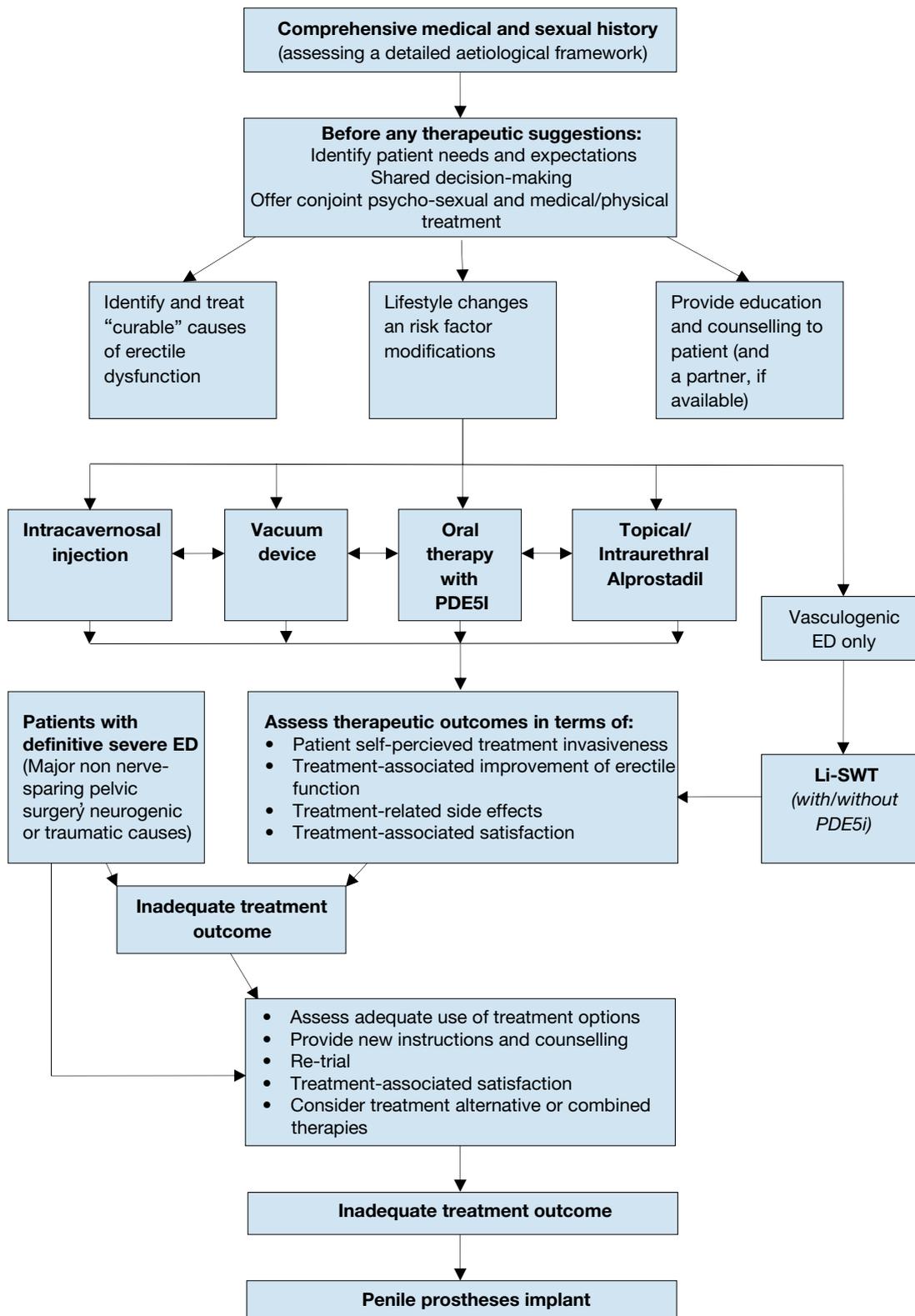
Based on the currently available evidence and the consensus of the panel, a novel comprehensive therapeutic and decision-making algorithm (Figure 6) for treating ED, which takes into account both the level of invasiveness of each therapy and the efficacy of the therapy itself, is presented. This newly-developed treatment algorithm has been extensively discussed within the guidelines panel as an alternative to the traditional three-level concept in order to better tailor a personalised therapy to individual patients, according to invasiveness, tolerability, effectiveness of the different therapeutic options and patients' expectations. In this context, patients should be fully counselled with respect to all available treatment modalities.

Erectile dysfunction may be associated with modifiable or reversible risk factors, including lifestyle or drug-related factors [308]. 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 (such as, endocrine disorders and metabolic disorders - e.g., diabetes - some cardiovascular problems - e.g., hypertension) which should always be well-controlled as the first step of any ED treatment [414]. Major clinical potential benefits of lifestyle changes may be achieved in men with specific comorbid cardiovascular or metabolic disorders, such as diabetes or hypertension [308, 415].

As a rule, ED can be treated successfully with current treatment options, but it cannot be cured. The only exceptions are psychogenic ED, post-traumatic arteriogenic ED in young patients, and hormonal causes (e.g., hypogonadism) [51, 382], which potentially can be cured with specific treatments. Most men with ED

will be treated with therapeutic options that are not cause specific. This results in a tailored treatment strategy that depends on invasiveness, efficacy, safety, and cost, as well as patient preference [412]. In this context, physician-patient (partner, if available) dialogue is essential throughout the management of ED.

Figure 6: Management algorithm for erectile dysfunction



ED = erectile dysfunction; PDE5Is = phosphodiesterase type 5 inhibitors.

5.6.2.1 Oral pharmacotherapy

Four potent selective PDE5Is have been approved by the EMA for the treatment of ED [416]. Phosphodiesterase type 5 catalyses the hydrolysis of the second messenger cyclic guanosine monophosphate (cGMP) in the cavernous tissue; cGMP is involved in intra-cellular signal pathways of cavernous smooth muscle. Indeed, the accumulation of cGMP sets in motion a cascade of events at the intracellular level, which induces a loss of contractile tone of the vessels at the penile level by lowering cytosolic Ca^{2+} . Nitric oxide (NO) has an essential role in promoting the formation of cGMP and other pathways leading to corporeal smooth muscle relaxation and erection of the penis [414, 417]. This is associated with increased arterial blood flow, eventually leading to compression of the sub-tunical venous plexus followed by penile erection [418]. Since they are not initiators of erection, PDE5Is require sexual stimulation to facilitate an erection. Efficacy is defined as an erection, with rigidity, sufficient for satisfactory intercourse [414].

Sildenafil

Sildenafil was launched in 1998 and was the first PDE5I available on the market [419]. It 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 side-effects [419]. Sildenafil is effective 30-60 minutes after administration [419]. Its efficacy is reduced after a heavy, fatty meal due to delayed absorption. Efficacy may be maintained for up to twelve hours [420]. The pharmacokinetic profile for sildenafil is presented in Table 14. Adverse events (Table 15) are generally mild in nature and self-limited [421, 422]. After 24 weeks in a dose-response study, improved erections were reported by 56%, 77% and 84% in a general ED population taking 25, 50 and 100 mg sildenafil, respectively, compared to 25% of men taking placebo [423]. Sildenafil significantly improved patient scores for IIEF, Sexual Encounter Profile (SEP)2, SEP3, and General Assessment Questionnaire (GAQ) and treatment satisfaction. The efficacy of sildenafil in almost every subgroup of patients with ED has been successfully established, irrespective of age [424]. Recently, an orally disintegrating tablet (ODT) of sildenafil citrate at a dosage of 50 mg has been developed mainly for the benefit of patients who have difficulty swallowing solid dosage forms.

Tadalafil

Tadalafil was licensed for treatment of ED in February 2003 and is effective from 30 minutes after administration, with peak efficacy after about two hours [425]. Efficacy is maintained for up to 36 hours [425] and is not affected by food [426]. Usually, it 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 side-effects [425, 427]. Pharmacokinetic data for tadalafil is presented in Table 14. Adverse events (Table 15) are generally mild in nature and self-limited by continuous use. In pre-marketing studies, after twelve weeks of treatment in a dose-response study, improved erections were reported by 67% and 81% of a general ED population taking 10 and 20 mg tadalafil, respectively, compared to 35% of men in the control placebo group [425]. Tadalafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction [425].

Efficacy has been confirmed in post-marketing studies [416, 428]. The efficacy of tadalafil in almost every subgroup of patients with ED, including difficult-to-treat subgroups (e.g., diabetes mellitus), has been successfully established [429], in addition to the evidence of a net clinical advantage in the short-term on ejaculatory and orgasmic functions in ED patients [430]. Daily tadalafil has also been licensed for the treatment of LUTS secondary to BPH. Therefore, it is useful in patients with concomitant ED and LUTS [431]. Recent data also confirms that 40% of men aged > 45 years were combined responders for ED and LUTS/BPH to treatment with tadalafil 5 mg once daily, with symptom improvement after twelve weeks [432].

Vardenafil

Vardenafil became commercially available in March 2003 and is effective from 30 minutes after administration [433], with up to one out of three patients achieving satisfactory erections within 15 minutes of ingestion [434]. Its effect is reduced by a heavy, fatty meal. Doses of 5, 10 and 20 mg have been approved for on-demand treatment of ED. The recommended starting dose is 10 mg and should be adapted according to the patient's response and side-effects [435]. Pharmacokinetic data for vardenafil is presented in Table 14. Adverse events (Table 15) are generally mild in nature and self-limited by continuous use [435]. After twelve weeks in a dose-response study, improved erections were reported by 66%, 76% and 80% of a general ED population taking 5, 10 and 20 mg vardenafil, respectively, compared with 30% of men taking placebo [435, 436]. Vardenafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ and treatment satisfaction.

Efficacy has been confirmed in post-marketing studies [435, 436]. The efficacy of vardenafil in almost every subgroup of patients with ED, including difficult-to-treat subgroups (e.g. diabetes mellitus), has been successfully established. More recently, an ODT form of vardenafil has been released [436]. Orodispersible tablet formulations offer improved convenience over film-coated formulations and may be

preferred by patients. Absorption is unrelated to food intake and they exhibit better bio-availability compared to film-coated tablets [437]. The efficacy of vardenafil ODT has been demonstrated in several RCTs and did not seem to differ from the regular formulation [437-439].

Avanafil

Avanafil is a highly-selective PDE5I that became commercially available in 2013 [440]. Avanafil has a high ratio of inhibiting PDE5 as compared with other PDE subtypes, ideally allowing for the drug to be used for ED while minimising adverse effects (although head-to-head comparison studies are not yet available) [441]. Doses of 50 mg, 100 mg, and 200 mg have been approved for on-demand treatment of ED [440]. The recommended starting dose is 100 mg taken as needed approximately 15 to 30 minutes before sexual activity and the dosage may be adapted according to efficacy and tolerability [440, 442, 443]. In the general population with ED, the mean percentage of attempts resulting in successful intercourse was approximately 47%, 58%, and 59% for the 50 mg, 100 mg, and 200 mg avanafil groups, respectively, as compared with approximately 28% for placebo [440, 442]. Data from sexual attempts made within fifteen minutes of dosing showed successful attempts in 64%, 67%, and 71% of cases, with avanafil 50, 100, and 200 mg, respectively. Dosage adjustments are not warranted based on renal function, hepatic function, age or gender [442]. Pharmacokinetic data for avanafil is presented in Table 14 [440, 442]. Adverse events are generally mild in nature (Table 15) [440, 442]. Pairwise meta-analytic data from available studies suggested that avanafil significantly improved patient scores for IIEF, SEP2, SEP3, and GAQ, with an evident dose-response relationship [440, 444]. Administration with food may delay the onset of effect compared with administration in a fasting state but avanafil can be taken with or without food [445]. The efficacy of avanafil in many groups of patients with ED, including difficult-to-treat subgroups (e.g., diabetes mellitus), has been successfully established. As for dosing, 36.4% (28 of 77) of sexual attempts (SEP3) at fifteen minutes or less were successful with avanafil versus 4.5% (2 of 44) after placebo ($p < 0.01$) [446]. A recent meta-analysis confirmed that avanafil had comparable efficacy with sildenafil, vardenafil and tadalafil treatments [445].

Choice or preference between the different PDE5Is

To date, no data are available from double- or triple-blind multicentre studies comparing the efficacy and/or patient preference for the most-widely available PDE5Is (i.e., sildenafil, tadalafil, vardenafil, and avanafil). Choice of drug will depend on the frequency of intercourse (occasional use or regular therapy, three to four times weekly) and the patient's personal experience. Patients need to know whether a drug is short- or long-acting, its possible disadvantages, and how to use it. A meta-analysis demonstrated that ED patients who prioritise high efficacy must use sildenafil 50 mg whereas those who optimise tolerability should initially use tadalafil 10 mg and switch to udenafil 100 mg if the treatment is not sufficient (however, udenafil 100 mg is not EMA or FDA approved and is not available in Europe) [428]. In addition, results of another clinical trial revealed that tadalafil 5 mg once daily may improve the erectile function outcomes among men who had a partial response to on-demand PDE5I therapy [447].

Continuous use of PDE5Is

Animal studies have shown that chronic use of PDE5Is significantly improves or prevents the intracavernous structural alterations due to age, diabetes, or surgical damage [448-452]. No data exists in humans. In humans, it has been clinically demonstrated that treatment with tadalafil 5 mg once-daily in men complaining of ED of various severities was well tolerated and effective [453]. In 2007, tadalafil 2.5 and 5 mg were approved by the EMA for daily treatment of ED. According to the EMA, a once-daily regimen with tadalafil 2.5 mg or 5 mg might be considered suitable, based on patient choice and the physician's judgement. In these patients, the recommended dose is 5 mg, taken once a day at approximately the same time. Overall, tadalafil, 5 mg once daily, provides an alternative to on-demand dosing of 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. The appropriateness of the continuous use of a daily regimen should be re-assessed periodically [453, 454]. A recently published integrated analysis showed that no clinical populations of patients with ED seemed to benefit overwhelmingly from tadalafil once daily over on-demand dosing regimen and vice versa [455]. Furthermore, a recent RCT showed that there is no clinical benefit on endothelial dysfunction measured by flow-mediated dilation deriving from daily tadalafil when compared to placebo [456]. Although some authors reported improved erectile function when long-term tadalafil 5 mg once daily is combined with sildenafil as needed [457], more safety analyses are required to give a formal recommendation on such a therapy.

Table 14: Summary of the key pharmacokinetic data for the four PDE5Is currently EMA-approved to treat 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 half-time; AUC = area under curve or serum concentration time curve.

Table 15: 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.

Safety issues for PDE5Is

- Cardiovascular safety**

Clinical trial results for the four PDE5Is and post-marketing data of sildenafil, tadalafil, and vardenafil have demonstrated no increase in myocardial infarction rates in patients receiving PDE5Is, as part of either RCTs or open-label studies, or compared to expected rates in age-matched male populations. None of the PDE5Is had an adverse effect on total exercise time or time-to-ischæmia during exercise testing in men with stable angina [416, 458]. Chronic or on-demand use is well tolerated with a similar safety profile. The prescription of all PDE5Is in patients with CVD or in those with high CV risk should be based on the recommendations of the 3rd Princeton Consensus Panel [389].

- Contraindication for the concomitant use of organic nitrates**

Absolute contraindication to PDE5Is is represented by patients who are using any form of organic nitrate (e.g., nitroglycerine, isosorbide mononitrate, and isosorbide dinitrate) or NO donors (e.g., other nitrate preparations used to treat angina, as well as amyl nitrite or amyl nitrate such as “poppers” which are used for recreation). They result in cGMP accumulation and unpredictable falls in blood pressure and symptoms of hypotension. The duration of interaction between organic nitrates and PDE5Is depends upon the PDE5I and nitrate used. If a PDE5I is taken and the patient develops chest pain, nitroglycerine must be withheld for at least 24 hours if sildenafil (and probably also vardenafil) is used (half-life, four hours), or at least 48 hours if tadalafil is used (half-life, 17.5 hours), and for no less than twelve hours if avanafil is used (half-life, 6-17 hours) [459-462].

- Use caution with antihypertensive drugs**

Co-administration of PDE5Is with antihypertensive agents (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium blockers, β-blockers, and diuretics) may result in small additive decreases in blood pressure, which are usually minor [389]. 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 [463].

- Interaction with Nicorandil**

In vitro studies in animals suggest that the potassium channel opener nicorandil may potentiate the vasorelaxation induced by isoproterenol in isolated rat aorta by increasing cyclic GMP levels [464]. This may be due to the nitric oxide donating properties of nicorandil. Therefore the concurrent use of nicorandil and PDE5Is is also contraindicated.

α -Blocker interactions

All PDE5Is show some interaction with α -blockers, which under some conditions may result in orthostatic hypotension.

- Sildenafil labelling advises that 50 or 100 mg sildenafil should be used with caution in patients taking an α -blocker (especially doxazosin). Hypotension is more likely to occur within four hours following treatment with an α -blocker. A starting dose of 25 mg is recommended [421].
- Concomitant treatment with vardenafil should only be initiated if the patient has been stabilised on their α -blocker therapy. Co-administration of vardenafil with tamsulosin is not associated with clinically significant hypotension [433, 435, 436].
- Tadalafil is not recommended in patients taking doxazosin, but this is not the case for tamsulosin [425, 465].
- Avanafil labelling currently reports that patients should be stable on α -blocker therapy prior to initiating avanafil. In these patients, avanafil should be initiated at the lowest dose of 50 mg. Conversely, in those patients already taking an optimised dose of avanafil, α -blocker therapy should be initiated at the lowest dose.

In the everyday clinical practice, a patient presenting for ED should be stable on one medication (every α -blocker except for doxazosin which should be avoided whenever possible) before starting a PDE5Is.

Dosage adjustment

Drugs that inhibit the CYP3A4 pathway will inhibit the metabolic breakdown of PDE5Is, thus increasing PDE5Is blood levels (e.g. ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir and telithromycin). Therefore, lower doses of PDE5Is are necessary. However, other agents, such as rifampin, phenobarbital, phenytoin and carbamazepine, may induce CYP3A4 and enhance the breakdown of PDE5Is, so that higher doses of PDE5Is are required. Severe kidney or hepatic dysfunction may require dose adjustments or warnings.

Management of non-responders to PDE5Is

The two main reasons why patients fail to respond to a PDE5I are either incorrect drug use or lack of efficacy of the drug. Data suggest that an adequate trial involves at least six attempts with a particular drug [466]. The management of non-responders depends upon identifying the underlying cause [467]. Check that the patient has been using a licensed medication. There is a large counterfeit market in PDE5Is. The amount of active drug in these medications varies enormously and it is important to check how and from which source the patient has obtained his medication.

Check that the medication has been properly prescribed and correctly used. The main reason why patients fail to use their medication correctly is inadequate counselling from their physician. The most common causes of incorrect drug use are: i) failure to use adequate sexual stimulation; ii) failure to use an adequate dose; and, iii) failure to wait an adequate amount of time between taking the medication and attempting sexual intercourse.

PDE5I action is dependent on the release of NO by the parasympathetic nerve endings in the erectile tissue of the penis. The usual stimulus for NO release is sexual stimulation, and without adequate sexual stimulation (and NO release), the medication is ineffective. Oral PDE5Is take different times to reach maximal plasma concentrations [420, 422, 437, 444, 468-470]. Although pharmacological activity is achieved at plasma levels well below the maximal plasma concentration, there will be a period of time following oral ingestion of the medication during which the drug is ineffective. Even though all four drugs have an onset of action in some patients within 15-30 minutes of oral ingestion [422, 437, 468-470], most patients require a longer delay between taking the medication [435, 444, 471, 472]. Absorption of both sildenafil and vardenafil can be delayed by a heavy, fatty meal [473]. Absorption of tadalafil is less affected, and food has negligible effects on its bioavailability [468]. When avanafil is taken with a high fat meal, the rate of absorption is reduced with a mean delay in T_{max} of 1.25 hours and a mean reduction in C_{max} of 39% (200 mg). There is no effect on the extent of exposure (AUC). The small changes in avanafil C_{max} are considered to be of minimal clinical significance [440, 441, 444].

It is possible to wait too long after taking the medication before attempting sexual intercourse. The half-life of sildenafil and vardenafil is about four hours, suggesting that the normal window of efficacy is six to eight hours following drug ingestion, although responses following this time period are well recognised. The half-life of avanafil is six to seventeen hours. Tadalafil has a longer half-life of ~17.5 hours, so the window of efficacy is much longer at ~36 hours. Data from uncontrolled studies suggest patient education can help salvage an apparent non-responder to a PDE5I [467, 474-477]. After emphasising the importance of dose, timing, and sexual stimulation to the patient, erectile function can be effectively restored following re-administration of the relevant PDE5I [467, 474, 475].

Recent data suggested that response to sildenafil treatment was also dependent on polymorphism in the PDE5A gene, which encodes the principal cGMP-catalysing enzyme in the penis, regulating cGMP clearance, and it is the primary target of sildenafil [478-480].

Clinical strategies in patients correctly using a PDE5Is

Overall, treatment goals should be individualised to restore sexual satisfaction for the patient and/or couple and improve QoL based on the patient's expressed needs and desires [481]. In this context, data suggests that almost half of patients abandon first-generation PDE5Is within one year, with no single specific factor playing a major role in PDE5Is dropout rates [482].

Uncontrolled trials have demonstrated that hypogonadal patients not responding to PDE5Is may improve their response to PDE5Is after initiating testosterone therapy [51, 414, 483]. Therefore, in the real-life setting most patients with ED will first be prescribed a PDE5I, which is usually effective; however, if diagnostic criteria suggestive for testosterone deficiency are present, testosterone replacement therapy may be a more appropriate treatment even in ED patients [5, 51].

Modification of other risk factors may also be beneficial as previously discussed. Limited data suggest that some patients might respond better to one PDE5I than to another [484] and although these differences might be explained by variations in drug pharmacokinetics, they do raise the possibility that, despite an identical mode of action, switching to a different PDE5I might be helpful. However it is important to emphasise that the very few randomised studies show any difference in clinical outcomes with different drugs and intake patterns both in patients with classic ED [485] and in special populations such as diabetics [486].

Moreover, in patients with severe ED, it has been suggested to combine tadalafil daily dosing with a short acting PDE5I (such as sildenafil), without any significant increase in terms of side-effects [457]; robust prospective data from RCTs to support combination treatments with any oral preparations are still lacking and should therefore be used with caution. If drug treatment fails, then patients can be offered an alternative therapy such as intracavernous injection therapy or use of a vacuum erection device (VED). Likewise, limited data suggest the combination of a PDE5I with alprostadil as intracavernosal, intraurethral or topical application in patients who have previously failed therapy with either drug [487]. Review findings indicated that with all three formulations the combination therapy resulted in an improved outcome compared with either of the drugs as monotherapy, even for patients with post-prostatectomy ED. Treatment-emergent side-effects of the combined treatment did not result in treatment discontinuation [487].

5.6.2.2 Topical/Intraurethral alprostadil

The vasoactive agent alprostadil can be administered per urethra with two different formulations. The first compound is the topical route using a cream that includes a permeation enhancer in order to facilitate absorption of alprostadil (200 and 300 µg) via the urethral meatus [488, 489]. 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 [490]. Side-effects include penile erythema, penile burning and pain that usually resolves within two hours of application. Systemic side effects are very rare. Topical alprostadil (VITAROSTM) at the dose of 300 µg is currently approved and it is available in some European countries. Recently a randomised cross-over clinical trial showed that, compared to the standard administration route, the direct delivery of the drug within the urethral meatus is able to increase the level of treatment efficacy and confidence among patients, without increasing the incidence of side-effects [491].

The second method of delivery is by the 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 be initiated at a dose of 500 µg, as it has a higher efficacy than the 250 µg dose, with minimal differences with regard to adverse events. In case of unsatisfactory clinical response the dose can be increased to 1000 µg [492-494]. The application of a constriction ring at the root of the penis may improve efficacy [493, 494].

Overall, the most common adverse events are local pain (29-41%) and dizziness with possible hypotension (1.9-14%). Penile fibrosis and priapism are very 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 intracavernous pharmacotherapy [495], with a ~30% of adherence to long-term therapy. Intraurethral pharmacotherapy provides an alternative to intracavernous injections in patients who prefer a less-invasive, although less-efficacious treatment.

5.6.2.3 Shockwave therapy

The use of LI-SWT has been increasingly proposed as a treatment for vasculogenic ED over the last decade, being the only currently marketed treatment that might offer a cure, which is the most desired outcome for most men suffering from ED [397, 496-503].

Overall, several single-arm trials have shown benefit of LI-SWT on patient-reported erectile function scores, but data from prospective randomised trials are conflicting, and many questions remain to be answered especially because of the variation in shockwave generators (electrohydraulic, electromagnetic, piezoelectric, electropneumatic), type of shockwaves delivered (focused, linear, semi-focused, unfocused), set-up parameters (energy flux density and number of pulses per session) and treatment protocols (duration of treatment course, number of sessions per week, total number of shockwaves pulses delivered, penile sites of application) [504]. As a whole, most of the studies suggest that LI-SWT can significantly increase the IIEF and Erection Hardness Score in patients with mild vasculogenic ED, rather than improve penile hemodynamic parameters [504, 505]. Likewise, data suggest that LI-SWT could ameliorate erection quality even in patients with severe ED who are PDE5Is non-responders [501, 506] or inadequate responders [507], reducing the immediate need for more invasive treatments. However, prospective RCTs and longer-term follow-up data would provide the clinician with more confidence regarding the use and efficacy of LI-SWT for ED. Further clarity is also needed in defining treatment protocols that can result in greater clinical benefits [508, 509]. Overall, according to the available data and the novel treatment decision algorithm, patients with vasculogenic ED may be treated with LI-SWT, although they should be fully counselled before treatment.

5.6.2.4 *Psychosexual counselling and therapy*

For patients with a recognised psychological problems [510], psychosexual therapy may be given either alone or with another therapeutic approach in order to improve couple's sexual satisfaction and partner's sexual function [511]. Psychosexual therapy requires ongoing follow-up and has had variable results [512]. Despite this psychological treatments including different modalities (e.g., sexual skills training, marital therapy, psychosexual education) [411], Cognitive and Behaviour Therapy (CBT), including group or couple format, has been recommended [406]. Cognitive and behaviour therapy is aimed at altering dysfunctional cognitive and behavioural patterns influencing ED, and increasing adjustment during the course of the disorder. Some of its techniques include identifying triggers preceding erectile difficulties, cognitive restructuring of dysfunctional thinking styles, learning coping skills aimed at dealing with erectile difficulties and emotional symptoms, and relapse prevention. The CBT approach combined with the medical treatment for ED has received empirical support and is considered an optimal procedure [406].

5.6.2.5 *Hormonal treatment*

The advice of an endocrinologist should be sought for managing patients with hormonal abnormalities or endocrinopathies [382]. Testosterone deficiency is either a result of primary testicular failure or secondary to pituitary/hypothalamic causes (e.g., a functional pituitary tumour resulting in hyperprolactinaemia) [382, 513]. When clinically indicated [514], testosterone replacement therapy (intramuscular, transdermal, or oral) can be considered for men with low or low-normal testosterone levels and concomitant problems with their sexual desire, erectile function and dissatisfaction derived from intercourse and overall sexual life (see section 3.6 for a comprehensive discussion of testosterone replacement therapy).

5.6.2.6 *Vacuum erection devices*

Vacuum erection devices (VED) provide passive engorgement of the corpora cavernosa, together with a constrictor ring placed at the base of the penis to retain blood within the corpora. 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% [515, 516]. Most men who discontinue use of VEDs do so within three months. Long-term use of VEDs decreases to 50-64% after two years [517]. The most common adverse events include pain, inability to ejaculate, petechiae, bruising, and numbness [516]. 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 [518, 519]. Vacuum erection devices may be the treatment of choice in well-informed older patients with infrequent sexual intercourse and comorbidities requiring non-invasive, drug-free management of ED [515, 516, 520].

5.6.2.7 *Intracavernous injections therapy*

Intracavernous administration of vasoactive drugs was the first medical treatment introduced for ED [477, 521]. According to invasiveness, tolerability, effectiveness and patients' expectations (Figure 6), patients may be offered intracavernous injections. The success rate is high (85%) [495, 522].

5.6.2.7.1 *Alprostadil*

Alprostadil (Caverject™, Edex/Viridal™) was the first and only drug approved for intracavernous treatment of ED [477, 523]. Intracavernous alprostadil is most efficacious as a monotherapy at a dose of 5-40 µg (of note 40 µg dose may be offered off label in some European countries). The erection appears after five to fifteen minutes and lasts according to the dose injected, but with significant heterogeneity among patients. An office-training

program is required for the patient to learn the injection technique. In men with limited manual dexterity, the technique may be taught to their partners. The use of an automatic pen that avoids a view of the needle may be useful to resolve fear of penile puncture and simplifies the technique.

Efficacy rates for intracavernous alprostadil of > 70% have been found in the general ED population, as well as in patient subgroups (e.g., diabetes or CVD), with reported satisfaction rates of 87-93.5% in patients and 86-90.3% in partners after the injections, respectively [477, 521]. Complications of intracavernous alprostadil include penile pain (50% of patients reported pain only after 11% of total injections), excessively-prolonged undesired erections (5%), priapism (1%), and fibrosis (2%) [477, 521, 524]. Pain is usually self-limited after prolonged use. It can be alleviated with the addition of sodium bicarbonate or local anaesthesia [477, 521, 525]. Cavernal fibrosis (from a small haematoma) usually clears within a few months after temporary discontinuation of the injection program. However, tunical fibrosis suggests early onset of Peyronie's disease and may indicate stopping intracavernous injections indefinitely. Systemic side-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 described for intracavernous pharmacotherapy [477, 521, 526, 527], with most drop-outs occurring within the first two to three months. In a comparative study, alprostadil monotherapy had the lowest discontinuation rate (27.5%) compared to overall drug combinations (37.6%), with an attrition rate after the first few months of therapy of 10% per year [528]. Reasons for discontinuation included desire for a permanent modality of therapy (29%), lack of a suitable partner (26%), poor response (23%) (especially among early drop-out patients), fear of needles (23%), fear of complications (22%), and lack of spontaneity (21%). Careful counselling of patients during the office-training phase as well as close follow-up is important in addressing patient withdrawal from an intracavernous injection program [529-531].

5.6.2.8 Combination therapy

Table 16 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 side-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 due to its high incidence of side-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.
- Sparse data in the literature support the use of other drugs, such as vasoactive intestinal peptide (VIP), NO donors (linsidomine), forskolin, potassium channel openers, moxislyte or calcitonin gene-related peptide, usually combined with the main drugs [532, 533]. Most combinations are not standardised and some drugs have limited availability worldwide.
- Bimix, Trimix: Papaverine (7.5-45 mg) plus phentolamine (0.25-1.5 mg) (also known as bimix), and papaverine (8-16 mg) plus phentolamine (0.2-0.4 mg) plus alprostadil (10-20 µg) (also known as trimix), have been widely used with improved efficacy rates, although they have never been licensed for ED [534, 535]. Trimix has the highest efficacy rates, reaching 92%; this combination has similar side-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 total dose).
- Invicorp: Vasoactive intestinal peptide (25 µg) plus phentolamine mesylate (1-2 mg Invicorp™), currently licensed in Scandinavia, is a combination of two active components with complementary modes of action. Clinical studies showed that the combination is an effective treatment 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 very low incidence of penile pain and a virtually negligible risk of priapism [536].

Despite high efficacy rates, 5-10% of patients do not respond to combination intracavernous injections. The combination of sildenafil with intracavernous injection of the triple combination regimen may salvage as many as 31% of patients who do not respond to the triple combination alone [537]. However, combination therapy is associated with an increased incidence of adverse effects in 33% of patients, including dizziness in 20% of patients. This strategy can be considered in carefully selected patients before proceeding to a penile implant.

Table 16: 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	Very poor efficacy as monotherapy	Systemic hypotension, reflaxtachycardia, nasal congestion, and gastrointestinal upset	Abandoned as monotherapy
Bimix	Papaverine + Phentolamine	30 mg /mL + 0.5 mg/mL	~ 90%	Similar as 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 + 1-2mg	~ 80%	Similar as Alprostadil without pain	Easily available

There are currently several potential novel treatment modalities for ED, from innovative vasoactive agents and trophic factors to stem cell therapy and gene therapy. Most of these therapeutic approaches require further investigation in large-scale, blinded, placebo-controlled randomised studies in order to achieve an adequate evidence base and clinically-reliable grade of recommendation [538-543].

5.6.2.8.1 Erectile dysfunction after radical prostatectomy

Use of pro-erectile drugs following RP is important in achieving post-operative erectile function and to allow patients to resume sexual activity. There is also some evidence in animal studies that this may avoid cavernous fibrosis and maintain penile length. Overall, a number of trials have shown improvements in erectile function after RP in patients receiving drug compounds (any therapeutic or prophylactic) for ED. Early compared with delayed erectile function treatment seems to impact on the natural recovery time for potency [544], although there is a lack of data to support any specific regimen, which is either optimal for penile rehabilitation or may result in the achievement of spontaneous, non-pharmacological assisted erections [343, 545, 546]. In prospective studies, there is no evidence that penile rehabilitation itself increases the chances of spontaneous recovery of erectile function in men following NSRP [546]. Currently available therapeutic armamentarium follows the treatment algorithm for ED which is shown in Figure 4.

Historically, also the management of post-RP ED has been revolutionised by the advent of PDE5Is, with their demonstrated efficacy, ease of use, good tolerability, excellent safety, and positive impact on QoL. In this context, it must be emphasised that post-RP, ED patients are poor responders to PDE5Is. Since their launch on the market, PDE5Is have been considered as the first-line therapy in patients who have undergone NS surgery, regardless of the surgical technique used [343, 352, 353]. A number of clinical parameters have been identified as potential predictors of PDE5Is in men undergoing RP. As detailed, patient age, baseline erectile function, and quality of NS technique are key factors in preserving post-RP erectile function [352, 353, 361, 547].

Analysing results in further detail, the response rate to sildenafil treatment for ED after RP in different trials has ranged from 35% to 75% among those who underwent NSRP and from 0% to 15% among those who underwent non-NSRP [352, 548]. Early use of high-dose sildenafil after RP is associated with preservation of smooth muscle within the corpora cavernosa [549]. A single study demonstrated that daily sildenafil also results in a greater return of spontaneous normal erectile function after RP compared to placebo following bilateral NSRP in patients who were fully potent before surgery [550]. Conversely, a recent prospective, randomised, placebo-controlled study, which assessed the effects of nightly sildenafil citrate therapy during penile rehabilitation using nocturnal penile rigidity score in addition to the IIEF-erectile function showed no

therapeutic benefit for nightly sildenafil when compared to on-demand dosing in recovery of erectile function post-prostatectomy [551].

A large multicentre trial in Europe and the USA investigated the effects of tadalafil in patients with ED following bilateral NSRP. Erectile function was improved in 71% of patients treated with 20 mg tadalafil versus 24% of those treated with placebo, while the rate of successful intercourse attempts was 52% with 20 mg tadalafil versus 26% with placebo [552]. Moreover, a randomised, double-blind, double-placebo trial in men < 68 years of age and with normal pre-operative erectile function who underwent NSRP at 50 centres from nine European countries and Canada, compared tadalafil once daily with placebo [546]. Tadalafil was most effective for drug-assisted erectile function in men with ED following NSRP and data suggested a potential role for tadalafil once daily (provided early after surgery) in contributing to the recovery of post-operative erectile function and maintaining penile length [546]. Conversely, unassisted or spontaneous recovery of erectile function was not improved after cessation of active therapy for nine months [546]. However, tadalafil once daily improved QoL post-operatively, both at double-blind treatment and open label treatment period [553].

Similarly, vardenafil has been tested in patients with ED following NSRP in a randomised, multicentre, prospective, placebo-controlled study [554]. Following bilateral NSRP, erectile function improved by 71% and 60% with 10 and 20 mg vardenafil, respectively. An extended analysis of the same cohort of patients showed the benefit of vardenafil compared to placebo in terms of intercourse satisfaction, hardness of erection, orgasmic function, and overall satisfaction with sexual experience [555]. A randomised, double-blind, double-dummy, multicentre, parallel-group study in 87 centres across Europe, Canada, South Africa and the USA, compared on-demand and nightly dosing of vardenafil in men with ED following bilateral NSRP [545]. In patients whose pre-operative erectile function domain score was > 26, vardenafil was efficacious when used on demand [545].

A double-blind, placebo-controlled, parallel-group study in 298 patients with ED after bilateral NSRP randomised to 100 or 200 mg avanafil or placebo (taken 30 minutes before sexual activity) for twelve weeks showed significantly greater increases in SEP question 2 and SEP3 as well as in mean change of IIEF erectile function domain score with 100 and 200 mg avanafil versus placebo ($p < 0.01$) [391].

A recent Cochrane database systematic review analysed data from eight RCTs [556]. It showed that scheduled PDE5I may have little or no effect on short-term (up to twelve months) self-reported potency when compared to placebo or no treatment. In this study, daily PDE5I made little to no difference in short-term and long-term erectile function (short term: RR 1.00, 95% CI 0.65 to 1.55; long term: RR 0.74, 95% CI 0.48 to 1.14; both very low quality evidence). The authors conclude that penile rehabilitation strategies using PDE5I following RP do not increase self-reported potency and erectile function compared to on-demand use. Therefore, daily PDE5Is appeared to result in little to no difference in both short-term and long-term (greater than twelve months) self-reported potency when compared to scheduled use. Finally, at short-term follow-up, daily PDE5I may result in little or no effect on self-reported potency when compared to scheduled intra-urethral application of PGE1.

Historically, the treatment options for post-RP ED have included intracavernous injections [557], urethral micro-suppository [352, 558], vacuum device therapy [343, 352, 559, 560], and penile implants [352, 561, 562]. Intracavernous injections and penile implants had been suggested as second- and third-line treatments, respectively, when oral PDE5Is are not adequately effective or not usable for post-operative patients [342, 343, 563]. A recent meta-analysis showed that the early use of vacuum device therapy appears to have excellent therapeutic effect on post-RP patients and no serious side-effects, therefore it should be considered as a therapeutic alternative to discuss with the patient [564].

5.6.2.9 *Vascular surgery*

5.6.2.9.1 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 [519, 565]. The stenosis must be confirmed by penile pharmaco-arteriography. Corporeal veno-occlusive dysfunction is a contraindication to revascularisation and must be excluded by dynamic infusion cavernosometry or cavernosography.

5.6.2.9.2 Venous ligation surgery

Venous ligation surgery for veno-occlusive dysfunction is no longer recommended because of poor long-term results [565].

5.6.2.9.3 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 pharmacological therapies (Figure 6) [566]. The two currently available classes of penile implants include inflatable (2- and 3-piece) and semi-rigid devices (malleable, mechanical, soft flexible) [352, 561, 567-569]. Patients may prefer the 3-piece inflatable devices due to the more “natural” erections obtained, although there are no prospective RCTs comparing 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 [352, 561, 567, 568]. Conversely, they can have the disadvantage of unnatural persistent erection and reduced concealability [568, 570]. 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 [567, 568, 570, 571]. The peno-scrotal approach has been suggested to provide an excellent exposure; afford proximal crural exposure; avoid dorsal nerve injury; and permit direct visualisation of pump placement. However, with this approach, the reservoir is either placed blindly into the retropubic space, which can result in visceral injury in patients with a history of major pelvic surgery (mainly radical cystectomy) or a separate incision in the abdomen is placed under direct vision. A recent systematic review comparing the satisfaction and complication rates of the different surgical approaches showed that there is no specific advantage between the two, but rather it is recommended that the surgeon has knowledge of both techniques and is capable of tailoring the incision strategy for complex cases [572]. Revision surgery is associated with poorer outcomes and may be more challenging. 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 [352, 561, 567, 573-581]. In patients with favourable oncologic prognosis after RP for PCa, combination surgery for treatment of ED, with the implant of a penile prosthesis, and stress urinary incontinence (male sling or artificial urinary sphincter) is effective and durable and has an established and definitive role to address both problems [352, 561, 582-584]. Structured psychosexual counselling may improve sexuality and sexual well-being in both patients and their partners after penile implant surgery [585].

5.6.2.9.4 Penile prostheses implantation: complications

The two main complications of penile prosthesis implantation are mechanical failure and infection. Several technical modifications of the most commonly used 3-piece prosthesis (e.g., AMS 700CX/CXR™ and Titan Zero degree™) resulted in mechanical failure rates of < 5% after five years of follow-up [561, 586, 587]. Careful surgical techniques with appropriate antibiotic prophylaxis against Gram-positive and Gram-negative bacteria reduced infection rates to 2-3% with primary implantation in low-risk patients and in high volume centres, although the definition of a high volume centre still needs clarity [588-591]. The infection rate may be further reduced to 1-2% by implanting an antibiotic-impregnated prosthesis (AMS Inhibizone™) or hydrophilic-coated prosthesis (Coloplast Titan™) [561, 588, 592-595]. Methods that decrease infections include using coated prostheses and strictly adhering to surgical techniques that avoid prolonged wound exposure and skin contact minimisation (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 prepping with chlorhexidine-alcohol [596]. Furthermore, identification and pre-treatment of patients who are colonised with nasal *Staphylococcus aureus* with mupirocin and chlorhexidine prior to surgery has been shown to reduce the incidence of surgical site infection after surgery from 4.4% to 0.9% in a placebo-controlled randomised trial [597]. On the whole, growing evidence suggests that the risk of penile prosthesis infection has reduced over the last few decades with device improvement and surgical expertise [598].

Higher-risk populations include patients undergoing revision surgery, those with impaired host defences (immunosuppression, diabetes mellitus, spinal cord injury) or those with penile corporal fibrosis [561, 567, 589, 599-601]. A recent large database-study showed that diabetes mellitus is a risk factor for penile prostheses infection, highlighting the need for an optimal patient selection other than raising the question of whether lowering this risk by optimising glycaemic control before surgery [602]. 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 [603].

Infection requires removal of the prosthesis and antibiotic administration. Alternatively, removal of the infected device with immediate replacement with a new prosthesis has been described using a wash-out protocol with successful salvages achieved in > 80% of cases [589, 600, 604, 605]. A final recommendation on how to proceed after removal in this setting cannot be given. The majority of revisions are secondary to mechanical

failure and combined erosion or infection [594, 596]. Ninety-three percent of cases are successfully revised, providing functioning penile prosthesis [588, 589, 604, 606, 607].

Besides infection and mechanical failure, impending erosion involving the distal lateral corpora, urethra, glans or other structures can occur in 1-6% of cases after surgery [608]. Similarly glans ischaemia and necrosis have been reported in about 1.5% of patients [609]. 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.

5.6.2.9.4.1 Conclusions penile prostheses implantation

Penile implants are an effective solution for patients who do not respond to more conservative therapies. There is sufficient evidence to recommend this approach in patients not responding to less-invasive treatments due to its high efficacy, safety and satisfaction rates [610]. There are also currently no head to head studies comparing the different manufacturers' implants, demonstrating superiority of one implant type over another.

Table 17: Penile prostheses models available on the market

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

5.6.3 Recommendations for the treatment of ED

Recommendations	Strength rating
Assess all patients for inadequate/incorrect information about the mechanism of action and the ways in which drugs should be taken, as they are the main causes of a lack of response to PDE5Is.	Weak
Use Cognitive Behaviour Therapy as psychological approach (include the partner) combined with medical treatment to maximise treatment outcomes.	Strong
Discuss with patients undergoing radical prostatectomy (any technique) about the risk of sexual changes other than ED, including libido reduction, changes in orgasm, anejaculation, Peyronie's like disease and penile size changes.	Strong
Initiate lifestyle changes and risk factor modification prior to or at the same time as initiating erectile dysfunction (ED) treatments.	Strong
Treat a curable cause of ED first, when found.	Weak
Use phosphodiesterase type 5 inhibitors (PDE5Is) as first-line therapeutic options.	Strong
Use topical/intraurethral alprostadil as an alternative first-line therapy in well-informed patients who do not wish or are not suitable for oral vasoactive therapy.	Weak
Use topical/intraurethral alprostadil as an alternative therapy to intracavernous injections in patients who prefer a less-invasive therapy.	Weak
Use low intensity shockwave treatment (LI-SWT) in patients with mild vasculogenic ED or as an alternative first-line therapy in well-informed patients who do not wish or are not suitable for oral vasoactive therapy or desire a curable option. Use LI-SWT in vasculogenic ED patients who are poor responders to PDE5Is.	Weak
Use vacuum erection devices as a first-line therapy in well-informed patients with infrequent sexual intercourse and comorbidities requiring non-invasive, drug-free management of ED.	Weak
Use intracavernous injections as an alternative first-line therapy in well-informed patients or as second-line therapy.	Strong
Use implantation of a penile prosthesis if other treatments fail or based upon patient preference.	Strong
Data is inadequate to support the use of any specific regimen for penile rehabilitation after radical prostatectomy.	Strong
Pro-erectile treatments should start at the earliest opportunity after radical prostatectomy/ pelvic surgery and other curative treatments for prostate cancer.	Weak

5.6.4 Follow-up

Follow-up is important in order to assess 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 which is composed of emission and expulsion and is mediated by interwoven neurological and hormonal pathways [611]. Any interference with those pathways may cause a wide range of ejaculatory disorders (Table 18).

Table 18: Spectrum of ejaculation disorders

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

6.2 Premature ejaculation

6.2.1 Epidemiology

Historically, the main problem in assessing the prevalence of premature ejaculation (PE) has been the lack of a universally recognised definition at the time the surveys were conducted [172]. In this context, the highest prevalence rate of 31% (men aged 18-59 years) was found by the USA National Health and Social Life Survey (NHSLs) study [177]. Prevalence rates were 30% (18-29 years), 32% (30-39 years), 28% (40-49 years) and 55% (50-59 years). It is, however, unlikely that PE prevalence was as high as 20-30% based on the relatively low number of men who presented for treatment of 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. The Internet-based survey PEPA [the PE Prevalence and Attitudes] revealed a 22.7% prevalence of PE (24.0% in the United States, 20.3% in Germany, and 20% in Italy), which did not vary significantly with age among men over 24 years of age [178]. According to the four PE subtypes proposed by Waldinger *et al.* [181], the prevalence rates were 2.3% (lifelong PE), 3.9% (acquired PE), 8.5% (variable PE) and, 5.1% (premature-like ED or subjective PE) [179]. A prevalence of approximately 5% of acquired PE and lifelong PE in the general population is consistent with epidemiological data indicating that around 5% of the population have an ejaculation latency time of less than two minutes [185].

6.2.2 Pathophysiology and risk factors

The aetiology of PE is unknown, with little data to support suggested biological and psychological hypotheses, including anxiety [612-616], penile hypersensitivity [617-623] and 5-hydroxytryptamine (HT) receptor dysfunction [624-629]. The classification of PE into four subtypes [181] has contributed to a better delineation of lifelong, acquired, variable and subjective PE [630-632]. It has been hypothesised that the pathophysiology of lifelong PE is mediated by a very complex interplay of central and peripheral serotonergic, dopaminergic, oxytocinergic, endocrinological, genetic and epigenetic factors [633]. On the other hand, acquired PE may occur due to either psychological problems - such as sexual performance anxiety, psychological or relationship problems - and/or comorbid medical conditions, including ED, prostatitis and hyperthyroidism [634-636].

A significant proportion of men with ED also experience PE [188, 334]. 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 NHSLs, the prevalence of PE is not affected by age [177], unlike ED, which increases with age. Conversely, other data depicted an increased prevalence with ageing [637]; for instance, Verze *et al.* reported that PE prevalence based on the Premature Ejaculation Diagnostic Tool (PEDT) score (≥ 11) [638] proportionally increased with age [639]. Premature ejaculation is not affected by marital or income status [177, 639]. However, PE is more common in Black men, Hispanic men, and men from regions where the Islamic background is particularly common [176, 640] and may be higher in men with a lower educational level [177, 188]. Other risk factors may include a genetic predisposition [629, 641-644], poor overall health status and obesity [177], prostate inflammation [323, 645-648], low prolactin levels [649], higher testosterone levels [650], vitamin D and B12 deficiency [651, 652], diabetes [653, 654], metabolic syndrome [654, 655], lack of physical activity [656], emotional problems and stress [177, 657, 658], depressive symptoms [658], and traumatic sexual experiences [177, 188]. In the only published study on risk modification/prevention strategies [659], successful eradication of causative organisms in patients with chronic prostatitis and PE produced marked improvements in intravaginal ejaculatory latency time (IELT) and ejaculatory control compared to untreated patients.

6.2.3 Impact of premature ejaculation 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 [257, 660, 661]. However, the negative impact of PE extends beyond sexual dysfunction. 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 [257, 662, 663]. Moreover, PE may impact on the partner's sexual functioning

and their satisfaction with the sexual relationship decreases with increasing severity of the patients' condition [664-666]. Despite the possible serious psychological and QoL consequences of PE, few men seek treatment. In the Global Study of Sexual Attitudes and Behaviors (GSSAB) survey, 78% of men who self-reported a sexual dysfunction sought no professional help or advice for their sexual problems [188], with men more likely to seek treatment for ED than for PE [188]. In the PEPA survey, only 9% of men with self-reported PE consulted a doctor [178]. The main reasons for not discussing PE with their physician are embarrassment and a belief that there is no treatment. Physicians are often uncomfortable discussing sexuality with their patients usually because of embarrassment and a lack of training or expertise in treating PE [667, 668]. Physicians need to encourage their patients to talk about PE.

6.2.4 **Classification**

There is still little consensus about the definition and classification of PE [669]. It is now universally accepted that "premature ejaculation" is a broad term that includes a number of 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 [670]: *"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 five categories: male early ejaculation, lifelong generalised and situational, acquired generalised and situational, unspecified.

In the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V), PE is defined as a sexual disorder with:

- consistent ejaculation within one minute or less of vaginal penetration;
- over a period of at least six months;
- experienced 75%-100% of the time;
- the condition results in clinically significant distress, sexual frustration, dissatisfaction, or tension between partners;
- this condition is not better accounted for by another non-sexual mental disorder, medication or illicit substance use, or medical condition [671].

The EAU Guidelines have adopted the definition of PE which has been developed by the International Society for Sexual Medicine (ISSM) as the first evidence-based definition [672]. According to this definition, PE (lifelong and acquired) is a male sexual dysfunction characterised by the following:

- Ejaculation that always or nearly always occurs prior to or within about one minute of vaginal penetration (lifelong PE) or a clinically significant and bothersome reduction in latency time, often to about three minutes or less (acquired PE).
- The inability to delay ejaculation on all or nearly all vaginal penetrations.
- Negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy.

Two more PE syndromes have been proposed [631]:

- '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.

The addition of these new types may help in overcoming the limitations of each individual definition and it may support a more flexible view of PE for patient stratification, diagnosis and treatment [673].

6.2.5 **Diagnostic evaluation**

Diagnosis of PE is based on the patient's medical and sexual history [185, 674, 675]. 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 [334, 676]. Furthermore, some patients are not aware that loss of erection after ejaculation is normal and may erroneously complain of ED, while the actual problem is PE [677]. There are several overlapping definitions of PE, with four shared factors (Table 19), resulting in a multi-dimensional diagnosis [678].

Table 19: Common factors in different definitions of PE

Time to ejaculation assessed by IELT
Perceived control
Distress, bother, frustration, interpersonal difficulty related to the ejaculatory dysfunction

6.2.5.1 Intravaginal ejaculatory latency time

Although it has been suggested as an objective diagnostic criterion and treatment outcome measure [679, 680], the use of IELT alone is not sufficient to define PE, as there is significant overlap between men with and without PE [681, 682]. 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. IELT has a significant direct effect on perceived control over ejaculation, but not a significant direct effect on ejaculation-related personal distress or satisfaction with sexual intercourse [683]. In addition, perceived control over ejaculation has a significant direct effect on both ejaculation-related personal distress and satisfaction with sexual intercourse (each showing direct effects on interpersonal difficulty related to ejaculation) [684]. In everyday clinical practice, self-estimated IELT is sufficient [173]. Self-estimated and stopwatch-measured IELT are interchangeable and correctly assign PE status with 80% sensitivity and 80% specificity [685]. Specificity can be improved further to 96% by combining IELT with a single-item patient-reported outcome (PRO) scale on control over ejaculation and satisfaction with sexual intercourse (scale ranging from 0 = very poor to 4 = very good) and on personal distress and interpersonal difficulty (0 = not at all, to 4 = extremely). However, self-estimated IELT may be over-estimated by approximately one minute and therefore it must be carefully substituted with stopwatch-measured IELT while identifying men with the complaint of lifelong PE in a clinical setting [686].

On the other hand, 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 IELT instead of using arithmetic mean IELT as 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 [687].

6.2.5.2 Premature ejaculation assessment questionnaires

The need to assess PE objectively has led to the development of several questionnaires based on the use of PROs. 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 [688]. A total score > 11 suggests a diagnosis of PE, a score of 9 or 10 suggests a probable diagnosis of PE while a score of < 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, anxiety or depression [689]. A cut-off score of 30 (range of scores 7-35) discriminated PE diagnosis best. Severity of PE was classified as severe (score: 7-13), moderate (score: 14-19), mild-to-moderate (score: 20-25) and mild (score: 26-30).

Although it is widely used, some studies reported a low correlation between a diagnosis provided by PEDT and a self-reported diagnosis. Only 40% of men with PEDT-diagnosed PE and 19% of men with probable PE self-reported the condition [274]. On the contrary, a recent study has shown that the PEDT was highly valid in screening the presence of evidence-based-defined lifelong PE and acquired PE [62]. Questionnaires are a significant step in simplifying the methodology of PE drug studies, although further cross-cultural validation is needed [690].

Other questionnaires used to characterise PE and determine treatment effects include the Premature Ejaculation Profile (PEP) [682], Index of Premature Ejaculation (IPE) [691] and Male Sexual Health Questionnaire Ejaculatory Dysfunction (MSHQ-EJD) [692]. Currently, their role is optional in everyday clinical practice.

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 [674].

6.2.5.4 Recommendations for the diagnostic evaluation of PE

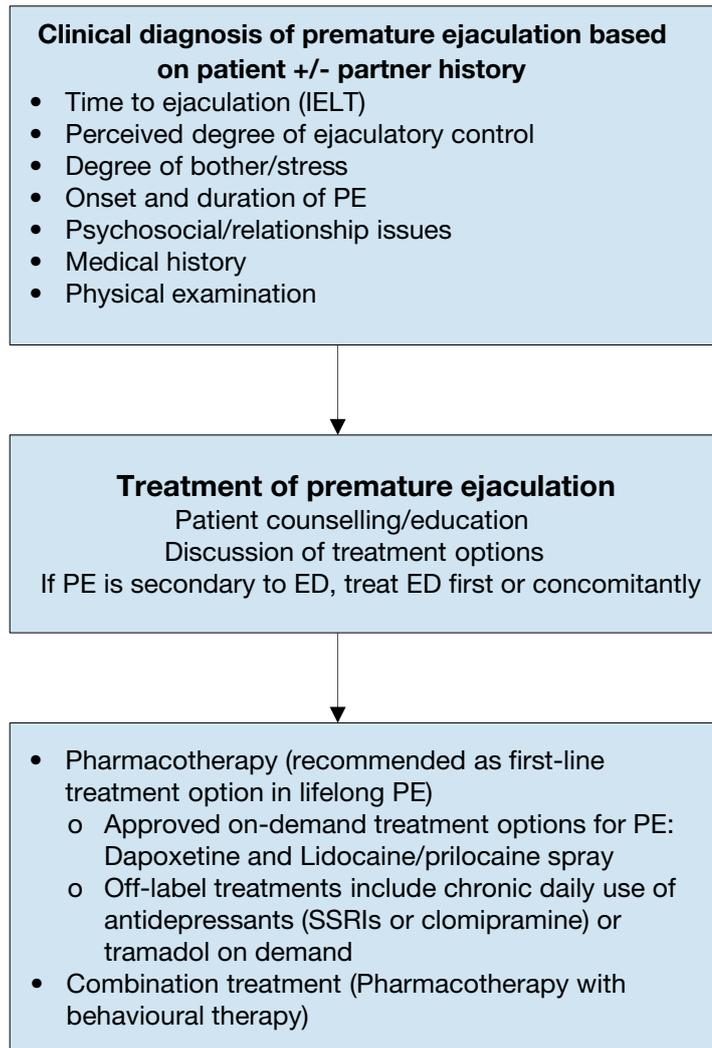
Recommendations	Strength rating
Perform the diagnosis and classification of premature ejaculation (PE) based on medical and sexual history, which should include assessment of intravaginal ejaculatory latency time (IELT) (self-estimated), perceived control, distress and interpersonal difficulty due to the ejaculatory dysfunction.	Strong
Use of stopwatch-measured IELT is not compulsory in clinical practice.	Weak
Use patient-reported outcomes in daily clinical practice.	Weak
Include physical examination in the initial assessment of PE to identify anatomical abnormalities that may be associated with PE or other sexual dysfunctions, particularly erectile dysfunction (ED).	Strong
Do not perform routine laboratory or neuro-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 as the first-line treatment for patients with lifelong PE, whereas treating the underlying cause (e.g., ED, prostatitis, LUTS, anxiety, hyperthyroidism) must be the initial goal for patients with acquired PE [185]. Various behavioural techniques may be beneficial in treating variable and subjective PE [693]. Psychotherapy can also be considered for PE patients who are uncomfortable with pharmacological therapy or in combination with pharmacological therapy [694, 695]. However, there is weak and inconsistent evidence regarding the effectiveness of these psychosexual interventions and their long-term outcomes in PE are unknown [696].

In lifelong PE, behavioural techniques are not recommended alone, and pharmacotherapy must be considered as the basis of treatment [185]. 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 [697]. Moreover, the metered-dose aerosol spray of lidocaine (150 mg/mL) and prilocaine (50 mg/mL) combination is the first topical formula to be officially approved for the on-demand treatment of lifelong PE by the EMA in the European Union [698]. All other medications used in PE are off-label indications [699]. 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 [700-703]. 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 7).

Figure 7: Management of premature ejaculation*



* Adapted from Lue *et al.* 2004 [704].

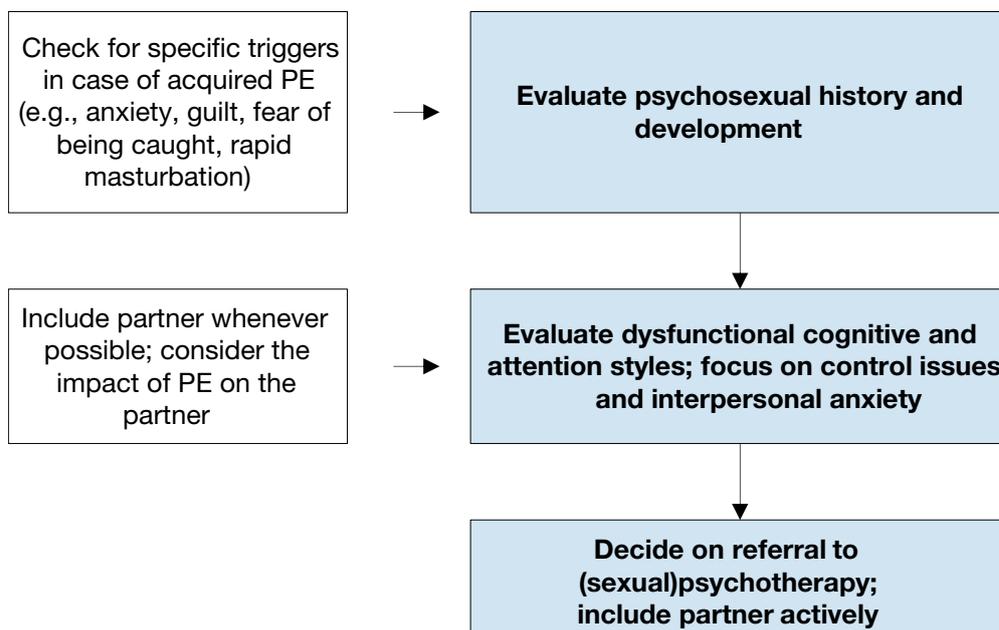
ED = erectile dysfunction; *PE* = premature ejaculation; *IELT* = intravaginal ejaculatory latency time; *SSRI* = selective serotonin receptor inhibitor.

6.2.6.1 Psychological aspects and intervention

Only a few studies have addressed the psychological factors underpinning PE. Men with PE were shown to present dysfunctional responsibility attribution patterns regarding their sexual experience. These men blamed themselves for their dysfunctional sexual response, even when the negative sexual outcome was unrelated to early ejaculation; additionally, they took less credit for any positive sexual experience they might have [705, 706]. In addition to this style of internalised blame, men with PE were found to focus on bodily sensations and partners' reactions during sex, in order to monitor potential signs of threat to their sexual performance. This monitoring process denotes a dysfunctional cognitive and attention style that contributes to the maintenance of PE [407]. Premature ejaculation has been further related to increased levels of anxiety, including social anxiety [407, 684]. Yet, it is not known whether anxiety is a precursor or a consequence of PE [613]. Furthermore, the negative impact of PE on the couple has been consistently mentioned. Female partners of men with PE present with an increased likelihood of sexual dysfunction [707]; the intimate sphere, as well as the overall relationship quality, was compromised by PE [696]. An important trigger for seeking help in PE is partner dissatisfaction and the negative impact of PE on the general QoL of the couple [708]. Accordingly, psychosexual interventions, whether these are 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 [693]. It is worth noting, however, that psychosexual interventions alone regarding PE lack empirical support. Behavioural therapy may be most effective when used to 'add value' to medical interventions. A combination of dapoxetine and behavioural treatment was more effective than dapoxetine alone in patients with lifelong PE in a prospective, randomised

trial [694]. Validated assessment instruments need to be used as end-points. Longer follow-up periods are necessary to confirm these findings.

Figure 8: Key aspects for psychosexual evaluation



6.2.6.1.1 Recommendation for the assessment and treatment (psychosexual approach) of PE

Recommendations for assessment	Strength rating
Consider sexual history and psychosexual development.	Strong
Consider anxiety, interpersonal anxiety; focus on control issues.	Strong
Include 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.	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 [699]. It has a rapid T_{max} (1.3 hours) and a short half-life (95% clearance rate after 24 hours) [709]. Dapoxetine has been investigated in 6,081 subjects to date [710]. 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 of < 0.5 minutes [697, 711, 712].

In RCTs, dapoxetine, 30 mg or 60 mg one to two hours before intercourse, was effective on IELT and increased ejaculatory control, decreased distress, and increased satisfaction [713]. Dapoxetine has shown a similar efficacy profile in men with lifelong and acquired PE [697, 714, 715]. Treatment-related side-effects were dose-dependent and included nausea, diarrhoea, headache, and dizziness. Treatment-emergent adverse events (TEAEs) were responsible for study discontinuation in 4% (30 mg) and 10% (60 mg) of subjects [173]. There was no indication of an increased risk of suicidal ideation or suicide attempts and little indication of withdrawal symptoms with abrupt dapoxetine cessation [716, 717]. Moreover, dapoxetine is found to be safer compared with formal anti-depressant compounds which are used for the treatment of PE [718].

A low rate (0.1%) of vasovagal syncope was reported in phase 3 studies [719]. According to the summary of product characteristics, orthostatic vital signs (blood pressure and heart rate) must be measured prior to starting dapoxetine and dose-titration must be considered [720]. The EMA assessment report for dapoxetine concluded that the potentially increased risk for syncope has been proven manageable with adequate risk minimisation measures [721]. No cases of syncope were observed in a post-marketing observational study, which had identified patients at risk for orthostatic reaction using the patient's medical history and orthostatic testing [722].

Many patients and physicians may prefer using dapoxetine in combination with a PDE5I in order 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 does not have any pharmacokinetic interactions with PDE5I (i.e. tadalafil 20 mg and sildenafil 100 mg) [723]. When dapoxetine is co-administered with PDE5Is, it is well tolerated, with a safety profile consistent with previous phase 3 studies of dapoxetine alone [724]. A recent RCT including PE patients without ED, demonstrated that combination of dapoxetine with sildenafil can significantly improve IELT values and PROs compared with dapoxetine alone or sildenafil alone, with tolerable adverse effects [725]. Efficacy and safety of dapoxetine/sildenafil combination tablets for the treatment of PE have also been reported [726].

6.2.6.2.2 Off-label use of antidepressants: SSRIs and clomipramine

Ejaculation is commanded by a spinal ejaculation generator [727, 728] under excitatory or inhibitory influences from the brain and the periphery [653]. 5-hydroxytryptamine (5-HT or serotonin) is involved in ejaculatory control, with its ejaculation-retarding effects likely to be attributable to activation of 5-HT_{1B} and 5-HT_{2C} receptors, both spinally and supraspinally. By contrast, stimulation of 5-HT_{1A} receptors precipitates ejaculation [729].

Selective serotonin re-uptake inhibitors are used to treat mood disorders but can delay ejaculation and therefore are widely used 'off-label' for PE since the 1990s [730]. For depression, SSRIs must be given for one to two weeks to be effective in PE [729]. Administration of chronic SSRIs causes prolonged increases in synaptic cleft serotonin, which desensitises the 5-HT_{1A} and 5-HT_{1B} receptors [731]. Commonly used SSRIs include continuous intake of citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, all of which have a similar efficacy, whereas paroxetine exerts the strongest ejaculation delay [679, 732, 733].

Clomipramine, the most serotonergic tricyclic antidepressant, was first reported in 1977 as an effective PE treatment [734, 735]. In a recent 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 to the placebo group (4.66 ± 5.64 vs. 2.80 ± 2.19 , $p < 0.05$). [736, 737]. The most commonly reported TEAEs were nausea in 15.7% of men and dizziness in 4.9% [736, 737].

Several SRs and meta-analyses of drug treatment studies reported that, despite methodological problems in most studies, there still remained several, well-designed, double-blind, placebo-controlled trials supporting the therapeutic effect of daily SSRIs on PE [679, 700-703]. Based on these meta-analyses, SSRIs may increase the geometric mean IELT by 2.6-fold to 13.2-fold. Paroxetine was found to be superior to fluoxetine, clomipramine and sertraline. Sertraline was superior to fluoxetine, whereas the efficacy of clomipramine was not significantly different from 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; there was no significant relationship between dose and response among the various drugs. There is limited evidence that citalopram may be less efficacious compared to other SSRIs, while fluvoxamine may not be effective [738, 739].

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 [734]. 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 [711, 734]. 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 with PE aged eighteen years or less, 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 associated with a SSRI withdrawal syndrome [173]. Moreover, PE patients who are trying to conceive should avoid using these medications because of their detrimental effects on sperm cells [740-743].

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 [744]. Several trials [620, 745, 746] 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 confirmed the efficacy and safety of these agents for the treatment of PE [747, 748].

6.2.6.2.3.1 Lidocaine-prilocaine cream

In a randomised, double-blind, placebo-controlled trial, lidocaine/prilocaine cream increased the IELT from one minute in the placebo group to 6.7 minutes in the treatment group [749]. In another randomised, double blind, placebo-controlled trial, lidocaine/prilocaine cream significantly increased the stopwatch-measured IELT from 1.49 to 8.45 minutes, while no difference was recorded in the placebo group (1.67 to 1.95 minutes) [750]. Although no significant TEAEs have been reported, topical anaesthetics are contraindicated in patients or partners with an allergy to any ingredient in the product. Moreover, these anaesthetic creams/gels may be transferred to the partner and result in vaginal numbness. Therefore, patients are advised to use a condom after applying the cream on their penises. Alternatively, the penis can be washed clean of any residual active compound prior to sexual intercourse. Since these chemicals may be associated with cytotoxic effects on fresh human sperm cells, couples who are wanting to achieve pregnancy should not use topical lidocaine/prilocaine containing substances [751].

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 males with lifelong PE [752]. 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 [753], without absorption through the penile shaft skin [754].

To date, one phase 2 proof-of-concept [754] and two phase 3 RCTs [755, 756] have demonstrated the efficacy of lidocaine/prilocaine spray in improving both IELT and the Index of Ejaculatory Control (IEC) of patients with primary PE, along with an improvement in scores assessing treatment satisfaction (IPE) [755, 756]. Based on these data, according to the patient information leaflet [757], the recommended dose of lidocaine/prilocaine spray is one dose (namely three sprays) to be applied on the glans penis at least five minutes before sexual intercourse [758]. 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 [759]. A low incidence of local TEAEs in both patients and partners have been reported, including genital hypoaesthesia (4.5% and 1.% in males and females partners, respectively) and ED (4.4%), and vulvovaginal burning sensation (3.9%), but is unlikely to be associated with systemic TEAEs [757, 760].

6.2.6.2.4 Tramadol

Tramadol is a centrally-acting analgesic agent that combines opioid receptor activation and re-uptake inhibition of serotonin and noradrenaline. Tramadol is a mild-opioid receptor agonist, but it also displays antagonistic properties on transporters of noradrenaline and 5-HT [761]. 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 five to seven hours.

A large, randomised, double-blind, placebo-controlled, multicentre twelve-week study was carried out to evaluate the efficacy and safety of two doses of tramadol (62 and 89 mg) by ODT in the treatment of PE [762]. A bioequivalence study had previously been performed demonstrating equivalence between tramadol ODT and tramadol HCl. In patients with a history of lifelong PE and an IELT < two minutes, increases in the median IELT of 0.6 minutes (1.6-fold), 1.2 minutes (2.4-fold) and 1.5 minutes (2.5-fold) were reported for placebo, 62 mg of tramadol ODT, and 89 mg of tramadol ODT, respectively. It should be noted that there was no dose-response effect with tramadol. Side-effects were reported at doses used for analgesic purposes (up to 400 mg daily) and include constipation, sedation and dry mouth. However, in May 2009, the US FDA released a warning letter about tramadol's potential to cause addiction and difficulty in breathing [763]. The tolerability during the twelve-week study period in men with PE was acceptable. Several other studies also reported that tramadol exhibits a significant dose-related efficacy and side-effects over placebo for the treatment of PE [764]. Moreover, the efficacy and safety of tramadol have been confirmed in SRs and meta-analyses [765-767].

6.2.6.2.5 Phosphodiesterase type 5 inhibitors

There is one well-designed, randomised, double-blind, placebo-controlled study comparing sildenafil to placebo in men with PE [768]. Although IELT was not significantly improved, sildenafil increased confidence, the perception of ejaculatory control and overall sexual satisfaction, reduced anxiety and decreased the refractory time to achieve a second erection after ejaculation. Another RCT demonstrated that once-daily use of 5 mg tadalafil for six weeks is effective in improving PROs and is well tolerated by patients with PE [769].

Several open-label studies showed that PDE5Is combined with an SSRI is superior to SSRI monotherapy:

- Sildenafil combined with paroxetine improved IELT significantly and satisfaction versus paroxetine alone [770];
- Sildenafil combined with sertraline improved IELT and satisfaction significantly versus sertraline alone [771];
- Sildenafil combined with paroxetine and psychological and behavioural counselling significantly improved IELT and satisfaction in patients in whom other treatments failed [772];
- Sildenafil combined with dapoxetine (30 mg.) improved IELT, satisfaction scores and PEDT vs. dapoxetine, paroxetine or sildenafil monotherapy [725];
- Tadalafil combined with paroxetine significantly improved IELT and satisfaction versus paroxetine and tadalafil alone [773];
- Finally, sildenafil combined with behavioural therapy significantly improved IELT and satisfaction versus behavioural therapy alone [774].

There are very limited data on the efficacy of other PDE5Is (tadalafil and vardenafil) [775, 776]. However, some meta-analyses demonstrated that the combined use of SSRIs and PDE5Is may be more effective as compared with SSRIs or PDE5Is monotherapy [702, 777-781].

6.2.6.2.6 Other drugs

In addition to the aforementioned drugs, there is continuous research for other treatment options. Considering the abundant α 1a-adrenergic receptors in seminal vesicles and the prostate, and the role of sympathetic system in the ejaculation physiology, the efficacy of selective α -blockers in the treatment of PE has been assessed [782-784]. A recent study demonstrated that wake-promoting agent modafinil may be effective in delaying ejaculation and improving PROMs [785]. The efficacy of acupuncture was compared to dapoxetine for the treatment of PE and although acupuncture showed a significant ejaculation-delaying effect, this was less effective as compared with that of dapoxetine [786].

Decreasing penile sensitivity with glans penis augmentation using hyaluronic acid for the treatment of PE has initially been proposed by Korean researchers in 2004 [787], and since then has gained popularity mainly in Asian countries [788, 789]. In a randomised controlled cross-over study, hyaluronic acid glans injection were found to be a safe treatment with a modest but significant increase in IELT [790]. However, these procedures may result in serious complications and more safety studies must be conducted before recommending this treatment to PE patients [791].

Considering the importance of central oxytocin receptors in ejaculation reflex, several researchers assessed the efficacy and safety of oxytocin receptor antagonists in the treatment of PE [792]. Epelsiban [793] and cligosiban [794-796] have been found to be safe and mildly effective in delaying ejaculation, but further controlled trials are needed [796].

6.2.7 Summary of evidence on the epidemiology/aetiology/pathophysiology of PE

Summary of evidence	LE
Pharmacotherapy includes either dapoxetine on-demand (an oral short-acting SSRI) and the eutectic lidocaine/prilocaine spray (a topical desensitising agent) that are the only approved treatments for PE, or other off-label antidepressants (daily/on-demand SSRIs and clomipramine).	1a

6.2.8 Recommendations for the treatment of PE

Recommendations	Strength rating
Treat erectile dysfunction (ED), other sexual dysfunction or genitourinary infection (e.g., prostatitis) first.	Strong
Use either dapoxetine or the lidocaine/prilocaine spray as first-line treatments for lifelong premature ejaculation (PE).	Strong
Use off-label topical anaesthetic agents as a viable alternative to oral treatment with selective serotonin re-uptake inhibitor (SSRIs).	Strong
Use tramadol on-demand as a weak alternative to SSRIs.	Weak
Use PDE5Is alone or in combination with other therapies in patients with PE (without ED).	Strong
Use psychological/behavioural therapies in combination with pharmacological treatment in the management of acquired PE.	Weak

6.3 Retarded or Delayed Ejaculation

6.3.1 Definition and classification

The American Psychiatric Association defines DE as requiring one of two symptoms as follows: marked delay, infrequency, or absence of ejaculation on 75-100% of occasions, that persists for at least six months, and which causes personal distress [671]. Delayed ejaculation is a medical and/or psychological condition that is not associated with other types of psychiatric diagnosis. This definition is paramount to understanding the psychologic implications and treatment strategies for DE.

6.3.2 Pathophysiology and risk factors

The causes of DE can be psychological, organic (e.g. incomplete spinal cord lesion or iatrogenic penile nerve damage), or pharmacological (e.g. selective serotonin re-uptake inhibitors (SSRIs), antihypertensive drugs, or antipsychotics) (Table 20) [797, 798]. Although low testosterone levels has been considered as a risk factor in the past [53, 650], more contemporary studies did not confirm any association between ejaculation times and serum testosterone levels [799, 800].

Table 20: Etiological Causes of Delayed Ejaculation and Anejaculation [801]

Ageing Male	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
Medication	Antihypertensives; thiazide diuretics Alpha-adrenergic blockers Antipsychotics and antidepressants Alcohol Antiandrogens Ganglion blockers Selective serotonin reuptake Inhibitors
Psychological	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. It is not uncommon for clinicians to feel uncomfortable with the level of sexual

information that is warranted in obtaining a full sexual history. Understanding the details of the ejaculatory response, sensation, frequency, and sexual activity/techniques; cultural context and history of the disorder; the quality of the sexual response cycle (desire, arousal, ejaculation, orgasm, and refractory period); the partners' 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 [802]. Investigation by a sexual therapist is often required to help get a complete psychological evaluation. 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. Good communication between the sexual therapist and medical practitioner is vital to successful diagnosis and treatment of DE.

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. Findings on psychological aspects revealed that men with DE showed a strong need for controlling their sexual experiences. Delayed ejaculation was associated with difficulties surrendering to sexual pleasure during sex, i.e., the sense of *letting go* [803], which denotes a psychological underlying mechanism influencing the reaching of orgasm [804]. 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) [802]. A basic understanding of the sexual cycle for their respective partners can assist men and women in managing expectations and in evaluating their own sexual practices. 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 [192]. Although masturbation with fantasy can be harmful when not associated with appropriate sexual arousal and context, fantasy can be quite supportive if it allows blockage of critical thoughts that may be preventing orgasm and ejaculation. Techniques geared towards reduction of anxiety are important skills that can help overcome the performance anxiety as this can often interrupt the natural erectile through orgasmic progression. Referral to a sexual therapist, psychiatrist or psychologist is appropriate and often warranted.

6.3.3.2 *Pharmacotherapy*

Pharmacologic agents have been used to treat DE with varied success. 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 have not been randomised, blinded, or placebo-controlled. Many drugs have been used as both primary treatments and/or as antidotes to other medications that can cause DE. A recent survey of sexual health providers demonstrated an overall treatment success of 40% with most providers commonly using cabergoline, bupropion, and oxytocin for treatments [805]. However, this survey measured the anecdotal results of practitioners and there was no proven efficacy or superiority of any drug due to a lack of placebo-controlled, randomised, blinded, comparative trials [801].

6.4 **Anejaculation**

6.4.1 **Definition and classification**

Anejaculation involves the complete absence of antegrade or retrograde ejaculation. It is caused by failure of semen emission from the seminal vesicles, prostate, and ejaculatory ducts into the urethra [806]. True anejaculation is usually associated with a normal orgasmic sensation and is always associated with central or peripheral nervous system dysfunction or with drugs [807].

6.4.2 **Pathophysiology and risk factors**

Generally, anejaculation shares the similar aetiologic factors with DE and retrograde ejaculation (see Table 20).

6.4.3 **Investigation and treatment**

Drug treatment for anejaculation caused by lymphadenectomy and neuropathy, or psychosexual therapy for anorgasmia, is not very effective. In all these cases, and in men who have a spinal cord injury, vibro-stimulation (i.e., application of a vibrator to the penis) is the first-line therapy. In anejaculation, vibro-stimulation evokes the ejaculation reflex [808], 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 vibro-stimulation has failed, electro-ejaculation can be the therapy of choice [809]. When electro-ejaculation fails or cannot be carried out, other sperm retrieval techniques may be used [810]. Anejaculation following either retroperitoneal surgery for testicular cancer or total mesorectal excision can be prevented using unilateral lymphadenectomy or autonomic nerve preservation [811], respectively.

6.5 Painful Ejaculation

6.5.1 Definition and classification

Painful ejaculation is a condition where a patient feels mild discomfort to severe pain during or after ejaculation. The pain can involve the penis, scrotum, and perineum [812].

6.5.2 Pathophysiology and risk factors

Many medical conditions can result in painful ejaculations, but it can also be an idiopathic problem. Initial reports demonstrated possible associations of painful ejaculation with calculi in the seminal vesicles [813], sexual neurasthenia [814], sexually transmitted diseases [812, 815], inflammation of the prostate [210, 816], PCa [817, 818], BPH [208], prostate surgery [819, 820], pelvic radiation [821], herniorrhaphy [822] and antidepressants [823-825], among others. Further case reports have suggested that mercury toxicity or Ciguatera toxin fish poisoning may also result in painful ejaculations [826, 827]. Psychological issues may also be the cause of painful ejaculations, especially if the patient does not experience this problem during masturbation [828].

6.5.3 Investigation and treatment

Treatment of painful ejaculation must be tailored according to the underlying cause, if detected. Psychotherapy or relationship counselling, withdrawal of suspected agents (drugs, toxins, or radiation) [823, 824, 829] or the prescription of appropriate medical treatment (antibiotics, α -blockers, anti-inflammatory agents) may ameliorate painful ejaculations. Behavioural therapies, myorelaxants, antidepressant pelvic floor exercises, anticonvulsant drugs and/or opioids may be administered if no underlying cause can be identified [830, 831].

6.5.3.1 Surgical intervention

If medical treatments fail, surgical operations such as TURP, transurethral resection of the ejaculatory duct and neurolysis of the pudendal nerve have been suggested [832, 833]. However, there is no strong evidence supporting that surgical therapy improves painful ejaculations and therefore 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, as a result of 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 [812].

6.6.2 Pathophysiology and risk factors

The process of ejaculation requires complex coordination and interplay between the epididymis, vas deferens, prostate, seminal vesicles, bladder neck and bulbourethral glands [834]. 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, in part maintained by coaptation of the bladder neck and rhythmic contractions of the periurethral muscles, coordinated by a centrally mediated reflex [834]. Closure of the bladder neck and seminal emission are 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 bulbocavernosal, ischiocavernosal and pelvic floor are initiated by the S 2-4 parasympathetic nervous system via the pelvic nerve [834].

Any factor, which disrupts this reflex and inhibits the bladder neck (internal vesical sphincter) contraction 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 21).

Table 21: Aetiology of retrograde ejaculation [797]

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 verumontanum hyperplasia Congenital dopamine beta-hydroxylase deficiency
Pharmacological	Antihypertensives, thiazide diuretics Alpha-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**

Medical and surgical strategies exist for the treatment of retrograde ejaculation. In recent years the reliance on medical treatment as first-line management has become common practice.

6.6.3.1 *Pharmacological*

Sympathomimetics stimulate the release of noradrenaline as well as activating α - and β -adrenergic receptors, resulting in closure of the internal urethral sphincter, restoring the antegrade flow of semen. The most common sympathomimetics are synephrine, pseudoephedrine hydrochloride, ephedrine, phenylpropanolamine and midodrine [835]. Unfortunately, as time progresses their effect diminishes [836]. Many of the studies published about the efficacy of sympathomimetics in the treatment of retrograde ejaculation suffer from small sample size with some represented by case reports.

A double-blind controlled study randomised patients to one of four α -adrenergic agents (dextroamphetamine, ephedrine, phenylpropanolamine, and pseudoephedrine) with or without histamine. The patients suffered from the failure of ejaculation following retroperitoneal lymphadenectomy. They found that four days of treatment prior to ejaculation was most effective and that all the adrenergic agonists restored antegrade ejaculation [835]. In a SR, the efficacy of this group of medications was found to be 28% [197]. The side-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 or antimuscarinics in combination with sympathomimetics are 22% versus 39%, respectively [197]. 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 the use of standard sperm retrieval techniques, such as testicular sperm extraction (TESE), three different methods of sperm acquisition have been identified for the management of infertility in the patient suffering from 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 either increase their fluid intake or to take sodium bicarbonate to dilute or alkalise

the urine respectively. Afterwards, a post-orgasmic urine sample is collected by either introducing a catheter or spontaneous voiding. This sample is then centrifuged and suspended in a medium. The types of suspension fluids employed are heterogeneous and can include bovine serum albumin, human serum albumin, Earle's/Hank's, phosphate-buffered medium and the patients urine. The resultant modified sperm mixture can then be used in assisted reproductive techniques. A SR of the literature in couples with the male partner suffering from retrograde ejaculation found a 15% pregnancy rate per cycle (0-100%) [197].

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 conditions of the bladder. The patient then ejaculates, and semen is retrieved by catheterisation or voiding [837]. Modified Hotchkiss methods involve a variance in the instillation medium. Pregnancy rates per cycle were 24% per cycle (0-100%) [197].
3. *Ejaculation on a full bladder.* Few papers have described results from this technique [838, 839]. 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 in total was 60% [197].

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 [840].

6.7.2 Pathophysiology and risk factors

Primary anorgasmia is defined as starting from the men's first sexual intercourse and lasts throughout his life, while for secondary anorgasmia patients should have a normal period before the problem starts [841]. Substance abuse, obesity and some non-specific psychological aspects, such as anxiety and fear, are considered the risk factors for anorgasmia. There are only a few studies available that describe anorgasmia alone and generally it has been considered as a symptom linked to ejaculatory disorders especially with DE and therefore they are believed to share the same risk factors. However, psychological factors are considered to be responsible for 90% of anorgasmia problems [842]. Causes of delayed orgasm and anorgasmia are shown in Table 22 [841].

Table 22: Causes of delayed orgasm and anorgasmia [841]

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 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, questioning penile sensitivity and psychological issues. Adjunctive laboratory tests can also be used to rule out organic causes, such as testosterone, prolactin and thyroid-stimulating hormone (TSH) levels. Patients who have loss of penile sensitivity require further investigations [841].

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 [804, 843]. However, it is very 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 [844-849]. 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 the choice of options for sperm retrieval in anorgasmia cases [841].

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 great anxiety in many men and may be indicative of underlying pathology [213].

6.8.2 Pathophysiology and risk factors

Several reasons 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 23) [850].

Table 23: Pathology associated with haemospermia [850]

Category	Causes
Congenital	Seminal vesicle (SV) or ejaculatory duct cysts
Inflammatory	Urethritis, prostatitis, epididymitis, tuberculosis, CMV, HIV, Schistosomiasis, hydatid, condylomata 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, testicle, instrumentation, post hemorrhoid injection, prostate biopsy, vaso-venous fistula
Systemic	Hypertension, hemophilia, 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) [851]. In an observational study of 300 consecutive patients over a 30-month period, 81% had no cause of their haemospermia identified. In those patients for whom a cause was identified, the diagnosis varied dependent upon the age of presentation. When the patients were divided into those under and those over 40 years of age, urinary tract infections were more common among younger patients compared to older patients (15% versus 10.3%). In the older group (> 40 years old), stones (2.2% versus 1.4%) and malignancy (6.2% versus 1.4%) were more common when compared with the younger cohort [60]. In the over 40 group, thirteen patients had PCa and one had a low-grade urethral carcinoma. In the under 40 group, one patient had testicular cancer [212].

6.8.3 Investigations

As with other clinical conditions, a systematic clinical history and assessment to help identify the reason of haemospermia is undertaken. Although the differential diagnosis is extensive, most cases are caused by infections or other inflammatory processes [213].

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 [812, 852, 853]. A sexual history should be taken to identify those whose haemospermia may be as a consequence of a sexually transmitted disease. Recent foreign travel to areas affected by schistosomiasis or tuberculosis should also be considered. The possibility of co-existing systemic disease such as hypertension, liver disease and coagulopathies should be investigated along with systemic features of malignancy such as weight loss, loss of appetite or bony pain. Examination of the patient should also include measurement of

the blood pressure, as there have been several case reports suggesting an association between uncontrolled hypertension and haemospermia [854, 855].

Most authors who propose an investigative baseline agree on the initial diagnostic tests, however, there is no consensus in this regard [850-852]. A urinalysis should be performed along with sending the urine for culture and sensitivities 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 taken and tested for *Chlamydia*, *Ureaplasma* and *Herpes*. Using this strategy, it may be possible to find an infectious agent among patients who would have been labelled as idiopathic haemospermia [856].

A serum PSA should be taken in men over the age of 40 years who have been appropriately counselled [214]. 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 [850]. Digital rectal examination should also be performed and the meatus re-examined after DRE for the presence of bloody discharge [857]. Detection of a palpable nodule in the prostate is of importance as an association between haemospermia and PCa has been postulated although not completely proven.

Magnetic Resonance Imaging 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 duct has enabled the modality to be particularly useful in determining the origin of midline or paramedian prostatic cysts and in determining optimal surgical management [858]. The addition of an endorectal coil can improve the diagnostic accuracy for identifying the site and cause of haemorrhage [859].

The use of cystoscopy has been included in the majority of suggested investigation protocols in patients with high-risk features (patients who are refractory to conservative treatments and patients with persistent haemospermia). It can provide invaluable information as it allows direct visualisation of the main structures in the urinary tract that can be attributed to causes of haemospermia such as although not limited to; polyps, urethritis, prostatic cysts, foreign bodies, calcifications and vascular abnormalities [860, 861].

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 [862]. In a prospective study of 106 patients with prolonged haemospermia patients underwent both transrectal US and seminal vesiculoscopy. With both modalities combined, diagnoses were made in 87.7% of patients. When compared, head-to-head, the diagnostic yield for TRUS versus seminal vesiculoscopy was 45.3% versus 74.5%, respectively ($p < 0.001$) [863].

Melanospermia that is a consequence of malignant melanoma involving the genitourinary tract is a very rare condition and has also been described in two case reports [864, 865]. 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**

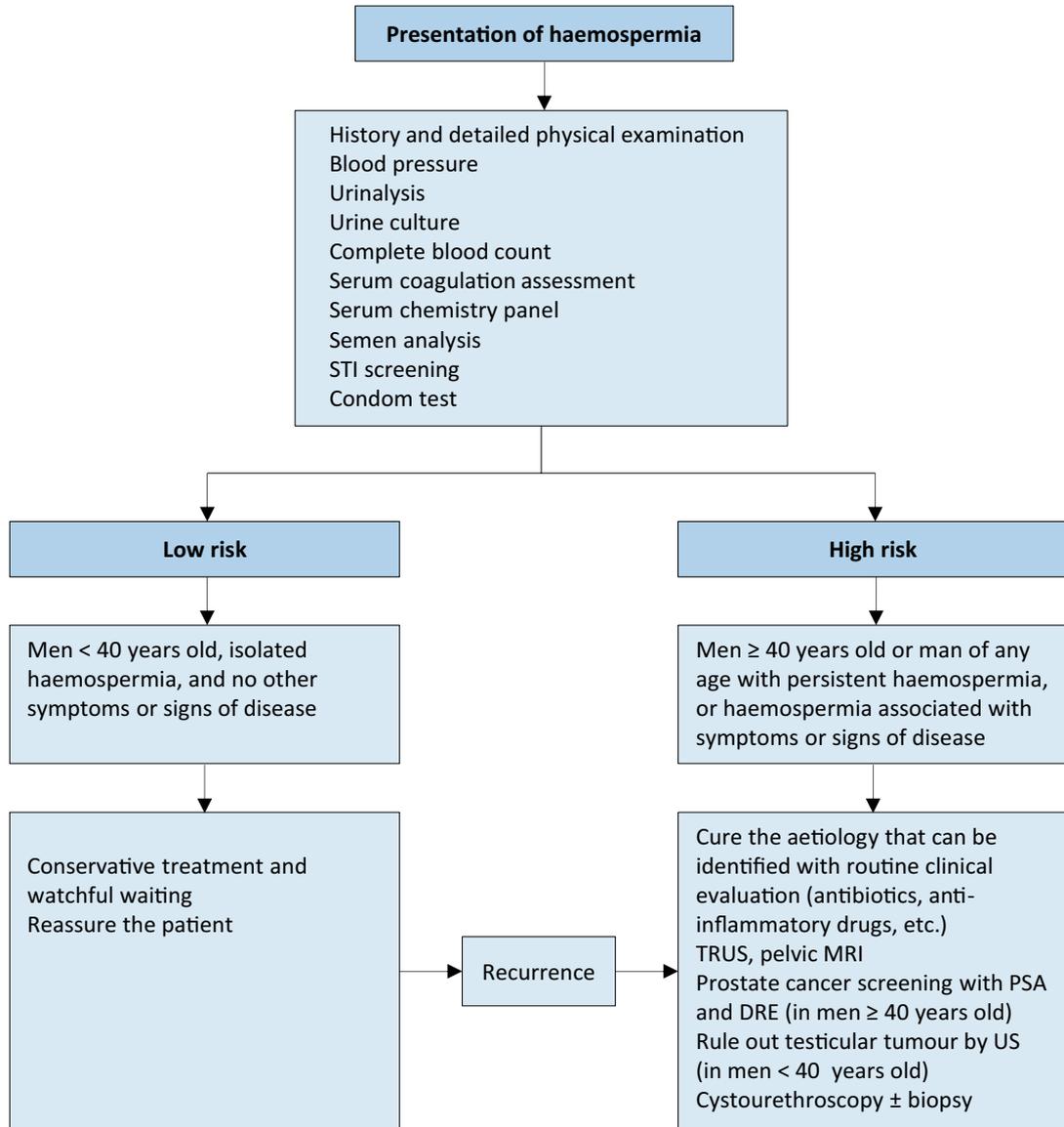
Conservative management is generally the primary treatment option when the patients are younger than 40 years of age and have a single episode of haemospermia. The primary goal of the treatment is to exclude malignant conditions like prostate and bladder cancer and treat any other underlying cause. If no pathology is found, then the patient can be reassured [213, 850].

Patients with recurrent haemospermia and who are middle-aged, warrant more aggressive intervention. Appropriate antibiotic therapy should be given to patients who have urogenital infections or STIs. Urethral or prostate varices or angiodysplastic vessels can be fulgurated, whereas cysts, either of the seminal vesicles or prostatic urethra, can be aspirated transrectally [213]. Ejaculatory duct obstruction is managed by a transurethral incision at the duct opening [866, 867]. Systemic conditions should be treated appropriately [851, 853, 868, 869].

Defining a management algorithm for haemospermia is based on the patient age and degree of haemospermia. Patients will often find the presence of blood in the ejaculate alarming, and investigations should be aimed at excluding a serious, despite infrequent, underlying cause (e.g., cancer), whilst at the same time preventing over investigation and alleviating patient anxiety. The literature describes a multitude of causes for haemospermia, although many of these pathologies are not commonly found after investigations have been

undertaken. However, men may be stratified into higher risk groups according to a number of factors including: men over 40 years of age, recurrent or persistent haemospermia, actual risk for PCa (e.g., positive family history), and concurrent haematuria. Based upon the literature, a management algorithm is proposed (Figure 9) [851, 853, 868, 869].

Figure 9: Management algorithm for haemospermia [851, 853, 868, 869]



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

6.9 Recommendations for the management of recurrent haemospermia

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

7. LOW SEXUAL DESIRE AND MALE HYPOACTIVE SEXUAL DESIRE DISORDER

7.1 Definition and classification

It has been always 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 ICD-10, lack or loss of sexual desire should be the principal problem and no other sexual problems accompanying it such as ED [870]. In the DSM-V, male hypoactive sexual desire disorder was defined as “the persistent or recurrent deficiency (or absence) of sexual or erotic thoughts or fantasies and desire for sexual activity”. The judgment of deficiency is made by the clinician, taking into account factors that affect sexual functioning, such as age and general and socio-cultural contexts of the individual's life [671]. According to the fourth International Consultation on Sexual Medicine, the definition of male hypoactive sexual desire disorder was proposed as a “persistent or recurrent deficiency or absence of sexual or erotic thoughts or fantasies and desire for sexual activity (clinical principle)” [871].

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 as drive (biological), motivation (psychological) and wish (cultural) [872]. However, it is believed that both in the surveys and clinical practice those three components are usually found interwoven [873].

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) predicted LSD in men [874]. Furthermore, feeling shame during sexual intercourse, because of negative sexual thoughts (e.g., concern about achieving erection), characterised men with LSD as opposed to women with the same condition [875]. Psychological models testing the interplay role between biopsychosocial factors revealed that reduced male sexual desire was best predicted by negative thoughts and emotions during sex, more than general psychopathology symptoms or age [876-878]. Similarly, having a low confidence achieving erection, no attraction toward the partner, living in long-term relationships, and stress resulting from work were predictors of LSD in men [879]. On the other hand, relationship factors such as marital satisfaction, cohesion or display of affection received little support [874, 879]. Even so, it is worth noting that, despite LSD being less common in men than in women [871], it is the most frequent complaint in couples' therapy [880]. Therefore, the role of relationship factors cannot be completely ruled out. 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 [881].

7.2.2 *Biological aspects*

Testosterone seems to be essential for a man's sexual desire; however, sexual desire does not directly relate with the circulating level of testosterone, especially in older men [882]. The biological and psychology components that take place in the pathophysiology of LSD are shown in Table 24 [873, 883]. In addition to these factors, there have been some speculations on the role of thyroid and oxytocin hormones [634, 884].

Table 24: The list of common causes of low sexual desire in men [873, 883]

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
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 between 60-69 and 70-80 years, poor overall health, vascular diseases, being a current smoker, belief that aging reduces sex, divorce in the past three years, financial problems in the last three years, major depression, being worried about the future of relation and less than one sexual relation in a week [188].

7.3 **Diagnostic work-up**

7.3.1 **Assessment questionnaires**

Sexual Desire Inventory (SDI) is a scale aimed at evaluating different components influencing the development and expression of sexual desire [885]. This self-administered questionnaire consists of fourteen questions which 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" [885].

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 [886] 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 [887], prolactin [888] and thyroid hormones [634] levels can be evaluated.

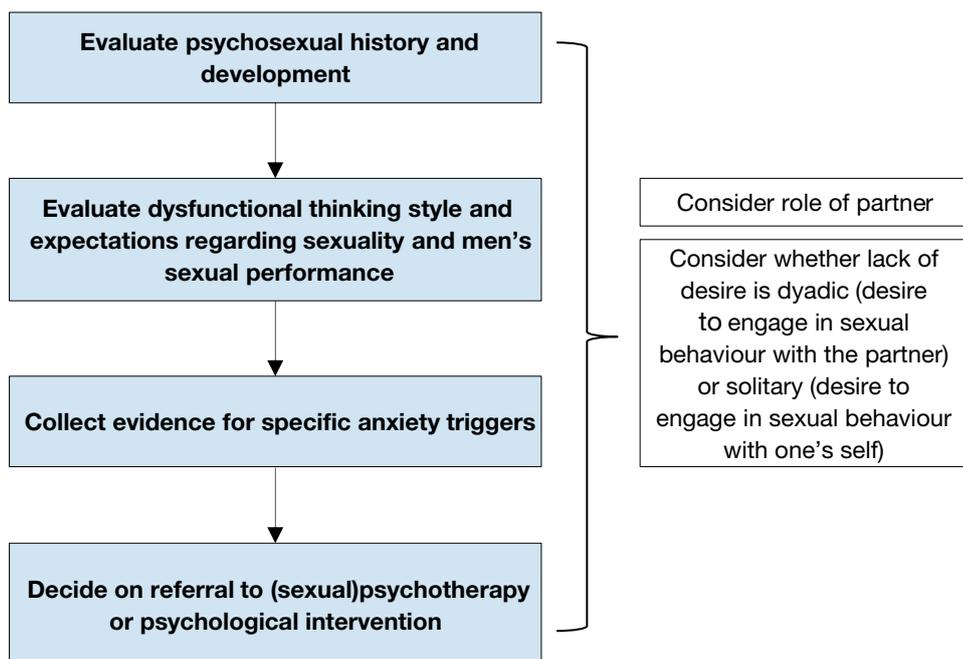
7.4 **Disease management**

The treatment of LSD should be tailored according to the underlying aetiology.

7.4.1 **Psychological intervention**

Data on treatment efficacy of psychological interventions 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 (Figure 10) [406]. 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 aging couple (thus including LSD) as a whole rather than treating the individual patient [889].

Figure 10: 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 administrations. The favourable effect of testosterone treatment on sexual motivation and the presence of sexual thoughts was shown in a meta-analysis [887]. The aim of the treatment should be to reach the physiological range of testosterone (see section 3.5).

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 MRI of the pituitary gland and can be treated with dopamine agonist agents [890]. The other accompanying endocrine disorders, such as hypothyroidism, hyperthyroidism or diabetes, should be treated accordingly.

Pharmacotherapy can also be used to treat major depression; however it should be kept in mind that antidepressants may negatively impact on sexual functioning; therefore, antidepressant compounds which have less effect on sexual function should be chosen. Psychotherapy can increase the efficacy of pharmacotherapy, especially for patients whose LSD is due to depression [891].

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
Replace testosterone 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 relatively rare condition, with a reported incidence of less than 1% [892], although there are studies which report higher prevalence rates of 4-10%, in the absence of hypospadias [893]. Congenital penile curvature results from disproportionate development of the tunica albuginea of the corporal bodies and is not associated with urethral malformation. In the majority of cases, the curvature is ventral, but it can also be lateral and, more rarely, dorsal [894].

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 more severe curvatures can make intercourse difficult or impossible. Physical examination during erection (alternatively photographic or preferably after intracavernous injection (ICI) of vasoactive drugs) is important to document the curvature and exclude other pathologies [894].

8.1.3 *Disease management*

The definitive treatment for this disorder remains surgical and can be deferred until after puberty, although results from a survey suggest that men with probable untreated ventral penile curvature reported more dissatisfaction with penile appearance, increased difficulty with intercourse, and psychological problems, therefore supporting surgical correction of CPC in childhood [895]. Surgical treatments for CPC generally share the same principles as in Peyronie's disease. Plication techniques (Nesbit, 16-dot, Yachia, Essed-Schröder, and others) with or without neurovascular bundle elevation (medial/lateral) and with or without complete penile degloving, have been described [896-905]. Other approaches are based on corporal body de-rotation proposed by Shaeer with different technical refinements that enable correction of a ventral curvature, with reported minimal narrowing and shortening [906-909]. There are no direct comparative studies therefore, no single technique can be advocated as superior in terms of surgical correction.

8.1.4 *Summary of evidence for congenital penile curvature*

Summary of evidence	LE
Medical and sexual history are usually sufficient to establish a diagnosis of CPC. Physical examination after ICI or a photograph during erection is mandatory for documentation of the curvature and exclusion of other pathologies.	3
There is no role for medical management of CPC. Surgery is the only treatment option, which can be deferred until after puberty and can be performed at any time in adult life in individuals with significant functional impairment during intercourse.	3

8.1.5 *Recommendation for the treatment congenital penile curvature*

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

8.2 Peyronie's Disease

8.2.1 *Epidemiology/aetiology/pathophysiology*

8.2.1.1 *Epidemiology*

Epidemiological data on Peyronie's disease (PD) are limited. Prevalence rates of 0.4-20.3% have been published, with a higher prevalence in patients with ED and diabetes [910-918]. A recent survey indicates that the prevalence of definitive and probable cases of PD in the US is 0.7% and 11%, respectively, suggesting that PD is an under-diagnosed condition [919]. Peyronie's disease often occurs in older males with the typical age of onset of 50-60 years. However, PD also occurs in younger men (< 40 years), but at a lesser prevalence than older men (1.5 to 16.9%) [914, 920, 921].

8.2.1.2 *Aetiology*

The aetiology of PD is unknown. However, repetitive microvascular injury or trauma to the tunica albuginea is still the most widely accepted hypothesis to explain the aetiology of the disease [922]. Abnormal wound healing

leads to the remodeling of connective tissue into a fibrotic plaque [922-924]. Penile plaque formation can result in a curvature, which, if severe, may impair penetrative sexual intercourse. The genetic underpinnings of fibrotic diatheses, including PD and Dupuytren's diseases, are beginning to be understood (Table 25) [925].

Table 25: Genes with involvement in Peyronie's and Dupuytren's diseases (adapted from Herati *et al.* [925])

Gene	Gene Symbol	Chromosomal Location	Gene Function
Matrix metalloproteinase 2	MMP 2	16q12.2	Breakdown of extracellular matrix
Matrix metalloproteinase 9	MMP 9	20q13.12	Breakdown of extracellular matrix
Thymosin beta-10	TMSB-10	2p11.2	Prevents spontaneous globular actin monomer polymerisation
Thymosin beta-4	TMSB-4	Xq21.3-q22	Actin sequestering protein
Cortactin; amplixin	CTTN	11q13	Organises cytoskeleton and cell adhesion structures
Transforming protein RhoA H12	RHOA	3p21.3	Regulates cytoskeletal dynamics
RhoGDP dissociation inhibitor	ARHGDI A	17q25.3	Regulates Rho GTPase signaling
Pleiotrophin precursors; osteoblast specific factor 1	PTN/OSF-1	7q33	Stimulates mitogenic growth of fibroblasts and osteoblasts
Amyloid A4 protein precursor; nexin II	PN-II	21q21.3	Cell surface receptor
Defender against cell death 1	DAD1	14q11.2	Prevents apoptosis
Heat Shock 27-kDa protein (HSP27)	HSP27	7q11.23	Actin organisation and translocation from cytoplasm to nucleus upon
Macrophage-specific stimulating factor	MCSF/CSF1	1p13.3	Controls the production, differentiation and function of macrophages
Transcription factor AP-1	AP1	1p32-p31	Key mediator of macrophage education and point of recruitment for immunosuppressive regulatory T cells
Human Early growth response protein 1	hEGR1	5q31.1	Promotes mitosis
Monocyte chemotactic protein 1	MCP1	17q11.2-q12	Chemotactic cytokine for monocytes and basophils
Bone Proteoglycan II precursor; Decorin	DCN	12q21.33	Matrix proteoglycan
T-Cell specific rantes protein precursor	RANTES	17q12	Chemoattractant for monocytes, memory T cells and eosinophils
Integrin Beta-1	ITGB1	10p11.2	Membrane receptor involved in cell adhesion and recognition in a variety of processes including immune response, tissue repair and hemostasis
Osteonectin	SPARC	5q31.3-q32	Matrix protein that facilitates collagen ossification
Ubiquitin	RBX1	6q25.2-q27	Targets substrate proteins for proteasomal degradation
Transcription factor ATF-4	ATF4	22q13.1	Transcriptional regulation of osteoblasts and down-regulates apelin to promote apoptosis
Elastase IIB	ELA2B	1p36.21	Serine protease that hydrolyzes matrix protein
c-myc	MYC	8q24.21	Transcription factor that regulates cell cycle progression, apoptosis, and cellular transformations
60 S ribosomal protein L13A	RPL13A	19q13.3	Repression of inflammatory genes

Prothymosin alpha	PTMA	2q37.1	Influences chromatin remodeling, anti-apoptotic factor
Fibroblast tropomyosin	TPM1	15q22.1	Actin-binding protein involved in contractile system of striated and smooth muscle
Myosin light chain	MYL2	12q24.11	Regulatory light chain associated with myosin Beta heavy chain
Filamin	FLN	Xq28	Actin-binding protein that crosslinks actin filaments and links actin to membrane glycoproteins. Interacts with integrins
Calcineurin A subunit alpha	PPP3CA	4q24	Promotes cell migration and invasion and inhibits apoptosis
DNA binding protein inhibitor Id-2	ID2	2p25	Transcriptional regulator that inhibits the function of basic helix-loop-helix transcription factors by preventing their heterodimerisation, negatively regulates cell differentiation
Smooth muscle gamma actin	ACTA2	10q23.3	Plays a role in cell motility, structure and integrity
Desmin	DES	2q35	Forms intra-cytoplasmic filamentous network connecting myofibrils
Cadherin FIB2	PCDHGB4	5q31	Cell adhesion proteins expressed in fibroblasts and playing a role in wound healing
Cadherin FIB1	DCHS1	11p15.4	Cell adhesion proteins expressed in fibroblasts and playing a role in wound healing
SMAD family member 7	SMAD7	18q21.1	Interacts with and promotes degradation of TGFBR1
Insulin-like growth factor binding protein 6	IGFBP6	12q13	Negative regulator of cellular senescence in human fibroblasts
Collagen 1 alpha	COL1A1	17q21.33	Encodes pro-alpha 1 chains of type 1 collagen
Transforming growth factor, beta 1	TGFB1	19q13.1	Cytokine that regulates proliferation, differentiation, adhesion and cell migration

8.2.1.3 Risk factors

The most commonly associated comorbidities and risk factors are diabetes, hypertension, dyslipidemias, ischaemic cardiopathy, autoimmune diseases [926], ED, smoking, excessive consumption of alcohol, low testosterone levels and pelvic surgery (e.g., radical prostatectomy) [343, 914, 918, 927-929]. Dupuytren's contracture is more common in patients with PD affecting 8.3-39% of patients [915, 930-932], whilst 4-26% of patients with Dupuytren's contracture report PD [931, 933].

8.2.1.4 Pathophysiology

Two phases of the disease can be distinguished [934]. The first is the active inflammatory phase (acute phase), which may be associated with painful erections and a palpable nodule or plaque in the tunica of the penis; typically, but not invariably, a penile curvature begins to develop. The second is the fibrotic phase (chronic phase) with the formation of hard, palpable plaques that can calcify, with stabilisation of the disease and of the penile deformity. With time, the penile curvature is expected to worsen in 21-48% of patients or stabilise in 36-67% of patients, while spontaneous improvement has been reported in only 3-13% of patients [927, 935-937]. Overall, penile deformity is the most common first symptom of PD (52-94%). Pain is the second most common presenting symptom of PD, which presents in 20-70% of patients during the early stages of the disease [938]. Pain tends to resolve with time in 90% of men, usually during the first twelve months after the onset of the disease [935, 936]. Palpable plaques were reported as initial symptom in 39% of the patients and mostly situated dorsally [48, 938].

In addition to functional effects on sexual intercourse, men may also suffer from significant psychological distress. Validated mental health questionnaires have shown that 48% of men with PD have moderate or severe depression, sufficient to warrant medical evaluation [939].

8.2.1.5 Summary of evidence on epidemiology/aetiology/pathophysiology of Peyronie's disease

Summary of evidence	LE
Peyronie's disease is a connective tissue disorder, characterised by the formation of a fibrotic lesion or plaque in the tunica albuginea, which may lead to penile deformity.	2b
The contribution of associated comorbidities or risk factors (e.g., diabetes, hypertension, lipid abnormalities and Dupuytren's contracture) to the pathophysiology of PD are still unclear.	3
Two phases of the disease can be distinguished. The first phase is the active inflammatory phase (acute phase-painful erections, nodule/plaque), and the second phase is the fibrotic/calcifying phase (chronic or stable phase) with formation of hard palpable plaques (disease stabilisation).	2b
Spontaneous resolution is uncommon (3-13%) and most patients experience disease progression (21-48%) or stabilisation (36-67%). Pain is usually present during the early stages of the disease, but tends to resolve with time in 90% of men within twelve months of onset.	2a

8.2.2 Diagnostic evaluation

The aim of the initial evaluation is to obtain information on the presenting symptoms and their duration (e.g., pain on erection, palpable nodules, deformity, length and girth and erectile function). It is important to obtain information on the distress caused by the symptoms and the potential risk factors for ED and PD. A disease-specific questionnaire (Peyronie's disease questionnaire [PDQ]) has been developed to be used both in clinical practice and trials. Peyronie's disease questionnaire measures three domains, including psychological and physical symptoms, penile pain and symptom bother [940].

Clinicians should take a focused history to distinguish between active and stable disease, as this will influence medical treatment or 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 well-accepted criteria of disease stabilisation and patients' referral for specific medical therapy [941, 942] or surgical intervention when indicated [943].

The examination should start with a focused genital assessment which is then extended to the hands and feet for detecting possible Dupuytren's contracture or Ledderhosen scarring of the plantar fascia [936]. Penile examination is performed to assess the presence of a palpable nodule or plaque. There is no correlation between plaque size and the degree of curvature [944]. 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 [945-947].

An objective assessment of penile curvature with an erection is mandatory. According to current literature, this can be obtained by several approaches, including a 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 is able to induce an erection similar to or better than that which the patient would experience when sexually aroused [948-950]. Computerised Tomography and MRI have a limited role in 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 [951]. Erectile dysfunction is common in patients with PD (30-70.6%) [952, 953]. It is mainly arterial or cavernosal (veno-occlusive) dysfunction in origin [927, 944, 954]. The presence of ED and psychological factors may also have a profound impact on the treatment strategy [953].

Ultrasound measurement of plaque size is inaccurate, and it is not recommended in everyday clinical practice [955]. Doppler US may be used for the assessment of penile haemodynamics [953].

8.2.2.1 Summary of evidence for the diagnosis of Peyronie's disease

Summary of evidence	LE
Ultrasound (US) measurement of the plaque's size is inaccurate and operator dependent.	3
Doppler US may be required for the assessment penile haemodynamic and vascular anatomy.	2a
Intracavernous injection method is superior to other methods to provide an objective assessment of penile curvature with an erection.	4

8.2.2.2 Recommendations for the diagnosis of Peyronie's disease

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

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 the progression of the disease or if the patient declines other treatment options during the active phase [936, 943]. Several options have been suggested, including oral pharmacotherapy, intralesional injection therapy, shock wave therapy (SWT) and other topical treatments (Table 26).

The results of the studies on conservative treatment for PD are often contradictory making it difficult to provide recommendations in the everyday, real-life setting [956]. The Panel does not support the use of oral treatments for PD including pentoxifylline, vitamin E, tamoxifen, procarbazine, potassium para-aminobenzoate (potaba), omega-3 fatty acids or combination of vitamin E and L-carnitine because of their lack of efficacy (tamoxifen, colchicine, vitamin E, procarbazine) or evidence (potaba, L-carnitine, pentoxifylline) [943, 957-959]. This statement is based on several methodological flaws in the available studies. These include their uncontrolled nature, the limited number of patients treated, the short-term follow-up and the different outcome measures used [960, 961]. Even in the absence of adverse events, treatment with these agents may delay the use of other efficacious treatments.

Table 26: Conservative treatments for PD

Oral treatments
Non-steroidal anti-inflammatory drugs (NSAIDs)
Phosphodiesterase type 5 inhibitors (PDE5I)
Intralesional treatments
Verapamil
Nicardipine
Clostridium collagenase
Interferon α 2B
Hyaluronic acid
Botulinum toxin
Topical treatments
H-100 gel
Extracorporeal shockwave treatment
Other
Traction devices
Multimodal treatment

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 [962, 963]. A retrospective study of 65 men suggested the use of PDE5I as an alternative for the treatment of PD. The results indicated that treatment with tadalafil was helpful in decreasing curvature and remodelling septal scar when compared to controls [964]. Another recent study concluded that sildenafil was able to improve erectile function and pain in PD patients. In the study, 39 patients with PD were divided into two groups receiving vitamin E (400 IU) or sildenafil 50 mg for twelve weeks and significantly better outcomes in pain and IIEF score were seen in the sildenafil group [965].

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) may be offered to patients in active-phase PD in order to manage penile pain, which is usually present in this phase. Pain levels should be periodically reassessed in 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 particular 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 [966, 967]. 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 [968-973]. In fact, most of the studies did not perform direct statistical comparison between groups.

Collagenase of clostridium histolyticum

Collagenase of *clostridium histolyticum* (CCH) is a chromatographically purified bacterial enzyme that selectively attacks collagen, which is known to be the primary component of the PD plaque [974-977]. Intralesional injection of CCH has been used in the treatment of PD since 1985. In 2014 the EMA approved CCH for the nonsurgical treatment of the stable phase of PD in men with palpable dorsal plaques in whom abnormal curvature of 30° to 90° and non-ventrally located plaques is present. It should be administered by a healthcare professional who is experienced and properly trained in the administration of CCH treatment for PD [978, 979].

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) I and II studies [976], as well as post approval trials [980], which demonstrated the efficacy and safety of this treatment, are summarised in the Table 27.

Table 27: Clinical evidence supporting CCH treatment

Author/Year	Study type	Special considerations	Number of patients	Number of injections	Decrease in PC in CCH group
Gelbard <i>et al.</i> (2013) [981]	Phase 3 randomised double-blinded controlled trial	Pilot study	551	8 (in 78.8% of patients)	34% (17.0 ± 14.8 degrees)
Levine <i>et al.</i> (2015) [982]	Phase 3 open-label	IMPRESS based	347	≤ 8	34.4% (18.3 ± 14.02 degrees)
Ziegelmann <i>et al.</i> (2016) [983]	Prospective, double-blinded trial	IMPRESS based	69	Mean = 6	38% (22.6 ± 16.2 degrees)
Yang and Bennett (2016) [984]	Prospective study	Included patients in acute phase	37 in SP 12 in AP	Median in SP = 6 Median in AP = 2.5	32.4% (15.4 degrees) AP = 20 degrees
Nguyen <i>et al.</i> (2017) [951]	Retrospective study	Included patients in acute phase	126 in SP 36 in AP	Mean = 3.2	SP = 27,4% (15.2 ± 11.7 degrees) AP = 27,6% (18.5 ± 16.2 degrees) N/S differences in final change in curvature between group 1 (16.7°) and group 2 (15.6°) p=0.654
Anaissie <i>et al.</i> (2017) [985]	Retrospective study	Included patients in acute phase	77	Mean = 6.6	29.6% (15.3 ± 12.9 degrees)
Abdel Raheem <i>et al.</i> (2017) [986]	Prospective study	Shortened protocol	53	Mean = 3	31.4% (17.6 degrees)
Capece <i>et al.</i> (2018) [987]	Prospective multicentric study	Shortened protocol	135	Mean = 3	42.9% (19.1 degrees)

SP = Stable phase; AP = Acute phase; N/S = Non-significant.

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 is for curvatures between 30° and 60°, longer duration of disease, an IIEF > 17, and no calcification [942]. An 18.2% improvement from baseline in the placebo arm was also observed. These findings raise questions regarding the alleged role of plaque injection and penile modeling, regardless of the medication, in improving outcomes in men with PD as the placebo or modeling arm resulted in a relatively high curvature reduction compared to treatment.

The conclusion of the IMPRESS I and II studies is that that CCH improves PD both physically and psychologically [981]. A post hoc meta-analyses of the IMPRESS studies demonstrated better results in patients with less than 60° of curvature, more than two years of evolution, no calcification in the plaque and good erectile function [980].

A relatively new modified short protocol which consists of the 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 four-weekly intervals, has been proposed, and replaces the physician modelling with a multimodal approach through penile stretching, modelling and vacuum device at home [986]. The results from this modified protocol were comparable to the results of the IMPRESS trials and appear to decrease the

cost and duration of the treatment, although these represent non-randomised study protocols. These results were further explored in a prospective non-randomised multi-centric 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 [988]. 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 [988]; however, these findings need to be externally validated.

Regarding safety concerns, the majority of PD's patients treated with CCH experienced at least one mild or moderate adverse reaction 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 fourteen days of the injection [989]. The adverse reaction profile was similar after each injection, regardless of the number of injections administered. Serious TEAE's (0.9%) include penile haematoma and corporeal rupture that require surgical treatment. According to both IMPRESS' data and the shortened protocol, in order to prevent serious TEAE men should be advised to avoid sexual intercourse in the four weeks following the injection. Recent preliminary data suggest that treatment in the acute phase of the disease can be effective and safe [946, 979-981].

In conclusion, CCH is a safe and established treatment for active-phase disease; more recent evidence would suggest that CCH may also have a role in affecting the progression of active-phase disease, thus suggesting that the indications for CCH use could be expanded, although there is the possibility of a high placebo effect. 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 [986]. However, further investigation is needed to validate these initial findings [951, 984]. The panel has agreed to keep the whole set of information and recommendations regarding the use of CCH in men with PD despite the recent report about the official withdrawal of the product from the European market by the company.

Interferon α -2b

Interferon α -2b (IFN- α 2b) has been shown to decrease fibroblast proliferation, extracellular matrix production and collagen production from fibroblasts and improve the wound healing process from PD plaques *in vitro* [990]. Intralesional injections (5×10^6 units of IFN- α 2b in 10 mL saline every two weeks over twelve 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 benefited in the IFN- α 2b group [979, 991, 992]. A study showed that regardless of plaque location, IFN- α 2b is an effective treatment option. Treatment with IFN- α 2b provided a greater than 20% reduction in curvature in the majority of men with PD, independent of plaque location [993]. Given the mild side-effects, which include sinusitis and flu-like symptoms, which can be effectively treated with NSAIDs drugs before IFN- α 2b injection, and the moderate strength of data available, IFN- α 2b 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 [994]. Adverse effects include tissue atrophy, thinning of the skin and immunosuppression [995]. Only a case-controlled single site study and a prospective non-controlled study support the use of hyaluronic acid injections in PD, with conflicting results related to penile curvature or penile pain [996, 997]. As only a single study evaluated intralesional botox injections in men with PD, the panel conclude that there is no robust evidence available to support these treatments [998].

8.2.3.1.3 Topical treatments

Topical verapamil and H-100 Gel

There is no sufficient and unequivocal evidence that topical treatments (neither verapamil, H-100 Gel [a compound with nifedipine, superoxide dismutase and emu oil] nor steroids) applied to the penile shaft, with or without the use of iontophoresis (now known as transdermal electromotive drug administration [EMDA]), result in adequate levels of the active compound within the tunica albuginea [999-1002]. Therefore, the panel does not support the use of topical treatments for PD applied to the penile shaft.

Extracorporeal shockwave treatment

The mechanical shear stress provoked by low-intensity extracorporeal shockwave treatment (LI-ESWT) on the treated tissue was deemed to induce neovascularisation and to enhance local blood flow [956]. The mechanism of action involved in ESWT for PD is still unclear, but there are two hypotheses. In the first hypothesis, shockwave therapy works by directly damaging and remodeling the penile plaque. In the second hypothesis, shockwave lithotripsy increases the vascularity of the area by generating thermodynamic changes resulting in an inflammatory reaction, with increased macrophage activity causing plaque lysis and eventually leading to plaque resorption [1003, 1004].

Four RCTs and one meta-analysis [1005-1009] assessed the efficacy of ESWT in the treatment of PD. Three were sham-controlled trials while one compared ESWT with the combination of ESWT and PDE5i (tadalafil) [1007].

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. The results are summarised in the Table 28.

Table 28: Efficacy of ESWT in the treatment of PD

Author/Year	N° cases/controls	Inclusion criteria	Comparator	Follow up	Protocol of treatment	Results	AES's
Palmieri <i>et al.</i> 2009 [1005]	50 / 50	PD <12 mo. No previous treatment	Sham therapy	6 month	1 session/week x 4 weeks 2000 sw, 0.25 mJ/mm ² , 4 Hz	Change in IIEF (+5.4points) Pain reduction (-5.1 points) Change in curvature (-1.4°) Plaque size (-0.6 in)	No
Chitale <i>et al.</i> 2010 [1006]	16 / 20	Stable PD > 6 mo. No previous treatment	Sham therapy	6 month	1 session/week x 6 weeks. No other parameters mentioned.	Change in IIEF N/S Pain reduction N/S Change in curvature N/S Plaque size N/S	No
Palmieri <i>et al.</i> 2011 [1007]	50 / 50	PD <12 mo. Painful erections Presence of ED	ESWT + tadalafil 5 mg OD	6 month	1 session/week x 4 weeks 2000 sw, 0.25 mJ/mm ² , 4 Hz	Change in IIEF Significant in both groups Pain reduction Significant in both groups Change in curvature N/S Plaque size N/S	No
Hatzichristodoulou <i>et al.</i> 2013 [1008]	51 / 51	Stable PD > 3 mo. Previous unsuccessful oral treatment	Sham therapy	1 month	1 session/week x 6 weeks 2000 sw, 0.29 mJ/mm ²	Change in IIEF N/A Pain reduction (-2.5 points) Change in curvature N/S Plaque size N/S	Ecchymosis 4,9%

N/A = no assessed; N/S = no significant; IIEF = International index of erectile function; VAS = Visual Analogic Scale; ED = Erectile dysfunction

Penile traction therapy

In men with PD, potential mechanisms for disease modification with penile traction therapy (PTT) have been described, including collagen remodelling via decreased myofibroblast activity and matrix metalloproteinase up-regulation [1010, 1011].

The stated clinical goals of PTT are to non-surgically reduce curvature, enhance girth, and recover lost length,

which are very attractive to patients suffering from PD. However clinical evidence is limited due to the limited number of patients included (267 in total), the heterogeneity in the study designs, and the non-standardised inclusion and exclusion criteria make it impossible to draw any definitive conclusions about this therapy [1012-1016].

Most of the included patients will need further treatment to ameliorate their curvature for satisfactory sexual intercourse. Moreover, the effect of PTT therapy 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 due to use of the device for an extended period (two to eight hours daily), but has been shown to be tolerated by highly motivated patients. There were no serious adverse effects, including skin changes, ulcerations, hypoesthesia or diminished rigidity [1014, 1017].

In conclusion, PTT seems to be effective and safe for patients with PD, but there is still lack of evidence to give any definitive recommendation in terms of monotherapy for PD.

Table 29: Summary of clinical evidence of PTT as monotherapy

Author/Year	Study type	Device	Number of patients	Hours of use	Result
Levine <i>et al.</i> (2008)	Pilot Prospective, uncontrolled	Fast Size®	10	2-8h 6 months	Mean reduction in PC 33% (51°-34°) SPL: + 0.5-2 cm EG: + 0.5-1 cm IIEF: + 5.3
Gontero <i>et al.</i> (2009)	Phase II Prospective Uncontrolled	Andropenis®	15	> 5h 6 months	Mean reduction in PC: N/S SPL: + 0.8 cm (6 mo) + 1.0 cm (12 mo)
Martinez-Salamanca <i>et al.</i> (2014)	Prospective, controlled, open label Men in AP	Andropenis®	96 55 (PD) 41 (NIG)	6-9h (4.6 h/d) 6 months	Mean reduction in PC: 20° (33°-15°) p < 0.05. SPL: + 1.5 cm (6 mo) EG: + 0.9 cm (6 mo)
Moncada <i>et al.</i> (2018)	Controlled multicenter trial Men in CP	Penimaster®PRO	80 41 (PTT) 39 (NIG)	3-8h 3 months	Mean reduction in PC: 31° (50°-15°). SPL: + 1.8 cm (3 mo) EG: +0.9 cm (6 mo) IIEF: + 2.5
Ziegelmann <i>et al.</i> (2019) [1016]	Randomised, prospective, controlled, single blind study Men in CP and controls 3:1	Restorex®	110	30-90 min/day 3 months	Mean reduction in PC (3 mo): 13.3° (PTT) +1.3° (control) p < 0.001 SPL: + 1.5 cm (PTT) + 0.cm (control) p < 0.001 IIEF: +4.3 (PTT) -0.7 (control) p=0.01

NIG = non-intervention group; IIEF = International Index of Erectile Function; N/S = Not Significant;
PD = Peyronie's Disease; AP = Acute phase; CP = Chronic phase; SPL - Stretched penile length; EG = Erect girth, mo = month.

Vacuum erection device

Vacuum erection device (VED) therapy results in dilation of cavernous sinuses, decreased retrograde venous blood flow and increased arterial inflow [1018]. Intracorporeal molecular markers are affected by VED application, including decreases in hypoxia-inducible factor-1a, transforming growth factor (TGF)-b1, collagenase, and apoptosis, and increases endothelial nitric oxide synthase and a-smooth muscle actin, given a role in the pathogenesis of PD [1019]. Only one clinical study assessed the efficacy of VED therapy in mechanically straightening the penile curvature of PD as monotherapy and further investigation is needed [1020].

8.2.3.1.4 Multimodal treatment

There is some data suggesting that a combination of different oral drugs can be used in the treatment of the acute phase of PD. However, there does not seem to be a consensus on which drugs to combine, 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 it is efficacious to treat PD patients. The authors concluded that combination therapy reduced pain more effectively than verapamil alone, making this specific combination treatment more effective compared to monotherapy [1019]. Furthermore, combination protocols including injectable therapies, such as CCH, have been studied in controlled trials. The addition of adjunctive PTT and VED have been described, however, limited data is available regarding its use [1021].

Penile traction therapy was evaluated as an adjunctive therapy to intralesional injections with interferon, verapamil, or CCH [969, 1022, 1023]. Results from these studies have failed to demonstrate statistically significant improvements in penile length or curvature, with the exception of one subset analysis identifying a 0.4 cm length increase among men using the devices for > 3 hours a day [1023]. A meta-analysis comparing the efficacy of PTT as an adjuvant treatment demonstrated that men who used PTT as an adjunct treatment to surgery or injection therapy in the treatment of PD had, on average, an increase in stretched penile length (SPL) of 1 cm compared to men who did not use adjunct PTT. There was no significant change in curvature between the two groups [1024].

Data available on the combined treatment of CCH and the use of VED between injection intervals reported statistically significant mean improvements in curvature (-17°) 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 [986, 1024].

Recent data suggested that the combination of PDE5I (sildenafil 25 mg twice a day) after CCH treatment (shortened protocol combined with VED) is superior to CCH alone for improving penile curvature and erectile function. Further studies are necessary to externally validate those findings.

8.2.3.1.5 Summary of evidence 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.	5
Intralesional treatment with calcium channel antagonists: verapamil and nicardipine are no longer recommended due to contradictory results.	1b
Intralesional treatment with collagenase of <i>clostridium histolyticum</i> 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 and density, and pain.	2b
Intralesional treatment with steroids are no longer recommended due to adverse effects include tissue atrophy, thinning of the skin and immunosuppression.	3c
No robust evidence is available to support treatment with intralesional hyaluronic acid or botulinum toxin.	3c
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
The use of iontophoresis is not recommended due to the absence of efficacy data.	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 studies have limitations.	3c

8.2.3.1.6 Recommendations for non-operative treatment of Peyronie's disease

Recommendations	Strength rating
Offer conservative treatment to patients not fit for surgery or when surgery is not acceptable to the patient.	Strong
Discuss with patients all the available treatment options and expected results before starting any treatment.	Strong
Do not offer oral treatment with vitamin E, potassium para-aminobenzoate (potaba), tamoxifen, pentoxifyline, colchicine and acetyl esters of carnitine to treat Peyronie's disease (PD).	Strong
Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used to treat penile pain in the acute phase of PD.	Strong
Extracorporeal shockwave treatment (ESWT) can be used to treat penile pain in the acute phase of PD.	Weak
Phosphodiesterase type 5 inhibitors can be used to treat concomitant erectile dysfunction or if the deformity results in difficulty in penetrative intercourse in order to optimise penetration.	Weak
Intralesional therapy with interferon alpha-2b may be offered in patients with stable curvature dorsal or lateral > 30° seeking a minimal invasive procedure.	Strong
Intralesional therapy with collagenase <i>clostridium histolyticum</i> may be offered in patients with stable PD and dorsal or lateral curvature > 30°, who request non-surgical treatment, although the placebo effects are high.	Strong
Do not offer intralesional treatment with steroids to reduce penile curvature, plaque size or pain.	Strong
Do not offer ESWT to improve penile curvature and reduce plaque size.	Strong
Penile traction devices and vacuum devices may be offered to reduce penile deformity or as part of a multimodal therapy approach, although outcome data is limited.	Weak

8.2.3.2 Surgical treatment

Although conservative treatment for PD may resolve painful erections in most men, only a small percentage will experience a 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) [934, 943, 1025]. In addition to this requirement, there are other situations that may precipitate the indication for surgery, such as failed conservative or medical therapies, extensive penile plaque(s), or patient preference, when the disease is stable [1026, 1027].

Before considering reconstructive surgery, it is highly recommended to document the size and location of plaques, the degree of curvature, complex deformities (hinge, hourglass), the penile length and also the presence or absence of ED. The potential aims and risks of surgery should be discussed fully with the patient so that he can make an informed decision [1025]. Specific issues that should be mentioned during this discussion are the risks of penile shortening, ED, penile numbness and delayed orgasm, the risk of recurrent curvature, the potential for palpation of knots and stitches underneath the skin, and the potential need for circumcision at the time of surgery, including residual curvature and the risk of further penile wasting with shortening procedures [943, 1028]. 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 [943]. 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 [1025, 1029].

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 adjunct straightening techniques in the presence of concomitant ED and residual curvature [1030, 1031].

Tunical shortening procedures achieve straightening of the penis by shortening the longer, convex side of the penis to make it even with the contralateral side. 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 in real life rarely lead to long-term penile length gain, they aim to minimise penile shortening caused by plication techniques of the tunica albuginea or correct complex deformities. In practice, tunical lengthening procedures are often combined with penile plication or shortening

procedures to correct the residual curvature [1032]. In patients with PD and ED not responding to medical treatments, penile prosthesis implantation can be considered with correction of the curvature including adjunct techniques (modeling, plication or incision/excision with grafting).

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) [1033]. Non-degloving techniques have been described that have been shown to prevent ischaemia and lymphatic complications after subcoronal circumcision [1034, 1035].

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 on expert opinion [943, 1036]. Therefore, surgical outcomes must be treated with caution.

8.2.3.2.1 Tunical shortening procedures

For men with good erectile function, adequate penile length, without complex deformities, such as an hourglass or hinge type narrowing abnormality, 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.

In 1965, Nesbit was the first to describe the removal of tunical ellipses opposite to the point of maximum curvature with a non-elastic corporal segment to treat CPC [1037]. Thereafter, this technique became a successful treatment option for PD-associated penile curvatures [1038]. This operation is based on a 5-10 mm transverse elliptical excision of the tunica albuginea or approximately 1 mm for each 10° of curvature. The overall short- and long-term results of the Nesbit operation are excellent [1039-1043]. Some modifications of the Nesbit procedure have been described (partial thickness shaving instead of conventional excision; underlapped U incision) with similar results, although these are in non-randomised studies [1044-1048].

The Yachia technique, on the other hand, is based on a completely different concept, as it utilises the Heinke-Mikowitz principle where a longitudinal tunical incision is closed transversely in order 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 ten cases [1049-1054].

Pure plication techniques are simpler to perform. They are based on single or multiple plications performed without making excisions or incisions, in order to limit the potential damage to the veno-occlusive mechanism [945, 1055-1071]. Another modification has been described as the '16-dot' technique which consists of the application of two pairs of parallel Essed-Schroeder plications tensioned more or less depending on the degree of curvature [1048, 1072-1074]. The use of non-absorbable sutures or longer lasting absorbable sutures may reduce recurrence of the curvature (panel expert opinion). Results and satisfaction rates are both similar to the incision/excision procedures.

In general, using these tunical shortening techniques, complete penile straightening is achieved in more than 85% of patients. Recurrence of the curvature and penile hypoesthesia are uncommon (about 10%) and the risk of post-operative ED is low. Penile shortening is the most commonly reported outcome of these procedures. Shortening of 1-1.5 cm has been reported for about 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, whatever the technique used (Table 30).

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

Table 30: Results of tunical shortening procedures for PD data from different, non-comparable studies) [945, 1044-1071]

	Tunical shortening procedures				
	Nesbit	Modified Nesbit	Yachia	16-dot / mod16-dot	Simple plication
Number 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)	58.1% (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 <i>de novo</i> 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 surgery is preferable in patients with significant penile shortening, severe curvature and/or complex deformities (hourglass, hinge) but without underlying ED. The definition of a severe curvature has been proposed to be greater than 60°, although there are no studies validating this threshold. However, it may be used as an informative guide to the patient and clinician in surgical counselling and planning, although there is no unanimous consensus based on the literature that such a threshold can predict surgical outcomes (panel expert consensus opinion). 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 [1075, 1076]. Patients who do not have pre-operative ED should be informed of the significant risk of post-operative ED of up to 50% [1028].

Since 1974, when the first study using dermal grafting to treat PD was published [1077], a large number of different grafts have been used. The ideal graft should be resistant to traction, easy to suture and manipulate, flexible (not too much, to avoid aneurysmal dilations), readily available, morbidity should be minimal especially when using autografts and cost effective. No one graft material meets all of these requirements. Moreover, the studies performed do not compare different types of grafts and biomaterials and are often single-centre retrospective studies so there is not a single graft that can be recommended for surgeons [1078]. In addition, grafting procedures are associated with long term ED rates as high as 50%. The presence of pre-operative ED, the use of larger grafts, age more than 60 years, and ventral curvature are considered poor prognostic factors for good functional outcomes after grafting surgery [1031]. Although the risk for penile shortening appears to be less than that compared to the Nesbit, Yachia or plication procedures, it is still an issue and patients must be informed accordingly [1030]. Higher rates (3-52%) of penile hypoesthesia have also been described after these surgeries, as damage of the neurovascular bundle with dorsal curves (in the majority) is inevitable. A recent prospective study showed that 21% of patients had some degree of sensation loss at one week, 21% at one month, 8% at six months, and 3% at twelve months. [1029, 1079-1082]. 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 [1083].

Grafts for PD surgery can be classified into four types (Table 31) [935]:

- 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 [1077, 1078, 1084-1094]. Vein grafts have the theoretical advantage of endothelial-to-endothelial contact when grafted to underlying cavernosal tissue. The Saphenous vein has been the most common vein graft used [1095-1110]. For some extensive albuginea defects, more than one incision may be needed. Tunica albuginea grafts have obviously perfect histological properties but have some limitations: the size that can be harvested, and the risk of weakening penile support and making future procedures (penile prosthesis implantation) more complicated [1111-1113]. Tunica vaginalis is easy to harvest and has little tendency to contract due to its low metabolic requirements, although better results could be obtained if a vascular flap is used [1114-1118]. 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 [1119-1125].

Cadaveric dura mater is no longer used due to concerns about the possibility of infection [1081, 1126]. Cadaveric pericardium (Tutoplast[®]) offers good results by coupling excellent tensile strength and multidirectional elasticity/expansion by 30% [1029, 1076, 1090, 1127, 1128]. Cadaveric or autologous fascia lata or temporalis fascia offers biological stability and mechanical resistance [1129-1131].

Xenografts have become more popular in recent years. Small intestinal submucosa, 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 the growth of endothelial cells, resulting in tissue structurally and functionally similar to the original [1132-1141]. As mentioned above, pericardium (bovine, in this case), has very good traction resistance and adaptability, and good host tolerance [1080, 1110, 1142-1144]. Grafting by collagen fleece (TachoSil[®]) in PD has some major advantages such as decreased operative times, easy application and an additional haemostatic effect [1079, 1145-1149].

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 [1052, 1150-1153].

Some authors recommend post-operative penile rehabilitation to improve surgical outcomes. Some studies have described using VED and PTT to prevent penile length loss of up to 1.5 cm [1154]. In addition, daily nocturnal administration of PDE5i enhances nocturnal erections, encourages perfusion of the graft, and may minimise post-operative ED [1155]. Massages and stretching of the penis have also been recommended once wound healing is complete.

Table 31: Results of tunical lengthening procedures for Peyronie's disease (data from different, non-comparable studies) [1029, 1052, 1076, 1077, 1079-1081, 1084-1149]

	Year of publication	Number 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 / 4	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	2002-2016	284 / 5	88.7% (81-100)	4.3% (0-41)	24.8% (0-50)	(14-67)
Bovine dermis	2016	28 / 1	93%	0%	25%	32
TachoSil®	2002-2018	477 / 6	93.1%	10.9% (0-93)	10.6% (0-21)	(0-63)

*Data are expressed as weighted average. Ranges are in parentheses.

ED = Erectile dysfunction; SIS = Small intestinal submucosa.

The results of tunical shortening and lengthening approaches are presented in Tables 30 and 31. It must be emphasised that there are no RCTs available comparing surgical outcomes in PD. The risk of ED seems to be greater for penile lengthening procedures [943]. Recurrent curvature is likely to be the result of failure to wait until the disease has stabilised, 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 strength before 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., PDS) should be used. Although 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., PDS) [1039]. Penile numbness is a potential risk of any surgical procedure, involving mobilisation of the dorsal neurovascular bundle. This will usually be a temporary neuropraxia, due to bruising of the dorsal sensory nerves. Given that the usual deformity is a dorsal deformity, the procedure most likely to induce this complication is a lengthening (grafting) procedure, or the association with although rare ventral curvatures [1030].

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 intracavernosal injections of vasoactive agents) [943]. Although inflatable prostheses (IPP) have been considered classically more effective in the general population with ED, some studies support the use of malleable prostheses (MPP) in these patients with similar satisfaction rates [943, 1156, 1157]. The evidence suggests that there is no real difference between the available IPPs [1158]. Surgeons can and should advise on which type of prosthesis best suits the patient but it is the patient who should ultimately choose the prosthesis to be implanted [1159].

Most patients with mild-to-moderate curvature can expect an excellent outcome simply by cylinder insertion [1108, 1160]. If the 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, on the other hand, the curvature is > 30°, the first-line treatment would 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) [1161, 1162]. If, after performing this manoeuvre, a deviation > 30° persists, next steps would be eventually incision with collagen fleece coverage or without (if the defect is small, it can be left uncovered) or plaque incision and grafting [1163-1168]. However, the defect may be covered if it is larger, and this can be accomplished using grafts commonly employed in the grafting surgery (described above) which will prevent herniation and recurrent deformity due to the scarring of the defect [1169].

The risk of complications (infection, malformation, etc.) is not increased compared to the general population. However, a small risk of urethral perforation (3%) has been reported in patients with ‘modeling’ over the inflated prosthesis [1161].

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 considered [1170]. Although the “sliding” technique is not recommended due to reported cases of glans necrosis because of the concomitant release of both the neurovascular bundle and the 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 in the hands of experienced high-volume surgeons and after full patient counseling [1171-1173].

While patient satisfaction after IPP placement in the general population is quite 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% to 10.9%) [1174]. The main cause of dissatisfaction after PPI in the general population is a shortened penile length. Therefore, patients with PD undergoing penile implant surgery must be counselled that they are not designed to restore their previous length [1174, 1175].

8.2.3.2.4 Summary of evidence for non-operative treatment of Peyronie’s disease

Summary of evidence	LE
Surgery for PD should only be offered in patients with stable disease 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 the erections, degree of curvature, presence of complex deformities and patient choice must be taken into account in order to decide on a tunical shortening or lengthening technique.	3

8.2.3.2.5 Recommendations for the surgical treatment of penile curvature

Recommendations	Strength rating
Perform surgery only when Peyronie's disease (PD) has been stable for at least three months (without pain or deformity deterioration), which is usually the case after twelve months from the onset of symptoms, and intercourse is compromised due to deformity.	Strong
Prior to surgery, assess penile length, curvature severity, erectile function (including response to pharmacotherapy in case of erectile dysfunction [ED]) and patient expectations.	Strong
Use tunical shortening procedures as the first treatment option for congenital penile curvature and for PD with adequate penile length and rigidity, non-severe curvature and absence of complex deformities (hour-glass, hinge). The type of procedure used is dependent on surgeon and patient preference, as no procedure has proven superior to its counterparts.	Weak
Use tunical lengthening procedures for patients with PD and normal erectile function, without adequate penile length, severe curvature or presence of complex deformities (hour-glass, hinge). The type of graft used is dependent on the surgeon and patient factors, as no graft has proven superior to its counterparts.	Weak
Use the sliding techniques with caution, as there is a significant risk of life changing complications (e.g., glans necrosis).	Strong
Do not use synthetic grafts in PD reconstructive surgery.	Strong
Use penile prosthesis implantation, with or without any additional procedure (modeling, plication, incision or excision with or without grafting), in PD patients with ED not responding to pharmacotherapy.	Strong

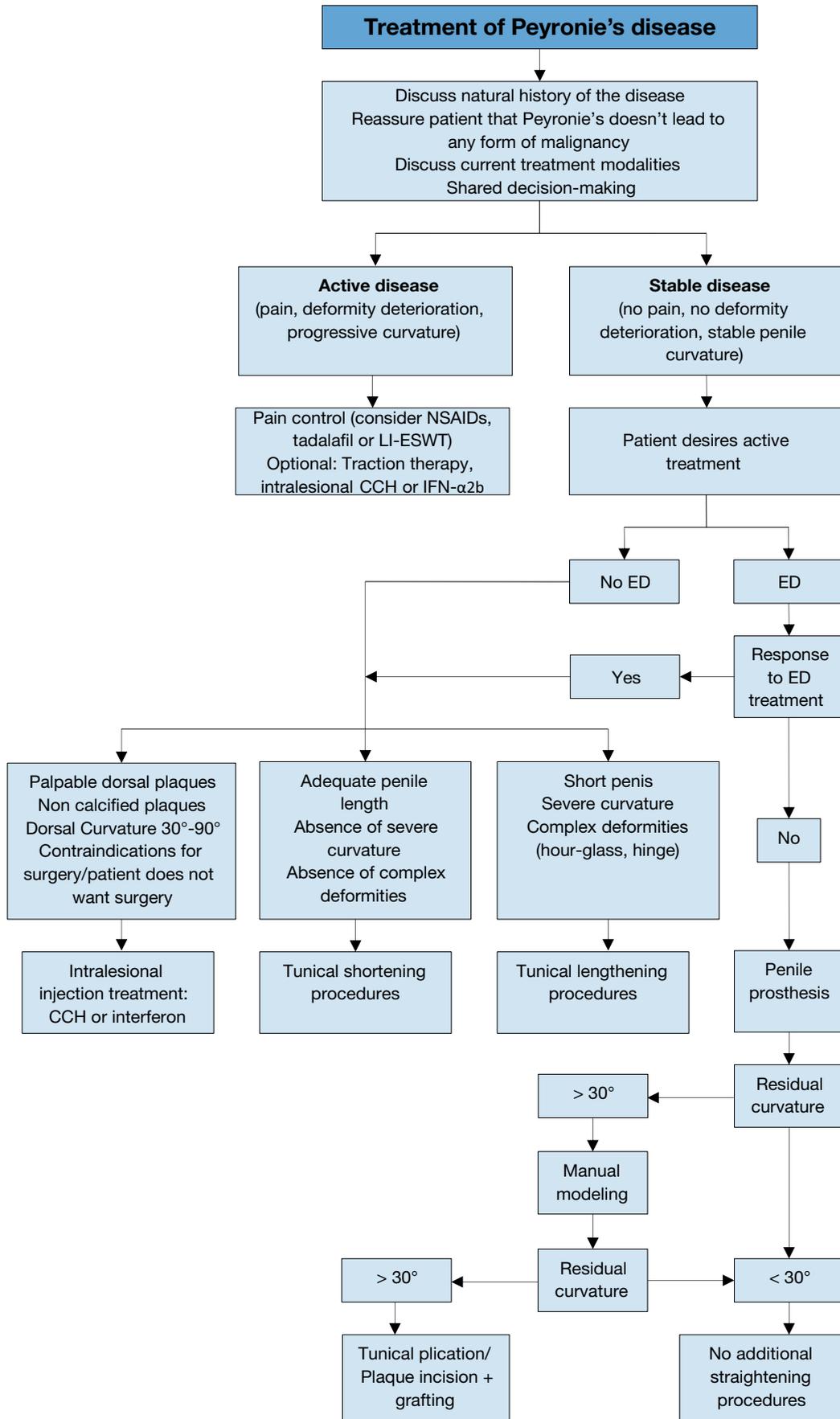
8.2.3.3 Treatment algorithm

As mentioned above, in the active phase of the disease, most therapies are experimental or with low evidence. In cases of pain, LI-ESWT, tadalafil and NSAIDs can be offered. In cases of curvature or shortening, traction therapy has demonstrated good responses.

When the disease has stabilised, intralesional treatments (mainly CCH) or surgery may be used. Intralesional treatments may reduce the indication of the surgery or change the technique to be performed but only after full patient counselling which should also include a cost benefit discussion with the patient.

The decision on the most appropriate surgical procedure to correct penile curvature is based on pre-operative assessment of penile length, the degree of the curvature and erectile function status. In non-complex and non-severe deformities, tunical shortening procedures are acceptable and are usually the method of choice. This is typically the case for PC. If a severe curvature or a complex deformation is present (hourglass, or hinge), or if the penis is significantly shortened in patients with a good erectile function (preferably without pharmacological treatment), then a tunical lengthening procedure is feasible, using any of the grafts previously mentioned. If there is concomitant ED, which is not responsive to pharmacological treatment, the best option is the implantation of a penile prosthesis, with or without a straightening procedure over the penis (modeling, plication, incision or excision with or without grafting). The treatment algorithm is presented in Figure 11.

Figure 11: Treatment algorithm for Peyronie's disease



ED = erectile dysfunction; LI-ESWT= Low-intensity Extracorporeal shockwave treatment.

9. MALE INFERTILITY

9.1 Definition and classification

Infertility is the inability of a sexually active, non-contraceptive couple to achieve spontaneous pregnancy in one year [1176]. Primary infertility refers to couples that have never had a child and cannot achieve pregnancy after at least twelve 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.

9.2 Epidemiology/aetiology/pathophysiology/risk factors

9.2.1 Introduction

About 15% of couples do not achieve pregnancy within one year and seek medical treatment for infertility. One in eight couples encounter problems when attempting to conceive a first child and one in six when attempting to conceive a subsequent child. Three percent of women who are currently trying to conceive remain involuntarily childless, while 6% of parous women are not able to have as many children as they would wish [1177]. In 50% of involuntarily childless couples, a male-infertility-associated factor is found, usually together with abnormal semen parameters [1176]. For this reason, all male patients belonging to infertile couples should undergo medical evaluation by a urologist trained in male reproduction.

Male fertility can be impaired as a result of [1176]:

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

In 30-40% of cases, no male-associated factor is found to explain 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 9.3.2). On the other hand, unexplained male infertility is defined as infertility of unknown origin with normal sperm parameters. 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/sperm DNA damage, or genetic and epigenetic abnormalities [1178].

Advanced paternal age has emerged as one of the main risk factors associated with the progressive increase in the prevalence of male factor infertility [1179-1182]. Table 32 summarises the main male-infertility-associated factors.

Table 32: Male infertility causes and associated factors and percentage of distribution in 10,469 patients
[1183]

Diagnosis	Unselected patients (n = 12,945)	Azoospermic patients (n = 1,446)
<i>All</i>	100%	11.2%
<i>Infertility of known (possible) cause</i>	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
<i>Idiopathic infertility</i>	30.0	13.3
<i>Hypogonadism</i>	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
<i>General/systemic disease</i>	2.2	0.5
<i>Cryopreservation due to malignant disease</i>	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
<i>Disturbance of erection/ejaculation</i>	2.4	-
Obstruction	2.2	10.3
Vasectomy	0.9	5.3
Cystic fibrosis (CBAVD)	0.5	3.0
Others	0.8	1.9

CBAVD = Congenital bilateral absence of the vas deferens.

9.2.2 Recommendations on epidemiology and aetiology

Recommendations	Strength rating
Investigate both partners simultaneously to categorise the cause of infertility.	Strong
Examine all men seeking medical help for fertility problems, including men with abnormal semen parameters for urogenital abnormalities.	Strong

9.3 Diagnostic work-up

A focused evaluation of the male patient must always be undertaken and should include: a medical and reproductive history; physical examination; semen analysis - with strict adherence to World Health Organization (WHO) reference values for human semen characteristics [1184], and hormonal evaluation. Other investigations (e.g., genetic analysis and imaging) may be required depending on the clinical features and semen parameters.

9.3.1 Medical/reproductive history and physical examination

9.3.1.1 Medical and reproductive history

Medical history should evaluate any risk factors and behavioural patterns which could affect the male partner's fertility, such as lifestyle, family history (including, testis cancer), comorbid conditions (including, systemic diseases; e.g., hypertension; diabetes mellitus; obesity; MetS; testis cancer, etc.), genito-urinary infections (including, sexually transmitted infections), past history of surgery of the testis and excluding any potential known gonadotoxins.

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 (anabolic drugs, chemotherapeutic agents, etc.);
- exposure to radiation or cytotoxic agents.

9.3.1.2 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, testis volume is assessed by Prader's orchidometer [1185]; orchidometry may over-estimate testis volume when compared with US assessment [1186]. There are no uniform reference values in terms of Prader's orchidometer-derived testis volume, due to differences in the populations studied (e.g., geographic area, nourishment, ethnicity and environmental factors) [1185-1187]. The mean Prader's orchidometer-derived testis volume reported in the European general population is 20.0±5.0 mL [1185], whereas in infertile patients it is 18.0±5.0 mL [1185, 1188, 1189]. The presence of the vas deferens, fullness of epididymis and presence of a varicocele should be always determined. Likewise, palpable abnormalities of the testis, the epididymis, and the 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.

9.3.2 Semen analysis

A comprehensive andrological examination is always indicated if semen analysis shows abnormalities as compared with reference values (Table 33). Important treatment decisions are based on the results of semen analysis; therefore, it is essential that the complete laboratory work-up is standardised. Ejaculate analysis has been standardised by the WHO and disseminated by publication of the most updated version of the WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn.) [1190]. There is consensus that modern semen analysis must follow these guidelines. However it has also become clear from studies that more complex testing than semen analysis may be required, particularly in men belonging to couples with recurrent pregnancy loss from natural conception or assisted reproductive technologies (ART) and men with unexplained male infertility. In these patients there is evidence that the sperm DNA may be damaged, thus resulting in pregnancy failure [1178] (see below).

Table 33: Lower reference limits (5th centiles and their 95% CIs) for semen characteristics

Parameter	Lower reference limit (range)
Semen volume (mL)	1.5 (1.4-1.7)
Total sperm number (10 ⁶ /ejaculate)	39 (33-46)
Sperm concentration (10 ⁶ /mL)	15 (12-16)
Total motility (PR + NP)	40 (38-42)
Progressive motility (PR, %)	32 (31-34)
Vitality (live spermatozoa, %)	58 (55-63)
Sperm morphology (normal forms, %)	4 (3.0-4.0)
Other consensus threshold values	
pH	> 7.2
Peroxidase-positive leukocytes (10 ⁶ /mL)	< 1.0
Optional investigations	
MAR test (motile spermatozoa with bound particles, %)	< 50
Immunobead test (motile spermatozoa with bound beads, %)	< 50
Seminal zinc (µmol/ejaculate)	≥ 2.4
Seminal fructose (µmol/ejaculate)	≥ 13
Seminal neutral glucosidase (mU/ejaculate)	≤ 20

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

If the results of semen analysis are 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. It is important to differentiate between the following:

- oligozoospermia: < 15 million spermatozoa/mL;
- asthenozoospermia: < 32% progressive motile spermatozoa;
- teratozoospermia: < 4% normal forms.

Often, all three anomalies occur simultaneously, which is defined as oligo-astheno-teratozoospermia (OAT) syndrome. As in azoospermia (namely, the complete absence of spermatozoa in semen), in severe cases of oligozoospermia (spermatozoa < 5 million/mL) [1191], there is an increased incidence of obstruction of the male genital tract and genetic abnormalities. In those cases, a more comprehensive assessment of the hormonal profile may be helpful to further and more accurately differentially diagnose among pathologic conditions.

In azoospermia, the semen analysis may present with normal ejaculate volume and azoospermia after centrifugation. A recommended method is semen centrifugation at 3,000 g for fifteen minutes and a thorough microscopic examination by phase contrast optics at $\times 200$ magnification of the pellet. All samples can be stained and re-examined microscopically [1190]. This is to ensure that small quantities of sperm are detected, which may be potentially used for intracytoplasmic sperm injection (ICSI) and obviate the need to surgical intervention.

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

Semen analysis is a descriptive evaluation, and may be unable to discriminate between the sperm of fertile and infertile men. Therefore, it is now apparent that sperm DNA damage may occur in men with infertility. DNA fragmentation, or the accumulation of single- and double-strand DNA breaks, is a common property of sperm, and an increase in the level of sperm DNA fragmentation has been shown to reduce the chances of natural conception. In this context, sperm DNA damage is more common in infertile men and sperm DNA damage has been identified as a major contributor to male infertility, as well as poorer outcomes following ART [1192, 1193], including impaired embryo development [1192], miscarriage, recurrent pregnancy loss [1192, 1194], and birth defects in the offspring [1192]. Sperm DNA damage can be increased by a number of factors including hormonal anomalies, varicocele, chronic infection and lifestyle factors (e.g., smoking) [1193].

A number of 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 controversy exists as whether to recommend them routinely for clinical use [1193, 1195]. Of those, terminal deoxynucleotidyl transferase mediated deoxyuridine triphosphate nick end labeling (TUNEL) and the alkaline comet test (COMET), are tests that directly measure DNA damage. Conversely, sperm chromatin structure assay (SCSA) and sperm chromatic dispersion test (SCD) are indirect tools for DNA fragmentation assessment. Sperm chromatin structure assay is still the most widely studied and one of the most commonly used techniques to detect DNA damage [1196, 1197]. In SCSA, the number of cells with DNA damage is indicated by the DNA fragmentation index (DFI,%) [1198], whereas the proportion of immature sperm with defects in the histone-to-protamine transition is indicated by high DNA stainability [1199]. It is suggested that a threshold value of DFI of 30% as measured with SCSA, is associated with reduced pregnancy rates via natural conception or Intra-uterine insemination (IUI) [1197]. Furthermore, DFI values of over 50% on SCSA have been associated with poorer outcomes from *in vitro* fertilisation (IVF) treatment. 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 [1193].

Testicular sperm has been reported to have lower levels of sperm DFI when compared to ejaculated sperm [1200]. Couples with elevated DNA fragmentation may benefit from the combination of testicular sperm extraction (TESE) and ICSI, an approach called TESE-ICSI, which may not overcome infertility when applied to an unselected population of infertile men with untested DNA fragmentation values [1197, 1200]. However, further evidence is needed to support this practice in the routine clinical setting [1200].

9.3.4 **Hormonal determinations**

In men with testicular deficiency, hypergonadotropic hypogonadism (also called primary hypogonadism) is usually present, with high levels of FSH and LH, with or without low levels of testosterone. Generally, the levels of FSH negatively correlate with the number of spermatogonia [1201]. When spermatogonia are absent or markedly diminished, FSH values are usually elevated; when the number of spermatogonia is normal, but maturation arrest exists at the spermatocyte or spermatid level, FSH values are usually within the normal range [1201]. 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 testis volume [1202, 1203]. Furthermore men with non-obstructive azoospermia (NOA) and high levels of FSH may still harbour focal areas of spermatogenesis at the time of TESE or microdissection TESE (mTESE) [1203].

9.3.5 **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. Men with very low sperm counts can still be offered a reasonable chance of paternity, using IVF, ICSI and sperm extraction from the testes in cases of azoospermia. However, the spermatozoa of infertile men shows an increased rate of aneuploidy, structural chromosomal abnormalities, and DNA damage, carrying the risk of passing genetic abnormalities to the next generation. Current routine clinical practice is based on the screening of genomic DNA from peripheral blood samples. However, screening of chromosomal anomalies

in spermatozoa (sperm aneuploidy) is also feasible and can be performed in selected cases (e.g., recurrent miscarriage) [1204-1206].

9.3.5.1 Chromosomal abnormalities

Chromosome abnormalities can be numerical (e.g. trisomy) or structural (e.g. inversions or translocations). In a survey of pooled data from eleven publications, including 9,766 infertile men, the incidence of chromosomal abnormalities was 5.8% [1207]. 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 newborn male infants, of which 131 (0.14%) were sex chromosome abnormalities and 232 (0.25%) autosomal abnormalities [1207]. The frequency of chromosomal abnormalities increases as testicular deficiency becomes more severe. Patients with sperm count < 5 million/mL already show a ten-fold higher incidence (4%) of mainly autosomal structural abnormalities compared with the general population [1208, 1209]. Men with NOA are at highest risk, especially for sex chromosomal anomalies (e.g., Klinefelter Syndrome) [1210, 1211].

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) [1209]. This broad selection criterion has been recently externally validated, with the finding that the suggested threshold has a relatively low sensitivity, specificity, and discrimination (namely, 80%, 37%, and 59%, respectively) [1212]. In this context, a novel nomogram, with a 2% probability cut-off, which allows for a more careful detection of karyotype alterations has been developed [1212]. 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 [1213]. If there is a family history of recurrent spontaneous abortions, malformations or mental retardation, karyotype analysis should be requested, regardless of the sperm concentration.

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

Klinefelter Syndrome is the most common sex chromosome abnormality [1214]. Adult men with Klinefelter Syndrome usually have small firm testicles along with features of primary hypogonadism. The phenotype is the final result of a combination between genetic, hormonal and age-related factors [15]. As a whole, the phenotype varies from that of a normally virilised male to one with the stigmata of androgen deficiency. In the vast majority of the cases infertility and reduced testis 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 that in the general population, although rarely observed during the peri-pubertal period, which usually occurs in a normal manner [15, 1215]. Rarely, more pronounced signs and symptoms of hypogonadism can be present, along with congenital abnormalities including heart and renal problems [1216].

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. Based on sperm fluorescence *in situ* hybridisation (FISH) studies showing an increased frequency of sex chromosomal abnormalities and increased incidence of autosomal aneuploidy (disomy for chromosomes 13, 18 and 21), concerns have been raised about the chromosomal normality of the embryos generated through ICSI [1217]. The production of 24,XY sperm has been reported in 0.9% and 7.0% of men with Klinefelter's mosaicism [1218, 1219] and in 1.36-25% of men with somatic karyotype 47,XXY [1220-1223]. In patients with azoospermia, TESE or mTESE are therapeutic options as spermatozoa can be recovered in up to 50% of cases [1224] [1225]. There is growing evidence that TESE or mTESE yields higher sperm recovery rates when performed at a younger age [1210, 1226].

Numerous healthy children have been born using ICSI without pre-implantation genetic diagnosis (PGD) although the conception of one 47,XXY foetus has been reported [1214]. Although data published so far have not reported any difference in the prevalence of aneuploidies in children conceived using ICSI in Klinefelter Syndrome compared to the general population, men with Klinefelter Syndrome undergoing fertility treatments should be counselled regarding the potential genetic abnormalities in their offspring.

Regular medical follow-up of men with Klinefelter Syndrome is recommended as androgen replacement therapy may be considered if testosterone levels are in the hypogonadal range when fertility issues have been addressed. Since this syndrome is associated with a number of general health problems, appropriate medical follow-up is therefore advised [16, 1227, 1228]. In particular, men with Klinefelter Syndrome are at higher risk

of metabolic and cardiovascular diseases (CVD), including venous thromboembolism (VTE). Therefore, men with Klinefelter Syndrome should be made aware of this risk, particularly when starting testosterone treatment TRT [1229]. In addition, a higher risk of haematological malignancies has been reported in men with Klinefelter Syndrome [16].

Testicular sperm extraction in peri-pubertal or pre-pubertal Klinefelter boys aiming at cryopreservation of testicular spermatogonial stem cells is to be still considered experimental and should only be performed within a research setting [1230]. The same applies to sperm retrieval in older boys who have not considered their fertility potential [1231].

9.3.5.1.2 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. As with Klinefelter Syndrome, sperm FISH analysis provides a more accurate risk estimation of affected offspring. However, the use of this genetic test is largely limited by the availability of laboratories able to perform this analysis [1232]. When IVF/ICSI is carried out for men with translocations, PGD or amniocentesis should be performed [1233, 1234].

9.3.5.2 Cystic fibrosis gene mutations

Cystic fibrosis (CF) is an autosomal-recessive disorder [1235]. 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. Congenital bilateral absence of the vas deferens (CBAVD) is associated with CFTR gene mutations and was also found in ~2% of men with obstructive azoospermia [1236]. Clinical diagnosis of absent vasa is easy to miss and all men with azoospermia should be very carefully examined to exclude CBAVD, particularly those with a semen volume < 1.0 mL and acidic pH < 7.0 [1237-1239]. Approximately 1,500 mutations are listed on the CFTR database <http://www.geneticsickkids.on.ca/cftr/>.

The most frequently found mutations are the F508, R117H and W1282X, but their frequency and the presence of other mutations largely depend on the ethnicity of the patient [1240, 1241]. Given the functional relevance of a DNA variant (the 5T allele) in a non-coding region of CFTR [1242], it is now considered a mild CFTR mutation rather than a polymorphism and it should be analysed in each CBAVD patient. As more mutations are defined and tested for, almost all men with CBAVD will probably be found to have mutations. It is not practical to test for all known mutations, because many have a very low prevalence in a particular population. Routine testing is usually restricted to the most common mutations in a particular community through the analysis of a mutation panel. 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 also his partner for CF mutations. If the female partner is found to be a carrier of CFTR mutations, the couple must consider very carefully whether to proceed with ICSI using the male's sperm, 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% [1243].

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

Unilateral absence of the vas deferens is usually associated with ipsilateral absence of the kidney and probably has a different genetic causation [1244]. Consequently, in these subjects CFTR mutation screening is not indicated. Men with unilateral absence of the vas deferens are usually fertile, and the condition is most commonly encountered as an incidental finding in the vasectomy clinic. 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 extremely rare for patients who have CBAVD and CFTR mutations [1245]. An abdominal US should be undertaken both in unilateral and bilateral absence of vas deferens without CFTR mutations. Findings may range from unilateral absence of the vas deferens with ipsilateral absence of the kidney, to bilateral vessel and renal abnormalities, such as pelvic kidney [1246].

9.3.5.3 Y microdeletions - partial and complete

Microdeletions on the Y-chromosome are termed AZFa, AZFb and AZFc deletions [1247]. 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 [1248]. In each AZF region,

there are several spermatogenesis candidate genes [1249]. Deletions occur *en bloc* (i.e. removing more than one gene), it is not possible to determine the role of a single AZF gene from the AZF deletion phenotype and it is unclear if they all participate in spermatogenesis. Gene-specific deletions, which remove a single gene, have been reported only in the AZFa region and concern the USP9Y gene. These studies have suggested that USP9Y is most likely to be a “fine tuner” of sperm production, and its specific screening is not advised [1250].

9.3.5.3.1 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 [1251].
- The highest frequency of Y-deletions is found in azoospermic men (8-12%), followed by oligozoospermic (3-7%) men [1252, 1253].
- Deletions are extremely rare with a sperm concentration > 5 million/mL (~0.7%).
- 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%) [1254].
- Complete deletion of the AZFa region is associated with severe testicular phenotype (Sertoli cell only syndrome), 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 at the time of TESE and sperm is not found in these patients. Therefore, TESE should not be attempted in these patients [1255, 1256].
- Deletions of the AZFc region causes a variable phenotype ranging from azoospermia to oligozoospermia.
- Sperm can be found in up to 50%-75% of men with AZFc microdeletions [1255-1257].
- Men with AZFc microdeletions who are oligozoospermic 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 [1258, 1259].

The specificity and genotype/phenotype correlation reported above means that Y-deletion analysis has both a diagnostic and prognostic value for testicular sperm retrieval [1258].

9.3.5.3.1.1 Testing for Y microdeletions

Historically, indications for AZF deletion screening are based on sperm count and include azoospermia and severe oligozoospermia (spermatozoa count < 5 million/mL). A recent single meta-analysis assessing the prevalence of microdeletions on the Y chromosome in oligozoospermic men in thirty-seven European and North American studies (n=12,492 oligozoospermic men) showed that the majority of microdeletions occur in men with sperm concentrations of ≤ 1 million sperm/mL, with < 1% identified in men with > 1 million sperm/mL [1259]. In this context, whilst an absolute threshold for clinical testing cannot be universally given, patients may be offered testing if sperm counts are less than 5 million sperm/mL, but should be necessarily tested if less than ≤1 million sperm/mL.

With the efforts of the European Academy of Andrology (EAA) guidelines and the European Molecular Genetics Quality Network external quality control program (<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 [1260].

9.3.5.3.1.2 Genetic counselling for AZF deletions

After conception, any Y-deletions are transmitted to the male offspring, and genetic counselling is therefore mandatory. In most cases, father and son will have the same microdeletion [1260], but occasionally the son may have a more extensive deletion [1261]. The extent of spermatogenic failure (still in the range of azoo-/oligozoospermia) cannot be predicted entirely in the son, due to the different genetic background and the presence or absence of environmental factors with potential toxicity on reproductive function. A significant proportion of spermatozoa from men with complete AZFc deletion are nullisomic for sex chromosomes [1262, 1263], indicating a potential risk for any offspring to develop 45,X0 Turner's syndrome and other phenotypic anomalies associated with sex chromosome mosaicism, including ambiguous genitalia [1264]. Despite this theoretical risk, babies born from fathers affected by Yq microdeletions are phenotypically normal [1258, 1260]. This could be due to the reduced implantation rate and a likely higher risk of spontaneous abortion of embryos bearing a 45,X0 karyotype.

9.3.5.3.1.3 Y-chromosome: 'gr/gr' deletion

A new type of Yq deletion, known as the gr/gr deletion, has been described in the AZFc region [1265]. This deletion removes half of the gene content of the AZFc region, affecting the dosage of multicopy genes mapping inside this region. This type of deletion confers a 2.5-8 fold increased risk for oligozoospermia [1260, 1266-1268]. The frequency of gr/gr deletion in oligozoospermic patients is ~5% [1269].

According to four meta-analyses, gr/gr deletion is a significant risk factor for impaired sperm production [1267-1269]. It is worth noting that both the frequency of gr/gr deletion and its phenotypic expression vary between different ethnic groups, depending on the Y-chromosome background. For example, in some Y haplo-groups, the deletion is fixed and appears to have no negative effect on spermatogenesis. Consequently, the routine screening for gr/gr deletion is still a debated issue, especially in those laboratories serving diverse ethnic and geographic populations. A large multicenter study has shown that gr/gr deletion is a potential risk factor for testicular germ cell tumours [1242]. However, these data need further confirmation in an ethnically and geographically matched case-control study setting. For genetic counselling it is worth noting that partial AZFc deletions, gr/gr and b2/b3, may predispose to complete AZFc deletion in the next generation [1270].

9.3.5.3.1.4 Autosomal defects with severe phenotypic abnormalities and infertility

Several inherited disorders are associated with severe or considerable generalised abnormalities and infertility (e.g., Prader-Willi Syndrome [1271], Bardet-Biedl Syndrome [1272], Noonan's Syndrome, Myotonic dystrophy, dominant polycystic kidney disease [1273, 1274], 5 α -reductase deficiency [1275-1278], etc). Pre-implantation genetic screening (PGS) may be necessary in order to improve the ART outcomes among men with autosomal chromosomal defects [1279, 1280].

9.3.5.4 Sperm chromosomal abnormalities

Sperm can be examined for their chromosomal constitution using FISH both in men with normal karyotype and with anomalies. Aneuploidy in sperm, particularly sex chromosome aneuploidy, is associated with severe damage to spermatogenesis [1207, 1281-1283] and with translocations and may lead to recurrent pregnancy loss (RPL) or recurrent implantation failure [1284]. In a large retrospective series, couples with normal sperm FISH had similar outcomes from IVF and ICSI on PGS. However, couples with abnormal FISH had better clinical outcomes after PGS, suggesting a potential contribution of sperm to aneuploidic abnormalities in the embryo [1285]. In men with sperm aneuploidy, PGS combined with IVF and ICSI can increase chances of live births [1206].

9.3.5.5 Measurement of Oxidative Stress

Oxidative Stress (OS) is considered to be central in male infertility by affecting sperm quality, function, and the integrity of sperm as well [1286]. Oxidative Stress may lead to sperm DNA damage and poorer sperm DNA integrity, which are associated with poor embryo development, miscarriage and infertility [1287, 1288]. Spermatozoa are vulnerable to OS 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 [1289]. However, this data has never been supported by RCTs. Furthermore, there are no standardised testing methods for reactive oxygen species (ROS) and the duration of antioxidant treatments. Although ROS can be measured by various assays (e.g., chemiluminescence), routine measurement of ROS testing should remain experimental until these tests are validated in randomised controlled studies [1290].

9.3.5.6 Outcomes from assisted reproductive technology and long-term health implications to the male and offspring

It is estimated that more than four million babies have been born with ART since the first baby conceived by IVF in 1978 [1291]. As the number of couples undergoing ART has increased [1292, 1293], safety concerns related to ART have been raised. Assisted reproductive technology-conceived offspring have poorer prenatal outcomes, such as lower birth weight, lower gestational age, premature delivery, and higher hospital admissions compared with naturally conceived offspring [1294, 1295]. However, the exact mechanisms resulting in these complications remain obscure. Birth defects have also been associated with children conceived via ART in numerous studies [1296-1298]. Furthermore, a 30%-40% increase of major malformations were linked with ART in meta-analyses [1299-1301]. However, debate still continues as to whether the increased risk of birth defects are related to parental age, ART or the intrinsic defects in spermatogenesis in infertile men [1302-1307].

As for the long-term outcomes, post-natal growth patterns are mostly not associated with ART [1296, 1308, 1309]. However, a number of studies showed that ART children are taller [1310, 1311]. This may be important as there is evidence showing that rapid weight gain during early childhood is linked with higher blood pressure levels in children conceived via ART [1312]. It is also suggested that ART-conceived children have similar

childhood illnesses and hospital services rates as compared with naturally conceived children [1313-1315]. Furthermore, some studies showed an increased risk for retinoblastoma [1316] and hepatoblastoma in children after ART. However, these studies have been challenged with other studies which have not supported these findings [1317]. The current evidence for cancer risk in children conceived with ART is inadequate and further studies are warranted [1318, 1319]. Finally, a number of epigenetic alterations seem to be caused by ART, which might be the molecular basis to a some complex traits and diseases [1320].

9.3.6 *Imaging in the infertile male*

In addition to physical examination, a scrotal US may be helpful in: i) measuring testis volume; ii) assessing testicular anatomy and testicular structure in terms of US patterns, thus detecting signs of testicular dysgenesis often related to an impaired spermatogenesis (e.g., non-homogeneous testicular architecture and microcalcifications) and testis tumours; and, iii) finding indirect signs of obstruction (e.g., dilatation of rete testis, enlarged epididymis with cystic lesions, or absent vas deferens) [1186]. In clinical practice, Prader's orchidometer-derived testis volume is considered a reliable surrogate of US-measured testis volume, is easier to perform and is cost-effective [1185]. Nevertheless, scrotal US has a relevant role in testis 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 testis volume [1185, 1186]. US-patterns of testicular inhomogeneity [1321, 1322] is usually associated with ageing, although it has also been reported in association with testis atrophy and fibrosis [1186]. At present, a diagnostic testicular biopsy is not recommended when testicular inhomogeneity is detected [1321, 1322].

9.3.6.1 *Testicular neoplasms*

Scrotal US is widely used in everyday clinical practice in patients with oligozoospermia or azoospermia, as infertility has been found to be an additional risk factor for testicular cancer [1323, 1324]. In one study, men with infertility had an increased risk of testicular cancer (hazard rate [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) [1325]. Furthermore, in a recent SR infertile men with testicular microcalcification (TM) were found to have an ~18-fold higher prevalence of testicular cancer [1326]. However, the utility of US as a routine screening tool in men with infertility to detect testis cancer remains a matter of debate [1323, 1324].

One issue in undertaking routine screening for testicular neoplasms in this cohort of patients is the risk of overdiagnosis and the increased detection of indeterminate lesions of the testis. These testicular lesions are often detected during the diagnostic work-up of infertile men and are difficult to characterise as 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. However, in a recent study 81 patients with a lesion size < 10 mm on histology were identified and of these, 56 (69%) were benign lesions, although of note one-third were malignant. Overall, 100% of lesions < 5 mm in diameter were benign [1327]. Overall, available data suggest that the smaller the nodule, the less likely that it is malignant [1328], and lesions < 5 mm could be monitored, as they have a low probability of malignancy.

Small hypoechoic/hyperechoic areas may be diagnosed as intra-testicular cysts, focal Leydig cell hyperplasia, fibrosis and focal testis inhomogeneity after previous pathologic conditions. Hence, they require careful periodic US assessment and follow-up, especially if additional risk factors for malignancy are present (i.e., infertility, bilateral testicular microcalcifications, history of cryptorchidism, testicular atrophy, inhomogeneous parenchyma, history of testicular tumour, history of /contralateral tumour) [1186].

In the case of interval growth of a lesion and/or of 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 sonographic abnormality; a hypoechoic lesion was found in 20 patients (14%), hyperechoic lesions were seen in 10 (7%); and, a heterogeneous appearance of the testicular parenchyma was seen in 19 patients (13%). Of 18 evaluable patients, 11 had lesions less than 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 are found to have incidental testicular lesions and negative tumour markers and lesions less than 5 mm, may be observed with serial scrotal US examinations and enlarging lesions or those of greater dimension can be considered for histological biopsy [1329].

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 [1330-1334]. 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 remains controversial, although a number of authors have proposed its value in the intra-operative diagnosis of indeterminate testicular lesions [1335]. Whilst, 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 those men who have severe abnormalities in semen parameters (e.g., azoospermia), a concurrent mTESE can also be performed at the time of diagnostic biopsy (panel recommendations).

In summary, if an indeterminate lesion is detected incidentally on US in an infertile male, a MDT discussion is highly recommended. Based upon the current literature, lesions < 5 mm in size are likely to be benign and serial US and self-examination can be performed. However, men with larger sized lesions (> 5 mm), which are hypoechoic or demonstrate vascularity, may be considered for open US-guided testis biopsy, testis sparing surgery with tumour enucleation for frozen section examination or radical orchidectomy. Therefore, in making a definitive treatment decision for surveillance versus intervention, consideration should be given to the size of the lesion, echogenicity, vascularity and previous history (e.g., cryptorchidism, previous history of germ cell tumour [GCT]). If intervention is to be undertaken in men with severe hypospermatogenesis (e.g., azoospermia), then a simultaneous TESE can be undertaken, along with sperm banking.

9.3.6.2 *Varicocele*

At present, the clinical management of varicocele is still mainly based on physical examination; nevertheless, scrotal color Doppler US is useful in assessing venous reflux and diameter, when palpation is unreliable and/or in detecting recurrence/persistence after surgery [1186]. Furthermore, definitive evidence of reflux and venous diameter may be utilised in the decision process to treat.

9.3.6.3 *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, presence or absence of the epididymis and/or seminal vesicles (SV) (e.g., abnormalities/agenesis). Likewise, TRUS has an important role in assessing obstructive azoospermia (OA) secondary to CBAVD or anomalies related to the ejaculatory ducts obstruction, such as ejaculatory duct cysts, SV dilatation or hypoplasia/atrophy, although retrograde ejaculation should be excluded as a differential diagnosis [1186, 1336].

9.3.7 Recommendations for the diagnostic work-up of male infertility

Recommendations	Strength rating
Include a parallel assessment of the fertility status, including ovarian reserve, of the female partner during the diagnosis and management of the infertile male, since this might determine decision making in terms of timing and therapeutic strategies (e.g., assisted reproductive technology (ART) versus surgical intervention)	Strong
A complete medical history taking, physical examination and semen analysis are the essential components of male infertility evaluation.	Strong
Prader's orchidometer-derived testis volume is a reliable surrogate of ultrasound (US)-measured testis volume in everyday clinical practice.	Weak
Perform semen analyses according to the WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn) indications and reference criteria.	Strong
Perform a full andrological assessment in all men with couple infertility, particularly when semen analysis is abnormal in at least two consecutive tests.	Strong
In cases of oligozoospermia and azoospermia, a hormonal evaluation should be performed, including a serum total testosterone and Follicle Stimulating Hormone FSH/Luteinising Hormone.	Weak
Offer standard karyotype analysis and genetic counselling to all men with azoospermia and oligozoospermia (spermatozoa < 10 million/mL) for diagnostic purposes.	Strong
Do not test for Y-chromosome microdeletions in men with pure obstructive azoospermia as spermatogenesis will be normal.	Strong
Y-chromosome microdeletion testing may be offered in men with sperm concentrations of < 5 million sperm/mL, but should be mandatory in men with sperm concentrations of ≤ 1 million sperm/mL.	Strong
Testicular sperm extraction (any type) should not be attempted in patients with complete deletions that include the aZFa and aZFb regions, since they are a poor prognostic indicator for retrieving sperm at surgery.	Strong
Inform men with Yq microdeletion and their partners who wish to proceed with intracytoplasmic sperm injection (ICSI) that microdeletions will be passed to sons, but not to their daughters.	Strong
In men with structural abnormalities of the vas deferens (unilateral or bilateral absence with no renal agenesis), test the male and his partner for cystic fibrosis transmembrane conductance regulator gene mutations, which should include common point mutations and the 5T allele.	Strong
Provide genetic counselling in all couples with a genetic abnormality found on clinical or genetic investigation and in patients who carry a (potential) inheritable disease.	Strong
For men with Klinefelter Syndrome offer long-term endocrine follow-up and appropriate medical treatment.	Strong
Do not routinely use reactive oxygen species testing in the diagnosis and management of the male partner of an infertile couple.	Weak
Sperm DNA fragmentation testing should be performed in the assessment of couples with recurrent pregnancy loss from natural conception and ART or men with unexplained infertility.	Strong
Perform scrotal ultrasound in patients with infertility, as there is a higher risk of testis cancer.	Weak
A multidisciplinary team discussion concerning invasive diagnostic modalities (e.g., US-guided testis biopsy with frozen section versus radical orchidectomy versus surveillance) should be considered in infertile men with US-detected indeterminate testicular lesions, especially if additional risk factors for malignancy are present.	Weak
Perform transrectal ultrasound if a partial or complete distal obstruction is suspected.	Strong
Consider imaging for renal abnormalities in men with structural abnormalities of the vas deferens and no evidence of cystic fibrosis transmembrane conductance regulator abnormalities.	Strong

9.4 Special Conditions and Relevant Clinical Entities

9.4.1 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 [1337]. Approximately 30% of undescended testes are non-

palpable and may be located within the abdominal cavity. This guideline will only deal with the management of cryptorchidism in adults.

9.4.1.1 Classification

The classification of cryptorchidism is based on the duration of the condition and the anatomical position of the testis. If the undescended testicle has been identified from birth then this is termed congenital whilst the diagnosis of acquired is used in males that have been previously noted to have testicles situated within the scrotum. Cryptorchidism is categorised on whether it is bilateral or unilateral and the location of the testicle (inguinal, intra-abdominal or ectopic).

Studies have shown that treatment of congenital and acquired cryptorchidism results in similar hormone profiles, semen analysis and testicular volumes [1338, 1339]. However, testicular volume and hormone function have been reported to be reduced in adults treated with congenital bilateral cryptorchidism compared to unilateral cryptorchidism [1340].

9.4.1.1.1 Aetiology 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 [1341]. Cryptorchidism has also been linked with maternal gestational smoking [1342] and premature birth [1343].

9.4.1.1.2 Pathophysiological effects in maldescended testes

9.4.1.1.2.1 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 testis [1344]. During the second year, the number of germ cells declines. Early treatment is therefore recommended (surgery should be performed within the subsequent year) to conserve spermatogenesis and hormone production, as well as to decrease the risk for tumours [1345]. Surgical treatment is the most effective. Meta-analyses on the use of medical treatment with GnRH and hCG have demonstrated poor success rates [1346, 1347]. It has been reported that hCG treatment may be harmful to future spermatogenesis therefore, the Nordic Consensus Statement on treatment of undescended testes does not recommend its use on a routine basis [1348]. See also the EAU Guidelines on Paediatric Urology [1349].

There is increasing evidence to suggest that in cases of a unilateral undescended testicle, the contralateral normal descended testicle may also have structural abnormalities, including smaller volume, softer consistency and reduced markers of future fertility potential (spermatogonia/tubule ratio and a dark spermatogonia) [1338, 1350]. This implies that unilateral cryptorchidism may affect the contralateral testis and patients and parents should be counselled appropriately.

9.4.1.1.2.2 Relationship with fertility

Semen parameters are often impaired in men with a history of cryptorchidism [1351]. Early surgical treatment may have a positive effect on subsequent fertility [1352]. In men with a history of unilateral cryptorchidism, paternity is almost equal (89.7%) to that in men without cryptorchidism (93.7%). In men with bilateral cryptorchidism, oligozoospermia can be found in 31% and azoospermia in 42%. In cases of bilateral cryptorchidism, the rate of paternity falls to 35-53% [1353]. 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 [1354].

9.4.1.1.2.3 Germ cell tumours

As a component of the 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 [1355]. 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 [1337]. Orchidopexy performed before the onset of puberty has been reported to decrease the risk of testicular cancer [1356]. 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 [1357]. Therefore all men with a history of cryptorchidism should be warned that they are at increased risk of developing testis cancer and should perform regular testicular self-examination [1358].

9.4.1.2 Disease management

9.4.1.2.1 Hormonal treatment

Human chorionic gonadotropin or GnRH is not recommended for the treatment of cryptorchidism in adulthood. Although some studies have recommended the use of hormonal stimulation as an adjunct to orchidopexy to improve fertility preservation, there is a lack of long-term data and also concerns regarding impairment to spermatogenesis with the use of these drugs [1359].

9.4.1.2.2 Surgical treatment

In adolescence removal of an intra-abdominal testis (with a normal contralateral testis) can be recommended, because of the risk of malignancy [1360]. In adults, with a palpable undescended testis and a normal functioning contralateral testis (i.e., biochemically eugonadal), an orchidectomy may be offered in this setting as there is evidence that the undescended testicle confers a higher risk of GCNIS and future development of GCT [1361] and regular testicular self-examination is not an option in these patients. In those patients with unilateral undescended testis (UDT) and impaired testicular function on the contralateral testis as demonstrated by biochemical hypogonadism and/or impaired sperm production (infertility), an orchidopexy may be offered in this setting to preserve androgen production and fertility if surgically feasible. However, multiple biopsies of the UDT are recommended at the time of orchidopexy to exclude intra-testicular GCNIS as a prognostic indicator of future development of GCT (panel consensus opinion). 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, if surgically feasible and or in patients who place a high utility on fertility preservation [1362]. 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 those cases with long vascular pedicles that enabled scrotal positioning. Post-operative atrophy in staged orchidopexy has been reported in up to 40% of patients [1363]. 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 [1364]).

9.4.1.3 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 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
If undescended testes are corrected in adulthood, perform simultaneous testicular biopsy, for the detection of intratubular germ cell neoplasia <i>in situ</i> (formerly carcinoma <i>in situ</i>).	Strong
Men with unilateral undescended testis and normal hormonal function/spermatogenesis should be offered orchidectomy.	Strong
Men with unilateral or bilateral undescended testis with biochemical hypogonadism and or spermatogenic failure (i.e., infertility) may be offered unilateral or bilateral orchidopexy, if technically feasible.	Weak

9.4.2 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 [1365]. The lifetime risk of TGCT varies between 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 nonseminomas are preceded by GCNIS, and untreated GCNIS will eventually progress to invasive cancer [1366-1368]. There has been a general decline in male reproductive health and an increase in testicular cancer seen in western countries [1369, 1370]. In almost all countries with reliable cancer registries, the incidence of testicular cancer has increased [1258, 1371]. This has been postulated to be related to the so-called TDS, which is a developmental disorder of the testes caused by environmental and/or genetic influences in

pregnancy. As detailed above, the adverse sequelae of TDS include cryptorchidism hypospadias, infertility and an increased risk of testicular cancer [1341]. Endocrine disrupting chemicals have also been associated with sexual dysfunction [1372] and abnormal semen parameters [1373]. These cancers arise from premalignant gonocytes or GCNIS [1374]. Testicular microcalcification, seen on US, can be associated with TGCT and GCNIS of the testes [1326, 1375, 1376].

9.4.2.1 *Testicular germ cell cancer and reproductive function*

Overall, sperm, cryopreservation is considered standard practice in patients with cancer, not only with testicular cancer [1377, 1378]. As such, it is important to stress that all men with cancer must be offered sperm cryopreservation prior to the therapeutic use of gonadotoxic agents or ablative surgery which may impair spermatogenesis or ejaculation (i.e., chemotherapy; radiation therapy; retroperitoneal surgery).

Men with TGCT have decreased semen quality, even before cancer treatment. Azoospermia has been observed in 5-8% of men with TGCT [1379] and oligospermia in 50% [1380]. 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 [1380, 1381]. Semen analysis and cryopreservation is therefore recommended prior to any gonadotoxic cancer treatment and all patients should be offered cryopreservation of ejaculated sperm or sperm extracted surgically (e.g., c/mTESE) if shown to be azoospermic or severely oligozoospermic. Given the fact that a significant number of men with testis cancer at the time of first presentation will have severe semen abnormalities (i.e., severe oligozoospermia/azoospermia) even prior to (any) treatment [1374], it is recommended that men should undergo sperm cryopreservation prior to orchidectomy. As mentioned above, in those who are either azoospermic or severely oligozoospermic this will allow an opportunity to perform TESE prior to further potential gonadotoxic/ablative surgery [1380]. The use of cryopreservation has been demonstrated to be the most cost effective strategy for fertility preservation in patients undergoing potential gonadotoxic treatments [1382, 1383]. In cases of azoospermia, testicular sperm may be recovered to safeguard patient's fertility (Onco-TESE) potential. The surgical principles in Onco-TESE do not differ from the technique of mTESE for men with infertility (e.g., NOA) [1384, 1385]. In this context, referral to a urologist adept in microsurgery is desirable with facilities for sperm cryopreservation.

Rates of under-utilisation of semen analysis and sperm cryopreservation have been reported to be high; resulting in the failure to identify the azoospermic or severely oligozoospermic patient at diagnosis who may eventually benefit from fertility-preserving procedures (e.g., Onco-mTESE at the time of orchidectomy). Therefore, counselling about fertility preservation is a priority and needs to be broached earlier in men with testis cancer [1380]. There are controversial arguments that performing cryopreservation prior to orchidectomy may delay subsequent treatment and have an adverse impact on survival. In this context, orchidectomy should not be unduly delayed if there are no facilities for cryopreservation or there is a potential delay in treatment.

Treatment of TGCT can result in additional impairment of semen quality [1386] and increased sperm aneuploidy up to two years following gonadotoxic therapy [1387]. Chemotherapy is also associated with DNA damage and an increased DNA fragmentation rate [1388]. However, sperm aneuploidy levels will often decline to pre-treatment levels 18-24 months post treatment [1387] and several studies reviewing the offspring of cancer survivors has not shown a significant increased risk of genetic abnormalities in the context of chemotherapy and radiotherapy treatment [1389].

In addition to spermatogenic failure, patients with TGCT have Leydig cell dysfunction, even in the contralateral testis [1390]. The risk of hypogonadism may therefore be increased in men treated for TGCT. 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. Men who have had TGCT and have low normal androgen levels should be advised that they may be at increased risk of developing hypogonadism, as a result of an age-related decrease in testosterone production and could potentially develop MetS; there is no current long term data supporting this. The risk of hypogonadism is increased in the survivors of testis cancer and serum testosterone levels should be evaluated during the management of these patients [1391]. However, this risk is greatest at six to twelve months post-treatment and suggests that there may be some improvement in Leydig cell function post treatment and it is therefore reasonable to delay initiation of TRT, until the patient shows continuous signs or symptoms of testosterone deficiency [1366]. The risk of low libido and ED is also increased in TGCT patients [1392]. Furthermore, patients treated for TGCT are also at increased risk of CVD [1388]. Therefore, patients may require a MDT approach and in this context, survivorship programmes incorporating a holistic view of patients psychological, medical and social needs could be beneficial to the patient. In those patients who place a high utility on fertility potential, the use of TRT in men

with symptoms suggestive for TDS will need to be balanced with worsening spermatogenesis. In these patients consideration can be given to the use of SERM (e.g., clomiphene) or gonadotrophin analogues (e.g., hCG), although these are off label treatments in this particular clinical setting.

9.4.2.2 Testicular microcalcification

Microcalcification inside the testicular parenchyma can be found in 0.6-9% of men referred for testicular US [1393, 1394]. Although the true incidence of testicular microcalcification (TM) in the general population is unknown, it is most probably rare. Ultrasound findings of TM have been associated in men with TGCT, cryptorchidism, infertility, testicular torsion and atrophy, Klinefelter's syndrome, hypogonadism, male pseudohermaphroditism and varicocele [1395]. The incidence reported seems to be higher with high-frequency US machines [1396]. The relationship between TM and infertility is unclear, but may relate to dysgenesis of the testes, 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% [1397-1399]. A recent SR 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; $p < 0.0001$) [1326].

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 [1400]. 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 will require testicular biopsies in large series of men without signs of TGCT with or without risk factors for TGCT. However, the clinician and patient should be reassured that testicular cancer will not develop in the majority of men with asymptomatic TM [1376] and available data indicates that only men in whom TM is found by US, and who have an increased risk of TGCT, should be offered testicular biopsy to exclude GCNIS. Men potentially at high-risk of harbouring or developing GCNIS includes men with infertility, atrophic testes, undescended testes, a history of TGCT, and contralateral TM and it has been suggested that men with these risk factors could be offered testicular biopsy [1370, 1375]. The normal mean testicular volume is estimated to range between 12-30 mL and less than 12 mL is considered small [1393]. 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 [1376], whilst there are only a few studies showing a further increase in GCNIS with TM in the context of cryptorchidism [1370, 1394, 1401]. A useful algorithm has been proposed [1370] 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. With the lack of availability of large cohort studies, these recommendations must be treated with caution given the risk of overtreatment (i.e. biopsy) in these patients.

Decastro *et al.* [1402] suggested that testicular cancer will not develop in the majority of men with TM (98.4%) during a five-year follow-up. As such, an extensive screening program would only benefit men at significant risk. In this context it would be prudent to advise those patients with TM and risk factors for developing 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 [1395]. As testicular atrophy and infertility have an association with testicular cancer, some authors recommend biopsy or follow-up US if TM is seen [1370]. However, the majority of patients who are azoospermic will be undergoing therapeutic biopsy (i.e. 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 those patients with incidental TM, the risk of GCNIS will be low and a logical approach would be to instruct patients to perform regular testicular self-examination.

9.4.2.3 Recommendations for germ cell malignancy and testicular microcalcification

Recommendations	Strength rating
Men with testicular microcalcification (TM) should learn to perform self-examination even without additional risk factors, as this may result in early detection of testicular germ cell tumour (TGCT).	Weak
Do not perform testicular biopsy, follow-up scrotal ultrasound, measure biochemical tumour markers, or abdominal or pelvic computed tomography, in men with isolated TM without associated risk factors (e.g., infertility, cryptorchidism, testicular cancer, and atrophic testis).	Strong
Testicular biopsy may be offered in infertile men with TM, who belong to one of the following higher risk groups: spermatogenic failure (infertility), bilateral TM, atrophic testes (less than 12 mL), history of undescended testes and TGCT.	Weak
If there are suspicious findings on physical examination or ultrasound in patients with TM with associated lesions, perform inguinal surgical exploration with testicular biopsy or offer orchidectomy after multidisciplinary meeting and discussion with the patient.	Strong
Men treated for TGCT are at increased risk of developing hypogonadism, sexual dysfunction and cardiovascular (CV) risk. Men should be managed in a multidisciplinary team setting with a dedicated late effects clinic.	Weak
Sperm cryopreservation should be performed prior to planned orchidectomy, since men with testis cancer may have significant semen abnormalities (including azoospermia).	Weak
Men with testis cancer and azoospermia or severe abnormalities in their semen parameters may be offered onco-testicular sperm extraction at the time of radical orchidectomy.	Weak

9.4.3 Varicocele

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

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

9.4.3.1 Classification

The following classification of varicocele [1176] 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 studies).
- Grade 1: palpable during Valsava manoeuvre.
- Grade 2: palpable at rest.
- Grade 3: visible and palpable at rest.

Overall, the prevalence varicocele in one study was 48%. Of 224 patients, 104 had unilateral, 120 had bilateral varicoceles; 62 (13.30%) were grade 3, 99 (21.10%) were grade 2, and 63 (13.60%) were grade 1 [1403, 1404]. Worsening semen parameters are associated with a higher grade of varicocele and age [1405, 1406].

9.4.3.2 Diagnostic evaluation

The diagnosis of varicocele is made by physical examination and if this examination is inconclusive scrotal Doppler US is indicated [1176, 1407]. A number of radiological thresholds for venous diameter on US are used to diagnose significant varicoceles, although multiple spermatic veins > 3 mm in the upright position and during the Valsalva manoeuvre correlate with the presence of a clinically significant varicocele [1408a].

9.4.3.3 Basic considerations

9.4.3.3.1 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 (1,3,7,9). 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% [1176, 1409].

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 OS and DNA damage [1409].

A meta-analysis showed that improvements in semen parameters are usually observed after surgical correction in men with abnormal parameters [1408b]. Varicocelectomy can also reverse sperm DNA damage and improve OS levels [1409, 1410].

9.4.3.3.2 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 showed 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 [1411-1415]. Moreover, pain resolution after varicocelectomy occurs in 48-90% of the patients [1416].

In RCTs varicocele repair in men with a subclinical varicocele was found to be ineffective in increasing the chances of spontaneous pregnancy [1417]. Also, in randomised studies that included mainly men with normal semen parameters no benefit was found in favour of treatment over observation. 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 for spontaneous pregnancy [1418]. In two recent meta-analysis of RCTs comparing treatment to observation in men with a clinical varicocele, oligozoospermia and otherwise unexplained infertility, the analyses favoured treatment, with a combined OR of 2.39-4.15 (95% CI 1.56 to 3.66) (95% CI, 2.31 to 7.45) [1415, 1418]. A recent meta-analysis has reported that varicocelectomy may improve outcomes following ART in oligozoospermic men with an OR of 1.69 (95% CI 0.95 to 3.02) [1419].

9.4.3.3.3 Prophylactic varicocelectomy

In adolescents with a varicocele, there is a significant risk of over-treatment since most adolescents with a varicocele will have no problem achieving pregnancy later in life [1420]. 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 [1421, 1422].

More novel considerations for varicocelectomy are patients with NOA, hypogonadism and DNA damage are described below:

Varicocelectomy and NOA

A number of 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 men led to sperm in the ejaculate post-operatively with an increase in ensuing natural or assisted pregnancies [1423]. There were further beneficial effects on sperm retrieval rates and ICSI outcomes. 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, sperm retrieval rates (SRR) 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 postoperative ejaculate. These findings indicate that varicocelectomy in patients with NOA and clinical varicocele is associated with improved SRR and overall 44% of the treated men will have sperm in the ejaculate and may avoid sperm retrieval. 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 [1413].

Varicocelectomy and hypogonadism

Evidence would also suggest that men with clinical varicoceles who are hypogonadal may benefit from varicocele intervention. In one meta-analysis studying the efficacy of varicocele intervention by comparing the pre-operative and post-operative serum testosterone, 712 patients were included for analysis. 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, $p < 0.00001$, $I^2 = 0.0\%$) compared with their pre-operative levels. In an analysis of surgery versus untreated control results showed that mean testosterone among hypogonadic patients increased by 105.65 ng/dL (95% CI: 77.99-133.32), favouring varicocelectomy [1424]. 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 TRT in this setting. Whilst, varicocelectomy may be offered in 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 randomised controlled studies.

9.4.3.3.4 Varicocelectomy for assisted reproductive technology and for raised DNA fragmentation

Varicocelectomy can improve sperm DNA integrity, with a mean difference of -3.37% (95% CI, -2.65 to -4.09) [1425]. There is now increasing evidence that varicocele treatment may improve DNA fragmentation

and outcomes from ART [1419, 1420]. As a consequence, more recently it has been suggested that the indications for varicocele intervention should be expanded to also 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 [1426] and exclusion of other causes of raised DNA fragmentation [1420, 1427]. The dilemma is whether varicocele treatment is indicated in men with raised DNA fragmentation and normal semen parameters.

In a meta-analysis study 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, $I^2 = 25\%$) and live birth rates (OR = 2.17, 95% CI: 1.55-3.06, $I^2 = 0\%$) in the varicocelectomy group compared to the group subjected to ICSI without previous varicocelectomy. A further study [1419] evaluated the effects of varicocele repair and its impact on pregnancy and live birth rates in infertile couples undergoing ART in male partners with oligospermia or azoospermia and a varicocele. In 1,241 patients, a meta-analysis demonstrated that varicocelectomy improved live birth rates for the oligospermic (OR = 1.699) men and combined oligospermic/azoospermic groups (OR = 1.761). Pregnancy rates were higher in the azoospermic group (OR = 2.336) and combined oligospermic/azoospermic groups (OR = 1.760). Live birth rates were higher for patients undergoing IUI after intervention (OR = 8.360).

9.4.3.4 Disease management

Several treatments are available for varicocele (Table 34). Current evidence indicates that microsurgical varicocelectomy is the most effective method among the different varicocelectomy techniques [1420, 1428]. Unfortunately, there are no large prospective RCTs comparing the efficacy of the various interventions for varicocele. However, microsurgical repair results in fewer complications and lower recurrence rates compared to the other techniques based upon case series [1429]. This procedure, however, requires microsurgical training. The various other techniques are still considered viable options, although recurrences and hydrocele formation appear to be higher [1430].

Radiological techniques (sclerotherapy and embolisation) are minimally invasive widely used approaches, although higher recurrence rates compared to microscopic varicocelectomy have been reported (4-27%) [1409]. Robot-assisted varicocelectomy has similar success rate compared to the microscopic varicocelectomy technique, although larger prospective randomised studies are needed to establish the most effective method [1431-1433].

Table 34: Recurrence and complication rates associated with treatments for varicocele

Treatment	Ref.	Recurrence/ Persistence %	Overall complications	Specific Complications
Antegrade sclerotherapy	[1434, 1435]	5-9	Hydrocele (5.5%), haematoma, infection, scrotal pain, testicular atrophy, epididymitis	Technical failure 1-9%, left-flank erythema.
Retrograde sclerotherapy	[1436, 1437]	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 embolisation	[1436, 1438]	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
<i>Open operation</i>				
Scrotal operation		-	Testicular atrophy, arterial damage with risk of devascularisation and testicular gangrene, scrotal haematoma, post-operative hydrocele	
Inguinal approach	[1439, 1440]	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	[1428, 1441]	15-29	Hydrocele (5-10%), testicular atrophy, scrotal edema	External spermatic vein ligation failure
Microsurgical inguinal or subinguinal	[1429, 1439, 1442, 1443]	0.4	Hydrocele (0.44%), scrotal haematoma	
Laparoscopy	[1406, 1428, 1429, 1444, 1445]	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; pneumoscrotum; peritonitis; post-operative pain in right shoulder (due to diaphragmatic stretching during pneumoperitoneum)

9.4.3.5 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 reduction in fertility.	2a
Although the treatment of varicocele in adolescents may be effective, there is a significant risk of over-treatment: 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
Although there are no prospective randomised studies evaluating this, meta-analysis suggest that varicocele repair may lead to sperm appearing in the ejaculate in 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 DNA fragmentation and intervention has been shown to reduce DNA fragmentation	2a

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

9.4.4 Male accessory gland infections and infertility

9.4.4.1 Introduction

Infections of the male urogenital tract are potentially curable causes of male infertility [1446-1448]. The WHO considers urethritis, prostatitis, orchitis and epididymitis to be male accessory gland infections (MAGIs) [1446]. The effect of symptomatic or asymptomatic infections on sperm quality is contradictory [1449]. A SR assessing the relationship between sexually transmitted diseases, such as *Chlamydia trachomatis*, genital mycoplasmas, *Neisseria gonorrhoeae*, *Trichomonas vaginalis* and viral infections, and infertility was unable to draw a strong association between STDs and male infertility due to the limited quality of reported data [1450].

9.4.4.2 Diagnostic evaluation

9.4.4.2.1 Semen analysis

Semen analysis (see Section 9.3.2) clarifies whether the prostate is involved as part of a generalised MAGI and provides information regarding sperm quality. In addition, leukocyte analysis allows differentiation between inflammatory and non-inflammatory chronic pelvic pain syndrome (CP/CPPS) (NIH IIa versus NIH 3b National Institutes of Health classification for CP/CPPS).

9.4.4.2.2 Microbiological findings

After exclusion of UTI (including urethritis), $> 10^6$ peroxidase-positive white blood-cells (WBCs) per millilitre of ejaculate indicate an inflammatory process. In these cases, a semen culture or PCR analysis should be performed for common urinary tract pathogens. A concentration of $> 10^3$ CFU/mL urinary tract pathogens in the ejaculate is indicative of significant bacteriospermia [1451]. 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 [1452]. The ideal diagnostic test for isolating *C. trachomatis* in semen has not yet been established [1453], but the most accurate method is PCR analysis [1454-1456].

Historical data showed that *Ureaplasma urealyticum* is pathogenic only in high concentrations ($> 10^3$ CFU/mL ejaculate). Less than 10% of samples analysed for ureaplasma exceeded this concentration [1457]. Normal colonisation of the urethra hampers the significance of mycoplasma-associated urogenital infections, using samples such as the ejaculate [1458].

A recent meta-analysis indicates that *Ureaplasma parvum* and *Mycoplasma genitalium* are not associated with male infertility, but a significant relationship existed between *Ureaplasma urealyticum* (OR 3.03 95% CI: 1.02-8.99) and *Mycoplasma hominis* (OR 2.8; 95% CI: 0.93- 3.64) [1459].

The prevalence of Human papilloma virus (HPV) in the semen ranges from 2-31% in the general population and is higher in men with unexplained infertility (10-35,7%) [1460,1461]. Recent systematic reviews have reported an association between male infertility, poorer pregnancy outcomes and semen HPV positivity [1462-1464]. 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 HSV-negative infertile men [1449]. However, it is unclear if anti-viral therapy improves fertility rates in these men.

9.4.4.2.3 White blood cells

The clinical significance of an increased concentration of leukocytes in the ejaculate is controversial [1465]. 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 [1466]. 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 [1467, 1468]. 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 seminal analysis. There is currently no evidence that treatment of leukocytospermia alone without evidence of infective organisms will improve conception rates [1469].

9.4.4.2.4 Sperm quality

The deleterious effects of chronic prostatitis (CP/CPPS) on sperm density, motility and morphology has been demonstrated in a recent SR based on case-controlled studies [1470]. Both *C. trachomatis* and *Ureoplasma spp.* can cause decreased sperm density, motility, altered morphology and increased DNA damage. HPV can also induce changes in sperm density, motility and DNA damage [1460, 1461]. *Mycoplasma spp.* can cause decreased motility and development of antisperm antibodies [1449].

9.4.4.2.5 Seminal plasma alterations

Seminal plasma elastase is a biochemical indicator of polymorphonuclear lymphocyte activity in the ejaculate [1448, 1471, 1472]. 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 [1473-1475].

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 [1476]. However, elevated cytokine levels do not depend on the number of leukocytes in expressed prostatic secretion (EPS) [1477].

9.4.4.2.6 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; the seminal plasma concentrations of these factors are usually altered during infection and inflammation. However, they are not recommended as diagnostic markers for MAGIs [1478].

9.4.4.2.7 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, the levels of ROS in infertile patients with asymptomatic *C. trachomatis* and *M. hominis* in the semen were low, making it difficult to draw any firm conclusions [1479]. Chronic urogenital infections are also associated with increased leukocyte numbers [1480]. However, their biological significance in prostatitis remains unclear [1448].

9.4.4.2.8 Disease management

Treatment of CP/CPPS is usually targeted at relieving symptoms [1481, 1482]. The indications and aims of therapy are:

- reduction or eradication of micro-organisms in prostatic secretions and semen;
- normalisation of inflammatory (e.g., leukocytes) and secretory parameters;
- improvement of sperm parameters associated with fertility impairment [1483].

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 [1483], there is no evidence that treatment of CP/CPPS increases the probability of natural conception [1448, 1484].

Asymptomatic presence of *C. trachomatis* and *M. hominis* in the semen can be correlated to impaired sperm quality, which recovers after antibiotic treatment. However further research is required to confirm these findings [1479].

9.4.4.3 Epididymitis

Inflammation of the epididymis causes unilateral pain and swelling, usually with acute onset. Among sexually active men < 35 years of age, epididymitis is most often caused by *C. trachomatis* or *N. gonorrhoea* [1485, 1486]. Sexually transmitted epididymitis is usually accompanied by urethritis. Non-sexually transmitted epididymitis is associated with urinary tract infection and occurs more often in men aged > 35 years [1487].

9.4.4.3.1 Diagnostic evaluation

9.4.4.3.1.1 Ejaculate analysis

Ejaculate analysis according to WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn) criteria, may indicate persistent inflammatory activity. Transient reductions in sperm counts and progressive motility can be observed [1485, 1488, 1489]. 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 Chapter 9.3.2).

9.4.4.3.1.2 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 [1490].

9.4.4.4 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

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

9.5 Non-Invasive Male Infertility Management

9.5.1 Idiopathic male infertility and OATS

Oligo-astheno-teratozoospermia (OAT) is a clinical condition, with a reduced number of spermatozoa in the ejaculate, which is also characterised by a reduced motility and morphology; often referred to as OAT syndrome (OATs). Several conditions can cause OATs, although the aetiology may be unknown in a significant number of cases [73, 1324].

9.5.2 Empirical treatments

9.5.2.1 Life-style

Studies suggest that environmental and lifestyle factors may contribute to idiopathic infertility acting additively on a susceptible genetic background [73, 1324]. Hence, lifestyle improvement can have a positive effect on sperm parameters (see below).

9.5.2.1.1 Weight loss

Few authors have investigated the role of weight loss on male fertility outcomes. Non-controlled studies have suggested that weight loss can result in improved sperm parameters [73, 1491, 1492]. However, data derived from RCTs are more conflicting. In particular, a meta-analysis including a total of 28 cohort studies and 1,022 patients, documented that bariatric surgery had no effects in improving sperm quality and function in morbidly obese men [1493]. Data on ART outcomes are lacking. However, it is important to recognise that weight loss is able to improve obesity-related secondary hypogonadism which may result in better outcomes in couples seeking medical care for infertility and is important for the general health of the male partner [1491, 1493].

9.5.2.1.2 Physical activity

Regular physical activity is recommended by the WHO in order to prevent and reduced the risk of several long-term chronic diseases [1494]. A recent meta-analysis has documented that moderate-intensity (20-40 METs-h/week) or even high-intensity (40-80 METs-h/week) recreational physical activity can result in better semen parameters [1495]. In addition, similar to what is observed from weight loss improvements in hormonal profile have also been reported [1496].

9.5.2.1.3 Smoking

Epidemiological data has indicated that about one in three men of reproductive age smokes, with the highest prevalence observed in Europe among all the WHO regions [1497]. Data derived from a large meta-analysis including twenty studies and 5,865 participants has clearly documented a negative association between smoking and sperm parameters [1497]. Experimental studies performed in rats showed that nicotine has a dose-dependent deleterious effect on the sperm, which can be improved by nicotine cessation [1498]. Data in men are lacking and only one case report has indicated an improvement of sperm parameters after a three months smoking cessation program [1499]. Similar data have been reported in a recent non-controlled study, which showed a possible benefit on ART after the male partner stopped smoking [1500].

9.5.2.1.4 Alcohol consumption

Data derived from a recent meta-analysis including fifteen cross-sectional studies and 16,395 men suggested that moderate alcohol did not adversely affect semen parameters whereas higher alcohol intake can result in a detrimental effect on male fertility [1501]. Similar to what has been reported for weight loss, however, heavy chronic ethanol consumption (defined as > two drinks per day [1502]) can reduce testosterone levels which can be restored by alcohol cessation [1503].

9.5.2.2 Antioxidant treatment

Inflammation is a positive reaction of the human body to overcome potential noxious stimuli. However, chronic inflammation can induce several negative biochemical and metabolic effects contributing to the development of several medical conditions. Oxidative stress (OS) is considered one of the most important contributing factors in the pathogenesis of idiopathic infertility. ROS, the final products of OS, can impair sperm function acting at several levels including plasma membrane lipid peroxidation and which can affect sperm motility, the acrosome reaction and chromatin maturation leading to increased DNA fragmentation [1504]. Accordingly, seminal levels of ROS have been negatively associated with ART outcomes [1505]. Despite this, evidence for the role of antioxidant therapy in male patients with infertility is still conflicting. In a meta-analysis Cochrane Data Base Systemic Review 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 [1506]. Similar results were also reported in the most recent meta-analysis including 61 studies with a total population of 6,264 infertile men, aged between 18 and 65 year [1507]. However, all the aforementioned studies also recognised important limitations. In particular, data were derived

from low-quality RCTs with serious risk of bias due to poor methods of reporting randomisation, failure to report on the clinical outcomes including live birth rate and clinical pregnancy rate, high attrition rates, and also imprecision due to often low event rates and small overall sample sizes [1507]. In addition, no clear conclusion regarding the specific antioxidants to use or and/or therapeutic regimes for improving sperm parameters and pregnancy rate were possible [1507].

9.5.2.3 Selective oestrogen receptor modulators (SERMs)

Selective oestrogen receptor modulators (SERMs) have been advocated as a possible empiric treatment in male idiopathic infertility. The proposed mechanism of action is based on the activity of these compounds to block oestrogen receptors at the level of the hypothalamus, which results in stimulation of GnRH secretion leading to an increase in pituitary gonadotropin release. The latter effect, by stimulating spermatogenesis, represents the rational basis for SERM administration to patients with reduced sperm number [1508]. In an initial meta-analysis including eleven RCTs, in which only five were placebo-controlled, it was concluded that SERMs were not associated with an increased pregnancy rate in the 459 patients analysed [1509]. In a subsequent Cochrane review published one year later, these findings were confirmed, in a larger number of studies (n=10 and 738 men), although positive effects on hormonal parameters were documented. More recently, Chua *et al.* meta-analysed data derived from eleven RCTs showing that the use of SERM was associated with a statistically significant increased pregnancy rate [1510]. In addition, a significant improvement in sperm parameters and hormonal parameters were detected. Similar results were confirmed in the latest updated meta-analysis including sixteen studies [1508]. However, it should be recognised that the quality of the papers included is low and only a few studies are 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 SERM are under reported.

9.5.2.4 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 estradiol and estrone, respectively. Estradiol negatively feeds back on the hypothalamus and pituitary to reduce gonadotropic secretions, ultimately affecting spermatogenesis. In this context, 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 [1511-1514]. Aromatase activity has been associated with male infertility characterised by testicular dysfunction with low serum testosterone and/or testosterone to estradiol ratio. In this context, Aromatase inhibitors (AIs) have been reported to increase endogenous testosterone production and improve spermatogenesis in the setting of infertility as an off-label option for treatment [1515]. Either steroidal (testolactone) or non-steroidal (anastrozole and letrozole) AIs were found to statistically 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 [1513, 1515].

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

9.5.3 Hormonal therapy

9.5.3.1 Gonadotrophins

Follicle Stimulating Hormone is primarily involved in the initiation of spermatogenesis and testicular growth during puberty. The role of FSH post puberty has not been clearly defined. Luteinising Hormone stimulates testosterone production in the testes, but due to its short half-life is not suitable for clinical use. Human Chorionic Gonadotrophin acts in a similar manner to LH and can be used pharmacologically to stimulate testosterone release in men with failure of their hypothalamic-pituitary axis. Human Chorionic Gonadotrophin

can adequately stimulate spermatogenesis in men whom have developed hypopituitarism after a normal puberty. Therefore, the treatment of men with secondary hypogonadism depends on whether or not they developed hypothalamic-pituitary failure before or after puberty [5].

9.5.3.2 Secondary Hypogonadism

(a) Pre-Pubertal-Onset

Congenital causes resulting in low gonadotropin production are associated with testicular size < 4 mL and/or cryptorchidism. Testes size of < 4 mL occurs when they have not been exposed to any gonadotropins at all. These conditions require combination therapy with both hCG and FSH with subcutaneous administration or GnRH by pulsed delivery using a subcutaneous pump [1516]. However, GnRH treatment requires a pulsatile secretion using specific devices for either intravenous or subcutaneous administration, which may limit patient compliance. Moreover, GnRH therapy should be limited to subjects with a residual pituitary gonadotropic activity [5].

As for the type of gonadotropin treatment, it is usual to commence hCG first and titrate the dose to achieve testosterone levels within the normal physiological range. However, FSH can be given first or in combination with hCG [105]. Human Chorionic Gonadotrophin is given twice weekly and in patients with congenital secondary hypogonadism in high dose, commencing at 1,000 IU twice weekly. Testosterone levels can be assayed every two weeks with dosage increases until ideally mid-range testosterone is achieved. Dose increases can be to 2,000 IU, 3,000 IU, 4,000 IU and 5,000 IU all two to three times a week, until normal testosterone levels are achieved [1517-1520]. Failure to achieve normal testosterone status at the high dose would indicate that primary testicular failure is present, probably as a result of cryptorchidism or failure of testicular development. Human Chorionic Gonadotrophin is also used to stimulate testicular descent into the scrotum in subjects with cryptorchidism. Once the hCG dose giving a normal level testosterone is established with the implication that intra-testicular testosterone has occurred FSH 75-150 IU three times per week subcutaneously should be commenced. Usually the higher 150 IU dose three times weekly is needed to be successful in men with testes size < 4mL. The trophic response of the testes to FSH is variable in these patients and it may range from no effect to achieving testicular sizes of 12-15 mL [1521]. A trophic response is usually an indication of an increase in spermatogenesis. The production of new spermatogenesis may be evident after three months of FSH therapy, but could occur even up to eighteen months of treatment [1519-1521]. A low baseline sperm concentration does not indicate a poor response to gonadotropin therapy [1522]. Semen analysis can be assessed at three monthly intervals. These patients can be fertile with low sperm counts much less than 20 million/mL as there is a high proportion of motile sperm. Follicle-stimulating hormone SH therapy prior to GnRH is also effective in stimulating testicular growth and fertility in men with congenital hypogonadotropic hypogonadism [1523]. A larger initial testicular volume is the best prognostic factor for induction of successful spermatogenesis [1524].

(b) Post-Pubertal Onset Secondary

If secondary hypogonadism develops after puberty, hCG alone is usually required first to stimulate spermatogenesis. Doses of subcutaneous hCG required may be lower than those used in individuals with pre-pubertal onset; therefore, a starting dose of 250 IU twice weekly is suggested, and if normal testosterone levels are reached, hCG doses may be increased up to 2,000 IU twice weekly as per pre-pubertal onset above. 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, a combination therapy with FSH and hCG can be administered from the beginning of treatment, promoting better outcomes in men with secondary hypogonadism [105]. No difference in outcomes have been observed when urinary-derived, highly purified FSH was compared to recombinant FSH [105].

Greater baseline testicular volume is a good prognostic indicator for response to gonadotrophin treatment [1524]. Data had suggested that previous testosterone therapy could negatively impact on gonadotropins treatment outcomes in men with secondary hypogonadism [1524]. However, this observation had been subsequently refuted by a meta-analysis which did not confirm a real negative role of testosterone therapy in terms of future fertility in this specific setting of men [105].

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 a drug which causes the condition. Dopamine agonists used include bromocriptine, cabergoline and quinagolide.

9.5.3.3 Primary Hypogonadism

There is no substantial evidence that gonadotrophin therapy has any beneficial effect in the presence of classical testicular failure. Likewise, there is no data to support the use of other hormonal treatments (including SERMs or AIs) in the case of primary hypogonadism to improve spermatogenesis [74, 1525].

9.5.3.4 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). It has also been reported that FSH may improve sperm DNA fragmentation rates as well as ameliorating AMH and inhibin levels [1526-1529]. High-dose FSH therapy is more effective in achieving a testicular response than lower doses. A Cochrane Database Systemic 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 to either placebo or no treatment. However, no significant difference among groups was observed when ICSI or IUI were considered [1530]. In a more recent meta-analysis including fifteen trials with more than 1,200 patients, similar findings after FSH treatment were observed in terms of both spontaneous pregnancies and pregnancies after ART [1531]. A further study showed that in azoospermic men undergoing TESE-ICSI there were improved sperm retrieval rates and higher pregnancy and fertilisation rates in men treated with FSH compared to non-treated subjects [1532]. In men with NOA, the combination of hCG/FSH therapy has in only one study been shown to increase sperm retrieval rates [1533]. Human Chorionic Gonadotrophin alone prior to TESE in NOA has not been found to have any benefit on sperm retrieval rates [1534].

9.5.3.5 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. If after this interval the condition persists, then hCG without or in combination with FSH as an alternative to clomiphene can be used to try and stimulate spermatogenesis [1535].

9.5.3.6 Recommendations for treatment of male infertility with hormonal therapy

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

9.6 Invasive Male Infertility Management

9.6.1 Obstructive azoospermia

Obstructive azoospermia is the absence of spermatozoa in the sediment of a centrifuged sample of ejaculate due to obstruction [1536]. Obstructive azoospermia is less common than NOA and occurs in 20-40% of men with azoospermia [1537, 1538]. Men with OA usually have a normal FSH, testes of normal size and epididymal enlargement [1539]. Of clinical relevance, men with late maturation arrest may present with normal gonadotrophins and testis size and may be only be distinguished from OA at the time of surgical exploration.

The vas deferens may be absent bilaterally (CBAVD) or unilaterally (CUAVD). Obstruction in primary infertile men is more frequently present at the epididymal level.

9.6.1.1 Classification of obstructive azoospermia

9.6.1.1.1 Intratesticular obstruction

Intratesticular obstruction occurs in 15% of men with OA [1540]. Congenital forms are less common than acquired forms (post-inflammatory or post-traumatic) (Table 35).

9.6.1.1.2 Epididymal obstruction

Epididymal obstruction is the most common cause of OA, affecting 30-67% of azoospermic men [1540-1543]. Congenital epididymal obstruction usually manifests as CBAVD, which is associated with at least one mutation of the CF gene in 82% of cases [1543]. Other congenital forms of epididymal obstruction include chronic sinu-pulmonary infections (Young's syndrome) [1544]. Acquired forms secondary to acute (e.g., gonococcal) and subclinical (e.g., chlamydial) epididymitis are most commonly due to infections [1545, 1546]. Other causes may be trauma or surgical intervention (Table 35) [1547, 1548].

9.6.1.1.3 Vas deferens obstruction

Vas deferens obstruction is the most common cause of acquired obstruction following vasectomy (Table 35) [1545]. Approximately 2-6 % of these men request vasectomy reversal (see section from EAU Guidelines on Male Infertility 2019 for this topic). Vasal obstruction may also occur after hernia repair [1549, 1550]. The most common congenital vasal obstruction is CBAVD, often accompanied by CF. Unilateral agenesis or a partial defect is associated with contralateral seminal duct anomalies or renal agenesis in 80% and 26% of cases, respectively [1245].

9.6.1.1.4 Ejaculatory duct obstruction

Ejaculatory duct obstruction is found in 1-5% of cases of OA and is classified as either cystic or post-inflammatory or calculi of one or both ejaculatory ducts (Table 35) [1380, 1551]. Cystic obstructions are usually congenital (i.e., Mullerian duct cyst or urogenital sinus/ejaculatory duct cysts) and are typically midline. In urogenital sinus abnormalities, one or both ejaculatory ducts empty into the cyst [1552], while in Mullerian duct anomalies, the ejaculatory ducts are laterally displaced and compressed by the cyst [1553]. Paramedian or lateral intraprostatic cysts are rare [1554]. Post-inflammatory obstructions of the ejaculatory duct are usually secondary to urethroprostatitis [1555]. Congenital or acquired complete obstructions of the ejaculatory ducts are commonly associated with low semen volume, decreased or absent seminal fructose, and acidic pH. The seminal vesicles (anterior-posterior diameter > 15 mm) and ejaculatory duct (> 2.3 mm in width) are usually dilated [1551, 1555-1557].

9.6.1.1.4.1 Functional obstruction of the distal seminal ducts

Functional obstruction of the distal seminal ducts might be attributed to local neurogenic dysfunction [1558]. This abnormality is often associated with urodynamic dysfunction. Impaired sperm transport can be observed as idiopathic or due to spinal cord injury, multiple sclerosis, retroperitoneal lymph node dissection, pelvic surgery and selective serotonin re-uptake inhibitors (SSRI), α -blockers and typical antipsychotic medication [1559].

Table 35: Causes of obstruction of the genitourinary system

Epydidimis
Infection (acute/chronic epididymitis)
Trauma
Post-surgical iatrogenic obstruction (i.e., MESA; hydrocelectomy; 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; herniorrhaphy)
Congenital unilateral (CUAVD) or bilateral absence of the vas deferens (CBAVD)
Ejaculatory ducts
Cysts (Mullerian utricular; prostatic; seminal vesicular)
Infection (acute/chronic epididymitis)

Traumatic
Postsurgical iatrogenic obstruction
Functional obstruction
Idiopathic/acquired local neurogenic dysfunction

9.6.1.2 Diagnostic evaluation

9.6.1.2.1 Clinical history

Clinical history taking should follow the investigation and diagnostic evaluation of infertile men (See section 10.3). Risk factors for obstruction include prior surgery, iatrogenic injury during inguinal herniorrhaphy, orchidopexy or hydrocelectomy.

9.6.1.2.2 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.

9.6.1.2.3 Semen analysis

Azoospermia means the inability to detect spermatozoa after centrifugation at $\times 400$ magnification. At least two semen analyses must be carried out [1536, 1560] (see section 10.3). When semen volume is low, 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.

9.6.1.2.4 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 [1561].

9.6.1.2.5 Genetic Testing

Inability to palpate the vas on one or both sides should raise concern for a CFTR mutation. Any patient with unilateral or bilateral absence of the vas deferens or seminal vesicle agenesis should be offered CFTR testing [1562].

9.6.1.2.6 Testicular biopsy

Testicular biopsy must be combined with TESE for cryopreservation. Although studies suggest that a diagnostic or isolated testis biopsy [1563] is the most important prognostic predictor of spermatogenesis and sperm retrieval, the panel recommends not to perform testis biopsies (including fine needle aspiration [FNA]) without performing simultaneously a therapeutic sperm retrieval, as this will require a further invasive procedure after biopsy. Furthermore, even patients with extremes of spermatogenic failure (e.g., Sertoli Cell Only syndrome [SCOS]) may harbour focal areas of spermatogenesis [1564, 1565].

9.6.1.3 Disease management

Sperm retrieval

9.6.1.3.1 Intratesticular obstruction

Only TESE allows sperm retrieval in these patients and is therefore recommended.

9.6.1.3.2 Epididymal obstruction

Microsurgical epididymal sperm aspiration (MESA) or percutaneous epididymal sperm aspiration (PESA) [1566] is indicated in men with CBAVD. Testicular sperm extraction (TESE) and percutaneous techniques, such as testicular sperm aspiration (TESA), are also options [1567]. The source of sperm used for ICSI in cases of OA and the aetiology of the obstruction does not affect the outcome in terms of fertilisation, pregnancy, or miscarriage rates [1568]. Usually, one MESA procedure provides sufficient material for several ICSI cycles [1569] and it produces high pregnancy and fertilisation rates [1570]. In patients with OA due to acquired epididymal obstruction and with a female partner with good ovarian reserve, microsurgical epididymovasostomy (EV) is recommended [1571]. Epididymovasostomy can be performed with different techniques such as end-to-site and intussusception [1572].

Anatomical recanalisation following surgery may require 3 to 18 months. A recent systematic review indicated that the time to patency in EV varies between 2.8 to 6.6 months. Reports of late failure are heterogenous and vary between 1-50% [1573]. Before microsurgery, and in all cases where recanalisation is impossible, epididymal spermatozoa should be aspirated intra-operatively by MESA and cryopreserved to be used for subsequent ICSI procedures [1555]. Patency rates range between 65% and 85% and cumulative pregnancy rates between 21% and 44% [1548, 1574]. Recanalisation success rates may be adversely affected by pre-operative and intra-operative findings. Robot-assisted EV has similar success rates and larger studies are needed [1431].

9.6.1.3.3 Vas deferens obstruction after vasectomy

Vas deferens obstruction after vasectomy requires microsurgical vasectomy reversal. The mean post-procedure patency and pregnancy rates weighted by sample size were 90-97% and 52-73%, respectively [1548, 1574]. The average time to patency is 1.7 to 4.3 months and late failures are uncommon (0-12%) [1573]. Robot-assisted vasovasostomy has similar success rates and larger studies are needed to establish its benefits over standard microsurgical procedures including cost-benefit analysis [1431].

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 has a thick “toothpaste” appearance; in this case microsurgical EV may be indicated [1575-1577]. A simultaneous sperm retrieval may be performed for future cryopreservation and use for ICSI; likewise, patients should be counselled appropriately.

9.6.1.3.4 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 [1578] can be used for cryopreservation for future ICSI. Prostate cancer patients who express an interest in future fertility should be counselled for cryopreservation [1579].

9.6.1.3.5 Ejaculatory duct obstruction

The treatment of ejaculatory duct obstruction depends on its aetiology. Transurethral resection of the ejaculatory ducts (TURED) can be used in post-inflammatory obstruction and cystic obstruction [1551, 1555]. 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 [1551, 1555].

Intra-operative TRUS makes this procedure safer. If distal seminal tract evaluation is carried out at the time of the procedure, installation of methylene blue dye into the seminal vesicles (chromotubation) can help to confirm intra-operative opening of the ducts. Pregnancy rates after TURED are approximately 20-25% [1380, 1551, 1580]. Complications following TURED include epididymitis, urinary tract infection, gross haematuria, haemospermia, azoospermia (in cases with partial distal ejaculatory duct obstruction) and urine reflux into the ejaculatory ducts and seminal vesicles [1551].

Alternative therapies for EDO include, seminal vesiculoscopy to remove debris or calculi and balloon dilation and laser incision for calcification on TRUS [1581]. The alternatives to TURED are MESA, PESA, TESE, proximal vas deferens sperm aspiration and seminal vesicle-ultrasonically guided aspiration.

9.6.1.4 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, 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

9.6.2 **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 consecutive semen analyses [1582]. 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.

9.6.2.1 *Investigation of Non-obstructive azoospermia*

The diagnosis of NOA is based on the evidence of two consecutive semen analyses confirming azoospermia. Moreover, causes of OA should be ruled out. Patients with NOA should undergo a comprehensive assessment aimed to identify genetically transmissible conditions, potential treatable causes of azoospermia, and potential health-relevant comorbidities (e.g., testis cancer and hypogonadism [any type]). A detailed medical history (e.g., history of cryptorchidism, previous gonadotoxic treatments for cancer), also including socio-demographic characteristics [1583], along with a comprehensive physical examination should be performed in every patient to detect conditions potentially leading to azoospermia, while ruling out comorbidities frequently associated with azoospermia. Indeed, NOA could be the first sign of pituitary tumours or germ cell tumours of the testis [1584-1586]. Patients with NOA have been shown to be also at increased risk of being further diagnosed with cancer [1587]. Moreover, other systemic conditions such as metabolic syndrome, type 2 diabetes, osteoporosis and cardiovascular diseases (CVDs) have been more frequently observed in patients with NOA compared to normozoospermic men [1588-1590]. Therefore investigation of the infertile male provides an opportunity for long-term risk stratification for other co-morbid conditions [1591].

Genetic tests should be performed in patients with NOA to detect genetic abnormalities. As discussed (see section 10.3), patients should undergo karyotype analysis [1208, 1209], along with a screening of Y-chromosome microdeletions [1259, 1592] and of the gene coding for CFTR in order to exclude concomitant mutations, and to rule out CBAVD [1240, 1241]. Genetic counselling for eventual transmissible and health-relevant genetic conditions should be provided to couples.

As detailed, all patients should undergo a complete hormonal investigation to exclude a concomitant hypogonadism, which has been found in about 30% of patients with NOA [341, 1593, 1594]. A correct definition of the type of the associated hypogonadism (i.e., hypogonadotropic hypogonadism versus hypergonadotropic vs. compensated hypogonadism) is fundamental to differentiate diagnostic and therapeutic approaches to the patient [1595].

Scrotal US may show signs of testicular dysgenesis (e.g., non-homogeneous testicular architecture and/or microcalcifications) and testis tumours. Testicular volume may be a predictor of spermatogenic function [1186] and is usually, but not invariably, low in patients with NOA. Some authors advocated that testicular perfusion detected at US Doppler assessment can predict surgical sperm retrieval at TESE and guide testicular biopsies [1596]; however, to date data are inconsistent to suggest a routine role of testis Doppler evaluation before TESE.

9.6.2.2 *Surgery for non-obstructive azoospermia*

Surgical treatment for NOA is mostly aimed to retrieve vital sperm directly from the testis (either uni- or bilaterally). This treatment is normally part of assisted reproductive technology (ART) protocols, including IVF cycles via intracytoplasmic sperm injection (ICSI). Techniques and indications for surgical sperm retrieval in patients with NOA are discussed below. As detailed, any surgical approach aimed at sperm retrieval must be considered not a routine and simple biopsy; in this context, performing a diagnostic biopsy before surgery (any type) unless dedicated to ART protocols is currently considered inappropriate.

9.6.2.3 *Indications and techniques of sperm retrieval*

Spermatogenesis within the testis 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 sperm retrieval rates have been reported in up to 50% of patients with NOA [1597, 1598]. Numerous predictive factors for positive sperm retrieval have been investigated, although no definitive factors have been demonstrated to predict sperm retrieval [1598].

Historically, there is a good correlation between the histology found at testicular biopsy and the likelihood of finding mature sperm cells during testicular sperm retrieval [1563, 1599, 1600]. The presence of hypospermatogenesis at testicular biopsy showed a good accuracy in predicting positive sperm retrieval after either single or multiple conventional TESE or mTESE compared to maturation arrest pattern or a SCOS [1563, 1599, 1600]. However, a diagnostic biopsy is not recommended in this clinical setting for the reasons outlined above.

Hormonal levels, including FSH, LH, inhibin B and AMH have been variably correlated with sperm retrieval outcomes at surgery, and data from retrospective series are still controversial [1601-1607]. Similarly, conflicting results have been published regarding testicular volume as a predictor of positive sperm retrieval [1563, 1604, 1605]. Therefore, no clinical variable may be currently considered as a reliable predictor for positive sperm retrieval throughout ART patient work-up [1598].

In case of complete AZFa and AZFb microdeletions, the likelihood of sperm retrieval is zero and therefore TESE procedures are contraindicated [1258]. Conversely, patients with Klinefelter syndrome [1225] and a history of undescended testes have been shown to have higher chance of finding sperm at surgery [1604].

Historically, surgical techniques for retrieving sperm in men with NOA include testicular sperm aspiration (TESA), single or multiple conventional TESE (cTESE) and mTESE.

Fine needle aspiration (FNA)

Fine needle aspiration (FNA) mapping technique has been proposed as a prognostic procedure aimed to select patients with NOA for TESE and ICSI [1608]. The procedure is performed under local anaesthesia in the office and percutaneous aspiration is performed with 23G needle in multiple sites, ranging from 4 to 18 [1608]. The retrieved tissue is sent for cytological and histological evaluation in order to provide information on the presence of mature sperm and on testicular histological pattern. Moreover, given that focal spermatogenesis may occur within the testis of patients with NOA, FNA mapping may provide information on the sites with the higher probability of retrieving sperms, thus serving as a guide for further sperm retrieval surgery in the context of ART procedures (e.g., ICSI). Turek *et al.* have shown that a higher number of aspiration sites may increase the chance of finding sperm [1609, 1610]. The extent and type of subsequent sperm retrieval procedure can be tailored according to the FNA mapping results: TESA or TESE could be suggested in case of multiple positive sites for sperm, while a more precise and potentially more invasive technique, such as mTESE, could be considered for patients with only few positive sites at FNA [1608]. However, there are no RCTs comparing the diagnostic yield from FNA vs. mTESE. Furthermore, a positive FNA will require a secondary therapeutic surgical approach, which may increase the risk of testis damage and without appropriate cost-benefit analysis is not justifiable. Furthermore, there are no studies evaluating the salvage rate of mTESE in men who have undergone FNA mapping. Therefore, FNA mapping cannot be 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 sperm retrieval rates with TESA range from 11 to 60% according to patients' profile and surgical techniques [1611-1614]. Data have shown that using larger needles with (18-21G) with multiple passes could yield a higher chance of positive sperm retrieval [1614]. Complications after TESA are very uncommon and mainly include minor bleeding with scrotal haematoma and post-operative pain [1614].

As a less invasive and less-costly procedure TESA has been proposed as a possible first-line approach before sending patients to a more invasive procedure [1614]. To date there are no RCTs comparing sperm retrieval rates from TESA, cTESE or mTESE. A recent 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 sperm retrieval as compared with TESA [1598]. Given the low success rates compared to TESE, TESA is no longer recommended in men with NOA.

Conventional TESE

Conventional TESE (cTESE) requires a scrotal incision and an open biopsy of the testis. Reported sperm retrieval rates in single-arm studies are about 50% [1597]. However, pooled data analysis of case-control studies comparing conventional TESE with mTESE showed a lower unadjusted sperm retrieval rate of 35% (95% CI 30-40) for cTESE [1598]. Observational studies have demonstrated that multiple biopsies yield a higher chance of sperm retrieval [1597, 1615].

The probability of finding vital sperm at TESE varies also according to testicular histology: data from non-randomised studies comparing cTESE with mTESE have shown a higher chance of sperm retrieval with mTESE only for patients with an histological finding of SCOS [1616]: in such cases results ranged from 22.5 to 41% and from 6.3 to 29% for mTESE versus cTESE, respectively [1616]. Conversely, no difference between the two techniques has been found when comparing patients with a histology suggestive for maturation arrest [1616]. A single study showed a small advantage of mTESE when hypospermatogenesis was found [1617]. In light of these findings some authors have advocated that cTESE could be the technique of choice in patients with a histological finding of maturation arrest or hypospermatogenesis [1598, 1616].

Conventional TESE has been associated with a higher rate of complications compared to other techniques [1597]. A total of 51.7% of patients have been found with intratesticular haematoma at scrotal US three months after surgery, with testicular fibrosis observed in up to 30% of patients at 6-month assessment [1618].

A recent meta-analysis has investigated the risk of hypogonadism after TESE due to testicular atrophy [1619]; patients with NOA experienced a mean 2.7 nmol/L decrease in total testosterone 6 months after cTESE, which recovered to baseline in a time frame between 18 and 26 months.

Microdissection TESE)

Microdissection TESE (mTESE) is aimed at identifying sites of focal spermatogenesis within the testis by performing focal biopsies in areas where larger dilated (and opaque) tubules are present by using optical magnification (20-25x) [1620]. The rationale of this technique is to increase the probability of retrieving sperm with a lower amount of sampled tissue and a consequent lower risk of complications.

Unadjusted sperm retrieval rate after mTESE was 52% (95% CI 47-58) in a pooled data analysis of studies comparing cTESE with mTESE [1598]. Specifically, mTESE resulted in a 1.5 higher chance of retrieving sperm compared to the conventional technique [1598]. 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 [1565]. Lower rates of complications have been observed with mTESE as compared to cTESE, both in terms of haematoma and fibrosis [1616]. Both procedures have shown a recovery of baseline testosterone levels at long-term follow-up [1617].

A recent meta-analysis of the currently available studies comparing cTESE vs. mTESE in patients with NOA showed a mean sperm retrieval rate of 47% (95% CI 45;49). No differences were observed when mTESE was compared to cTESE (46[range 43;49]% for cTESE versus 46[range 42;49]% for mTESE, respectively). Meta-regression analysis demonstrated that SRR per cycle was independent of age and hormonal parameters at enrolment. However, the SRR increased as a function of testis volume. Retrieved sperms resulted in a live birth rate of up to 28% per ICSI cycle [1621].

Although no difference between cTESE/mTESE techniques in subjects with NOA was found, to conclusively clarify if one technique is superior to the other, there is a need for a sufficiently powered and well-designed RCTs to compare mTESE to cTESE; therefore, a clear recommendation regarding the technique of choice cannot be given. Several variables should be considered before counselling patients for one specific technique including surgical skills, testicular histology, costs of the procedure and risk of complications.

Follow-up after TESE

When compared with cTESE, mTESE has been reported to have fewer post-operative complications and negative effects on testicular function. In a recent meta-analysis analysing the complications of TESE, men with Klinefelter syndrome and NOA had the largest decrease in total testosterone levels 6 months after TESE (mean decrease of 4.1 and 2.7 nmol/l) respectively, which recovered to baseline levels 26 and 18 months after TESE, respectively [1619]. Therefore, it would be reasonable to provide long-term endocrinological follow-up after TESE (any type) to detect hypogonadism, particularly for patients with Klinefelter syndrome; testosterone levels assessment could be offered in asymptomatic men at 18 months post TESE or in those men who become symptomatic for hypogonadism after surgery [1622].

Hormonal therapy prior to surgical sperm retrieval approaches

Stimulating spermatogenesis by optimising intratesticular testosterone (ITT) has been proposed to increase the chance of sperm retrieval at the time of surgery in men with NOA. Similarly, increasing FSH serum levels could stimulate spermatogenesis. There is evidence that treatment with hCG can lead to an increase in ITT [1528] and Leydig cells within the testis [1623]. Moreover, it has been shown that in azoospermic patients with elevated gonadotropins levels, administration of HCG and/or FSH can lead to a so-called “gonadotropins reset”, with a reduction in FSH plasma concentrations and an improvement in Sertoli cells function [1624]. Similarly, clomiphene citrate may increase pituitary secretion by blocking feedback inhibition of estradiol, thus inducing an increase in FSH and LH in patients with NOA [1625]. Overall, whilst azoospermic patients with secondary hypogonadism should be treated accordingly to stimulate sperm production [341], there is currently no RCT showing a benefit of hormonal treatment to enhance the chances of sperm retrieval among patients with idiopathic NOA. In a large multicentre case-control study, 496 patients with idiopathic NOA treated with a combination of clomiphene, HCG and human menopausal gonadotropin according to hormonal profile, were compared to 116 controls subjected to mTESE without receiving any pre-operative treatment [1533]. A total of 11% of treated patients had sperm in the ejaculate at the end of treatment; of the remaining patients, 57% had positive sperm retrieval at mTESE as compared with 33% in the control group. Likewise, a small case-control study including 50 men with idiopathic NOA, of whom 25 were treated with recombinant FSH before mTESE,

the authors observed a 24% sperm retrieval rate compared to 12% in the control group [1532]. Conversely, Gul *et al.* [1626] failed to find any advantage of pre-operative treatment with HCG compared to no treatment, in 34 idiopathic NOA patients candidates for mTESE.

Moreover, hormonal therapy has been proposed to increase the chance of sperm retrieval at salvage surgery after a previous failed cTESE or mTESE. Retrospective data have shown that treatment with HCG and recombinant FSH could lead to a 10-15% sperm retrieval rate at salvage mTESE [1528, 1627]. In a small case-control study 28 NOA patients were treated with HCG with or without FSH for 4-5 months before salvage mTESE and compared with 20 controls subjected to salvage surgery [1628]. Sperm retrieval rate was 21% in the treated group compared to 0% in the control group. The histological finding of hypospermatogenesis emerged as predictor of sperm retrieval at salvage surgery after hormonal treatment [1628]. Further prospective trials are needed to elucidate the effect of hormonal treatment before salvage surgery in NOA patients, with a previously failed cTESE or mTESE. However, 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 [1629]. Currently, it is not recommended in routine practice.

9.6.2.4 Recommendations for Non-Obstructive Azoospermia

Recommendations	Strength rating
Patients with non-obstructive azoospermia should undergo a comprehensive assessment, including detailed medical history, hormonal profile and genetic tests to investigate the underlying aetiology and associated comorbidities. Genetic counselling is mandatory in couples with genetic abnormalities prior to any assisted reproductive technology protocols.	Strong
Surgery for sperm retrieval can be performed in men who are candidates for ART (i.e., ICSI). In patients with complete AZFa and AZFb microdeletions surgery is contraindicated since the chance of sperm retrieval is zero.	Strong
Fine needle aspiration (FNA) and testicular sperm aspiration (TESA) should not be considered the treatments of choice in patients with NOA, given the lower probability of positive sperm retrieval compared to cTESE and mTESE.	Weak
Fine needle aspiration as a prognostic procedure prior to definitive testicular sperm extraction (any type) in patients with NOA is not recommended for use in routine clinical practice.	Weak
Conventional TESE (cTESE) or microdissection TESE (mTESE) are the techniques of choice for retrieving sperm in patients with NOA.	Weak
No pre-operative biochemical and clinical variables may be considered sufficient and reliable predictors of positive sperm retrieval at surgery in patients with NOA.	Weak
No conclusive recommendations on the routine use of medical therapy (e.g., recombinant follicle-stimulating hormone (FSH); highly purified FSH; human chorionic gonadotrophin (hCG); aromatase inhibitors or selective oestrogen receptor modulators [SERMs]) in patients with NOA can be drawn and are not therefore currently recommended routinely before TESE.	Weak

9.7 Assisted Reproductive Technologies

9.7.1 Types

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 a pregnancy [1630].

Once couples have been prepared for treatment, the following are the steps that make up an ART cycle:

1. Pharmacological stimulation of growth of multiple ovarian follicles, while at the same time other medications are given to suppress the natural menstrual cycle and down-regulate the pituitary gland.
2. Careful monitoring at intervals to assess the growth of the follicles.
3. Ovulation triggering: when the follicles have reached an appropriate size, a drug is administered to bring about final maturation of the eggs.
4. Egg collection (usually with a trans-vaginal US probe to guide the pickup) and, in some cases of male infertility, sperm retrieval.
5. Fertilisation process, which is usually completed by IVF or ICSI.
6. Laboratory procedures follow for embryo culture: culture media, oxygen concentration, co-culture, assisted hatching etc.
7. The embryos are then placed into the uterus. Issues of importance here include endometrial preparation, the best timing for embryo transfer, how many embryos to transfer, what type of catheter to use, the use of US guidance, need for bed rest etc.
8. Then there is luteal phase support, for which several hormonal options are available.

Fertility treatments are complex and each cycle consists of several steps. If one of the steps is incorrectly applied, conception may not occur [1630].

Several ART techniques are available:

9.7.1.1 Intra-uterine insemination (IUI): IUI is an infertility treatment that involves the placement of the prepared sperm into the uterine cavity timed around ovulation. This can be done in combination with ovarian stimulation or in a natural cycle. The aim of the stimulated cycle is to increase the number of follicles available for fertilisation and to enhance the accurate timing of insemination in comparison to the natural cycle IUI [1631-1633].

Intra-uterine insemination is generally, though not exclusively, used when there is at least one patent fallopian tube with normal sperm parameters and regular ovulatory cycles (unstimulated cycles) and when the female partner is less than 40 years of age.

The global pregnancy rate (PR) and delivery rate (DR) per IUI cycles with husband sperm are 12.0% and 8.0%, respectively. Using donor sperm the resultant PR and DR per cycle are 17.0% and 12.3%, respectively [1634]. The rates of successful treatment cycles for patients decrease with the increase in age, and the birth rates across all age groups have remained broadly stable over time. The highest birth rates were reported in patients younger than 38 years (14% in patients younger than 35 years and 12% in patients aged 35-37 years). The rates of successful treatments are low for patients older than 42 years. The multiple pregnancy rate (MPR) for IUI is approximately 8% [1632]. IUI is not recommended in couples with unexplained infertility, male factor and mild endometriosis, unless the couples have religious, cultural or social objections to proceed with IVF [1635].

Intra-uterine insemination with ovarian stimulation is a safe, cheaper, patient-friendly and non-inferior alternative to IVF in the management of couples with unexplained and mild male factor infertility [1631, 1632]. A recent RCT showed lower multiple pregnancy rates and comparable live birth rates in patients submitted to IUI with hormonal stimulation when compared to women undergoing IVF with single embryo transfer [1636]. Additionally, IUI was found to be a more cost-effective treatment than IVF for couples with unexplained or mild male subfertility [1637].

9.7.1.2 In vitro fertilisation IVF involves using controlled ovarian hyperstimulation to recruit multiple oocytes during each cycle from the female partner. Follicular development is monitored ultrasonically, and ova are harvested before ovulation with the use of US-guided needle aspiration. The recovered oocytes are mixed with processed semen to perform *in-vitro* fertilisation. The developing embryos are incubated for two to three days in culture and then placed trans-cervically into the uterus.

The rapid refinement of embryo cryopreservation methods has resulted in better perinatal outcomes of frozen-thawed embryo transfer (FET) and make it a viable alternative to fresh embryo transfer (ET) [1638, 1639]. FET

seems to be associated with lower risk of gestational complications than fresh ET. Individual approaches remain appropriate to balance the options of FET or fresh ET at present [1640].

Generally, only 20% to 30% of transferred embryos result in clinical pregnancies. The global PR and DR per aspiration for non-donor IVF is 24.0% and 17.6%, respectively [1634].

According to the NICE guidelines, IVF treatment is appropriate in cases of unexplained infertility for women who have not conceived after two years of regular unprotected sexual intercourse [1641].

9.7.1.3 Intracytoplasmic sperm injection is a procedure through which a single sperm is injected directly into the egg using a glass micropipette.

The difference between ICSI and IVF is the method used to achieve fertilisation. In conventional IVF, oocytes are incubated with sperm in a Petri dish, and the male gamete fertilises the oocyte naturally. In ICSI, the cumulus-oocyte complexes go through a denudation process in which the cumulus oophorus and corona radiata cells are removed mechanically or by an enzymatic process. This step is essential to enable microscopic evaluation of the oocyte regarding its maturity stage, as ICSI is performed only in metaphase II oocytes [1642]. A thin and delicate glass micropipette (injection needle) is used to immobilise and pick up morphologically normal sperm selected for injection. A single spermatozoon is aspirated by its tail into the injection needle, which is inserted through the zona pellucida into the oocyte cytoplasm. The spermatozoon is released at a cytoplasmic site sufficiently distant from the first polar body. During this process, the oocyte is held still by a glass micropipette [1642].

With this technique the oocyte can be fertilised independently of the morphology and/or motility of the spermatozoon injected.

Intracytoplasmic sperm injection is currently the most commonly used assisted reproductive technology, accounting for 70-80% of the cycles performed [1643].

The procedure was first used in cases of fertilisation failure after standard IVF or when an inadequate number of sperm cells were available. The consistency of fertilisation independent of the functional quality of the spermatozoon has extended the application of ICSI to immature spermatozoa retrieved surgically from the epididymis and testis [1644]. ICSI is the natural treatment for couples with severe male factor infertility and is also used for a number of non-male factor indications (Table 36) [1645].

Moreover, the need to denude the oocyte has allowed assessment of the nuclear maturity of the oocyte. ICSI is also preferred in conjunction with pre-implantation genetic diagnosis and has recently been used to treat HIV discordant couples, where there is a pressing need to minimise the exposure of the oocyte to a large number of spermatozoa [1644].

The global PR and DR per aspiration for ICSI is 26.2% and 19.0%, respectively [1634]. For all ages and with all the different sperm types used, fertilisation after ICSI is at approximately 70% to 80% and it ensures a clinical pregnancy rate of up to 45% [1643, 1644].

Existing evidence does not support ICSI in preference over IVF in the general non-male factor ART population; however, in couples with unexplained infertility, ICSI is associated with lower fertilisation failure rates than IVF [1645].

Overall, pregnancy outcomes from ICSI are comparable between epididymal and testicular sperm and also between fresh and frozen-thawed epididymal sperm in men with OA [1646]. However these results are from studies of low evidence [1645].

Sperm injection outcomes with fresh or frozen-thawed testicular sperm have also been compared in men with NOA. In a meta-analysis of 11 studies and 574 ICSI cycles, no statistically significant difference was observed between fresh and frozen-thawed testicular sperm with regards to fertilisation rate (RR 0.97, 95% CI 0.92-1.02) and clinical pregnancy rates (RR 1.00, 95% CI 0.75-1.33) [1647]. However, no meta-analysis was performed on data regarding implantation rate, miscarriage rate, and low birth rate.

Testicular sperm in men with raised DNA fragmentation in ejaculated sperm

The use of testicular sperm for ICSI is associated with possibly improved outcomes compared to ejaculated

sperm in men with high sperm DNA fragmentation [1200, 1645]. Men with unexplained infertility with raised DNA fragmentation may be considered for TESE after failure from ARTs, 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 [1648].

In terms of a practical approach, Urologists may offer the use of testicular sperm in patients with high DNA fragmentation. 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, dietary/lifestyle factors and accessory gland infections.

Table 36: Fertilisation methods for male-factor and non-male factor infertility (adapted from [1645])

	Fertilisation method
Male Factor Infertility	
Sperms derived from men with azoospermia	ICSI mandatory
Severe OAT	ICSI highly recommended
Moderate OAT	IVF and ICSI equally effective
Isolated teratozoospermia	IVF and ICSI equally effective
Absolute asthenozoospermia	ICSI mandatory
Globozoospermia	ICSI mandatory
Anti-sperm antibodies	IVF and ICSI equally effective
Sperm DNA fragmentation	ICSI recommended
Non-male factor infertility	
Unexplained infertility	Equally effective. Couples should be informed that ICSI improves fertilisation rates compared to IVF alone, but once fertilisation is achieved the pregnancy rate is no better than with IVF. It should be noted for clarification that in the absence of male factors, ICSI should not be offered in the first treatment cycle [1649].
General non-male factor population	Equally effective, slightly in favour of IVF
Poor quality oocytes and advanced maternal age	Equally effective, slightly in favour of IVF
Pre-implantational genetic testing	ICSI highly recommended
Poor responders	Equally effective, slightly in favour of IVF
Tubal ligation	IVF preferable
Sero-discordant couples	Equally effective

ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilisation; OAT = oligo-astheno-atozoospermia

ICSI is carried out using viable sperm populations. A number of semen processing techniques have been developed to select the optimal sperm fraction for ICSI. The density gradient centrifugation (DGC) and the swim-up procedures have been used as standard semen preparation techniques for ICSI for more than two decades [1650]. However, these traditional sperm selection techniques are unable to select sperm fractions with optimal DNA integrity and functional characteristics. Advanced sperm selection techniques have been introduced to optimise the selection of high quality sperm for ICSI [1651]. These selection methods are based on sperm surface charge (electrophoresis and Zeta potential), apoptosis (magnetic-activated sperm cell sorting (MACS) and glass wool), membrane maturity (hyaluronic acid binding), or ultra-morphological sperm assessment [1652].

9.7.1.4 *Intra-cytoplasmic morphologically selected sperm injection (IMSI)* was first introduced in 2002 as a modification of the ICSI technique [1653]. This technology introduced the magnification of sperm to more than 6,000 times its size, the purpose of which is to perform the motile sperm organelle morphology examination (MSOME), a method used to select spermatozoa that have the choicest morphology in couples with the most severe male factor. Bartoov *et al.* showed that, for patients with histories of ICSI failure, the addition of IMSI resulted in a 60% pregnancy rate, compared with a 30% rate for patients not using IMSI [1654]. Moreover, the pregnancy rate following IVF-IMSI was significantly higher and the miscarriage rate significantly lower,

than in the routine IVF-ICSI procedure (60.0% vs. 25.0%, and 14% vs. 40%, respectively) [1655]. However, a meta-analysis reviewed nine RCTs evaluating 2,014 couples and concluded that the current evidence does not adequately support the use of IMSI [1656].

Because IMSI is also a costly procedure, more studies with larger sample sizes are needed to confirm its value before recommending it for ART.

9.7.1.5 *PICSI technique: a selection based on membrane maturity of sperm*

The human oocyte is surrounded by hyaluronic acid, which acts as a natural selector. In fact, only mature sperm that express receptors specific to HA can reach the oocyte and fertilise it. Those sperm have normal shapes, low DNA fragmentation rates, and low frequency of chromosomal aneuploidies [1657]. Several studies have attempted to verify whether sperm selection based on HA binding could affect IVF outcomes. A meta-analysis included six prospective randomised studies and one retrospective study, all of which used either the PICSI sperm selection dish (a plastic culture dish with microdots of HA hydro gel on its inner surface) or the Sperm Slow method (a viscous medium containing HA). No improvements in fertilisation and pregnancy rates were recorded, although embryo quality was superior in PICSI compared with conventional ICSI [1657]. A recent large-sample multicentre randomised trial provided conclusive evidence against the use of PICSI in ART (PICSI live birth rate versus ICSI: OR 1.12, 95% CI 0.95-1.34) [1658]. A time-lapse study found no difference in embryo development dynamics in oocytes fertilised via HA-ICSI vs. conventional ICSI [1659].

9.7.1.6 *Magnetic-activated cell sorting (MACS)* is an advanced sperm selection technique used to isolate sperm that do not show signs of apoptosis and, therefore, are presumed to have a lower rate of DNA damage [1651]. Use of MACS after density gradient centrifugation (DGC) has been found to improve sperm morphology and decrease DNA fragmentation and apoptotic markers, but it reduces the motility of the selected sperm [1651, 1652]. Magnetic-activated cell sorting failed to improve ICSI outcomes compared with DGC or swim-up, although a slightly higher pregnancy rate (RR) 1.5, 95% CI 1.14-1.98) was observed in MACS patients relative to the control group [1660]. No difference in implantation or miscarriage rate was noted (RR 1.03 [95% CI 0.8-1.31] and 2 [95% CI 0.19-20.9], respectively).

Finally, another randomised controlled trial performed on infants conceived via ovum-donation IVF cycles did not report any differences in terms of obstetrical and perinatal outcomes between pregnancies or babies conceived with sperm selected via MACS or swim-up [1661].

9.7.2 **Safety**

The most significant risk of pre-implantation ART treatment is the ovarian hyperstimulation syndrome, a potentially life-threatening condition resulting from excessive ovarian stimulation during ART techniques, ranging from 0.6% to 5% in assisted reproduction cycles [1662].

Other problems include the risk of multiple pregnancies due to the transfer of more than one embryo and the associated risks to mother and baby, including multiple and preterm birth. The most prevalent maternal complications include pre-eclampsia, gestational diabetes, placenta previa, placental abruption, postpartum haemorrhage, and preterm labour and delivery [1663-1665]. The risks of foetal demise during the third trimester, perinatal mortality, preterm birth, and low birth weight increase with the number of foetuses in the pregnancy. The foetal consequences of preterm birth (cerebral palsy, retinopathy, and broncho-pulmonary dysplasia) and foetal growth restriction (polycythemia, hypoglycemia, and necrotizing enterocolitis) are significant [1666].

The average number of embryos transferred in fresh non-donor IVF and ICSI cycles in 2011 was 1.91, compared with 2.09 in 2008, 2.00 in 2009, and 1.95 in 2010, reflecting a continuing decrease from previous years. The average number of embryos transferred in frozen ET cycles decreased from 1.72 in 2008 to 1.65 in 2009 to 1.60 in 2010 and to 1.59 in 2011 [1667].

The global multiple birth rate for fresh cycle transfer has decreased from 21.5% in 2010 to 20.5% in 2011 and for frozen ET cycles from 12.0% to 11.5% [1634].

In 2011, the rate of early pregnancy loss was 20.1% after fresh ET, compared with 25.4% after frozen ET. Both rates showed wide regional variation [1634]. The multiple birth rates after fresh non-donor ET was 19.6% (twins) and 0.9% (triplets and higher order births); for frozen ET non-donor cycles, twin and triplet and higher order birth rates were 11.1% and 0.4%, respectively [1634].

Rates of premature delivery and perinatal mortality were lower for frozen ETs than for fresh ETs. The global preterm DR after non-donor fresh ET was 19.1%, and after frozen ET was 13.1%. The perinatal mortality rate per 1,000 births after non-donor fresh ET was 16.3 and after frozen ET was 8.6.

In terms of potential adverse effects of ICSI-conceived offspring, a greater neonatal morbidity, obstetric complications and congenital malformations compared to spontaneous conceptions [1668-1670]. Additionally, epigenetic disorders and impaired neurodevelopment have been observed in infants born using ICSI compared with naturally conceived children [1645]. Among singleton infants born at 37 weeks of gestation or later, those following IVF had a risk of low birth weight that was 2.6 times (95% CI 2.4-2.7) than in the general population (absolute risk of low birth weight with spontaneous versus resulting from IVF was 2.5% versus 6.5%) [1295]. Singleton infants after IVF were 39% more likely (adjusted RR of 1.39, 95% CI 1.21-1.59) to have a non-chromosomal birth defect (particularly gastrointestinal and musculoskeletal) compared with all other singleton births. No single ART procedure (e.g., ICSI, fresh, or frozen ETs) was found to substantially increase the risk of birth defects.

Analyses from the Massachusetts Outcome Study of ART reported a 50% increase (adjusted prevalence ratio of 1.5, 95% CI 1.3-1.6) in birth defects in infants after IVF vs. spontaneous pregnancy, and a 30% increase (adjusted prevalence ratio of 1.3, 95% CI 1.1-1.5) in birth defects in infants after subfertility vs. spontaneous pregnancy [1671-1673]. No difference in risk of cancer was found between ART-conceived children and those spontaneously conceived [1674].

Health differences between ICSI and IVF conceptions have not been comprehensively assessed and results are contradictory. Some authors found a significantly reduced risk of birth defects in IVF- compared to ICSI conceived infants [1298] (while two meta-analyses demonstrated no difference in risk of congenital malformations between IVF and ICSI conception) [1301, 1675]. Data about ICSI- and IVF-conceived adolescents or young adults is scarce but it seems that there is no difference in outcomes between the two techniques. Further research into health outcomes in adolescence and adulthood is required before conclusions can be drawn about the long-term safety of ICSI compared to IVF [1676].

10. 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 overall male sexual and reproductive health.

A systematic literature search for original English-language publications and review articles published up to December 2019 was performed using both Pubmed and Google, yielding only a very 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 decades, the panel observed that there is still a significant gender gap between male and female in life expectancy [1677, 1678]. The main contributors to male mortality in Europe are non-communicable diseases (namely cardiovascular diseases [CVD]), 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 amongst men is a natural phenomenon [1678, 1679].

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 [1583, 1589, 1680-1684]. 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 [1685]. Considering that the infertile male seems to be at greater risk of death, simply because of their inability to become fathers, is unacceptable [1686]. The Panel aim 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; f.i. men with varicoceles have a higher incidence of heart disease, a higher risk of diabetes and hyperlipidaemia following diagnosis [1685]. 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” [1688]. A combination of factors, personality, sociocultural background, and specific treatments/professional support, will determine how men cope with this diagnosis [1687].

The most common cancer among European men (excluding non-melanoma skin cancer) is PCa [351]. Due to new therapeutic approaches, survival rates have improved significantly [1689] and as men live longer, health-related quality of life and related sexual well-being will become increasingly important [1691]. Regardless of the type of treatment used [1692], sexual dysfunction is one of the most common post-treatment complications [342, 343, 1690].

Furthermore, relatively little is known about the relevance of fertility and fertility preservation strategies in cancer survivors [1693, 1694, 1695-1697]. In PCa, it has been documented that the psychological consequences persist, even after complete remission or cure and erectile function is restored [1698]. 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 now [288, 289, 291, 1710-1713]. Cardiovascular disease is the leading cause of both male mortality and premature mortality [1699-1702]. Studies indicate that all major risk factors for CVD, including hypertension, smoking and elevated cholesterol are more prevalent in men than women [1703-1709]. Given that ED is an established early sign of atherosclerotic disease and predicts cardiovascular events as an independent factor [291], it provides urologists with the unique opportunity for CVD screening and health modification and to optimise CVD risk factors, whilst 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 [1714-1716] (see sections 3.7.3 and 5.2).

There is clearly a need to prospectively collect data addressing all aspects of male health, including CVD screening protocols and to assess the impact of primary and secondary preventive strategies. The EAU Guidelines panel on Male sexual and reproductive health aims to promote and develop a long-term strategy to raise men’s health at a global level.

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12. CONFLICT OF INTEREST

All members of the EAU Sexual and Reproductive Health Guidelines working 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 publically 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.

13. CITATION INFORMATION

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