EAU Guidelines on

Management of Non-Neurogenic Female Lower Urinary Tract Symptoms (LUTS)

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1. INTRODUCTION

Lower urinary tract symptoms (LUTS) is the overarching term encompassing storage, voiding and post-micturition symptoms [1]. Storage symptoms commonly described include frequency, urgency, nocturia and urinary incontinence (UI) (stress UI [SUI], urgency UI [UUI] and mixed UI [MUI]). Voiding symptoms include hesitancy, intermittency, slow stream, straining, splitting or spraying of the urinary stream and terminal dribble. Post-micturition symptoms include post-void dribbling and feeling of incomplete bladder emptying. Lower urinary tract symptoms are often broadly classified into clinical syndromes/entities such as overactive bladder (OAB), underactive bladder (UAB), UI, nocturia, dysfunctional voiding, or genito-urinary fistulae.

Lower urinary tract symptoms are an extremely common complaint in the female population in every part of the world [2-5]. It causes a great deal of distress and embarrassment [6], as well as significant costs to both individuals and societies. Estimates of prevalence vary according to the definition and the population studied. However, there is universal agreement about the importance of the problem in terms of human suffering and economic cost [7].

1.1 Aim and objectives

These Guidelines from the European Association of Urology (EAU) Working Panel on Non-neurogenic Female LUTS are written by a multidisciplinary group, primarily for urologists, but are likely to be referred to by other professional groups. They aim to provide sensible and practical evidence-based guidance on the clinical problems associated with female LUTS rather than an exhaustive narrative review. Such reviews for UI and other LUT syndromes are already available from the International Consultation on Incontinence (ICI) [8] and other sources, so these EAU Guidelines do not describe the causation, basic science, epidemiology and psychology of LUTS/UI in detail. The focus of these Guidelines is entirely on assessment and treatment, reflecting clinical practice. These guidelines also do not consider women with LUTS caused by neurological disease, or LUTS occurring in children, as this is covered by complementary EAU Guidelines [9, 10].

The current Guidelines provide:

- A clear description of the assessment and treatment of common clinical problems. This can provide the basis for thinking through a patient's management and for planning and designing clinical services;
- A brief but authoritative summary of the current state of evidence on clinical topics, complete with references to the original sources;
- Clear guidance on what to do or not to do, in most clinical circumstances. This should be particularly helpful in those areas of practice for which there is little, or no, high-quality evidence.

The latest edition of the guidelines has seen a significant expansion of scope from 'urinary incontinence' to 'non-neurogenic female LUTS'. The primary consideration here was to include the significant population of women with functional urological conditions not necessarily associated with UI that were hitherto not accounted for in previous guidelines. Secondary considerations were to align more cohesively with the existing Non-neurogenic Male LUTS Guideline. As a consequence of the anatomical and physiological differences between the male and female LUT, the prevalence, pathophysiology, diagnostic approach and management of male and female LUTS differ widely. For that reason, the EAU Guidelines Office decided to provide gender-specific guidelines on LUTS and UI going forward. As a result, the section on post-prostatectomy UI has been moved to the Non-neurogenic Male LUTS Guideline. This reconfiguration has also seen some additional sections added to this Guideline (including non-obstetric fistulae, female bladder outlet obstruction [BOO], UAB and nocturia) and over the course of the next two or three iterations the scope is likely to widen further.

1.2 Panel composition

The EAU Non-neurogenic Female LUTS Panel consists of a multidisciplinary group of experts, including urologists, a uro-gynaecologist, a urodynamic scientist and a physiotherapist. All experts involved in the production of this document have submitted potential conflict of interest statements which can be viewed on the EAU website: https://uroweb.org/guideline/non-neurogenic-female-luts/.

The Panel acknowledge the support of Mrs. M. de Heide (Bekkenbodem4all), Mrs. T. van den Bos (Bekkenbodem4All), Mrs. M.L van Poelgeest-Pomfret (World Federation for Incontinence and Pelvic Problems [WFIP]) and Dr. H. Cobussen-Boekhorst (nurse practitioner) in the development of these guidelines.

1.3 Available publications

A quick reference document (Pocket Guidelines) is available, both in print and as an app for iOS and Android devices. These are abridged versions which require consideration together with the full text versions. All

documents are accessible through the EAU website: https://uroweb.org/guideline/non-neurogenic-female-luts/.

1.4 Publication history

The first EAU Urinary Incontinence Guidelines were published in 2001. The guideline has been modified since to broaden its scope specifically to include other female LUTS as of 2021.

2. METHODS

2.1 Introduction

For the 2021 Non-neurogenic Female LUTS Guideline, the existing text of the 2018 Urinary Incontinence Guidelines was re-structured and significantly expanded. The PICO question-based format of the text was modified to improve readability, although the underlying PICO structure still informs search strategies.

Databases searched for the 2021 update included Medline, EMBASE, and the Cochrane Libraries, covering a time frame between Jan 1st, 2000 and June 16th, 2020 with a focus on high level evidence only (systematic reviews and meta-analyses). Detailed search strategies are available online: https://uroweb.org/guideline/non-neurogenic-female-luts/?type=appendices-publications.

For the 2021 edition of the Guidelines a number of *de novo* systematic reviews have been undertaken by the Panel on the subjects of OAB syndrome and the diagnosis and treatment of female BOO [11, 12]. Full publication of the systematic review results are pending; however, the preliminary results have informed the corresponding sections of this Guidelines update.

For each recommendation within the guidelines there is an accompanying online strength rating form, the basis of which is a modified GRADE methodology [13, 14]. 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 [15];
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’ [16]. The strength rating forms will be available online.

Additional information can be found in the general Methodology section of this document, and online at the EAU website: https://uroweb.org/guidelines/policies-and-methodological-documents/.

A list of Associations endorsing the EAU Guidelines can also be viewed online at the above address.

2.2 Review

The guideline has been peer reviewed prior to publication in 2021.

2.3 Future goals

- A systematic review on the topic of Pelvic Organ Prolapse (POP);
- A systematic review on synthetic/mesh-related mid-urethral sling (MUS) complications;
- A systematic review on the diagnosis and treatment of underactive bladder (UAB) in women.

3. DIAGNOSTIS

3.1 History and physical examination

Taking a thorough clinical history is fundamental to the process of clinical evaluation. Despite the lack of high-level evidence to support it, there is universal agreement that taking a history should be the first step in the assessment of anyone with LUTS. The history should include a full evaluation of LUT symptoms (storage, voiding and post-micturition symptoms), sexual, gastrointestinal and neurological symptoms. Details of urgency episodes, the type, timing and severity of UI, and some attempt to quantify symptoms should also be made. The history should help to categorise LUTS as storage, voiding and post-void symptoms, and classify UI as SUI, UUI, MUI or overflow incontinence, the latter being defined as 'the complaint of UI in the symptomatic presence of an excessively (over-) full bladder (no cause identified)' [17]. It should also identify patients who need referral to an appropriate clinic/specialist. These may include patients with associated pain, haematuria, a history of recurrent urinary tract infection (UTI), pelvic surgery or radiotherapy, constant leakage suggesting a fistula (see Section 4.8), new-onset enuresis or suspected neurological disease. A neurological, obstetric and gynaecological history may help to understand the underlying cause and identify factors that may impact on treatment decisions. Guidance on history taking and diagnosis in relation to UTIs, neuro-urological conditions and chronic pelvic pain can be found in the relevant EAU Guidelines [9, 18, 19]. The patient should also be asked about other co-morbidities as well as smoking status, previous surgical procedures and for the details of current medications, as these may impact on symptoms of LUTS.

Similarly, there is little evidence from clinical trials that carrying out a clinical examination improves outcomes, but wide consensus suggests that it remains an essential part of assessment of patients with LUTS. It should include abdominal examination, to detect an enlarged urinary bladder or other abdominal mass, and digital examination of the vagina and/or rectum. Examination of the perineum in women includes an assessment of oestrogen status, pelvic floor muscle (PFM) function and a careful assessment of any associated POP. A cough stress test is necessary to look for SUI. The urethral mobility can be assessed visually and with an Ulmsten/Pinch or Marshall/Bonney test. Pelvic floor contraction strength can also be assessed digitally. A focused neuro-urological examination should also be routinely undertaken.

3.1.1 Summary of evidence and recommendation for history taking and physical examination

Summary of evidence	LE
History taking including symptoms and comorbidities and a focussed physical examination is an essential part of the evaluation of a woman with LUTS.	4

Recommendation	Strength rating
Take a complete medical history including symptoms and comorbidities and a focused physical examination in the evaluation of women with lower urinary tract symptoms.	Strong

3.2 Patient questionnaires

This section includes symptom scores, symptom questionnaires/scales/indices, patient-reported outcome measures (PROMs) and health-related quality of life (HRQoL) measures. The latter include generic or condition-specific measures. Questionnaires should have been validated for the language in which they are being used, and, if used for outcome evaluation, should have been shown to be sensitive to change. The US Food and Drug Administration (FDA) published guidance for industry on patient-reported outcome instruments (questionnaires) in 2009 [20].

Although many studies have investigated the validity and reliability of urinary symptom questionnaires and PROMs most of these studies include mixed populations (men and women). This limits the extent to which results and conclusions from these studies can be applied to particular LUT syndromes in women. Some questionnaires (ICIQ-FLUTS, QUID, 3IQ, ICIQ-SF) have potential to discriminate UI types in women [21-23]. Others have been developed to measure symptoms and bother in OAB (OABQ-SF, B-SAQ) and other specific conditions. Some questionnaires are responsive to change and may be used to measure outcomes, though evidence on their sensitivity is inconsistent [24, 25]. No evidence was found to indicate whether use of QoL or condition-specific questionnaires has an impact on outcome of treatment.

Detailed description of the different urinary symptoms questionnaires and PROMs is beyond the scope of this guideline. For more information we recommend the 6th ICI review on patient reported outcomes assessment [26]. To date, there is no one questionnaire that fulfils all requirements for assessment of women

with LUTS. Clinicians must evaluate the tools that exist, for use alone or in combination, for assessment and monitoring of treatment outcome [27]. The questionnaires can be found on the following websites: www.iciq.net, https://eprovide.mapi-trust.org, www.pfizerpcoa.com, www.ncbi.nlm.nih.gov.

3.2.1 Summary of evidence and recommendation for patient questionnaires

Summary of evidence	LE
Validated condition-specific symptom scores assist in the screening for, and categorisation of LUTS.	3
Validated symptom scores measure the severity of UI and LUTS.	3
Both condition-specific and general health status questionnaires measure current health status and change following treatment.	3
Patient questionnaires cannot replace a detailed patient consultation and should only be used as part of a complete medical history.	4

Recommendation	Strength rating
Use a validated and appropriate questionnaire as part of the standardised assessment of female lower urinary tract symptoms.	Strong

3.3 Bladder diaries

Measurement of the frequency and severity of LUTS is an important step in the evaluation and management of lower urinary tract (LUT) dysfunction. Bladder diaries are a semi-objective method of quantifying symptoms, such as frequency of UI events, number of nocturia episodes etc. They also quantify urodynamic variables, such as voided volume, 24-hour urine volume or nocturnal total urine volume. Voiding diaries are also known as micturition time charts, frequency/volume charts and bladder diaries.

Discrepancy between diary recordings and the patient rating of symptoms, e.g. frequency of UI, can be useful for patient counselling. In addition, fluid intake and voided volume measurement can be used to support diagnoses and management planning, for example in OAB, and for identifying polyuria, either 24-hour or nocturnal polyuria. Diaries can also be used to monitor treatment response and are widely used in clinical trials. In patients with severe UI, a bladder diary is unlikely to accurately report 24-hour urine output.

Consensus terminology is now well-defined and widely accepted [1, 28]. However, the terms micturition diary, frequency volume chart, bladder diary and voiding diary, have been used interchangeably for many years, but only bladder diaries include information on fluid intake, times of voiding, voided volumes, UI episodes, pad usage, degree of urgency and degree of UI recorded for at least 24 hours. When reviewing the evidence all synonymous search terms have been included.

Two studies have demonstrated the reproducibility of diaries in both men and women [29, 30]. Another two studies have shown the feasibility, reliability and validity of the bladder diary [31, 32]. Further studies have demonstrated variability of diary data within a 24-hour period and compared voided volumes recorded in diaries with those recorded by uroflowmetry [33, 34]. Another study found that keeping a bladder diary had a therapeutic benefit [35].

A number of observational studies have demonstrated a close correlation between data obtained from bladder diaries and standard symptom evaluation [36-39]. The optimum number of days required for bladder diaries appears to be based on a balance between accuracy and compliance [40, 41]. Diary durations between 3 and 7 days are routinely used in the literature.

3.3.1 Summary of evidence and recommendations for bladder diaries

Summary of evidence	LE
Bladder diaries of three to seven days duration are a reliable tool for the objective measurement of mean voided volume, day- and night-time frequency, and UI episode frequency.	2b
Bladder diaries are sensitive to change and are a reliable outcome measure.	2b

Recommendations	Strength rating
Ask patients with lower urinary tract symptoms to complete a bladder diary as part of the standardised assessment of female LUTS.	Strong
Use a bladder diary with a duration of at least three days.	Strong

3.4 Urinalysis and urinary tract infection

Reagent strip ('dipstick') urinalysis may indicate proteinuria, haematuria or glycosuria or suggest UTI requiring further assessment. Refer to the Urological Infections Guidelines for diagnosis and treatment of UTI [18].

Urine dipstick testing is a useful adjunct to clinical evaluation in patients in whom urinary symptoms are suspected to be due to UTI. Urinalysis negative for nitrite and leucocyte esterase may exclude bacteriuria in women with LUTS [42], and should be included, with urine culture when necessary, in the evaluation of all patients with LUTS. Urinary incontinence or worsening of LUTS may occur during a UTI [43] and existing UI may worsen during UTI [44]. The rate and severity of UI was unchanged after eradication of asymptomatic bacteriuria in nursing home residents [45].

3.4.1 Summary of evidence and recommendations for urinalysis

Summary of evidence	LE
Urinalysis negative for nitrite and leucocyte esterase may exclude bacteriuria in women with LUTS.	3
Urinary incontinence may be a symptom during a UTI, and LUTS may deteriorate during a UTI.	3
The presence of a UTI worsens existing symptoms of UI.	3
Elderly nursing home patients with UI do not benefit from treatment of asymptomatic bacteriuria.	2

Recommendations	Strength rating
Perform urinalysis as a part of the initial assessment of a patient LUTS.	Strong
If a urinary tract infection is present with LUTS, reassess the patient after treatment.	Strong
Do not routinely treat asymptomatic bacteriuria in elderly patients to improve urinary incontinence.	Strong

3.5 Post-void residual volume

Post-void residual (PVR) volume is the amount of urine that remains in the bladder after voiding. It indicates poor voiding efficiency, which may result from a number of contributing factors. Assessment of PVR is important because it may worsen symptoms and, more rarely, may be associated with UTI, upper urinary tract (UUT) dilatation and renal insufficiency. Both BOO and detrusor underactivity (DU) potentially contribute to the development of PVR. Post-void residual can be measured by catheterisation or ultrasound (US). The prevalence of PVR in patients with LUTS is uncertain, partly because of the lack of a standard definition of an abnormal PVR volume. Bladder voiding efficiency (BVE) is the proportion of the total bladder volume that is voided by the patient. The BVE can be defined as a percentage: BVE = (voided volume/[VV]+PVR) × 100. This may be a more reliable parameter to evaluate poor voiding [46].

Most studies investigating PVR assessed mixed populations. Although some studies have included women with UI and men and women with LUTS, they have also included children and adults with neurogenic UI. In general, the data on PVR can be applied with caution to women with non-neurogenic LUTS. The results of studies investigating the best method of measuring PVR [45, 47-51] have led to the consensus that US measurement of PVR is preferable to catheterisation due to its favourable risk-benefit profile.

In peri- and post-menopausal women without significant LUTS or pelvic organ symptoms, 95% of women had a PVR < 100 mL [52]. In women with UUI, a PVR > 100 mL was found in only 10% of cases [53]. Other research has found that a high PVR is associated with POP, voiding symptoms and an absence of SUI [52, 54-56]. In women with SUI, the mean PVR was 39 mL measured by catheterisation and 63 mL measured by US, with 16% of women having a PVR > 100 mL [57]. Some authors have suggested that it is reasonable to consider a PVR of > 100 mL to be significant, although many women may remain asymptomatic and hence it is imperative to consider the clinical context [53]. There is no consensus on what constitutes a significant PVR in women; therefore, the Panel suggests the additional use of BVE.

3.5.1 Summary of evidence and recommendations for post-void residual

Summary of evidence	LE
Lower urinary tract symptoms are associated with a higher PVR compared to asymptomatic population groups.	2

Recommendations	Strength rating
Measure post-void residual volume (PVR) in patients with LUTS during initial assessment.	Strong
Use ultrasound to measure PVR.	Strong
Monitor PVR in patients receiving treatments that may cause or worsen voiding dysfunction.	Strong
Provide Bladder Voiding Efficiency as an additional parameter when measuring PVR.	Weak

3.6 Urodynamics

Urodynamic testing is widely used as an adjunct to clinical diagnosis, in the belief that it may help to provide or confirm diagnosis, predict treatment outcome or facilitate discussion during counselling. The simplest form of urodynamic evaluation is uroflowmetry. The maximum flow rate (Q_{max}), the volume voided and the shape of the curve in addition to the PVR volume (see above) are the most important aspects to be assessed [26]. The bladder should be sufficiently full because of the volume dependency of Q_{max} [58, 59]. A minimum voided volume of 150 mL is advised in males, but there is very little evidence to suggest a volume threshold in females. It is of relevance to ask the patient whether or not the voiding was representative.

Invasive urodynamic tests are often performed prior to invasive treatment of LUTS. These tests include multichannel cystometry and pressure-flow studies, ambulatory monitoring and video-urodynamics, and different tests of urethral function, such as urethral pressure profilometry and Valsalva leak point pressure (VLPP). The ICS and the United Kingdom Continence Society provide standards to optimise urodynamic test performance and reporting [60, 61]. A characteristic of a good urodynamic study is that the patient's symptoms are replicated, recordings are checked for quality control and results interpreted in the context of the clinical problem, remembering that there may be physiological variability within the same individual [60]. Non-invasive alternatives for measurement of detrusor pressure and BOO include transabdominal wall near-infrared spectroscopy and US detrusor wall thickness analysis, but as yet these techniques have not been adopted into routine clinical practice [26].

In common with most physiological tests there is variability in urodynamic results. This has consequences for the reproducibility, diagnostic accuracy and predictive value of urodynamic testing (UDS). It has been stated that, at least in the case of cystometry and pressure-flow studies, one set of measurements suffice, but only if the patient's symptoms have been replicated [60]. It can nevertheless be sometimes necessary or advisable to repeat the urodynamic measurements. The risk-benefit profile of repeating urodynamic testing should always be considered.

Further condition-specific information regarding the role of urodynamic testing in OAB, SUI, BOO and UAB can be found in respective sections of this Guideline.

3.6.1 Variability

Contradictory findings were reported in studies assessing same-session repeatability of cystometric and pressure-flow studies [62, 63]. There is also conflicting evidence about the reproducibility of maximum urethral closure pressure (MUCP) measurement [64, 65]. One method of recording MUCP cannot be compared meaningfully to another [65, 66]. Valsalva leak point pressure measurement is not standardised and there is minimal evidence about its reproducibility. No studies on the reproducibility of ambulatory monitoring in non-neurological patients have been published [26].

3.6.2 Diagnostic accuracy

Clinical diagnosis and cystometric findings often do not correlate [67, 68] and asymptomatic women may have abnormalities on urodynamic testing. As the urodynamic diagnosis is often taken as the benchmark in the assessment of LUT function, this implies that the evaluation of other tests of LUT function may be biased as a result. The diagnostic accuracy of urethral pressure profilometry [69] and urethral retro-resistance pressure measurement in SUI is generally poor [26]. Valsalva leak point pressure did not reliably assess UI severity in a cohort of women selected for surgical treatment of SUI [70]. Urethral pressure reflectometry may have greater diagnostic accuracy but its clinical role remains unclear [71]. Ambulatory urodynamics may detect unexpected physiological variance from normal more often than conventional cystometry, but the clinical relevance of this is also uncertain [72, 73].

A pressure-flow study, that is, the simultaneous measurement of flow rate and detrusor pressure during voiding, can reveal whether a poor flow rate and PVR's are due to BOO, poor bladder contraction strength (DU) or a combination of both. Also, it may provide information on the degree of pelvic floor relaxation and thus diagnose dysfunctional voiding. As with uroflowmetry, its representativeness must be verified. Several proposals to define BOO in women have been made. These definitions are based on detrusor pressure values,

either the value at Q_{max} or the maximum value, and the Q_{max} value, either during the pressure-flow study or during uroflowmetry; sometimes combined with the findings during fluoroscopic imaging (see Section 4.5.4.8 for more detailed information) [74, 75]. Unlike the situation in men, there is no generally accepted definition or nomogram in women. Bladder contraction strength parameters are derived from the detrusor pressure and flow rate values during a pressure flow study or from stop tests [75], but again validation is poor. In addition, while these parameters estimate the strength of the contraction, they ignore its speed and persistence (see Section 4.4.3.2 for more detailed information) [76]. A video-urodynamic study can be useful to detect the site of obstructed voiding, which may be anatomical or functional [77]. Also, video-urodynamics may detect a bladder diverticulum or gross reflux as a pressure absorbing reservoir.

*3.6.3 **Predictive value***

Performing urodynamic evaluation is only useful if it leads to more effective clinical care and better outcomes. A Cochrane review of eight randomised controlled trials (RCTs) showed that use of urodynamic tests in women with UI increased the likelihood of prescribing drugs and did not increase the likelihood of undergoing surgery. However, there was no evidence that this influence on decision-making altered the clinical outcome of treatment [78]. Most RCTs addressed the utility of urodynamic tests on SUI only, include women with uncomplicated SUI. A meta-analysis including four RCTs comparing surgical outcomes in women with self-reported SUI (or stress-predominant MUI) who were investigated via urodynamics with women who had office evaluation only found that there was no difference in cure and complication rate [79]. On the other hand, in a large retrospective multicentre study it was found that only 36% of patients were defined as “uncomplicated” according to the definitions used in large RCTs [80]. The urodynamic observations were not consistent with the pre-urodynamic diagnosis in 1,276 out of 2,053 patients (62.2%). Voiding dysfunctions were urodynamically diagnosed in 394 patients (19.2%) and planned surgery was cancelled or modified in 304 patients (19.2%), due to the urodynamic findings [81].

The predictive value of urethral function tests remains unclear. In observational studies, there was no consistent correlation between the results of these tests and subsequent success or failure of SUI surgery [37-39, 82]. The same was true in a secondary analysis of an RCT [83].

The presence of pre-operative DO in women with stress-predominant MUI has been associated with post-operative UUI but did not predict overall treatment failure following MUS surgery or colposuspension [83]. The urodynamic diagnosis of detrusor overactivity (DO) had no predictive value for treatment response in studies on fesoterodine, onabotulinumtoxinA and sacral nerve stimulation (SNS) in patients with OAB symptoms [84-87]. Augmentation cystoplasty aims to abolish DO, improve bladder compliance and increase functional bladder capacity but there is no evidence to guide whether or not pre-operative urodynamics is predictive of outcome. Most clinicians would however consider pre-operative urodynamics as essential prior to contemplating augmentation cystoplasty.

A pressure-flow study is capable of discriminating BOO from DU as a cause of voiding dysfunction. The predictive value of parameters derived from such a study for voiding dysfunction after a surgical procedure for SUI is however low. A low pre-operative flow rate and a low detrusor voiding pressure have been shown to correlate with voiding dysfunction after a tension-free vaginal tape (TVT) and an autologous fascial sling procedure, respectively [88-90]. Bladder contraction strength parameters combining flow rate and detrusor pressure values only poorly predicted voiding dysfunction after autologous fascial sling [91]. *Post-hoc* analysis of two high-quality surgical trials on TVT, Burch colposuspension and autologous fascial sling showed that no pre-operative urodynamic parameter could predict post-operative voiding dysfunction in a selected population of women with low pre-operative PVR [92, 93].

The Panel recognises that it may be valuable to use urodynamic test results to select the optimum management strategy; however, there is inconsistent evidence regarding the predictive value of such tests. When urodynamics and clinical assessment (i.e. by history and examination) are in disagreement, there needs to be a careful re-evaluation of the clinical symptoms of the patient and the investigation results to ensure that the diagnosis is correct before invasive treatments are contemplated.

3.6.4 Summary of evidence and recommendations for urodynamics

Summary of evidence	LE
Most urodynamic parameters show variability within the same session and over time, and this may limit their clinical interpretation.	3
Different techniques of measuring urethral function may have good test-retest reliability, but do not consistently correlate to other urodynamic tests or to the severity of UI.	3
There may be inconsistency between history and urodynamic results.	3
Urodynamic diagnosis of DO does not influence treatment outcomes in patients with OAB.	1a
Pre-operative urodynamics in women with uncomplicated, clinically demonstrable, SUI does not improve the outcome of surgery for SUI.	1b
There is no consistent correlation between the result of urethral function tests and subsequent success or failure of SUI surgery.	3
There is no consistent evidence that pre-operative DO is associated with surgical failure of MUS in women.	3
The presence of pre-operative DO may be associated with persistence of urgency post-operatively.	3

Recommendations	Strength rating
Adhere to 'Good Urodynamic Practice' standards as described by the International Continence Society when performing urodynamics in patients with LUTS.	Strong
Do not routinely carry out urodynamics when offering treatment for uncomplicated stress urinary incontinence.	Strong
Do not routinely carry out urodynamics when offering first-line treatment to patients with uncomplicated overactive bladder symptoms.	Strong
Perform urodynamics if the findings may change the choice of invasive treatment.	Weak
Do not use urethral pressure profilometry or leak point pressure to grade severity of urinary incontinence as they are primarily tests of urethral function.	Strong

3.7 Pad testing

Measurement of urine loss using an absorbent pad worn over a set period of time or during a protocol of physical exercise can be used to quantify the presence and severity of UI, as well as a patient's response to treatment.

The clinical utility of pad tests for people with UI has been assessed in two systematic reviews [94, 95]. A one-hour pad test using a standardised exercise protocol and a diagnostic threshold of 1.4 g shows good specificity but lower sensitivity for symptoms of SUI and MUI. A 24-hour pad test using a threshold of 4.4 g is more reproducible but is difficult to standardise with variation according to activity level [96]. A pad test with a specific short graded exercise protocol also has diagnostic value but a negative test should be repeated with the degree of provocation increased [97]. The usefulness of pad tests in quantifying severity and predicting outcome of treatment is uncertain [94, 98, 99]. Pad tests are responsive to change following successful treatment [100]. Pad testing using a standardised bladder volume (50% of cystometric capacity) has been suggested to allow for a more reliable assessment of UI in a small study including 25 women [101]. There is no evidence that one type of pad test is superior to another.

3.7.1 Summary of evidence and recommendations for pad testing

Summary of evidence	LE
A pad test can diagnose UI accurately.	2
Standardisation of bladder volume and degree of provocation improves reproducibility.	2
Twenty-four hours is sufficient duration for home-based testing balancing diagnostic accuracy and adherence.	2
Change in leaked urine volume on pad tests can be used to measure treatment outcome.	2
Pad tests can be a useful tool in the research setting and are an optional investigation in clinical practice.	4

Recommendations	Strength rating
Use a pad test of standardised duration and activity protocol.	Strong
Use a pad test when quantification of urinary incontinence is required, especially to assess response to treatment.	Weak

3.8 Imaging

Imaging improves our understanding of the anatomical and functional abnormalities that may cause LUTS. In clinical research, imaging is used to understand the relationship between anatomy and function, between conditions of the central nervous system (CNS) or of the LUT, and to investigate the relationship between LUT and pelvic floor imaging and treatment outcomes.

Ultrasound and magnetic resonance imaging (MRI) have largely replaced X-ray imaging in the evaluation of the pelvic floor. Ultrasound is preferred to MRI because of its ability to produce three-dimensional and four-dimensional (dynamic) images at lower cost and wider availability.

In general, there is no need for UUT imaging unless a high-pressure bladder, severe POP or chronic urinary retention is suspected or diagnosed or abnormal renal function tests are observed. In cases of suspected UI caused by an UUT anomaly or uretero-vaginal fistula, UUT imaging (intravenous urography or CT scan) may be indicated [102].

*3.8.1 **Ultrasound***

Ultrasonography of the LUT plays a role in the differential diagnosis of women with LUTS, when there is a suspicion of bladder tumour, stones, etc. and in cases presenting with haematuria.

Ultrasonography has been used in the evaluation of UI and pelvic floor since the 1980s. Different imaging approaches, such as abdominal, transvaginal, transrectal, perineal and transurethral are described. The bladder neck and urethra are easily visible and measurements can be done at rest, during straining, coughing and during pelvic floor contraction. Ultrasonography can be used to assess PFMs and their function. Contraction of the pelvic floor results in displacement of pelvic structures that can easily be imaged on US. Integrity of the levator ani muscle can be determined by 3D transperineal US. The specific role of US is discussed in the condition-specific sections of this guideline.

*3.8.2 **Detrusor wall thickness***

As OAB syndrome is linked to DO, it has been hypothesised that frequent detrusor contractions may increase detrusor/bladder wall thickness (DWT/BWT). Transvaginal US seems to be more accurate with less inter-observer variability than transabdominal and transperineal approaches [103]. Several cut-off points have been suggested, from 4.4 to 6.5 mm. Other studies are contradictory and did not find this correlation. No consensus exists as to the relationship between OAB and increased BWT/DWT [104], and there is no evidence that BWT/DWT imaging improves management of OAB in practice. There is no widely accepted, standardised bladder volume for bladder wall thickness measurement.

In a retrospective study including 227 women with symptoms of voiding difficulty (hesitancy, intermittency and poor stream), 74 (32.6%) were diagnosed with voiding dysfunction on the basis of free uroflowmetry and residual urine. While controlling for the effect of DO, the relationships between DWT and different parameters of voiding function in pressure–flow studies and free uroflowmetry were examined. The results indicated that DWT was not associated with any urodynamic parameters that may indicate BOO [105].

*3.8.3 **Magnetic resonance imaging***

There is a general consensus that MRI provides good global pelvic floor assessment, including POP, defecatory function and integrity of the pelvic floor support [106]. However, there is a large variation in MRI interpretation between observers [107] and little evidence to support its clinical usefulness in the management of LUTS/UI. There is no conclusive evidence that MRI evaluation of POP is more clinically useful than vaginal examination. Studies have assessed the use of imaging to assess the mechanism of MUS insertion for SUI. One study suggested that MUS placement decreased mobility of the mid-urethra but not of the bladder neck [108]. Following MUS, a wider gap between pubic symphysis and sling (assessed by imaging) has been shown to correlate with a lower chance of cure of SUI [109].

3.8.4 *Summary of evidence and recommendation for imaging*

Summary of evidence	LE
There is no consistent evidence that routine urinary tract imaging is useful in the evaluation or management of lower urinary tract symptoms.	3
There is no consistent evidence that bladder (detrusor) wall thickness measurement is useful in the management of OAB.	3

Recommendation	Strength rating
Do not routinely carry out imaging of the upper or lower urinary tract as part of the assessment of lower urinary tract symptoms.	Strong

4. DISEASE MANAGEMENT

4.1 Overactive bladder

4.1.1 *Epidemiology, aetiology, pathophysiology*

Overactive bladder is defined by the ICS as 'urinary urgency, usually accompanied by frequency and nocturia, with or without UUI, in the absence of urinary tract infection (UTI) or other obvious pathology' [110]. Overactive bladder is a chronic condition and can have debilitating effects on QoL. The hallmark urodynamic feature is DO, although this may not be demonstrated in a large proportion of OAB patients, which may, in part, be due to failure to reproduce symptoms during urodynamic assessment.

The EPidemiology of InContinence (EPIC) study was one of the largest population-based surveys that studied the prevalence of LUTS and OAB [111]. Conducted in five countries, including Canada, Germany, Italy, Sweden, and the UK, it was a cross-sectional telephone survey of adults aged > 18 years. The study included over 19,000 participants and demonstrated an overall prevalence of OAB symptoms of 11.8% (10.8% in men and 12.8% in women). Other studies have reported prevalence of up to 30–40%, with rates generally increasing with age [5].

Various theories have been proposed to explain the pathophysiology of OAB, mainly relating to imbalances in inhibitory and excitatory neural pathways to the bladder, or the sensitivity of bladder muscle receptors. However, no definite identifiable cause has been established.

4.1.2 *Classification*

Overactive bladder is generally classified into 'wet' and 'dry', based on the presence or absence of associated UI.

4.1.3 *Diagnostic evaluation*

The evaluation of a patient with symptoms of OAB follows the general pathway of evaluation of the female LUTS patient.

4.1.3.1 *Bladder diaries*

Diaries are particularly helpful in establishing and quantifying symptoms of frequency, urgency and UI, and may be valuable in assessing change over time or response to treatment. A number of observational studies have demonstrated a close correlation between data obtained from bladder diaries and standard symptom evaluation [36-39]. The optimum number of days required for bladder diaries appears to be based on a balance between accuracy and compliance. Diary durations between 3 and 7 days are routinely used in the literature.

4.1.3.2 *Urodynamics*

Urodynamics is essential in establishing the presence of DO, but its absence does not preclude the diagnosis of OAB which is based on symptoms alone.

A Cochrane review of seven RCTs showed that use of urodynamic tests increased the likelihood of prescribing drugs or avoiding surgery. However, there was no evidence that this influence on decision-making altered the clinical outcome of treatment [112]. A sub-analysis of an RCT comparing fesoterodine to placebo [84, 85] showed that the urodynamic diagnosis of DO had no predictive value for treatment response.

4.1.3.3 Summary of evidence and recommendations regarding associated conditions

Summary of evidence	LE
Bladder diaries of three to seven days duration may be helpful in quantifying symptoms of OAB, and assessing response to treatment.	3
Urodynamic diagnosis of DO does not influence treatment outcomes in patients with OAB.	1a

Recommendations	Strength rating
Request that patients complete at least a three-day bladder diary at initial valuation and before each therapeutic intervention for overactive bladder (OAB).	Strong
Do not routinely carry out urodynamics when offering first-line treatment to patients with uncomplicated OAB symptoms.	Strong

4.1.4 ***Disease management***

4.1.4.1 Conservative management

In clinical practice, it has long been the convention that non-surgical therapies are recommended first because they usually carry the lowest risk of harm. While this remains true for non-pharmacological conservative treatments (e.g. pelvic floor muscle training [PFMT]), increasing concerns regarding the adverse events of some pharmacological treatments used to treat LUTS (e.g. anticholinergic drugs), particularly regarding cognitive function have emerged and patients should be fully counselled regarding this potential risk.

4.1.4.1.1 Addressing underlying disease/cognitive impairment

Lower urinary tract symptoms, especially in the elderly, have been associated with multiple comorbid conditions including:

- cardiac failure;
- chronic renal failure;
- diabetes;
- chronic obstructive pulmonary disease;
- neurological disease;
- general cognitive impairment;
- sleep disturbances, e.g. sleep apnoea;
- depression;
- metabolic syndrome.

It is possible that improvement of associated disease may reduce the severity of urinary symptoms. However, this is often difficult to assess as patients frequently suffer from more than one condition. In addition, interventions may be combined and individualised, making it impossible to decide which alteration in an underlying disease has affected a patient's symptoms.

One study involving middle-aged women with type 1 diabetes mellitus showed that 10% of these women had UUI. The study showed no correlation between earlier intensive treatment of type 1 diabetes mellitus and the prevalence of UI in later life vs. conventional treatment [113].

4.1.4.1.1.1 Summary of evidence and recommendation regarding associated conditions

Summary of evidence	LE
There is a lack of evidence that improving any associated comorbid condition improves OAB.	3

Recommendation	Strength rating
Review any new medication associated with the development or worsening of UI.	Weak

4.1.4.1.2 Adjustment of other medication

Although LUTS are listed as an adverse effect of many drugs in drug compendia, this mainly derives from uncontrolled individual patient reports and post-marketing surveillance. Few controlled studies have used the occurrence of LUTS as a primary outcome, or were powered to assess the occurrence of statistically significant LUTS or worsening rates against placebo. In most cases, it is therefore not possible to be sure that any drug causes OAB/LUTS.

A structured literature review failed to identify any studies addressing whether adjustment of specific medications could alter existing symptoms of OAB. Also, there is little evidence relating to the occurrence or worsening of OAB in relation to prescription of any specific drugs.

4.1.4.1.2.1 Summary of evidence and recommendations for adjustment of non-LUTS medication

Summary of evidence	LE
There is very little evidence that alteration of non-uroselective medications can cure or improve symptoms of OAB.	3

Recommendations	Strength rating
Take a history of current medication use from all patients with overactive bladder (OAB).	Strong
Review any new medication associated with the development or worsening of OAB symptoms.	Weak

4.1.4.1.3 Urinary containment

Urinary containment is important for people with OAB-wet or UUI when active treatment does not cure the problem, is delayed, or when it is not available or not possible. Some individuals may prefer urinary containment rather than to undergo active treatment with its associated risks. Containment includes the use of absorbent pads, urinary catheters, external collection devices and intravaginal devices. Detailed literature summaries can be found in the current ICUD monograph [114] and in a European Association of Urology Nurses guidance document [115].

A systematic review of six RCTs comparing different types of pads found that pads filled with superabsorbent material were better than standard pads, whilst evidence that disposable pads were better than washable pads was inconsistent [116]. A series of three crossover RCTs examined performance of different pad designs for differing populations [117, 118]. For women with light UI, disposable insert pads (within washable pouch pants) were most effective. In adults with moderate/severe UI, disposable pull-up pants were more effective for women.

A Cochrane review summarised three RCTs comparing different types of long-term indwelling catheters and found no evidence that one catheter material or type of catheter was superior to another [119]. A systematic review of non-randomised studies found no differences in UTI outcome or UUT changes between use of suprapubic or urethral catheter drainage; however, patients with suprapubic catheters were less likely to have urethral complications [120].

Clean intermittent self-catheterisation (CISC) is the most commonly used therapy to manage high PVR volumes and urinary retention [115]. It reduces the risk of complications such as UTI, UUT deterioration, bladder stones and overflow UI etc. It has not yet been established whether the incidence of UTI, other complications and user satisfaction are affected by either sterile or clean IC, coated or uncoated catheters or by any other strategy [121]. The use of hydrophilic catheters may be associated with a lower rate of UTI, but further evidence is needed, as most of it comes from neurogenic patients [122]. The average frequency of catheterisation is four to six times per day [123] and the catheter sizes most often used are 12-16 Fr. In aseptic IC, an optimum frequency of five times showed a reduction of UTI [123]. Frequency of catheterisation needs to be based on individual need and capability, to prevent chronic and repeated over-filling of bladder [124]. Thorough counselling regarding techniques, frequency, equipment and adverse effects of CISC should be given to all potential patients in line with good medical practice.

For people using CISC, a Cochrane review found no evidence that one type of catheter or regimen of catheterisation was better than another [125]. However, there is recent evidence from a narrative review suggesting that in certain populations using single-use catheters may reduce urethral trauma and UTI [126]. A Cochrane review summarising five trials comparing bladder washout policies in adults with indwelling urinary catheters found inconsistent evidence of benefit [127].

A further Cochrane review summarising eight trials testing whether antibiotic prophylaxis was beneficial for adults using CISC or indwelling catheterisation found it reduced incidence of symptomatic UTI but possible harms were not assessed [128]. A multicentre RCT from the UK reported that prophylaxis was well-tolerated but development of antibiotic resistance was a concern [129].

4.1.4.1.3.1 Summary of evidence and recommendations for urinary containment

Summary of evidence	LE
Pads are effective in containing urine.	1b
Antibiotic prophylaxis may help reduce incidence of UTI in patients who self-catheterise or have an indwelling catheter, but at the cost of increasing antimicrobial resistance.	1a

Recommendations	Strength rating
Ensure that women with overactive bladder (OAB) and/or their carers are informed regarding available treatment options before deciding on urinary containment alone.	Strong
Offer incontinence pads and/or containment devices for management of OAB-wet, either for temporary symptom control or where other treatments are not feasible.	Strong
Offer prophylactic antibiotics to patients with recurrent urinary tract infections who perform clean intermittent self-catheterisation, or have an indwelling catheter, after discussion regarding the risk of increasing antimicrobial resistance.	Strong

4.1.4.1.4 Lifestyle interventions

Examples of lifestyle factors that may be associated with UI include obesity, smoking, level of physical activity and liquid intake. Modification of these factors may improve symptoms of OAB.

4.1.4.1.4.1 Caffeine intake

Many drinks contain caffeine, particularly coffee, tea and cola. Conflicting epidemiological evidence of urinary symptoms being aggravated by caffeine intake has focused attention on whether caffeine reduction may improve LUTS [130, 131]. A recent review of 14 interventional and 12 observational studies reported that reduction in caffeine intake may reduce symptoms of urgency, but the certainty of evidence was low with significant heterogeneity [132].

4.1.4.1.4.2 Fluid intake

Modification of fluid intake, particularly restriction, is a strategy commonly used by people with OAB to relieve symptoms. Advice on fluid intake given by healthcare professionals should be based on 24-hour fluid intake and urine output measurements. From a general health point of view, it should be advised that fluid intake should be sufficient to avoid thirst and that an abnormally low or high 24-hour urine output should be investigated.

The few RCTs that have been published provide inconsistent evidence [133-135]. In most studies, the instructions for fluid intake were individualised and it is difficult to assess participant adherence to protocol. All available studies were in women. An RCT showed that a reduction in fluid intake by 25% improved symptoms in patients with OAB but not UI [135]. Personalised fluid advice compared to generic advice made no difference to continence outcomes in people receiving anticholinergics for OAB, according to an RCT comparing drug therapy alone to drug therapy with behavioural advice [136]. Patients should be warned of the possibility of worsening constipation as a consequence of fluid restriction.

4.1.4.1.4.3 Obesity and weight loss

Being overweight or obese has been identified as a risk factor for LUTS in many epidemiological studies [137, 138].

There is evidence that the prevalence of both UUI and SUI increases proportionately with rising body mass index (BMI) [139]. However, the evidence base largely relates to obesity and SUI rather than UUI and OAB. Therefore, no definite inference can be drawn between obesity and the prevalence of OAB.

4.1.4.1.4.4 Smoking

Smoking cessation is a generalised public health measure and has been shown to be weakly associated with improving urgency, frequency and UI [140, 141].

The effect of smoking cessation on LUTS was described as uncertain in a health technology assessment (HTA) review [142].

4.1.4.1.4.5 Summary of evidence and recommendations for lifestyle interventions

Summary of evidence	LE
Reduction of caffeine intake may reduce symptoms of frequency and urgency.	2
Addition of personalised fluid intake advice to pharmacotherapy provided no additional benefit in patients with OAB.	2
Reduction in fluid intake by 25% may help improve symptoms of OAB but not UI.	1b
Obesity is a risk factor for UI in women, but the relationship to other OAB symptoms remains unclear.	1b
There is weak evidence that smoking cessation will improve the symptoms of OAB.	3

Recommendations	Strength rating
Encourage overweight and obese adults with overactive bladder (OAB)/urinary incontinence to lose weight and maintain weight loss.	Strong
Advise adults with OAB that reducing caffeine intake may improve symptoms of urgency and frequency, but not incontinence.	Strong
Review type and amount of fluid intake in patients with OAB.	Weak
Provide smoking cessation strategies to patients with OAB who smoke.	Strong

4.1.4.1.5 Behavioural and physical therapies

Terminology relating to behavioural and physical therapies remains confusing because of the wide variety of ways in which treatment regimens and combinations of treatments have been delivered in different studies [143]. The terms are used to encompass all treatments which require a form of self-motivated personal retraining by the patient and also include techniques which are used to augment this effect.

Approaches include bladder training (BT) and PFMT, but terms such as bladder drill, bladder discipline, bladder re-education and behaviour modification are also used. Almost always in clinical practice, these will be introduced as part of a package of care including lifestyle changes, patient education and possibly some cognitive therapy as well. The extent to which individual therapists motivate, supervise and monitor these interventions is likely to vary but it is recognised that these influences are important components of the whole treatment package.

4.1.4.1.5.1 Prompted voiding and timed voiding

The term ‘prompted voiding’ implies that carers, rather than the patient, initiate the patient going to void with the aim of preventing or reducing UI. This applies largely to an assisted care setting.

Two systematic reviews (nine RCTs) [144, 145] confirmed a positive effect on continence outcomes for prompted voiding in comparison to standard care [145]. Timed voiding is defined as fixed, pre-determined, time intervals between toileting, applicable for those with or without cognitive impairment. A Cochrane review of timed voiding reviewed two RCTs, finding inconsistent improvement in continence compared with standard care in cognitively impaired adults [146].

4.1.4.1.5.2 Bladder Training

Bladder training (BT) is a programme of patient education along with a scheduled voiding regimen with gradually increasing voiding intervals. Specific goals are to correct faulty habit patterns of frequent urination, improve control over bladder urgency, prolong voiding intervals, increase bladder capacity, reduce incontinent episodes and restore patient confidence in controlling bladder function. The ideal form or intensity of a BT programme for OAB/UI is unclear. It is also unclear whether or not BT can prevent the development of OAB/UI.

There have been three systematic reviews on the effect of BT compared to standard care confirming that BT is more effective than no treatment in improving UUI [67, 142, 147]. The addition of BT to anticholinergic therapy did not improve UUI compared to anticholinergics alone but it did improve frequency and nocturia [148]. This review identified seven RCTs in which BT was compared to drug therapy alone and only showed a benefit for oxybutynin in cure and improvement of UUI [148].

4.1.4.1.5.3 Pelvic floor muscle training

An immediate effect of contracting the PFMs is a simultaneous inhibition of urgency, detrusor contraction and incontinence [149]. Intensive and regular strength training of the PFMs over time increases PFM strength and endurance, and changes the morphology of the pelvic floor which may yield a more effective inhibition of the

detrusor and help to stabilize the proximal urethra and improve urethral function. To date, there is a lack of basic and mechanistic studies to confirm that change of pelvic floor morphology improves OAB symptoms.

A systematic review of 11 RCTs [150] including women with OAB compared the efficacy of PFMT vs. inactive control, usual care, other lifestyle modification or other intervention. The descriptive analysis revealed that PFMT significantly reduced OAB symptoms (frequency and UUI) in five RCTs, while the remaining six reported no significant difference. Significant heterogeneity in protocols precluded meaningful comparisons.

4.1.4.1.5.4 Electrical stimulation

The details and methods of delivery of electrical stimulation (ES) vary considerably. Electrical stimulation of the pelvic floor can also be combined with other forms of conservative therapy, e.g. PFMT with and without biofeedback. Electrical stimulation is often used to assist women who cannot initiate contractions to identify their PFMs and in patients with OAB and UUI with the aim of inhibiting detrusor contraction. There is, however, lack of basic and mechanistic studies to confirm this theory.

A systematic review has been done on 51 trials on 3,443 adults with OAB symptoms [151], with quality of evidence ranging from very low to moderate. Moderate quality evidence suggests ES is more likely to improve OAB symptoms compared to sham control, no treatment or placebo. Moderate quality evidence also suggested that ES was more likely to improve OAB symptoms compared to anticholinergic therapy. There was insufficient evidence for comparisons to PFMT and between different types of ES.

4.1.4.1.5.5 Acupuncture

In a systematic review with meta-analysis of 10 RCTs including 794 patients (590 women), the authors reported that acupuncture might have an effect in reducing OAB symptoms compared to sham treatment [152]. The studies were of low quality and compared electro-acupuncture (EA) vs. sham acupuncture, or EA plus tolterodine vs. tolterodine alone.

4.1.4.1.5.6 Posterior tibial nerve stimulation

Electrical stimulation of the posterior tibial nerve (PTNS) delivers electrical stimuli to the sacral micturition centre via the S2–S4 sacral nerve plexus. Stimulation is percutaneous with a fine (34-G) needle, inserted just above the medial aspect of the ankle (P-PTNS). Transcutaneous stimulation is also available (T-PTNS) that delivers stimulation via surface electrodes which do not penetrate skin. Treatment cycles typically consist of twelve weekly treatments of 30 minutes.

4.1.4.1.5.6.1 Percutaneous posterior tibial nerve stimulation

The reviewed studies included two 12-week RCTs of P-PTNS against sham treatment [153, 154], one comparing PTNS to tolterodine, and a 3-year extension trial utilising a maintenance protocol in patients with UUI [155, 156]. The results of studies of PTNS in women with refractory UUI are consistent. Considered together, these results suggest that PTNS improves UUI in women who did not have adequate improvement or could not tolerate anti-muscarinic therapy. However, there is no evidence that PTNS cures UUI in women. In addition, PTNS is no more effective than tolterodine for improvement of UUI in women overall.

4.1.4.1.5.6.2 Transcutaneous posterior tibial nerve stimulation

A small RCT compared transcutaneous PTNS plus standard treatment (PFMT and BT) with PFMT and BT alone in older women [157]. Women in the T-TPNS group were more likely to achieve improvement at the end of therapy.

A systematic review of 13 trials (10 RCTs and 3 cohort studies) compared the efficacy of T-PTNS (treatment period between 4 and 12 weeks) with sham treatment, anticholinergics, and exercise in treatment of adults with OAB symptoms [158]. Of note, the populations were adult women and men, and some studies included patients with neurogenic OAB. Meta-analysis was possible in 2 RCTs comparing T-PTNS with sham treatment, and revealed mean reduction in total ICIQ-UI SF associated with T-PTNS of –3.79 points.

4.1.4.1.5.7 Summary of evidence and recommendations for behavioural and physical therapies

Summary of evidence	**LE**
Bladder training is effective for improvement of UUI in women.	1b
The combination of BT with anticholinergic drugs does not result in greater improvement of UUI, but may improve frequency and nocturia.	1b

Prompted voiding, either alone or as part of a behavioural modification programme, improves continence in elderly, care-dependent people.	1b
Pelvic floor muscle training may improve symptoms of frequency and incontinence in women.	1b
Electrical stimulation may improve symptoms of OAB in some women, but the type and mode of delivery of ES remains variable and poorly standardised.	1a
Percutaneous posterior tibial nerve stimulation appears effective for improvement of UUI in women who have had no benefit from anticholinergic medication.	2b
A maintenance programme of P-PTNS has been shown to be effective up to three years.	1b
Percutaneous-PTNS has comparable effectiveness to tolterodine for improvement of UUI in women.	1b
No serious adverse events have been reported for P-PTNS in UUI.	3
Transcutaneous-PTNS appears to be effective in reducing OAB symptoms compared to sham treatment.	1a

Recommendations	**Strength rating**
Offer prompted voiding for adults with overactive bladder (OAB) who are cognitively impaired.	Strong
Offer bladder training as a first-line therapy to adults with OAB/urgency urinary incontinence (UUI).	Strong
Ensure that pelvic floor muscle training programmes are as intensive as possible.	Strong
Consider posterior tibial nerve stimulation as an option for improvement of OAB/UUI in women who have not benefited from anticholinergic medication.	Strong

4.1.4.2 Pharmacological management

4.1.4.2.1 Anticholinergic drugs

Anticholinergic (antimuscarinic) drugs are currently the mainstay of treatment for OAB. They differ in their pharmacological profiles, e.g. muscarinic receptor affinity and other modes of action and in their pharmacokinetic properties, e.g. lipid solubility and half-life.

The evaluation of cure or improvement of OAB is made harder by the lack of standard definitions. In general, systematic reviews note that the overall treatment effect of drugs is usually small but larger than placebo. In addition, some RCTs have UI as an outcome rather than UUI. Dry mouth is the commonest side effect, though constipation, blurred vision, fatigue and cognitive dysfunction may occur with anticholinergic drugs [147].

Immediate-release (IR) anticholinergic preparations provide maximum dosage flexibility, including an off-label 'on-demand' use. Immediate-release drugs have a greater risk of side effects than extended release (ER) formulations because of differing pharmacokinetics. A transdermal delivery system (TDS) and gel developed for oxybutynin gives a further alternative formulation.

Seven systematic reviews of individual anticholinergic drugs vs. placebo were reviewed [147, 159-164]. Most studies included patients with a mean age of 55–60 years. The evidence reviewed was consistent, indicating that ER and IR formulations of anticholinergics offer clinically significant short-term improvement rates for OAB compared to placebo. On balance, IR formulations tend to be associated with more side effects compared to ER formulations [163].

A network meta-analysis of 128 RCTs comparing anticholinergics with placebo or with other anticholinergics revealed that all anticholinergics, except imidafenacin, showed significant cure or improvement in OAB symptoms in women and men [165].

Cure of UUI was deemed to be the most important outcome measure. Table 1 shows a summary of the findings from systematic reviews [147]. In summary, every drug where cure outcomes for UUI were available showed superiority compared to placebo, but the absolute size of effect was small. There is limited evidence that patients who do not respond to a first-line anticholinergic treatment may respond to a higher dose or a different anticholinergic agent [166, 167]. Risk of adverse events was often represented by trial-withdrawal because of adverse events, although this does not reflect clinical practice.

The cure rates for darifenacin were not included in the United States (U.S.) Agency for Healthcare Research and Quality (AHRQ) review. Continence rates were 29–33% for darifenacin compared to 17–18% for placebo [147]. Transdermal oxybutynin has shown a significant improvement in the number of incontinence episodes and micturitions per day vs. placebo and other oral formulations but cure of incontinence was not reported as an outcome [147].

Oxybutynin topical gel was superior to placebo for improvement of UUI with a higher proportion of participants being cured [147, 168].

Table 1: Summary of cure rates and discontinuation rates of anticholinergic drugs from RCTs which reported these outcomes [147]

Drug	No. of studies	n	RR (95% CI) (of curing UI)	NNT (95% CI) (to achieve one cure of UI)
Cure of incontinence				
Fesoterodine	2	2,465	1.3 (1.1–1.5)	8 (5–17)
Oxybutynin (includes IR)	4	992	1.7 (1.3–2.1)	9 (6–16)
Propiverine (includes IR)	2	691	1.4 (1.2–1.7)	6 (4–12)
Solifenacin	5	6,304	1.5 (1.4–1.6)	9 (6–17)
Tolterodine (includes IR)	4	3,404	1.2 (1.1–1.4)	12 (8–25)
Trospium (includes IR)	4	2,677	1.7 (1.5–2.0)	9 (7–12)
Discontinuation due to adverse events				
			RR (95% CI) (of discontinuation)	**NNT (95% CI) (for one discontinuation)**
Darifenacin	7	3,138	1.2 (0.8–1.8)	
Fesoterodine	4	4,433	2.0 (1.3–3.1)	33 (18–102)
Oxybutynin (includes IR)	5	1,483	1.7 (1.1–2.5)	16 (8–86)
Propiverine (includes IR)	2	1,401	2.6 (1.4–5)	29 (16–77)
Solifenacin	7	9,080	1.3 (1.1–1.7)	78 (39–823)
Tolterodine (includes IR)	10	4,466	1.0 (0.6–1.7)	
Trospium (includes IR)	6	3,936	1.5 (1.1–1.9)	56 (30–228)

CI = confidence interval; IR = immediate release; n = number of patients; NNT = number to treat; UI = urinary incontinence; RR = relative risk.

4.1.4.2.1.1 Comparison of different anticholinergic agents

Head-to-head comparison trials of the efficacy and side effects of different anticholinergic agents are of interest for decision making in practice.

A network meta-analysis revealed no clear best anticholinergic preparation for cure or improvement [165]. Darifenacin (40%), tolterodine IR and oxybutynin ER (13% each) appeared to score highest in indirect comparisons. Fesoterodine and oxybutynin IR were more effective than both oxybutynin (transdermal) and tolterodine ER. There were no clinically significant differences between anticholinergics for voiding and UI outcomes.

Another network meta-analysis of 53 RCTs compared the efficacy and tolerability of solifenacin 5 mg with other oral anticholinergics in the treatment of adults with OAB symptoms [169]. The analysis revealed that solifenacin 5 mg/day was significantly more effective than tolterodine 4 mg/day for reducing UUI episodes, but significantly less effective than solifenacin 10 mg/day for micturition episodes. Solifenacin 5 mg/day showed significantly lower risk of dry mouth compared with other anticholinergics. There were no significant differences for risk of blurred vision or constipation.

It is notable that nearly all the primary studies in this category were industry-sponsored. Upward dose titration is often included in the protocol for the experimental arm, but not for the comparator arm. In general, these studies have been designed to achieve regulatory approval. They have short treatment durations (twelve weeks) and a primary outcome of a change in OAB symptoms rather than a cure of, or an improvement in, UUI, which were generally analysed as secondary outcomes. The clinical utility of these trials in real life practice is debatable. Most trials were of low or moderate quality [161]. The 2012 AHRQ review included a specific section addressing comparisons of anticholinergic drugs (Table 1).

No single anticholinergic agent improved QoL more than another [161]. Dry mouth is the most prevalent adverse effect. Good evidence indicates that, in general, higher doses of any drug are likely to be associated with higher rates of adverse events. Also, ER formulations of short-acting drugs and longer-acting drugs are generally associated with lower rates of dry mouth than IR preparations [161, 170]. Oxybutynin IR showed higher rates of dry mouth than tolterodine IR and trospium IR, but lower rates of dry mouth than darifenacin,

15 mg daily [161, 170]. Overall, oxybutynin ER has higher rates of dry mouth than tolterodine ER, although the incidence of moderate or severe dry mouth were similar. Transdermal oxybutynin had a lower rate of dry mouth than oxybutynin IR and tolterodine ER, but had an overall higher rate of withdrawal due to adverse skin reactions [161]. Solifenacin 10 mg daily, had higher rates of dry mouth than tolterodine ER [161]. Fesoterodine 8 mg daily, had a higher rate of dry mouth than tolterodine 4 mg daily [171-173]. In general, similar discontinuation rates were observed, irrespective of differences in the occurrence of dry mouth (doses have been given where the evidence relates to a specific dose level typically from trials with a dose escalation element).

4.1.4.2.1.2 Anticholinergic drugs versus conservative treatment

The choice of drug vs. conservative treatment of OAB patients is an important question. More than 100 RCTs and high-quality reviews are available [148, 161, 162, 174-176]. Most of these were independent studies. A U.S. HTA [174] found that trials were of a low- or moderate-quality. The main focus of the review was to compare the different drugs used to treat UUI. In one study, multi-component behavioural modification produced significantly greater reductions in incontinence episodes compared to oxybutynin and higher patient satisfaction for behavioural vs. drug treatment.

The combination of BT and solifenacin in female patients with OAB conferred no additional benefit in terms of continence vs. solifenacin monotherapy [177]. A recent Cochrane review on the benefit of adding PFMT to other active treatments of UI in women showed insufficient evidence of any benefit in adding PFMT to drug treatment [178].

One RCT reported a similar improvement in subjective parameters with either transcutaneous electrical nerve stimulation (T-PTNS) or oxybutynin [179]. One study compared tolterodine ER to transvaginal/anal ES in female patients with OAB symptoms and/or UUI without differences in UI outcomes [180].

4.1.4.2.1.3 Anticholinergic drugs: adherence and persistence

Most studies on anticholinergic medication are short term (twelve weeks). Adherence in clinical trials is considered to be much higher than in clinical practice [181]. This topic has been reviewed for the development of a previous version of these Guidelines [182]. Two open-label extensions of RCTs of fesoterodine 8 mg showed adherence rates at two years of 49–84% [183, 184]. The main drugs studied were oxybutynin and tolterodine IR and ER. Non-persistence rates were high for tolterodine at twelve months, and particularly high (68–95%) for oxybutynin.

Five articles reported ‘median days to discontinuation’, but follow-up periods varied from < 30 days up to 50 days [185-189]. In a military health system where free medication was provided, the median time to discontinuation extended to 273 days [186].

Data on adherence/persistence from open-label extension populations are questionable as it could be argued that these patients are self-selected on the basis of their compliance. A Longitudinal Disease Analyser database study has indicated an increasing discontinuation rate, following treatment with anticholinergics, from 74.8% at one year to 87% at three years [190].

Several of the RCTs tried to identify the factors associated with low/lower adherence or persistence of anticholinergics. These were identified as:

- low level of efficacy (41.3%);
- adverse events (22.4%);
- cost (18.7%), although higher adherence rates were observed when drugs were provided at no cost to the patient [186].

Other reasons for poor adherence included:

- IR vs. ER formulations;
- age (lower persistence among younger adults);
- unrealistic expectations of treatment;
- gender distribution (better adherence/persistence in female patients);
- ethnic group (African-Americans and other ethnic minorities are more likely to discontinue or switch treatment).

4.1.4.2.1.4 Summary of evidence and recommendations for anticholinergic drugs

Summary of evidence	LE
No anticholinergic drug is clearly superior to another for cure or improvement of OAB/UUI.	1a
Higher doses of anticholinergic drugs are more effective to improve OAB symptoms, but exhibit a higher risk of side effects.	1a
Once daily (extended release) formulations are associated with lower rates of adverse events compared to immediate release preparations, although similar discontinuation rates are reported in clinical trials.	1b
Dose escalation of anticholinergic drugs may be appropriate in selected patients to improve treatment effect although higher rates of adverse events can be expected.	1b
Transdermal oxybutynin (patch) is associated with lower rates of dry mouth than oral anticholinergic drugs, but has a high rate of withdrawal due to skin reaction.	1b
There is no consistent evidence to show superiority of drug therapy over conservative therapy for treatment of OAB.	1b
Behavioural treatment may have higher patient satisfaction rates than drug treatment.	1b
There is insufficient evidence as to the benefit of adding PFMT to drug treatment for OAB.	1b
Adherence to anticholinergic treatment is low and decreases over time because of lack of efficacy, adverse events and/or cost.	2a
Most patients will stop anticholinergic agents within the first three months.	2a

Recommendations	Strength rating
Offer anticholineric drugs to adults with overactive bladder (OAB) who fail conservative treatment.	Strong
Consider extended release formulations of anticholinergic drugs, whenever possible.	Strong
If an anticholinergic treatment proves ineffective, consider dose escalation or offering an alternative anticholinergic formulation, or mirabegron, or a combination.	Strong
Encourage early review (of efficacy and side effects) of patients on anticholinergic medication for OAB.	Strong

4.1.4.2.2 Beta-3 agonists

Mirabegron was the first clinically available beta-3 agonist. Beta-3 adrenoceptors are the predominant beta receptors expressed on the smooth muscle cells of the detrusor and their stimulation is thought to induce detrusor relaxation. Vibegron is another beta-3 agonist commercially available in some countries.

Mirabegron has undergone evaluation in industry-sponsored phase II and phase III trials [191-194]. Three systematic reviews assessing the clinical effectiveness of mirabegron [191, 192, 195] reported that mirabegron at doses of 25, 50 and 100 mg, results in significantly greater reduction in UI episodes, urgency episodes and micturition frequency than placebo, with no difference in the rate of common adverse events [192]. The dry rates in most of these trials are between 35–40% for placebo, and between 43 and 50% for mirabegron. In all trials the statistically significant difference is consistent only for improvement but not for cure of UI. Similar improvements in frequency of UI episodes and micturitions/24 hours was found whether or not patients had previously tried anticholinergic agents. One systematic review showed that mirabegron is similarly efficacious as most anticholinergics in reducing UUI episodes [196].

The most common treatment adverse events in the mirabegron groups were hypertension (7.3%), nasopharyngitis (3.4%) and UTI (3%), with the overall rate similar to placebo [191, 194, 197].

In a twelve-month, active-controlled RCT of mirabegron 50/100 mg vs. tolterodine ER 4 mg, the improvement in efficacy seen at twelve weeks was sustained at 12-month evaluation in all groups. The reported dry rates at twelve months were 43%, 45% and 45% for mirabegron 50 mg, 100 mg and tolterodine 4 mg respectively [197]. *Post-hoc* analyses of RCTs showed that clinical improvement observed in parameters of OAB severity translates into an improvement in HRQoL and efficacy is maintained in patients with more severe degree of UI [198, 199].

No risk of QTc prolongation on electrocardiogram [200] and no raised intraocular pressure [201] were observed up to the 100 mg dose; however, patients with uncontrolled hypertension or cardiac arrhythmia were excluded from these trials. There is no significant difference in rate of side effects at different doses of mirabegron [197]. Patients on certain concurrent medications (e.g. metoprolol) should be counselled that, due to common metabolism pathways, their medication dosage may need to be adjusted. In the case of patients taking

metoprolol, blood pressure should be monitored after starting mirabegron and, if necessary, the metoprolol dosing may need to be changed.

Equivalent adherence was observed for tolterodine and mirabegron at twelve months (5.5% and 3.6%), although the incidence of dry mouth was significantly higher in the tolterodine group [197]. In mirabegron treated patients, improvement in objective outcome measures correlates directly with clinically relevant PROMs (Overactive Bladder questionnaire [OAB-q] and Patient Perception of Bladder Condition [PPBC]) [198, 202]. Data from a large Canadian Private Drug Plan database suggest a higher adherence rate for mirabegron compared to anticholinergics [203].

An RCT in patients who had inadequate response to solifenacin monotherapy 5 mg, demonstrated that combination treatment with mirabegron 50 mg had a higher chance of achieving clinically meaningful improvement in UI as compared to dose escalation of solifenacin [204].

4.1.4.2.2.1 Summary of evidence and recommendation for mirabegron

Summary of evidence	**LE**
Mirabegron is better than placebo and as efficacious as anticholinergics for improvement of OAB/UUI symptoms.	1a
Adverse event rates with mirabegron are similar to placebo.	1a
Patients inadequately treated with solifenacin 5 mg may benefit more from the addition of mirabegron than dose escalation of solifenacin.	1b

Recommendation	**Strength rating**
Offer mirabegron as an alternative to anticholinergics to women with overactive bladder who fail conservative treatment.	Strong

4.1.4.2.3 Anticholinergics and beta-3 agonists: the elderly and cognition

Trials have been conducted in elderly people with OAB. Considerations in this patient group include the multifactorial aetiology of OAB in the elderly, comorbidities such as cognitive impairment, the effect of co-medications and the risk of adverse events. The effects of anticholinergic agents on cognition have been studied in more detail.

Systematic reviews have included sections on the efficacy and safety of anticholinergics in elderly patients [147, 161]. A 2012 systematic review found inconclusive evidence as to the impact of anticholinergics on cognition [205].

Two recent longitudinal cohort studies in patients using drugs with anticholinergic effect showed a deterioration in cognitive function, alteration in CNS metabolism and an association with brain atrophy [206, 207]. In general, the long-term impact of anticholinergic agents specifically approved for OAB treatment on specific patient cohorts is poorly understood [208-211].

- *Oxybutynin:* There is evidence that oxybutynin IR may cause/worsen cognitive dysfunction in adults [208, 210, 212, 213]. One RCT with oxybutynin topical gel focused on cognitive and psychomotor function after one week of treatment showed no clinical meaningful effect on recent memory or other cognitive functions in healthy old adults [213]. Another retrospective study did not show cognitive impairment after 4 weeks of treatment with transdermal oxybutynin [210]. Recent evidence has emerged from a prospective cohort study showing cumulative cognitive deterioration associated with prolonged use of anticholinergic medication including oxybutynin [206]. More rapid functional deterioration might result from the combined use of cholinesterase inhibitors and anticholinergic agents in elderly patients with cognitive dysfunction [214].

- *Solifenacin:* One pooled analysis [215] has shown that solifenacin does not increase cognitive impairment in the elderly. No age-related differences in the pharmacokinetics of solifenacin in different age groups was found, although more frequent adverse events in subjects over 80 years of age were observed. No cognitive effect on healthy elderly volunteers was shown [216]. In a sub-analysis of a large trial, solifenacin 5–10 mg improved symptoms and QoL in people ≥ 75 years who had not responded to tolterodine [217]. In patients with mild cognitive impairment, ≥ 65 years, solifenacin showed no difference in efficacy between age groups and a lower incidence of most side effects compared to oxybutynin IR [213, 218].

- *Tolterodine:* No change in efficacy or side effects related to age has been reported, although a higher discontinuation rate was found for both tolterodine and placebo in elderly patients [208]. Two RCTs in the elderly found a similar efficacy and side effect profile to younger patients [219-222]. *Post-hoc* analysis has shown little effect on cognition. One non-randomised comparison showed lower rates of depression in elderly participants treated with tolterodine ER compared to oxybutynin IR [223].

- *Darifenacin:* Two RCTs in the elderly population (one in patients with UUI and the other in volunteers) concluded that darifenacin was effective with no risk of cognitive change, measured as memory scanning tests, compared to placebo [224, 225]. Another study on darifenacin and oxybutynin ER in elderly subjects concluded that the two agents had a similar efficacy, but that cognitive function was more often affected in the oxybutynin ER arm [210].

- *Trospium chloride:* Trospium does not appear to cross the blood brain barrier in healthy individuals due to its molecular characteristics (quaternary amine structure and hydrophilic properties). Two studies in healthy volunteers using electro-encephalography (EEG) showed no effect from trospium whilst tolterodine caused occasional changes and oxybutynin caused consistent changes [226, 227]. No evidence as to the comparative efficacy and side effect profiles of trospium in different age groups is available. However, there is some evidence that trospium does not impair cognitive function [211, 228] and that it is effective compared to placebo in the elderly [229].

- *Fesoterodine:* Pooled analyses of the RCTs of fesoterodine confirmed the efficacy of the 8 mg but not the 4 mg dose in over 75-year olds [183]. Adherence was lower in the over-75-year-old group but the effect on mental status was not reported [173, 183, 230]. A more recent RCT showed efficacy of fesoterodine in the vulnerable elderly with no differences in cognitive function at twelve weeks [231].

- *Mirabegron:* Analysis of pooled data from three RCTs showed efficacy and safety of mirabegron in elderly patients [232].

4.1.4.2.3.1 Applicability of evidence to the general elderly population

It is not clear how much the data from pooled analyses and subgroup analyses from large RCTs can be extrapolated to a general ageing population. Community-based studies of the prevalence of anticholinergic side effects may be the most helpful [233]. When starting anticholinergics in elderly patients, mental function should be assessed objectively and monitored [234]. No consensus exists as to the best mental function test to detect changes in cognition [214, 235].

4.1.4.2.3.2 Anticholinergic burden

A number of medications have anticholinergic effects and if another anticholinergic drug is added the possible greater cumulative effects on cognition should be considered. Lists of drugs with anticholinergic properties are available from several sources [236].

No studies were identified specifically in older people with LUTS, but evidence was available from observational cohort studies relating to the risk in a general population of older people.

Two systematic reviews of largely retrospective cohort studies showed a consistent association between long-term anticholinergic use and cognitive dysfunction [237, 238]. Longitudinal studies in older people over 2–4 years have found increased rates of decline in cognitive function for patients on anticholinergics or drugs with anticholinergic effects [206, 207, 239, 240]. It is unclear whether there is a direct correlation between cognitive dysfunction caused by medication and the long-term risk of the development of dementia.

4.1.4.2.3.3 Summary of evidence and additional recommendations for use of anticholinergic drugs in the elderly

Summary of evidence	**LE**
Anticholinergic drugs are effective in elderly patients suffering from OAB/UUI.	1b
Mirabegron has been shown to be efficacious and safe in elderly women suffering from OAB.	1b
In older women the cognitive impact of drugs which have anticholinergic effects is cumulative and increases with length of exposure.	2
Oxybutynin may worsen cognitive function in elderly women.	2
Darifenacin, fesoterodine, solifenacin and trospium have not been shown to cause cognitive dysfunction in elderly women in short-term studies.	1b

Recommendations	Strength rating
Long-term anticholinergic treatment should be used with caution in elderly women, especially those who are at risk of, or have pre-existing cognitive dysfunction.	Strong
Assess anticholinergic burden and associated co-morbidities in patients being considered for anticholinergic therapy for overactive bladder syndrome.	Weak

4.1.4.2.4 Oestrogens

Oestrogenic drugs including conjugated equine oestrogens, oestradiol, tibolone and raloxifene, are used as hormone replacement therapy (HRT) for women with natural or therapeutic menopause.

Oestrogen treatment for UI has been tested using oral, transdermal and vaginal routes of administration. Vaginal (local) treatment is primarily used to treat symptoms of vaginal atrophy in post-menopausal women. Available evidence related mainly to SUI and although some reviews include participants with UUI, it is difficult to generalise the results to women with predominantly OAB/UUI.

The association of LUTS with Genitourinary Syndrome of Menopause (GSM) should be considered [241]. GSM is a relatively new term that describes various menopausal symptoms and signs associated with physical changes of the vulva, vagina, and LUT. These include mucosal pallor/erythema, loss of vaginal rugae, tissue fragility/fissures, vaginal petechiae, urethral mucosal prolapse, introital retraction and vaginal dryness. There is evidence from a systematic review to suggest benefit from vaginal oestrogen therapy in GSM [242]. All vaginal oestrogens demonstrated superiority in objective endpoints and subjective endpoints of GSM compared to placebo. Only some trials demonstrated superiority vs. placebo in urogenital symptoms (UI, recurrent UTI, urgency, frequency). No significant difference was observed between various dosages and dosage forms of vaginal oestrogen products. Vaginal oestrogen showed superiority over vaginal lubricants and moisturizers for the improvement of objective clinical endpoints of vulvovaginal atrophy but not for subjective endpoints [242].

Available evidence suggests that vaginal oestrogen treatment with oestradiol and oestriol is not associated with the increased risk of thromboembolism, endometrial hypertrophy, and breast cancer seen with systemic administration [243-245].

4.1.4.2.4.1 Summary of evidence and recommendation for oestrogen therapy

Summary of evidence	LE
Vaginal oestrogen therapy may improve symptoms associated with GSM, of which OAB may be a component.	1a

Recommendation	Strength rating
Offer vaginal oestrogen therapy to women with lower urinary tract symptoms and associated symptoms of genito-urinary syndrome of menopause.	Weak

4.1.4.3 Surgical management

4.1.4.3.1 Bladder wall injection of botulinum toxin A

Onabotulinum toxin A (onabotA; BOTOX®) 100 U is licenced in Europe to treat OAB with persistent or refractory UUI in adults of both genders [246, 247]. Surgeons should be aware that other doses of onabotA and other formulations of botulinum toxin A, abobotulinum toxin A and incobotulinum toxin A, are not licensed for use in OAB/UUI. Doses for onabotA are not transposable to the other brands of botulinum toxin A. The continued efficacy of repeat injections is usual, but discontinuation rates may be high [248, 249]. The most important adverse events related to onabotA 100U injection detected in the regulatory trials were UTI and an increase in PVR that may require CISC [250].

Following a dose ranging study in which the 100 U of onabotA was established as the ideal dose, a phase III trial randomised (1:1) the same group of 557 OAB-wet patients whose symptoms were not adequately managed with anticholinergics to receive bladder wall injections of onabotA (100 U) or saline. At baseline, the population had on average more than five episodes of UUI, around twelve micturitions per day and a small PVR. At week twelve, in patients treated with onabotA, UUI episodes/day were halved and the number of micturitions/day reduced by more than two. A total of 22.9% of the patients in the onabotA arm were fully dry, against 6.5% in the saline arm [250]. Rates of urinary retention are not reported in systematic reviews, and a Cochrane review reported no significant difference in PVR between the onabotA and placebo groups [251].

Quality of life was substantially improved in the onabotA arm, as shown by the > 2.5 times improvement in I-QOL scores compared to baseline. Cohort studies have shown the effectiveness of bladder wall injections of onabotA in the elderly and frail elderly [252], though the success rate might be lower and the PVR (> 150 mL) higher in this group.

The median time to request re-treatment in the pooled analysis of the two RCTs was 24 weeks [247, 250]. Follow-up over 3.5 years showed consistent or increasing duration of effect for each subsequent treatment, with a median of 7.5 months. Considerable differences between patients have been observed on secondary analysis [253].

A recent RCT compared onabotA injection 100 U to solifenacin (with dose escalation or switch to trospium possible in the solifenacin group) and showed similar rates of improvement in UUI over the course of six months [254]. However, patients receiving onabotA were not only more likely to have cure of UUI (27% vs. 13%, p = 0.003), but also had higher rates of urinary retention during the initial two months (5% vs. 0%) and of UTIs (33% vs. 13%). Patients taking anticholinergics were more likely to have dry mouth. These results are further strengthened by a 2017 systematic review and network meta-analysis of onabotulinum toxin A vs. oral therapies (anticholinergics and mirabegron) for OAB at 12 weeks [255]. This review reported that patients receiving onabotulinum toxin had the greatest reduction in UUI episodes, urgency episodes, micturition frequency and the highest odds of achieving dryness as well as ≥ 50% reduction from baseline UI episodes/day (type not specified). However, adverse events were not reported in this network meta-analysis.

Identification of DO in urodynamics does not appear to influence the outcome of onabotulinum toxin A injections in patients with UUI [85].

4.1.4.3.1.1 Summary of evidence and recommendations for bladder wall injection of botulinum toxin A

Summary of evidence	**LE**
A single treatment session of onabotulinum toxin A (100 U) injected in the bladder wall is more effective than placebo at curing and improving UUI/OAB symptoms and QoL.	1a
There is no evidence that repeated injections of onabotulinum toxin A have reduced efficacy but discontinuation rates are high.	2a
There is a risk of increased PVR and UTI with onabotulinum toxin A injections.	2
The risk of bacteriuria after onabotulinum toxin A (100 U) injection is high but the clinical significance of this remains uncertain.	1b
Onabotulinum toxin A (100 U) is superior to anticholinergics and mirabegron for cure of UUI and improvement of symptoms of OAB at twelve weeks.	1a

Recommendations	**Strength rating**
Offer bladder wall injections of onabotulinum toxin A (100 U) to patients with overactive bladder/urgency urinary incontinence refractory to conservative therapy (such as pelvic floor muscle training and/or drug treatment).	Strong
Warn patients of the limited duration of response, risk of urinary tract infection and the possible prolonged need for clean intermittent self-catheterisation (ensure that they are willing and able to do so).	Strong

4.1.4.3.2 Sacral nerve stimulation

Sacral nerve stimulation involves placing electrodes adjacent to the sacral nerve roots and delivering an electric current to the area via an attached battery implanted in the buttock which delivers low-amplitude stimulation resulting in modulation of neural activity and stabilisation of bladder electrical activity through a mechanism that is, as yet, not fully understood. In most centres, test stimulation with a temporary or permanent electrode will be performed to assess response, before undertaking permanent stimulator implantation.

All randomised studies suffer from the limitation that patients cannot be blinded to the treatment allocation since all recruited subjects had to respond to a test phase before randomisation. A Cochrane review of the literature until March 2008 [256] identified three RCTs that investigated sacral nerve stimulation in patients with refractory UUI. The majority of included studies compared a strategy of immediate implantation vs. delayed implantation.

One study compared implantation to controls who stayed on medical treatment and received delayed implantation at six months. Fifty percent of the immediately implanted group had > 90% improvement in UUI at six months compared to 1.6% of the control group [257]. The effect on generic QoL measured by the SF-36, was unclear as it differed between the groups in only one of the eight dimensions. The other RCT achieved similar results, although these patients had already been included in the first report [258].

The results of seventeen case series of patients with UUI, who were treated early with SNS, were reviewed [259]. After a follow-up duration of between one and three years, approximately 50% of patients with UUI demonstrated > 90% reduction in UI, 25% demonstrated 50–90% improvement, and another 25% demonstrated < 50% improvement. Two case series describing the outcome of SNS, with a mean or median follow-up of at least four years [260, 261] reported continued success (> 50% improvement of original symptoms) in patients available for follow-up. Cure rates for UUI were 15% [261].

A more recent RCT comparing a strategy of onabotulinum toxinA injection (200 IU), repeated as required, against a strategy of test and, if indicated, subsequent permanent SNS showed lower cure rates with SNS at six months: 20% in the onabotulinumtoxinA group and 4% in the SNS group had complete resolution of UUI ($p < 0.001$) [262]. Forty-six per cent in the onabotulinumtoxinA group and 26% in the SNS group had at least a 75% reduction in the number of episodes of UUI ($p < 0.001$). This 4% cure rate is also lower than the six month cure rate in another RCT of SNS vs. standard medical therapy which reported a 39% continence rate in the SNS group at six months; however, the mean (SD) baseline leaks per day (2.4 [± 1.7]) for the SNS group in this study were lower , reflecting a less severely affected population [263]. Two-year follow-up data from 87% of participants in this trial suggests no significant deterioration in treatment outcomes over two years, although satisfaction rates and treatment endorsement remain higher with onabotulinum toxin. Interestingly, the rates of complete resolution of UI (5% for both) as well as ≥ 75% reduction in UUI episodes (22% onabotulinum toxin vs. 21% SNM) were equivalent at the 2-year mark [264]. Sacral nerve stimulation revision and removal occurred in 3% and 9% of this cohort, respectively. Some of these differences in outcome could potentially be explained by performance bias particularly the difference in type of permanent lead used and potential learning curve effects within the SNS cohort as well as the use of a relatively high (200 U) dose of onabotulinum toxin A.

A 2018 review of studies including SNS with at least 6 months follow-up reported dry rates of between 43 and 56% [265]. Adverse events occurred in 50% of implanted cases, with surgical revision necessary in 33–41% [261, 262]. In a sub-analysis of the RCT, the outcomes of UUI patients, with or without pre-implant DO, were compared. Similar success rates were found in patients with or without urodynamic DO [266].

4.1.4.3.2.1 Summary of evidence and recommendation for sacral nerve stimulation

Summary of evidence	**LE**
Sacral nerve stimulation is more effective than continuation of failed conservative treatment for OAB/ UUI, but no sham controls have been used.	1b
Sacral nerve stimulation is not more effective than onabotulinumA toxin 200 U injection at 24 months.	1b
In patients who have been implanted 50% improvement of UUI is maintained in at least 50% of patients and 15% may remain cured at four years.	3
The use of tined, permanent electrodes in a staged approach results in more patients receiving the final implant than occurs with temporary test stimulation.	4

Recommendation	**Strength rating**
Offer sacral nerve stimulation to patients who have overactive bladder/urgency urinary incontinence refractory to anticholinergic therapy.	Strong

4.1.4.3.3 Cystoplasty/urinary diversion

4.1.4.3.3.1 Augmentation cystoplasty

In augmentation cystoplasty (also known as clam cystoplasty), a detubularised segment of bowel is inserted into the bivalved bladder wall. The distal ileum is the bowel segment most often used but any bowel segment can be utilised if it has the appropriate mesenteric length. Most of the evidence pertaining to cystoplasty comes from patients with neuropathic bladder dysfunction. One study did not find any difference between bivalving the bladder in the sagittal or in the coronal plane [267, 268]. The procedure can be done, with equal success by open or robotic techniques, although the robotic consumes considerably more operative time [269].

There are no RCTs comparing bladder augmentation to other treatments for patients with OAB/UUI. Most often, bladder augmentation is used to correct neurogenic DO, small capacity or low-compliant bladders caused by fibrosis, chronic infection such as tuberculosis, radiation or chronic inflammation from interstitial cystitis.

The largest case series of bladder augmentation in a mixed population of idiopathic and neurogenic UUI included 51 women [270]. At an average follow-up of 74.5 months, only 53% were continent and satisfied with the surgery, whereas 25% had occasional leaks and 18% continued to have disabling UUI. It seems that the results for patients with idiopathic DO (58%) appeared to be less satisfactory than for patients with neurogenic UUI (90%). Malignant transformation was not reported in this series; however, it has been documented in other series and a systematic review [271-273]. Less than 60 cases have been reported worldwide, and almost all are exclusively beyond 10 years after the original cystoplasty surgery [274].

Adverse effects were common and have been summarised in a review over five to seventeen years of more than 267 cases, 61 of whom had non-neurogenic UUI [275]. In addition, many patients may require CISC to obtain adequate bladder emptying (Table 2). It is unclear if mucolytic agents will effectively reduce mucus accumulation. The only RCT that was identified comparing various mucolytic agents did not find significant benefits with the use of N-acetylcysteine, aspirin, or ranitidine. In one small study (n = 40), the use of subcutaneous octreotide immediately before, and for 15 days after surgery was reported to yield significant reductions in mucus production, the need for bladder irrigation to clear blockages, and the mean duration of hospital stay [276]. Before cystoplasty all potential complications should be outlined and both before and after surgery patients should be well supported by stoma/continence nurses.

Depending on the relative costs of Onabotulinum Toxin A and augmentation cystoplasty, the latter can be cost effective within five years if the complication rate is low and duration of effect of Onabotulinum Toxin A < 5 months [277].

Table 2: Complications of bladder augmentation

Short-term complications	**Affected patients (%)**
Bowel obstruction	2
Infection	1.5
Thromboembolism	1
Bleeding	0.75
Fistula	0.4
Long-term complications	**Affected patients (%)**
Clean intermittent self-catheterisation	38
Urinary tract infection/bacteriuria	70% asymptomatic 20% symptomatic
Urinary tract stones	13
Metabolic disturbance	16
Deterioration in renal function	2
Bladder perforation	0.75
Change in bowel symptoms	25

4.1.4.3.3.2 Detrusor myectomy (bladder auto-augmentation)
Detrusor myectomy aims to increase bladder capacity and reduce storage pressures by incising or excising a portion of the detrusor muscle, to create a bladder mucosal 'bulge' or pseudo-diverticulum. It was initially described as an alternative to bladder augmentation in children [278].

Two case series in adult patients with idiopathic and neurogenic bladder dysfunction, demonstrated poor long-term results caused by fibrosis of the pseudo-diverticulum [279, 280]. This technique is rarely, if ever, used nowadays.

4.1.4.3.3.3 Urinary diversion
Urinary diversion remains a reconstructive option for patients with intractable UI after multiple pelvic procedures, radiotherapy or pelvic pathology leading to irreversible sphincteric incompetence or fistula formation. These patients may be offered irreversible urinary diversion surgery. Options include ileal conduit urinary diversion, orthotopic neobladder and heterotopic neobladder with Mitrofanoff continent catheterisable conduit. There is insufficient evidence to comment on which procedure leads to the most improved QoL.

A small study comparing ileal with colonic conduits concluded that there were no differences in the relative risks of UUT infection and uretero-intestinal stenosis. However, there are no studies that have specifically examined these techniques in the treatment of intractable OAB/UUI [267]. Therefore, careful consideration on which operation is undertaken will depend on thorough pre-operative counselling, access to stoma/continence nurses as well as patient factors to allow for fully informed patient choice.

4.1.4.3.3.4 Summary of evidence and recommendations for cystoplasty/urinary diversion

Summary of evidence	LE
There is limited evidence of the effectiveness of augmentation cystoplasty and urinary diversion in treatment of idiopathic OAB.	3
Augmentation cystoplasty and urinary diversion are associated with high risks of short- and long-term severe complications.	3
The need to perform CISC following augmentation cystoplasty is very common.	3
There is no evidence comparing the efficacy or adverse effects of augmentation cystoplasty to urinary diversion.	3
Detrusor myectomy is ineffective in adults with UUI.	3

Recommendations	Strength rating
Offer augmentation cystoplasty to patients with overactive bladder (OAB)/urgency urinary incontinence (UUI) who have failed all other treatment options and have been warned about the possible small risk of malignancy.	Weak
Inform patients undergoing augmentation cystoplasty of the high risk of having to perform clean intermittent self-catheterisation (ensure they are willing and able to do so) and that they need life-long surveillance.	Strong
Do not offer detrusor myectomy as a treatment for UUI.	Weak
Only offer urinary diversion to patients who have failed less invasive therapies for the treatment of OAB/UUI, who will accept a stoma and have been warned about the possible small risk of malignancy.	Weak

*4.1.5 **Follow-up***

Follow-up for women with OAB is guided by the type of treatment instituted and local service capacity. Standardisation of follow-up pathways can therefore be difficult. Here we provide recommendations based on best practice and standards from clinical trials.

4.1.5.1 Recommendations for follow-up of patients with overactive bladder

Recommendations	Strength rating
Offer early follow up to women who have been commenced on anticholinergic or beta-3 agonist therapy.	Strong
Offer repeat injections of onabotulinum toxin, as required, to women in whom it has been effective (refer to the manufacturers guidance regarding the minimum timeframe for repeat injections).	Strong
Offer life-long surveillance to women who have a sacral nerve stimulation implant to monitor for lead displacement, malfunction and battery wear.	Strong
Offer cystoscopic surveillance to women with an augmentation cystoplasty due to the small risk of malignancy.	Weak

4.2 Stress Urinary Incontinence

*4.2.1 **Epidemiology, aetiology, pathophysiology***

Stress urinary incontinence, defined as 'involuntary loss of urine on effort or physical exertion', is a significant health problem worldwide with social and economic impact on women and society. It is estimated that the number of women in the U.S. with UI will increase from 18.3 million in 2010 to 28.4 million in 2050 [281]. The prevalence of SUI appears to peak between the ages of 45–59 years [282].

Data regarding the association of UI with ethnicity are conflicting. In several studies, SUI is more common in white women than in women of African-American or Asian-American origin [283, 284]. Other factors positively associated with SUI include parity, obesity, previous hysterectomy or pelvic surgery, diabetes mellitus [285] and pulmonary disease [286]. Physical activity level is another important factor which also positively correlates with severity of the problem [287].

Two common, often overlapping, mechanisms for SUI have been described: 1) urethral hypermobility resulting from loss of support of the bladder neck and urethra and 2) weakness of the urinary sphincter itself (intrinsic sphincter deficiency) which can result from trauma, radiotherapy, previous pelvic or urogynaecological surgery, neurological disease or ageing.

The mechanism behind urethral hypermobility as a cause of SUI is based on the "vaginal hammock" hypothesis [288]. The endopelvic fascia, that is attached to the upper (abdominal) side of the PFMs, links the muscles to the vagina and represents the 'hammock' which can compress the urethra during both rest and activity. This compression, combined with 'intrinsic' urethral sphincter pressure, supports and maintains the urethra in the correct and closed position preventing involuntary loss of urine, despite any increases in intravesical pressure. Damage to the supporting tissues (particularly the arcus tendinous fasciae pelvis, the central part of the fascia) can result in hypermobility of the urethra. Consequently, rather than being compressed at times of increased intra-abdominal pressure, the urethra moves caudally funnelling the bladder neck, and is no longer compressed, resulting in SUI [288, 289]. In general, almost all treatments are used for both subtypes of SUI, but most treatments are more successful in patients with some degree of urethral hypermobility than for isolated intrinsic weakness of the urinary sphincter [290].

*4.2.2 **Classification***

Patients with SUI can be classified as 'uncomplicated' and 'complicated' [291]. The Panel reached consensus on the definition to be used throughout this Guideline document:

- Women with uncomplicated SUI: no history of prior surgery for SUI, no prior extensive pelvic surgery, no prior pelvic radiation treatment, no neurogenic LUT dysfunction, no bothersome genitourinary prolapse, absence of voiding symptoms, and no medical conditions that affect the LUT. In cases where additional significant storage symptoms, especially OAB, are present, consider a possible diagnosis of MUI (see Section 4.3).
- Women with complicated SUI: previous surgery for incontinence or previous extensive pelvic surgery, a history of pelvic irradiation, the presence of anterior or apical POP, the presence of voiding symptoms or the presence of neurogenic LUT dysfunction, and with significant OAB/UUI. Neurogenic LUT dysfunction is reviewed in the EAU Guidelines on Neuro-Urology and will not be considered further in this guideline [9]. The treatment of LUTS associated with genitourinary prolapse has been included in this Guideline (see Section 4.7).

*4.2.3 **Diagnostic evaluation***

4.2.3.1 History and physical examination

There is universal agreement that taking a history should be the first step in the assessment of anyone with UI. When the history categorises UI as probable SUI the presence of complicated or uncomplicated SUI can also be determined. Those patients who require rapid referral to an appropriate specialist can also often be identified from the clinical history.

There is little evidence from clinical trials that carrying out a clinical examination improves clinical outcomes, but there is widespread consensus that it remains an essential part of the assessment of women with SUI. It should include abdominal examination, vaginal examination and a careful assessment of any associated pelvic POP, examination of the perineum and evaluation of PFM strength, as well as a neuro-urological examination. An attempt to reproduce the SUI should be made. A standing cough test has a higher sensitivity for the diagnosis of SUI compared to a supine cough test [292]. Despite this, the ICS has proposed a standardisation of the female cough stress test that includes a supine/lithotomy position with 200-400 mL of fluid in the bladder and 1–4 coughs [293].

4.2.3.1.1 Summary of evidence and recommendation for history and physical examination for SUI

Summary of evidence	LE
A standing cough stress test is more sensitive than a supine test.	1b

Recommendation	Strength rating
Take a full clinical history and perform a thorough physical examination in all women presenting with stress urinary incontinence.	Strong

4.2.3.2 Patient questionnaires

Although many studies have investigated the validity and reliability of urinary symptom questionnaires and PROMs, most of these studies did not include homogenous populations of adult women diagnosed with SUI. This limits the extent to which results and conclusions from these studies can be applied in women with SUI. Some questionnaires are used for prevalence studies, others are responsive to change and may be used to measure outcomes, though evidence on their sensitivity is inconsistent [24, 25]. No evidence was found to indicate whether use of QoL or condition-specific questionnaires have an impact on the outcome of treatment. To date, there is no one questionnaire that fulfils all requirements for the assessment of women with SUI.

4.2.3.2.1 Summary of evidence and recommendation for patient questionnaires

Summary of evidence	LE
Validated condition-specific symptom scores assist in the screening for, and categorisation of UI.	3
Validated symptom scores measure the severity and bother of SUI.	3
Both condition-specific and general health status questionnaires measure current health status, and are responsive to change following treatment.	3

Recommendation	Strength rating
Use a validated and appropriate questionnaire as part of the standardised assessment of patients with stress urinary incontinence.	Strong

4.2.3.3 Post-void residual volume

It is important to evaluate PVR in patients with SUI, in particular in patients who also have voiding symptoms or POP. The prevalence of a significant PVR in patients with SUI is uncertain, partly because of the lack of a standard definition of an abnormal PVR volume. Most studies investigating PVR have not included patients with SUI. In general, the data on PVR can only be applied with caution to adults with non-neurogenic SUI.

In a cohort study of over 900 women with SUI, there was good correlation between PVR estimated by US and measured by catheterisation. The mean PVR was 39 mL measured by catheterisation and 63 mL estimated by US, with only 16% of women having a PVR > 100 mL [57].

4.2.3.3.1 Summary of evidence and recommendations for post-void residual volume

Summary of evidence	LE
The majority of women with SUI will not have a significant PVR.	3
There is good correlation between PVR estimated using US and measured via catheterisation in women with SUI.	3

Recommendations	Strength rating
Measure post-void residual (PVR) volume, particularly when assessing patients with voiding symptoms or complicated stress urinary incontinence (SUI).	Strong
When measuring PVR, use ultrasound in preference to catheterisation.	Strong
Monitor PVR in patients scheduled for treatment which may cause or worsen voiding dysfunction, including surgery for SUI.	Strong

4.2.3.4 *Urodynamics*

Urodynamic testing is widely used as an adjunct to clinical diagnosis, based on the assumption that it may help to provide or confirm diagnosis. The role of urodynamics in SUI evaluation remains poorly defined and is still under debate.

Invasive urodynamic tests are often performed prior to surgical treatment of SUI. Clinical diagnosis of incontinence and cystometric findings often do not correlate [67, 68]. The diagnostic accuracy of urethral pressure profilometry [69] and VLPP measurement in SUI is generally poor [294]. Measurement of MUCP correlates, although weakly, with incontinence severity [69] and there is conflicting evidence about its reproducibility [64, 65]. One method of recording MUCP cannot be compared meaningfully to another [66]. Valsalva leak point pressures are not standardised and there is minimal evidence about reproducibility. Valsalva leak point pressure did not reliably assess incontinence severity in a cohort of women selected for surgical treatment of SUI [70]. The predictive value of the tests, regarding the outcome of treatment remains unclear.

A Cochrane systematic review including seven RCTs showed that the use of urodynamic tests increased the likelihood of avoiding surgery for SUI. However, there was no evidence that this influence on decision making altered the clinical outcome of treatment within trial populations [112].

A high-quality RCT (n = 630) compared office evaluation alone to office evaluation and urodynamics in women with clinical demonstrable SUI about to undergo surgery for SUI. Whilst urodynamics changed the clinical diagnosis in 56% of women [295], there was no difference in levels of SUI or any secondary outcome at twelve months follow-up after SUI surgery [80]. Another similar study also found that the omission of urodynamics was not inferior in the pre-operative work up of SUI [296]. Patients in whom urodynamics were discordant with clinical assessment (n = 109) were randomly allocated to receive either immediate surgery or individually tailored therapy based on the urodynamic findings. In this trial, performing immediate surgery, irrespective of the result of urodynamics, did not result in inferior outcomes [297]. An RCT, in which 145 women were randomised to retropubic or transobturator MUS, concluded that when patients were stratified according to pre-operative VLPP (≤ or > 60 cm H_2O), it was not linked to outcome after both synthetic MUS procedures [298].

In another study conflicting evidence was reported. A VLPP or maximum urethral closure pressure in the lowest quartile was predictive in terms of failure at twelve months [83].

The Panel recognise that it may be valuable to use urodynamic test results to help select the optimum surgical procedure, but the evidence outlined above would suggest that performing urodynamics in patients with uncomplicated SUI, which can be diagnosed based on a detailed clinical history and demonstrated at examination, is not necessary. The role of urodynamics in complicated SUI is still under debate [81, 299]. However in cases of SUI with associated storage symptoms, cases in which the type of incontinence is unclear, cases where voiding dysfunction is suspected, cases with associated POP or those with a previous history of SUI surgery, the Panel consensus is that urodynamics should be carefully considered. This is in line with other guideline documents in this topic area [67].

4.2.3.4.1 Summary of evidence and recommendations for urodynamics

Summary of evidence	**LE**
Pre-operative urodynamics in women with uncomplicated, clinically demonstrable, SUI does not improve the outcome of surgery for SUI.	1b
There is no consistent correlation between the result of urethral function tests and subsequent success or failure of SUI surgery.	3
There is no consistent evidence that pre-operative DO is associated with surgical failure of MUS in women.	3

Recommendations	**Strength rating**
Do not routinely carry out urodynamics when offering treatment for uncomplicated stress urinary incontinence (SUI).	Strong
Perform pre-operative urodynamics in cases of SUI with associated storage symptoms, cases in which the type of incontinence is unclear, cases where voiding dysfunction is suspected, cases with associated pelvic organ prolapse or those with a previous history of SUI surgery.	Weak

Perform urodynamics if the findings may change the choice of invasive treatment.	Weak
Do not use urethral pressure profilometry or leak point pressure to grade severity of incontinence as they are primarily tests of urethral function.	Strong

4.2.3.5 Pad testing

Measurement of urine loss using an absorbent pad worn over a set period of time or during a protocol of physical exercise can be used to quantify the presence and severity of SUI, as well as a patient's response to treatment.

The clinical utility of pad tests for people with UI has been assessed in two systematic reviews [94, 95]. A one-hour pad test using a standardised exercise protocol and a diagnostic threshold of 1.4 g shows good specificity but low sensitivity for the diagnosis of SUI and MUI. A 24-hour pad test using a threshold of 4.4 g is more reproducible but is difficult to standardise with variation according to activity level [96]. A pad test with a specific short graded exercise protocol also has diagnostic value but a negative test should be repeated or the degree of provocation increased [97]. The usefulness of pad tests in quantifying severity and predicting outcome of treatment is uncertain [94, 99]. Pad testing is responsive to change following successful treatment [100]. Pad testing using a standardised bladder volume (50% of cystometric capacity) has been suggested to allow for a more reliable assessment of UI in a small study including 25 women [101]. There is no evidence that one type of pad test is superior to another.

4.2.3.5.1 Summary of evidence and recommendations for pad testing

Summary of evidence	**LE**
A pad test can diagnose UI accurately, but cannot determine the aetiology.	2
Standardisation of bladder volume and degree of provocation improves reproducibility.	2
Twenty-four hours is sufficient duration for home-based testing balancing diagnostic accuracy and adherence.	2
Change in leaked urine volume on standardised pad tests can be used to measure treatment outcome.	2

Recommendations	**Strength rating**
Use a pad test of standardised duration and activity protocol.	Strong
Use a standardised pad test when quantification of urinary incontinence is required, especially to assess response to treatment.	Weak

4.2.3.6 Imaging

The role of imaging in SUI patients is limited. Many studies have evaluated imaging of bladder neck mobility by US and MRI, and concluded that SUI cannot be identified by a particular pattern of urethro-vesical movement [300]. In addition, the generalised increase in urethral mobility after childbirth does not appear to be associated with *de novo* SUI [301]. Studies have assessed the use of imaging to investigate the mechanism of action of MUS inserted for SUI. One study suggested that MUS placement decreased mobility of the mid-urethra but not mobility of the bladder neck [108]. Following MUS surgery, a wider gap between symphysis and sling (assessed by imaging) has been shown to correlate with a lower chance of cure of SUI [109]. One study of 72 women post-synthetic sub-urethral MUS surgery has investigated the usefulness of translabial US to assess tape functionality. In this study different parameters were measured (distance tape to urethra, position and shape during Valsalva, etc.) and concluded that tape position relative to the patient's urethra seems to play a role in treatment outcome [302]. The general role of US in the evaluation and follow-up of women with SUI is unclear, future research is needed to establish its place in the clinical pathway.

Several imaging studies have investigated the relationship between sphincter volume and function in women [303] and between sphincter volume and outcome from surgery in women [304]. However, no imaging test has been shown to predict the outcome of treatment for SUI. Imaging of the pelvic floor can identify levator ani detachment and hiatus size, although there is little evidence of a relationship to clinical benefit after treatment of SUI.

4.2.3.6.1 Summary of evidence and recommendation for imaging

Summary of evidence	LE
Imaging can reliably be used to measure bladder neck and urethral mobility, although there is no evidence of clinical benefit for patients with UI.	2b

Recommendation	Strength rating
Do not carry out imaging of the upper or lower urinary tract as part of the routine assessment of stress urinary incontinence.	Strong

4.2.4 ***Disease management***

4.2.4.1 *Conservative management*

4.2.4.1.1 Obesity and weight loss

Being overweight or obese has been identified as a risk factor for LUTS and UI in many epidemiological studies [137, 138]. There is evidence that the prevalence of both UUI and SUI increases proportionately with rising BMI [305]. The proportion of patients who undergo surgery for incontinence who are overweight or obese is higher than that of the general population [139].

All the available evidence relates to women. Three systematic reviews concluded that weight loss was beneficial in improving UI [137, 138, 306]. Five further RCTs reported a similar beneficial effect on incontinence following surgical weight reduction programmes [307-311]. Two large studies in women with diabetes mellitus, for whom weight loss was the main lifestyle intervention, showed UI did not improve but there was a lower subsequent incidence of UI among those who lost weight [307, 312]. There have been other cohort studies and case-control studies suggesting similar effects, including surgery for the morbidly obese [313-317].

In a prospective study in 160 consecutive women who underwent bariatric surgery, surgically-induced weight loss was associated with a significant improvement in pelvic floor disorders, including UI [318]. Similar results reported by prospective single-centre studies investigating the effect of bariatric surgery induced weight loss, revealed that bariatric surgery was associated with substantially reduced UI at 11 months and 3 years [319, 320].

4.2.4.1.1.1 Summary of evidence and recommendation for obesity and weight loss

Summary of evidence	LE
Obesity is a risk factor for LUTS and UI in women.	3
Non-surgical weight loss improves UI in overweight and obese women.	1a
Surgical weight loss improves UI in obese women.	1b

Recommendation	Strength rating
Encourage overweight and obese women with lower urinary tract symptoms/stress urinary incontinence to lose weight and maintain weight loss.	Strong

4.2.4.1.2 Urinary containment

The evidence for urinary containment derives from the same literature as for containment in OAB-wet. The readers are therefore referred to Section 4.1.4.1.3.

4.2.4.1.2.1 Summary of evidence and recommendations for urinary containment

Summary of evidence	LE
Pads are effective in containing urine.	1b

Recommendations	Strength rating
Ensure that women with stress urinary incontinence (SUI) and/or their carers are informed regarding available treatment options before deciding on urinary containment alone.	Strong
Offer incontinence pads and/or containment devices for management of SUI, either for temporary symptom control or where other treatments are not feasible.	Strong

4.2.4.1.3 Pelvic floor muscle training

Pelvic floor muscle training is used to improve function of the pelvic floor, thus improving urethral stability. An immediate effect of a single PFM contraction is narrowing of the levator hiatus area, increase of urethral closure pressure and lift of the bladder and rectum preventing the occurrence of UI [321-323]. In an RCT comparing intensive PFMT over a six-month period with no treatment, authors reported increased muscle strength and endurance, narrowing of the levator hiatus, reduced PFM length, increased muscle volume and lift of the bladder neck and rectal ampulla [324]. Pelvic floor muscle training may be used to prevent UI, e.g. in childbearing women before birth, or as part of a planned recovery programme after childbirth. Most often, PFMT is used to treat existing SUI; sometimes in combination with observation and/or palpation of the muscle contraction by the therapist or biofeedback (by use of an apparatus measuring the contraction either by electromyography (EMG), manometry, dynamometry, US or MRI). Electrical stimulation and vaginal cones are also used in treatment of SUI based on an assumption of the same mechanism of action.

4.2.4.1.3.1 Efficacy of pelvic floor muscle training in stress urinary incontinence

A Cochrane systematic review compared PFMT with no treatment or inactive control treatment and found that women with SUI in the PFMT groups were eight times more likely to report cure (56% vs. 6%; 4 trials including 165 women; high-quality evidence) [325]. The review also documented significant improvement in UI (7 trials, 376 women; moderate-quality evidence), and improvement in UI QoL (6 trials, 348 women; low-quality evidence). Pelvic floor muscle training reduced leakage by one episode per day in women with SUI (7 trials, 432 women; moderate-quality evidence). Women with SUI in the PFMT groups lost significantly less urine in short (up to one hour) pad tests. The comparison of short pad tests showed considerable heterogeneity but the findings still favoured PFMT when using a random-effects model (mean difference 9.71 g in 4 trials including 185 women; moderate-quality evidence). Women in the PFMT group were also more satisfied with treatment and their sexual outcomes were better. Adverse events were rare and minor.

A Cochrane review concluded that there may be some additional effect of adding biofeedback to PFMT. However, this was based on RCTs with training dosage and attention favouring biofeedback [326]. In a recent RCT (61.3% had MUI) comparing the exact same training dosage and attention between groups, use of biofeedback did not yield any additional effect [327]. Group training is cost effective in treatment of SUI/UI compared to individual treatment [328]. A Cochrane review concluded that a combination of individual assessment/education and group training was equally effective compared to individual treatment, but again the dosage and attention differed between comparison groups [329]. In a more recent RCT with the exact same training dosage and attention in individual and group training, group training was not inferior to individual treatment [328]. It is worth noting that all of the PFMT interventions in these reviews follow individual assessment and teaching before starting PFMT, and most interventions use some sort of measurement tool (biofeedback) in the assessment.

Both the Cochrane review and the ICI concluded that the use of vaginal cones to train the PFM is more effective than no treatment, but it is inconclusive whether it is more or less effective than structured PFMT [325, 330, 331]. Some women are unable to maintain the cone inside, some report discomfort and motivation problems and adherence may be low [330].

The Cochrane review [325], the ICI [331] and the National Institute for Health and Care Excellence (NICE) guidelines (2019) [67] all conclude that there is the highest level evidence (1a) to support PFMT in the treatment of SUI/MUI. All systematic reviews conclude that PFMT is less effective if women with MUI and UUI are included in the studies and more effective with more intensive and supervised training. According to the NICE guidelines literature review, PFMT is as effective as surgery for around half of women with SUI, and due to the risks following surgery and absence of side effects of PFMT, they recommend three months of supervised PFMT as first-line treatment for SUI and MUI [67].

Pelvic floor muscle training was compared to synthetic MUS surgery in an RCT involving 460 women with moderate to severe SUI [332]. Crossover between treatment arms was allowed and 49.0% of women in the physiotherapy group and 11.2% of women in the surgery group crossed over to the alternative treatment. Subjective improvement was reported by 90.8% of women in the surgery group and 64.4% of women in the physiotherapy group at 12 months.

4.2.4.1.3.2 Efficacy of electrical stimulation

There is lack of consensus regarding the use of ES to treat SUI. For subjective cure of SUI, a Cochrane review found moderate quality evidence that ES is probably better than no active treatment (risk ratio [RR] 2.31) [333]. Similar results were found for cure or improvement of SUI (RR: 1.73), but the quality of evidence was low. There

is uncertainty as to whether there is a difference between ES and sham treatment in terms of subjective cure alone because of very low quality of evidence (RR: 2.21). For subjective cure or improvement, ES may be better than sham treatment (RR: 2.03). Any comparison between ES and PFMT and other treatments is hampered by low quality evidence. Side effects such as pain and discomfort have been reported, and ES is not tolerated by all women [333].

In an RCT, 132 women assessed by vaginal palpation to have 0-1 on the modified Oxford grading scale (unable to contract the PFM) were randomly assigned to an 8-week intervention of either learning to contract via palpation, palpation with pelvic tilt, intravaginal ES or verbal instruction [334]. The results showed that 63.6%, 69.7%, 33.3% and 18.2% in the four groups, respectively, scored 2 after the intervention. Palpation was significantly more effective that ES, but one third of the ES group had learned a correct PFM contraction [334]. The effect on UI measured by ICIQ-UI-SF was significantly better in the palpation group.

4.2.4.1.3.3 Long-term efficacy of pelvic floor muscle training

In a systematic review including 19 studies, 1,141 women were followed-up long term (between 1 and 15 years) after PFMT for SUI [335]. Meta-analysis was not performed due to high heterogeneity of outcome measures and training dosage (frequency, intensity, duration and adherence). Only two studies provided interventions during the follow-up period. Losses to follow-up during the long-term period ranged between 0% and 39%. Long-term adherence to PFMT varied between 10% and 70%. Five studies reported that the initial success rate on SUI and MUI was maintained at long term. Long-term success based on responders in the original trial varied between 41% and 85%. Surgery rates at long term varied between 4.9% and 58%. It was concluded that short-term outcome of PFMT can be maintained at long-term follow-up without incentives for continued training, but there is a high heterogeneity in both interventional and methodological quality in short- and long-term PFMT studies [335].

4.2.4.1.3.4 Efficacy of pelvic floor muscle training in childbearing women

Pelvic floor muscle training to prevent SUI has been studied during pregnancy and in the postpartum period and the results are not reported separately for SUI and other subgroups of UI. A Cochrane review concluded that PFMT in women with and without UI (combined primary and secondary prevention) during pregnancy, produced a 26% reduced risk of UI during pregnancy and the mid-postnatal period [336]. Furthermore, pregnant continent women (primary prevention) who exercise the PFM during pregnancy are 62% less likely to experience UI in late pregnancy and have 29% lower risk of UI 3 to 6 months after giving birth. To date there is insufficient evidence for a long-term effect of antenatal PFMT beyond 6 to 12 months postpartum. In treatment studies; compared with “usual” care, there is no evidence that antenatal PFMT in incontinent women decreases incontinence in late pregnancy (very low-quality evidence), or in the mid- (low-quality evidence), or late postnatal periods (very low-quality evidence).

There are fewer RCTs in the postpartum period than during pregnancy [336]. No primary prevention studies were found in women after birth. For PFMT started after delivery, in a mixed group of continent and incontinent women, there was uncertainty about the effect on UI risk in the late postnatal period (3 trials, 826 women; moderate-quality evidence), and in postnatal women with persistent UI, there is no evidence that PFMT results in a difference in UI at more than six to twelve months postpartum (3 trials; 696 women; low-quality evidence). However, another RCT found that UI was less frequent in the intervention group, with 57% of patients still symptomatic, compared to 82% of controls ($p = 0.03$), as was bladder-related bother with a prevalence of 27% in the intervention vs. 60% in the control group ($p = 0.005$) [337]. Randomised controlled trials of high interventional and methodological quality are needed in the postpartum period.

4.2.4.1.3.5 Pelvic floor muscle training in the elderly

There are few RCTs on conservative treatment of SUI in the elderly (> 65 years) and many of the studies combine different modalities e.g. bladder training, lifestyle modifications and PFMT [338]. Some of the studies on PFMT and SUI in the general population have included women > 65 years and PFMT seems to be equally effective in elderly women. A systematic review on conservative management included 23 trials, 9 of moderate to high methodological quality, and concluded that PFMT in combination with physical training was effective in reducing UI and improving QoL [339]. Prompted voiding and toileting assistance with functional exercise reduced UI. Other behavioural interventions such a night-time prompted voiding and waking routine had no effect on UI reduction. The most recent ICI consensus publication stated that although there are limited studies of PFMT on UI in frail elderly populations, age and frailty alone should not preclude the use of PFMT in appropriate patients with sufficient cognition to participate [338]. More high-quality RCTs, both in frail and healthy older women (> 80 years of age) are needed.

4.2.4.1.3.6 Summary of evidence and recommendations for pelvic floor muscle training

Summary of evidence	LE
Pelvic floor muscle training is better than no treatment for improving SUI and QoL in women with SUI and MUI across a range of outcomes including cure rate, improvement rate, QoL, number and volume of urine leaks and treatment satisfaction.	1a
Pelvic floor muscle training exhibits a low rate of adverse events.	1a
Higher-intensity, supervised, treatment regimens confer greater benefit in women receiving PFMT.	1a
There is no extra benefit of combining PFMT with biofeedback.	1b
Short-term benefits of intensive PFMT can be maintained in the long-term.	2a
Pelvic floor muscle training in the antenatal period is associated with a reduced risk of UI in late pregnancy and in the short-term post-natally.	1a
Postpartum PFMT is effective in women with persistent UI.	1b
There is no benefit of postpartum PFMT in mixed (continent and incontinent) groups of women.	1b
Mid-urethral sling surgery is superior to PFMT for women with moderate to severe SUI.	1b
Pelvic floor muscle training commencing in the early postpartum period improves UI in women for up to 6 months.	1b
There is conflicting evidence on whether the addition of ES increases the effectiveness of PFMT alone.	2a

Recommendations	Strength rating
Offer supervised intensive pelvic floor muscle training (PFMT), lasting at least three months, as first-line therapy to all women with stress urinary incontinence (SUI) or mixed urinary incontinence (MUI) (including the elderly and pre- and post-natal).	Strong
Ensure that PFMT programmes are as intensive as possible.	Strong
Balance the efficacy and lack of adverse events from PFMT against the expected effect and complications from invasive surgery for SUI.	Strong
Do not offer electrical stimulation with surface electrodes (skin, vaginal, anal) alone for the treatment of SUI.	Strong

4.2.4.1.4 Electromagnetic stimulation

Electromagnetic stimulation (EMS) has been evaluated for its role in SUI therapy. In a double-blind RCT of EMS including 70 women with SUI, no effect of EMS over sham in any outcome was recorded [340].

4.2.4.2 Pharmacological management

4.2.4.2.1 Oestrogen

Oestrogenic drugs including conjugated equine oestrogens, oestradiol, tibolone and raloxifene, are used as hormone replacement therapy (HRT) for women with natural or therapeutic menopause.

Oestrogen treatment for SUI has been tested using oral, transdermal and vaginal routes of administration. Available evidence suggests that vaginal oestrogen treatment with oestradiol and oestriol is not associated with the increased risk of thromboembolism, endometrial hypertrophy, and breast cancer seen with systemic administration [243-245]. Vaginal (local) treatment is primarily used to treat symptoms of vaginal atrophy in post-menopausal women.

A Cochrane systematic review looked at the use of oestrogen therapy in post-menopausal women given local oestrogen therapy and 17 studies are focused on SUI [243]. There is also a narrative review of oestrogen therapy in urogenital diseases [341]. The Cochrane review found that vaginal oestrogen treatment improved symptoms of SUI in the short term [243]. The review found small, low-quality trials comparing vaginal oestrogen treatment with phenylpropanolamine, PFMT, ES and its use as an adjunct to surgery for SUI. Local oestrogen was less likely to improve UI than PFMT but no differences in UI outcomes were observed for the other comparisons. A single trial of local oestrogen therapy comparing a ring device to pessaries found no difference in UI outcomes although more women preferred the ring device. In one trial no significant adverse effects following vaginal administration of oestradiol for vulvovaginal atrophy over two years were reported [342].

Vaginal oestrogen therapy can be given as conjugated equine oestrogen, oestriol or oestradiol in vaginal pessaries, vaginal rings or creams. The ideal treatment duration and the long-term effects are uncertain. A review of local oestrogen treatment showed improvement of UI over placebo with vaginal rings, which were favoured subjectively over pessaries [343].

One RCT in post-menopausal women showed benefit in adding intravaginal oestriol to vaginal ES and PFMT in female SUI [344].

Studies of systemic HRT with non-urogenital primary outcomes have looked for change in urinary continence in secondary analyses. Large trials using conjugated equine oestrogens showed a higher rate of development or worsening of UI compared to placebo and no SUI improvement [345-350]. In a single RCT, use of raloxifene was not associated with development or worsening of UI [351]. Three small RCTs using oral oestriol or oestradiol as HRT for vulvovaginal atrophy suggested that UI symptoms were improved although the evidence was unclear [67, 352, 353].

4.2.4.2.1.1 Summary of evidence and recommendations for oestrogens

Summary of evidence	**LE**
Vaginal oestrogen therapy improves SUI for post-menopausal women in the short term.	1a
Neoadjuvant or adjuvant use of local oestrogens are ineffective as an adjunct to surgery for SUI.	2b
Systemic hormone replacement therapy using conjugated equine oestrogens does not improve SUI and may worsen pre-existing UI.	1a

Recommendations	**Strength rating**
Offer vaginal oestrogen therapy to post-menopausal women with stress urinary incontinence (SUI) and symptoms of vulvo-vaginal atrophy.	Strong
In women taking oral conjugated equine oestrogen as hormone replacement therapy who develop or experience worsening SUI discuss alternative hormone replacement therapies.	Strong

4.2.4.2.2 Duloxetine

Duloxetine inhibits the presynaptic re-uptake of neurotransmitters, serotonin (5-HT) and norepinephrine (NE). In the sacral spinal cord, an increased concentration of 5-HT and NE in the synaptic cleft increases stimulation of 5-HT and NE receptors on the pudendal motor neurons, which in turn increases the resting tone and contraction strength of the urethral striated sphincter.

Duloxetine was evaluated as a treatment for female SUI or MUI in three systematic reviews [162, 354, 355]. Improvement in UI compared to placebo was observed with no clear differences between SUI and MUI. One study reported cure for UI in about 10% of patients. An improvement in the Urinary Incontinence Quality of Life questionnaire (I-QoL) was not found in the study, which used this as a primary endpoint. In a further study comparing duloxetine, 80 mg daily, with PFMT alone, PFMT + duloxetine, and placebo [356], duloxetine reduced leakage compared to PFMT or no treatment. Global improvement and QoL were better for combined therapy than no treatment. There was no significant difference between PFMT and no treatment in this trial.

Two open-label studies with a follow-up of one year or more evaluated the long-term effect of duloxetine in controlling SUI [357, 358]. Both studies had a high patient withdrawal rate, due to lack of efficacy and a high incidence of adverse events, including nausea and vomiting (40% or more of patients), dry mouth, constipation, dizziness, insomnia, somnolence and fatigue, amongst other causes.

A systematic review showed significant efficacy for duloxetine compared to placebo in women with SUI, but with increased risk of adverse events [355]. The reported adverse effects of duloxetine include mental health problems and suicidal ideation. A meta-analysis of four RCTs including 1,910 women with SUI reported that “no suicidality, violence or akathisia events were noted”, but suggested that the discontinuation rate due to adverse events was around 1 in 7 and that the harms of this treatment may outweigh the benefit [359]. Furthermore, a meta-analysis of twelve placebo-controlled trials involving almost 3,000 patients showed that in patients with major depressive disorders there were no significant differences in the incidence of suicide-related events with duloxetine vs. placebo [360].

4.2.4.2.2.1 Summary of evidence and recommendations for duloxetine

Summary of evidence	**LE**
Duloxetine improves SUI in women, but the chances of cure are low.	1a

Duloxetine may cause significant gastrointestinal and central nervous system side effects leading to a high rate of treatment discontinuation, although these symptoms may be limited to the first weeks of treatment.	1a

Recommendations	Strength rating
Offer duloxetine (where licensed) to selected patients with SUI unresponsive to other conservative treatments and who want to avoid invasive treatment, counselling carefully about the risk of adverse events.	Strong
Duloxetine should be initiated and withdrawn using dose titration because of the high risk of adverse events.	Strong

4.2.4.3 Surgical management

4.2.4.3.1 General considerations

The use of polypropylene mesh, synthetic MUS for the treatment of SUI, has recently come under scrutiny following concerns raised regarding long-term complications. In some European countries such as the United Kingdom the use of synthetic MUS has been paused and pelvic mesh was the subject of a UK parliamentary review published in July 2020 [361]. This review has concluded that *"For many women mesh surgery is trouble-free and leads to improvements in their condition. However, this is not the case for all. There is no reliable information on the true number of women who have suffered complications. While they may be in the minority, that does not diminish the catastrophic nature of their suffering or the importance of providing support to them and learning from what has happened to them"*.

The range of complications highlighted during the process of this parliamentary review included [361]:

- pain;
- recurrent infections;
- mobility issues;
- recurring or new incontinence/urinary frequency;
- recurring or new prolapse;
- haemorrhage;
- bowel issues;
- erosion of mesh; this can be into the vagina and/or other organs;
- sexual difficulties; including pain on intercourse and a loss of sex life;
- autoimmune issues;
- psychological impacts.

When considering the choice of surgical treatments for SUI the Panel would advise individual clinicians to abide by any national or local rules that may be in place regarding mesh surgery. Furthermore it is essential for clinicians to point out the deficiencies in the long-term evidence regarding mesh use in SUI with specific reference to the complications highlighted above.

In line with the recommendations from NICE [67] and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) paper [362] the Panel agreed that surgeons and centres performing surgery should:

- be trained in the field of incontinence and for each surgical procedure they perform/offer;
- perform sufficient numbers of a procedure to maintain expertise of him/herself and the surgical team;
- be able to offer alternative surgical treatments;
- be able to deal with the complications of surgery;
- provide suitable arrangements for long-term follow-up.

Furthermore, the establishment of accurate and complete databases registering the interventions, patient profile and surgical complications or all surgical treatments for SUI is recommended to allow the generation of robust long-term data.

Many surgical procedures are available for uncomplicated SUI patients and the Panel analysed the results of the different procedures in terms of clinical effectiveness, safety and cost-effectiveness based on the recent ESTER systematic review and economic evaluation [363] and previous systematic reviews including those from the Cochrane collaboration [364-368].

The outcome parameters used to evaluate surgery for SUI have been limited to:

- continence rate;
- patient-reported outcome measures;
- general and procedure-specific complications;
- generic, specific (UI) and associated (sexual and bowel) QoL.

In this context, it has to be taken into account that a number of products may no longer be available and therefore the recommendations may not be transferable to current devices. The Panel makes a strong recommendation that new devices are only used as part of a structured research programme and their outcomes monitored in a registry, until there is adequate evidence of safety and efficacy.

4.2.4.3.1.1 Recommendations for surgical treatment of SUI

Recommendations	Strength rating
Offer patients who have explored/failed conservative treatment options a choice of different surgical procedures, where appropriate, and discuss the advantages and disadvantages of each approach.	Strong
Use new devices for the treatment of SUI only as part of a structured research programme. Their outcomes must be monitored in a registry or as part of a well-regulated research trial.	Strong

4.2.4.3.2 Surgery for women with uncomplicated stress urinary incontinence

The principal procedures evaluated are:

- open and laparoscopic colposuspension;
- autologous “traditional” slings;
- bulking agents;
- synthetic MUS.

4.2.4.3.2.1 Open- and laparoscopic colposuspension surgery

Open colposuspension was previously considered the most appropriate surgical intervention for SUI, and was used as the comparator in RCTs of newer, less invasive, surgical techniques. These include laparoscopic techniques, which have enabled colposuspension to be performed with a minimally invasive approach.

Open colposuspension

A number of systematic reviews were found, which covered the subject of open surgery for SUI, with a large number of RCTs [363, 365-368]. The Cochrane review on open colposuspension [368] included 55 trials comprising 5,417 women. In most of these trials, open colposuspension was used as the comparator to an experimental procedure. Within the first year, complete continence rates of approximately 85–90% were achieved for open colposuspension, while failure rates in terms of recurrent UI were 17% up to five years and 21% at over five years. The risk of re-operation after Burch colposuspension is estimated at 6% within 5 years [112] and 10.8% within 9 years [113]. The re-operation rate specifically for UI was only 2%. Colposuspension was associated with a higher rate of development of enterocoele/vault/cervical prolapse (42%) and rectocele (49%) at five years compared to TVT (23% and 32%, respectively). The rate of cystocoele was similar post-colposuspension (37%) and after TVT (41%). The Cochrane review concluded that open colposuspension is an effective treatment for SUI and around 70% of women can expect to be dry at five years after surgery.

Laparoscopic colposuspension

A Cochrane review reported on twelve trials comparing laparoscopic colposuspension to open colposuspension [366]. Although these procedures had a similar subjective cure rate, there was limited evidence suggesting the objective outcomes were less good for laparoscopic colposuspension. The ESTER systematic review [363] showed, based on a network meta-analysis, that at 12 months open colposuspension was more effective than laparoscopic colposuspension (9 trials, OR: 0.68, p = 0.009) but these findings are based on low quality evidence. The Surface Under the Cumulative Ranking Scores (SUCRA), which is a numerical representation of the overall ranking and presents a single number associated with each intervention, were 76.7% after open colposuspension, and 48.9% after laparoscopic colposuspension (out of a maximum score of 100%). Laparoscopic colposuspension had a shorter duration of surgery and subsequent hospital stay and may be slightly more cost-effective when compared with open colposuspension after 24 months follow-up.

Single-port laparoscopic Burch can be an alternative treatment, although data confirming efficacy are limited [369].

Complications

Voiding difficulties appeared to be more common after laparoscopic colposuspension than after retropubic MUS (7.5% vs. 5.1%) [363]. There was no evidence of a difference for the comparison assessing open colposuspension vs. retropubic MUS (7.8% vs. 7.5%; OR: 0.87) [363]. The results for the comparisons of *de novo* symptoms of urgency or UUI between open colposuspension and retropubic MUS (11% vs. 8%, OR: 1.49) did not favour either treatment and showed wide confidence intervals [363]. The rate of bladder or urethral perforation was higher for laparoscopic colposuspension compared with open colposuspension (3.7% vs. 0.7%; OR: 4.65) [363].

4.2.4.3.2.1.1 Summary of evidence and recommendation for open- and laparoscopic colposuspension surgery for stress urinary incontinence

Summary of evidence	**LE**
High subjective cure rates are associated with both open- and laparoscopic colposuspension for the treatment of SUI.	1a
Objective cure rates are higher for open colposuspension compared to laparoscopic colposuspension.	1a
Colposuspension is associated with a higher long-term risk of POP than MUS.	1a
Laparoscopic colposuspension has a shorter hospital stay and may be more cost-effective than open colposuspension.	1a
Laparoscopic colposuspension is associated with higher rates of intra-operative bladder perforation and post-operative voiding dysfunction compared to open colposuspension.	1a
The rates of *de novo* urinary urgency following colposuspension are similar to other surgical treatments for SUI.	1a

Recommendation	**Strength rating**
Offer colposuspension (open or laparoscopic) to women seeking surgical treatment for stress urinary incontinence following a thorough discussion of the risks and benefits relative to other surgical modalities.	Strong

4.2.4.3.2.2 Autologous sling

In the past, autologous, cadaveric, xenograft, and synthetic materials have been used for bladder neck pubovaginal sling (PVS). Nowadays, use of autologous tissue, either rectus sheath or fascia lata, is the most studied material with the strongest evidence base to support its use [370].

The ESTER systematic review included 3 trials of autologous sling vs. open colposuspension, six trials of autologous sling vs. retropubic MUS and one trial comparing autologous sling vs. transobturator MUS. The quality of evidence was overall very low. The pooled estimate showed that fascial sling had a higher cure rate at one year, than open colposuspension (OR: 1.24), retropubic MUS (OR: 1.06) and transobturator MUS (OR: 1.44) but without statistical significance. The SUCRA score was 89.4% for women cured after autologous fascial sling.

A sub-analysis from a Cochrane review showed autologous slings had better effectiveness compared to colposuspension at one to five years follow-up [368]. In an RCT of Burch colposuspension vs. autologous slings complete continence rates decreased substantially over time in both arms. At five years, the continence rate of colposuspension was 24.1% compared to 30.8% for fascial slings. Satisfaction remained higher in the sling group (83% vs. 73%) and was directly related to the continence status [371].

Complications

Adverse events rates were similar for the two treatment groups (Burch 10% and sling 9%) although post-operative obstruction was found exclusively in the sling group. Voiding difficulties appear to be more common after autologous sling [15.4% vs. 10.2%; OR: 1.46] than after retropubic MUS. Compared with open colposuspension, the rate of bladder or urethral perforation was lower for traditional sling [0.6% vs. 3.0%; OR: 0.20] [363].

4.2.4.3.2.2.1 Summary of evidence and recommendation for autologous sling

Summary of evidence	**LE**
High cure rates are associated with autologous sling placement for the treatment of SUI.	1a
Autologous sling is more effective in terms of cure rate than colposuspension.	1a

Autologous sling has a similar rate of adverse events compared to open colposuspension, with higher rates of voiding dysfunction and post-operative UTI, but a lower rate of bladder- or urethral perforation.	1a

Recommendation	Strength rating
Offer autologous sling placement to women seeking surgical treatment for stress urinary incontinence following a thorough discussion of the risks and benefits relative to other surgical modalities.	Strong

4.2.4.3.2.3 Urethral bulking agents

The concept of this procedure originates from the idea that intra- or peri-urethral injection of an agent able to form artificial cushions under/around the urethra will increase the resistance at the bladder outlet and facilitate continence.

Two Cochrane reviews (2012 and updated in 2017) identified fourteen RCTs or quasi-RCTs of treatment for UI in which at least one management arm involved peri-urethral or transurethral injection therapy [372, 373]. Following this review, five additional reviews investigated the effect of injectables for the treatment of female SUI [374-378], independently of the injected material. One review included results from RCTs only [378]. In the most recent Cochrane systematic review, 1,814 patients were included from fourteen trials of seven different types of intra-urethral injection: glutaraldehyde cross-linked collagen (Contigent©), a porcine dermal implant (Permacol©), solid silicone elastomer (Macroplastique©), autologous fat, pyrolytic carbon (Durasphere©), calcium hydroxylapatite (Coaptite©), hydrogel (Bulkamid®) and dextran polymer (Zuidex©). The conclusions state that "the available evidence base remains insufficient to guide practice" [373].

A systematic review of 23 studies using Macroplastique© including 958 patients showed a 75% improvement with 43% dry rate at less than 6 months and a 64% improvement and 36% cure rate at more than 18 months [375]. A review of 514 elderly women with SUI treated with various agents showed a reduced pad weight in 73% at 1-year follow-up, independent of the material injected [379]. The heterogeneity of the populations, the variety of materials used and the lack of long-term follow-up limit guidance of practice. Most of the studies show a tendency for a short-term improvement in UI, with the exception of one RCT, which could not find a difference between saline and fat injection [380].

One trial of 30 women showed a weak (but not clinically significant) advantage in terms of patient satisfaction after mid-urethral injection in comparison to bladder neck injection but with no demonstrable difference in continence levels [373]. Two trials found a higher risk of urinary retention with intra-urethral injections compared with transurethral injections, although the latter is associated with a higher risk of temporary urinary retention [372, 381]. A small RCT found no difference in efficacy between mid-urethral and bladder neck injection of collagen [382]. One study treated patients who had received radiotherapy with injection of Bulkamid® and reported around 25% cure at short-term follow-up [383].

Bulking agent injection is generally safe, the most frequent adverse event being UTI. However, autologous fat or hyaluronic acid should not be used due to the risk of fatal embolism and local abscess formation, respectively [372, 380].

Comparison with other surgical procedures

Two RCTs compared collagen injection to conventional surgery for SUI (silicon particles vs. autologous sling and collagen vs. other surgical procedures). The studies reported greater efficacy but higher complication rates for open surgery [384, 385].

In a recent non-inferiority clinical trial women with primary SUI were randomised to TVT or polyacrylamide hydrogel urethral bulking agent injection (Bulkamid®) [386]. Mid-urethral TVT slings were associated with better satisfaction and cure rates than Bulkamid® in primary SUI. In term of objective cure rate the cough stress test was negative in 95.0% of patients who underwent TVT vs. 66.4% who underwent Bulkamid®.

4.2.4.3.2.3.1 Summary of evidence and recommendations for urethral bulking agents

Summary of evidence	LE
Urethral bulking agents may provide short-term improvement and cure, in women with SUI.	1b

Bulking agents are less effective than MUS, colposuspension or autologous sling for cure of SUI and repeat injections may be required in order to achieve sustained benefits.	1b
Autologous fat and hyaluronic acid as bulking agents have a higher risk of adverse events.	1a
Adverse event rates for urethral bulking agents are lower compared to open surgery.	2a
There is no evidence that one type of bulking agent is better than another type.	1b
The peri-urethral route of injection of bulking agents may be associated with a higher risk of urinary retention compared to the transurethral route.	2b

Recommendations	Strength rating
Offer urethral bulking agents to women seeking surgical treatment for stress urinary incontinence (SUI) following a thorough discussion of the risks and benefits relative to other surgical modalities.	Strong
Offer urethral bulking agents to women with SUI who request a low-risk procedure with the understanding that efficacy is lower than other surgical procedures, repeat injections are likely and long-term durability and safety are not established.	Strong
Do not offer autologous fat and hyaluronic acid as urethral bulking agents due to the higher risk of adverse events.	Strong

4.2.4.3.2.4 Mid-urethral slings

Early clinical studies identified that non-autologous synthetic slings should be made from monofilament, non-absorbable material, typically polypropylene, constructed as a 1–2 cm wide mesh with a relatively large pore size (macroporous) and coloured to facilitate removal [387]. Mid-urethral slings are now the most frequently used surgical intervention in Europe for women with SUI.

Transobturator route versus retropubic route

A Cochrane meta-analysis of MUS procedures for SUI in women was performed in 2017 spanning January 1947 to June 2014 [388]. Moderate quality evidence from 55 studies showed variable, but comparable, subjective cure rates between retropubic and transobturator slings (62–98% in the transobturator groups and 71–97% in the retropubic groups) in the short term (up to one year). No difference in the objective cure rate in the short term was found. However, the ESTER systematic review [363], based on a network meta-analysis including 36 trials of overall moderate quality, showed that at 12 months retropubic MUS was, on average, more effective than transobturator MUS (OR: 0.74); SUCRA scores for women cured after retropubic MUS were 89.1% vs. 64.1% after transobturator MUS. However there was no statistically significant difference in these cure rates between the two approaches (p = 0.4). Similarly, based on 40 moderate quality trials, retropubic MUS performed better than the transobturator approach in terms of symptom improvement (RR: 0.76) but the difference was again not statistically significant (p = 0.16).

Analysis of a randomised equivalence trial of retropubic vs. transobturator MUS for the treatment of SUI in women shows similar findings. This trial confirms equivalence of objective cure rates at 12 months but not at 24 months (77.3% and 72.3% objective cure rate for retropubic and transobturator surgery). For both types of MUS subjective and objective treatment success decreased over time and equivalence of the retropubic and the transobturator routes could not be confirmed at 24 and 60 months with retropubic demonstrating a slightly increased level of benefit, despite satisfaction remaining high in both arms [389]. Five years after surgical treatment objective success was 7.9% greater in women assigned to retropubic sling compared to transobturator sling (51.3% vs. 43.4%), not meeting pre-specified criteria for equivalence. Patient satisfaction decreased over 5 years but remained high and similar between treatment arms (retropubic sling 79% vs. transobturator sling 85%, p = 0.15) [390].

In terms of long-term complications, data are scant but in one study *de novo* OAB developed in 14% of patients at ten years with no significant differences between groups (TOT vs. TVT) [391]. In a multicentre prospective study of women undergoing TOT a history of failure of previous anti-incontinence procedures was the only predictor of recurrence of SUI (HR: 5.34, p = 0.009) [391].

A long-term cohort study of retropubic TVT showed an 89.9% objective cure rate and a 76.1% subjective cure rate at ten years. Overall, 82.6% of patients reported to be highly satisfied with the surgery [392]. A long-term prospective study on transobturator sling showed that at 145 months the objective and subjective cure rates were 78.9% and 62.6% respectively; with no significant deterioration in SUI cure rates over time [393]. Another long-term follow-up study of patients treated with TVT showed a sustained response with 95.3%, 97.6%, 97.0% and 87.2% of patients being cured or improved at 5, 7, 11 and 17 years, respectively [394].

The ESTER network meta-analysis based on cure and improvement suggested that, when comparing surgical treatments for SUI, retropubic MUS, transobturator MUS and traditional sling had the highest efficacy rates, but this ranking does not consider the complication profile of these techniques. The short- to medium-term adverse event data were sparse [363]. The nine procedures compared in ESTER with their associated SUCRA ratings are shown in Table 3 below.

Table 3: SUCRA curve values for the outcome - number of women cured (indicated by %)*

Procedure*	Number of women cured
Traditional sling operations	89.4%
Retropubic MUS operations	89.1%
Open colposuspension	76.7%
Transobturator MUS operations	64.1%
Laparoscopic colposuspension	48.9%
Single-incision sling operations	39.8%
Bladder neck needle suspension	26.9%
Anterior vaginal repair.	12.5%
PFMT	2.6%

**Adapted from ESTER [363].*

Several health economic analyses of MUS procedures have been published with conflicting results. In a review of 26 economic evaluations and on the basis of a cost-utility and value of information analysis over a 10-year time period, the authors concluded that MUS remains among the most cost-effective approaches [364]. A primary economic evaluation of retropubic vs. transobturator tapes over a 5-year time period suggested that the latter may be cost-effective and cost-saving compared to the standard TVT approach [395]. Conversely, the findings from the ESTER network meta-analysis stated that over a lifetime, retropubic MUS was, on average, the least costly and most effective surgery but the level of uncertainty in these analyses was high.

Insertion using a skin-to-vagina direction versus a vagina-to-skin direction
The Cochrane review on MUS for female SUI showed no difference in the short- and medium-term subjective cure rates in vagina-to-skin (inside-out) vs. skin-to-vagina (outside-in) approaches based on moderate quality evidence [396]. Voiding dysfunction seems to be more frequent in the vagina to skin (inside-out) TOT group but this approach is associated with a lower frequency of vaginal perforations (RR: 0.25). Due to the low quality of the evidence it is unclear whether the lower frequency of vaginal perforations of this approach is responsible for the observed lower rate of vaginal tape erosions.

Likewise, a further meta-analysis of RCTs demonstrated no significant difference in efficacy between outside-in vs. inside-out approaches, but vaginal perforations were, again, less frequent in the latter group (2.6% vs. 11.8%, OR: 0.21, p = 0.0002) [397]. The five-year data of a prospective, non-randomised study of the two techniques showed a very high objective success rate (82.6 vs. 82.5%, respectively) with no difference between the two approaches [398].

In a secondary analysis of the E-TOT study (a study of transobturator TVTs in the treatment of women with urodynamic MUI), no difference in the patient-reported success rates was found between the vagina-to-skin (inside-out) and the skin-to-vagina (outside-in) groups (63.2% and 65.5%, respectively; OR: 1.11) at 9 years follow-up [399].

Complications of synthetic mid-urethral slings
In the ESTER network meta-analysis it was noted that comparative assessment of adverse events between different procedures was not always possible due to the lack of available data [363]. Direct comparisons using head-to-head meta-analyses were mainly carried out for retropubic MUS, transobturator MUS or single-incision slings. The authors did, however, comment that "For other intervention comparisons, the number of studies was generally small and the CIs wide. However, there was some evidence to suggest that bladder perforation was more likely to occur after retropubic MUS than after transobturator MUS, open colposuspension or traditional sling". In particular, the retropubic approach for MUS was associated with a significantly higher rate of bladder perforation than transobturator MUS (5% vs. 0.2%). Regarding *de novo* voiding dysfunction, 36 studies compared transobturator MUS with retropubic MUS, favouring transobturator MUS (OR: 0.51). While for pain, it is worth pointing out that it was defined and measured in many different ways across individual trials and across Cochrane systematic reviews. Some pain outcomes were categorised

by location (e.g. suprapubic) or time (e.g. short- or long-term). These discrepancies made it difficult to combine data from different studies. Data were available mainly for the comparison between retropubic MUS and transobturator MUS and other surgical procedures. However, groin pain was more frequent after transobturator MUS than retropubic MUS [6.3% vs. 1.3%; OR: 3.80]. Converse findings were reported for suprapubic pain which was higher following TVT (1.2% vs. 4.0%; OR: 0.37). Visceral injury (0.5% vs. 2.4% OR: 0.36), mean operative time, operative blood loss and hospital stay were lower in the transobturator groups than retropubic MUS. The overall vaginal erosion risk was low and comparable in both groups [363].

The rate of tape/mesh exposure or extrusion between retropubic and transobturator MUS was similar (2.1% vs. 2.4%; OR: 1.10). The exact time points at which measurements occurred could not be derived from the Cochrane systematic reviews but most studies were reported to have a short follow-up period (≤ 12 months), with only a few studies having a follow-up period of ≥ 2 years [363]. Re-do surgery for UI was more common in the transobturator group (RR = 8.79); however the data are limited and of low quality.

A population-based study performed in Scotland in over 16,000 women operated on for SUI showed a similar rate of complications between mesh and non-mesh surgery [400]. However, a recent study of over 92,000 patients followed in the National Health Service (UK) showed a significant (9.8%) rate of complications using a more broad definition and following patients for a longer period of time [401]. The level of detail regarding the precise nature of complications in this paper was poor. These findings suggest that, as with any SUI surgery, MUS surgery can be associated with complications and fully informed consent is mandatory.

In general, the available published evidence would suggest that MUS do not seem to be associated with significantly higher rates of morbidity and complications compared to other surgeries for SUI such as open retropubic colposuspension. Pelvic organ prolapse is more common after colposuspension whilst voiding dysfunction occurs more often after MUS [368]. The ESTER review has commented that the level of detail regarding short-to-medium adverse event data is poor for all SUI surgeries [363] and the Panel is aware of the recent findings from the Independent Medicines and Medical Devices Safety Review in the UK which has raised the possibility that the level of complications from synthetic MUS may be higher than the medical literature would suggest [361].

The ESTER systematic review included seven studies comparing re-intervention after transobturator MUS and retropubic MUS [363]. Pooled analysis of these studies showed wide CIs and considerable uncertainty around the estimated OR (12-month post-surgery: OR: 1.37). At 12 to 60 months after the procedure, rates of repeat continence surgery were considerably higher in women undergoing transobturator MUS (18.3%) compared with retropubic MUS (0.5%), although only two studies were available for the analysis. A similar trend was observed in studies with a longer follow-up period (> 60 months) but the pooled analysis of these studies showed wide CIs. For retropubic MUS surgery, the bottom-to-top route was 10% more efficacious than top-to-bottom in terms of subjective cure and it was associated with less voiding dysfunction, bladder perforations and vaginal erosion [363].

Single-incision mid-urethral slings

Although there have been many studies published on single-incision devices, it should be noted that there are significant differences in technical design between devices and it may be misleading to make general statements about them as a class of operation. It should also be noted that some devices have been withdrawn from the market (e.g. TVT Secur®, Minitape, MiniArc®), and yet evidence relating to these devices may still be included in current meta-analyses. There was evidence to suggest single-incision slings are quicker to perform and cause less post-operative thigh pain, but there was no difference in the rate of chronic pain. There was insufficient evidence for direct comparisons between single-incision slings, and no conclusions have been reached about differences between devices.

The ESTER systematic review showed, based on low quality evidence, that at 12 months retropubic MUS and transobturator MUS were, on average, more effective than single-incision sling (TVT, OR: 0.50, p = 0.01 and TOT, OR: 0.68, p = 0.02). The SUCRA score was 39.8% for women cured after single-incision slings. However, since not all single-incision devices have been assessed in a comparative RCT, it may be unsafe to assume that they are collectively technically similar or exhibit the same levels of efficacy.

Complications of single-incision slings

The meta-analysis results for the comparison between single-incision sling and transobturator MUS showed similar rates of mesh erosion or extrusion between interventions (4.8% vs. 3.7%; OR: 1.23). Rates of 'post-operative pain' were higher after retropubic MUS than after single-incision slings (19.2% vs. 6.8% OR: 0.21).

The rate of unspecified pain was higher after transobturator MUS than after single-incision sling both at twelve months (1.0% vs. 5.2%, OR: 0.24) and at 24 months (1.4% vs. 10.4%, OR: 0.16). Single-incision sling was associated with more repeat surgeries compared with transobturator MUS (5.1% vs. 2.9%, OR: 1.57). At over 36 months after the procedure, the repeat surgery rate was 10.3% for single-incision slings vs. 7.6% for transobturator MUS (OR: 1.42) [363].

Sexual function after synthetic mid-urethral sling surgery
A systematic review examining the effect of synthetic MUS on female sexual function suggested different and contradictory results between studies. Overall, more papers show an improvement, or no change, in sexual function because of a reduction in coital incontinence, anxiety and avoidance of sex. Dyspareunia was the most common cause of worsening of sexual function and the precise incidence is difficult to estimate as a lot of studies do not report it [402]. A meta-analysis of outcome measures in trials of sling procedures suggests that single-incision slings are associated with a significantly higher improvement in sexual function compared to standard MUS procedures [403].

4.2.4.3.2.4.1 Summary of evidence and recommendations for mid-urethral slings

Summary of evidence	**LE**
The retropubic MUS appears to provide better patient-reported subjective and objective cure of SUI, compared with colposuspension.	1a
Mid-urethral synthetic slings inserted by either the transobturator or retropubic route provide equivalent patient-reported outcomes at one year.	1a
Mid-urethral synthetic slings inserted by the retropubic routes have higher patient-reported cure rates in the longer term.	1b
Long-term analyses of MUS cohorts showed a sustained response beyond ten years.	2b
The retropubic route of insertion is associated with a higher intra-operative risk of bladder perforation and a higher rate of voiding dysfunction than the transobturator route.	1a
The transobturator route of insertion is associated with a higher risk of groin pain than the retropubic route.	1a
Long-term analysis of MUS showed no difference in terms of efficacy for the skin-to-vagina (outside-in) compared to vagina-to-skin (inside-out) directions up to nine years.	2a
The top-to-bottom (inside-out) direction in the retropubic approach is associated with a higher risk of post-operative voiding dysfunction.	1b
The comparative efficacy of single-incision slings against conventional MUS is uncertain.	1a
Operation times for insertion of single-incision MUS are shorter than for standard retropubic slings.	1b
Blood loss and immediate post-operative pain are lower for insertion of single-incision slings compared with conventional MUS.	1b
There is no evidence that other adverse outcomes from surgery are more or less likely with single-incision slings than with conventional MUS.	1b
In women undergoing surgery for SUI, coital incontinence is likely to improve.	3
Overall, there is conflicting evidence regarding sexual function following SUI surgery.	2a
Improvement in sexual function appears higher with single-incision slings than with standard MUS.	1a

NB: Most evidence on single-incision slings is from studies using the tension-free vaginal tape secure (TVT-S) device and although this device is no longer available, it is, however, still included in many systematic reviews and meta-analyses.

Recommendations	**Strength rating**
Offer a mid-urethral sling (MUS) to women seeking surgical treatment for stress urinary incontinence following a thorough discussion of the risks and benefits relative to other surgical modalities.	Strong
Inform women that long-term outcomes from MUS inserted by the retropubic route are superior to those inserted via the transobturator route.	Strong
Inform women of the complications associated with MUS procedures and discuss all alternative treatments in the light of recent publicity surrounding surgical mesh.	Strong
Inform women who are being offered a single-incision sling that long-term efficacy remains uncertain.	Strong

4.2.4.3.2.5 Other treatments for uncomplicated SUI

Intravesical balloon treatment has been explored for women with SUI. The Vesair® gas-filled intravesical balloon differs from other SUI treatment modalities in that it is not intended to increase outlet resistance or minimise urethral hypermobility but to attenuate the fluctuation of intravesical pressure when the abdominal pressure increases [404, 405]. Two sham-controlled randomised trials evaluating the Vesair® intravesical balloon have been published so far [404, 406]. Both reported significant reductions in incontinence symptoms and pad weight but QoL was not significantly different between study arms. High levels of adverse events were reported in both trials as well as significant numbers of withdrawals/device removals. The most common adverse events were dysuria, urgency, gross haematuria and UTIs.

Mechanical devices have been used to treat SUI for centuries. There are several devices available which act either by supporting the bladder neck or urethra to address urethral hypermobility, or by occluding the urethral lumen.

A 2014 Cochrane systematic review of eight RCTs that included three small trials comparing mechanical devices to no treatment found inconclusive evidence of benefit [407]. Another 2014 review of mechanical devices concluded that there was insufficient evidence to support their use in women [408]. The place of mechanical devices in the management of SUI remains in question. Currently there is little evidence from controlled trials on which to judge whether their use is better than no treatment and large well-conducted trials are required for clarification. There was also insufficient evidence in favour of one device over another and little evidence to compare mechanical devices with other forms of treatment [407].

Systematic reviews regarding compression devices such as the adjustable compression therapy and artificial urinary sphincter devices have published evidence to support their use [409, 410]. Although these procedures are largely reserved for those with recurrent or complicated SUI (see Section 4.2.4.3.3.3 - External compression devices) these recent additions to the literature include the use of some compression devices for uncomplicated SUI.

4.2.4.3.2.5.1 Summary of evidence and recommendations for other treatments for uncomplicated SUI

Summary of evidence	**LE**
Vesair® intravesical pressure-attenuating balloon improves SUI compared to sham control at three months.	1b
Vesair® intravesical pressure-attenuating balloon is associated with significant levels of adverse events.	1b
Implantation of an artificial sphincter can improve or cure incontinence in women with uncomplicated SUI.	3
Implantation of the adjustable compression therapy (ACT©) device may improve uncomplicated SUI.	3
Complications, mechanical failure and device explantation often occur with both the artificial sphincter and the ACT©.	3

Recommendations	**Strength rating**
Offer Vesair® intravesical balloon to women with mild-to-moderate stress urinary incontinence (SUI) who failed conservative treatments only as part of a well-conducted research trial.	Weak
Offer mechanical devices to women with mild-to-moderate SUI who failed conservative treatments only as part of a well-conducted research trial.	Strong
Inform women receiving artificial urinary sphincter or adjustable compression device (ACT©) that although cure is possible, even in expert centres there is a high risk of complications, mechanical failure or a need for explantation.	Strong

4.2.4.3.3 Surgery for women with complicated stress urinary incontinence

This section will address surgical treatment for women with complicated SUI as defined in Section 4.2.2 - Classification above. Neurogenic LUT dysfunction is reviewed by the EAU Guidelines on Neuro-Urology [9]. Women with associated genitourinary prolapse are included in Section 4.7 - Pelvic organ prolapse and LUTS.

The principal procedures included are:

- Colposuspension or MUS (synthetic or autologous) following failed primary SUI surgery;
- External compression devices: adjustable compression therapy (ACT©) and artificial urinary sphincter (AUS);
- Adjustable slings.

4.2.4.3.3.1 Colposuspension or sling (synthetic or autologous) following failed primary SUI surgery
Urinary incontinence following SUI surgery may indicate persistent or recurrent SUI, or the development of *de novo* UUI, or both. Careful evaluation including urodynamics is an essential part of the work-up of these patients.

Most of the data on surgery for SUI refer to primary operations. Even when secondary procedures have been included, it is unusual for the outcomes in this subgroup to be separately reported. When they are, the numbers of patients is usually too small to allow meaningful comparisons. This means that no firm recommendations can be made regarding which modality is best for the treatment of recurrent SUI and previous systematic reviews have commented that in view of the absence of any evidence, clinicians must rely largely on expert opinion or personal experience when advising patients about treatment options [411].

The ESTER network meta-analysis revealed that women with transobturator MUS were more likely to undergo re-do surgery than those who had retropubic MUS and in general fewer repeat surgeries were observed after retropubic MUS compared with other interventions [363]. A recent update of two Urinary Incontinence Treatment Network trials [412] compared the re-treatment-free survival rates by initial surgical procedure. Five-year re-treatment-free survival rates (and standard errors) were 87% (3%), 96% (2%), 97% (1%), and 99% (0.7%) for Burch colposuspension, autologous fascial sling, transobturator, and retropubic MUS groups respectively ($p < 0.0001$). Types of surgical re-treatment included autologous fascial sling (19), bulking agent (18), and synthetic sling (1). This suggests that MUS, may not be preferred in cases of recurrent SUI [412]. In these cohorts, 6% of women after standard anti-incontinence procedures were retreated within five years, mostly with injection therapy or autologous fascial sling. Not all women with recurrent SUI chose surgical re-treatment.

A 2019 Cochrane Review attempted to summarise the data regarding different types of MUS procedures for recurrent SUI after failure of primary surgical therapy [413]. The literature search identified 58 records but all were excluded from quantitative analysis because they did not meet eligibility criteria. Overall, there were no data to recommend or refute any of the different management strategies for recurrent or persistent SUI after failed MUS surgery. Another systematic review looking at the effectiveness of MUS in recurrent SUI included 12 studies and reported an overall subjective cure rate following MUS for recurrent SUI after any previous surgery of 78.5% at an average 29 months of follow-up [414]. The subjective cure rate following MUS after previous failed MUS was 73.3% at a follow-up of 16 months. The authors commented that there was a lower cure rate with transobturator compared to the retropubic tape for recurrent SUI after previous surgery. A further systematic review aimed to assess the effectiveness and complications of various surgical procedures for the treatment of female recurrent SUI and reported on data from 350 women in 10 RCTs with a mean follow-up of 18.1 months [415]. Conversely, the authors found no difference in patient-reported and objective cure/improvement rates between retropubic and transobturator MUS in the setting of recurrent SUI. There was also no significant difference between Burch colposuspension and retropubic MUS in terms of patient-reported improvement or objective cure/improvement.

Systematic review of older trials of open surgery for SUI suggests that the longer-term outcomes of redo open Burch colposuspension may be poor compared to autologous fascial slings [416]. Similarly, one large non-randomised comparative series suggested that cure rates after more than two previous operations were 0% for open colposuspension and 38% for autologous fascial sling [417].

4.2.4.3.3.1.1 Summary of evidence for surgery in those with recurrent SUI following failed primary SUI surgery

Summary of evidence	**LE**
Failure rates of single-incision slings appear higher than with other types of MUS.	1a
The incidence of repeat surgery is higher in those women who underwent primary transobturator MUS compared to retropubic MUS.	1a
The 5-year failure rate of Burch colposuspension appears higher than for synthetic- or traditional sling procedures.	2b
Some studies suggest that retropubic synthetic MUS procedures appear to be more effective than transobturator MUS for the treatment of recurrent SUI, but this is not a consistent finding in the literature.	1a
Most procedures will be less effective when used as a second-line procedure.	2a
Burch colposuspension has similar short-term patient-reported or objective cure rates when compared to TVT for the treatment of recurrent SUI.	1b
Autologous sling appears superior to Burch colposuspension for the treatment of recurrent SUI.	2b

4.2.4.3.3.2 Adjustable slings

Although adjustable slings are most commonly used as a treatment for complicated SUI, they may also be considered as a treatment for uncomplicated SUI. There are no RCTs investigating outcome of adjustable sling insertion for women with SUI. There are limited data from cohort studies on adjustable tension slings with variable selection criteria and outcome definitions. Few studies include sufficient numbers of patients or have a long enough follow-up to provide useful evidence.

One adjustable sling is the Remeex system (Neomedic International®, Terrassa, Spain), which was investigated in a prospective study of 230 women with SUI [418]. After a mean follow-up of 89 months, 165 patients were cured of SUI (71.7% in the intention-to-treat [ITT] analysis, 80.5% in per protocol analysis [PP]). Forty patients remained incontinent (17.4% in ITT, 19.5% in PP). Eighty-eight patients required re-adjustment of the sling during the follow-up. The tension was increased in 82 cases due to recurrence of SUI and reduced in six due to outlet obstruction.

However the currently available adjustable sling devices have differing designs, making it difficult to draw general conclusions about adjustable slings as a class of procedure.

4.2.4.3.3.2.1 Summary of evidence for adjustable slings

Summary of evidence	**LE**
There is only low level evidence to suggest that adjustable mid-urethral synthetic sling devices may be effective for cure or improvement of SUI in women.	3
There is no evidence that adjustable slings are superior to standard MUS.	4

4.2.4.3.3.3 External compression devices

External compression devices are usually used in the treatment of recurrent SUI after failure of previous surgery but can be considered as a primary treatment. Publications in the literature have largely included patients with profound intrinsic failure of the sphincter mechanism, characterised by very low VLPPs or low urethral closure pressures [409, 410]. The two intracorporeal external urethral compression devices available are the adjustable compression therapy (ACT©) device and AUS.

ACT®: Using US or fluoroscopic guidance, the ACT© device is inserted by placement of two inflatable spherical balloons, one on either side of the bladder neck. The volume of each balloon can be adjusted through a subcutaneous port placed within the labia majora. A systematic review including eight studies published between 2007 and 2013 with follow-up ranging from 1-6 years revealed 15-44% of patients considered that their SUI had been cured and 66–78.4% were satisfied with the result [409]. The explantation rate ranged between 19 and 31%. In these studies a significant reduction in the number of pads used per day was consistently observed after ACT® balloon placement and QoL was significantly improved. The authors concluded that ACT® balloons constitute a reasonable, minimally-invasive alternative for the treatment of female SUI due to intrinsic sphincter deficiency, especially in patients who have already experienced failure of standard surgical treatment.

AUS: The major advantage of AUS over other anti-incontinence procedures is the perceived ability to be able to void normally [407]. There are a few case series of AUS in women, including four series (n = 611), with study populations ranging from 45 to 215 patients and follow-up ranging from one month to 25 years [419-422]. Case series have been confounded by varying selection criteria, especially the proportion of women who have neurological dysfunction or who have had previous surgery. Most patients achieved an improvement in SUI, with reported subjective cure in 59–88%. Common side effects included mechanical failure requiring revision (up to 42% at ten years) and explantation (5.9–15%). In a retrospective series of 215 women followed up for a mean of six years, the risk factors for failure were older age, previous Burch colposuspension and pelvic radiotherapy [422].

Early reports of laparoscopically implanted AUS do not have sufficient patient populations and/or sufficient follow-up to be able to draw any conclusions [423, 424].

A more recent systematic review included 17 studies but all were retrospective or prospective non-comparative case series [410]. Most patients in the included trials had undergone at least one anti-incontinence surgical procedure prior to AUS implantation (69.1–100%). Outcomes revealed that complete continence rates ranged from 61 to 100%. The rates of explantation were 0–45%, erosion rates were 0–22% and mechanical failure rates were 0–44%. The authors concluded that AUS can provide excellent functional outcomes in female patients with SUI resulting from intrinsic urethral sphincter deficiency but at the cost of a relatively high morbidity.

4.2.4.3.3.3.1 Summary of evidence for external compression devices

Summary of evidence	LE
Implantation of an artificial sphincter improves or cures incontinence in women with SUI caused by sphincter insufficiency.	3
Implantation of the artificial urinary sphincter (AUS) device may improve complicated SUI.	3
Implantation of the adjustable compression therapy (ACT©) device may improve complicated SUI.	3
Complications, mechanical failure and device explantation often occur with both the artificial sphincter and the ACT©.	3
Explantation of AUS is more frequent in older women and among those who have had previous Burch colposuspension or pelvic radiotherapy.	3

4.2.4.3.3.4 Recommendations for complicated stress urinary incontinence

Recommendations	Strength rating
Management of complicated stress urinary incontinence (SUI) should only be offered in centres with appropriate experience (see Section: 4.2.4.3.1).	Strong
Base the choice of surgery for recurrent SUI on careful evaluation, including individual patient factors and considering further investigations such as cystoscopy, multichannel urodynamics, as appropriate.	Strong
Inform women with recurrent SUI that the outcome of a surgical procedure, when used as a second-line treatment, is generally inferior to its use as a first-line treatment, both in terms of reduced efficacy and increased risk of complications.	Weak
Only offer adjustable mid-urethral sling as a primary surgical treatment for SUI as part of a structured research programme.	Strong
Consider secondary synthetic sling, bulking agents, colposuspension, autologous sling or artificial urinary sphincter (AUS) as options for women with complicated SUI.	Weak
Inform women receiving AUS or adjustable compression device (ACT©) that although cure is possible, even in expert centres, there is a high risk of complications, mechanical failure or a need for explantation.	Strong

4.2.4.3.4 Surgery for stress urinary incontinence in special patient groups

4.2.4.3.4.1 Stress urinary incontinence surgery in obese women

There is no agreement as to the outcome of incontinence surgery in obese women. Secondary analysis of an RCT on retropubic and transobturator tapes in the treatment of women with SUI suggests that obese women experience inferior outcome compared to non-obese women. Stratification of patients according to BMI (< 30 and ≥ 30) shows significant difference in objective dry rates (negative pad test) at one (85.6% vs. 67.8%) and five years (87.4% vs. 65.9%) and subjective cure (absence of SUI symptoms) at one (85.8% vs. 70.7%) and five years (76.7% vs. 53.6%, respectively). Between one and five years, 6.7% and 16.3% of patients initially dry (negative pad test) after surgery developed a positive pad test, respectively [425, 426].

Conversely, short-term outcome of single-incision MiniArc® sling showed comparable objective cure rates (negative cough stress test) at two years (86% and 81% in non-obese and obese women, respectively); similar improvement of the Urinary Distress Inventory 6 and Incontinence Impact questionnaire 7 was observed in non-obese and obese women [427].

4.2.4.3.4.2 Stress urinary incontinence surgery in elderly women

Age appears to be a significant factor in outcome from SUI surgery but there is conflicting evidence in the literature. An RCT of 537 women comparing retropubic to transobturator tape, showed that increasing age was an independent risk factor for failure of surgery over the age of 50 [428]. An RCT assessing risk factors for the failure of TVT vs. transobturator tension-free vaginal tape (TVT-O) in 162 women also found that age is a specific risk factor (adjusted OR: 1.7 per decade) for recurrence at one year [429]. In addition, based on a sub-analysis of a trial cohort of 655 women at 2 years follow-up, it was shown that elderly women were more likely to have a positive stress test at follow-up (OR: 3.7) were less likely to report objective or subjective improvement in stress and UUI, and were more likely to undergo re-treatment for SUI (OR: 3.9). There was no difference in time to post-operative normal voiding [430].

Another RCT comparing immediate TVT vs. no surgery (or delayed TVT) in older women, confirmed efficacy of surgery in terms of QoL and satisfaction, but with more complications in the surgical arm [431].

Conversely, a cohort study evaluating 181 women undergoing TVT-O surgery, found that women over 70 years had similar outcomes when compared to women under 70 years old in terms of cure rates (92.5% vs. 88.3%, p = 0.40), voiding dysfunction, vaginal erosion and groin pain at a median follow-up of 24 months [432].

Furthermore, a systematic review of the efficacy of treatments of UI in older patients suggests that MUS are successful in older patients (≥ 65 years) with 5.2-17.6% reporting persistent SUI after surgery. No difference in the frequency of *de novo* UUI, persistent UUI and persistent SUI was found in older patients [365].

A cohort study of 256 women undergoing vagina-to-skin (inside-out) TOT reported similar efficacy in older vs. younger women, but there was a higher risk of *de novo* urgency in older patients [433].

4.2.4.3.4.3 Summary of evidence and recommendations for SUI surgery in special patient groups

Summary of evidence	LE
Incontinence surgery may be safely performed in obese women, however, outcomes may be inferior.	1
The risk of failure from surgical repair of SUI, and the risk of suffering adverse events, appears to increase with age.	2b
There is no evidence that any surgical procedure has greater efficacy or safety in older women than another procedure.	4

Recommendations	Strength rating
Inform obese women with stress urinary incontinence (SUI) about the increased risks associated with surgery, together with the lower probability of benefit.	Weak
Inform older women with SUI about the increased risks associated with surgery, together with the likelihood of lower probability of benefit.	Weak

*4.2.5 **Follow-up***

The follow-up of patients with SUI will be dependent on the treatment given. For conservative and physical therapies sufficient time should be allowed for the demonstration of treatment effect. For pharmacological treatment early follow-up is recommended. For most surgical interventions short-term follow-up should be arranged to assess efficacy and identify any surgical complications in the early post-operative phase.

The Panel is supportive of long-term outcome assessment via registries and recognises the paucity of high-quality long-term data specifically regarding complications from surgery.

4.3 Mixed urinary incontinence

The term ‘mixed urinary incontinence’ is extremely broad because it may refer to equal stress and urgency symptoms, stress-predominant symptoms, urgency-predominant symptoms, urodynamic SUI (USUI or USI) with DO or USUI with clinical urgency symptoms, but no DO [434]. The challenge of this broad definition is that it leads to inconsistencies when evaluating treatment options and outcomes.

*4.3.1 **Epidemiology, aetiology and pathophysiology***

The prevalence rates of MUI vary widely in the literature. A large majority of epidemiological studies have either not considered subtypes of UI, or only reported on SUI, UUI and MUI. The current literature is unclear regarding the population prevalence and risks for the different UI subtypes [8]. There are a large number of urinary symptom questionnaires employed in epidemiological research all with varying evidence of validity. Caution is needed when comparing epidemiological studies that do or do not report a separate MUI subgroup, and when generalising from population level data to clinical practice. The problems arise from significant heterogeneity in terms of types of questionnaires/surveys used, population parameters, variable response rates, varying definitions of MUI, and outcome measures.

It seems apparent, however, that MUI is the second most common form of UI, after SUI, with most studies reporting a 7.5–25% prevalence [8]. Furthermore, one can extrapolate that of women with UI, approximately one-third have MUI [435]. In a secondary analysis of a large clinical trial 655 women were evaluated for the presence of incontinence and their response to treatment [436]. They found that 50–90% of women fell into the category of MUI based on patient-reported answers to the Medical Epidemiologic and Social Aspects of Aging (MESA) and Urinary Distress Inventory (UDI) questionnaires. However, when objective criteria such as urodynamic findings were used, only 8% of women were categorised as having MUI.

Mixed incontinence is usually caused by a combination of the same factors that cause stress and urgency incontinence. Several factors may be responsible for its development, including oestrogen deficiency, abnormalities in histomorphology, and microstructural changes [437]. One report postulates that an incompetent sphincter and bladder neck allows urine to enter the proximal urethra during stress, causing a urethro-detrusor reflex that triggers an involuntary detrusor contraction, which then causes urgency and UUI [438]. Another paper also showed that urine flow across urethral mucosa led to an increase in the excitability of the micturition reflex [439]. Ultimately, it is likely that one theory or risk factor does not explain the development of MUI and its symptoms; it is more probable that disturbances in several elements and the inability of the bladder to compensate results in the development of MUI [437].

*4.3.2 **Diagnostic evaluation***

Assessment of patients with MUI begins with a thorough history of the patient's urinary symptoms and follows the recommendations set out in the general evaluation and diagnosis of LUTS section. It is conventional to try and categorise MUI as either stress or urge predominant.

Mixed UI is difficult to diagnose, as the condition comprises many phenotypes. Some women exhibit detrusor contractions provoked by physical stressors, some have unprovoked detrusor contractions, and many have no abnormal detrusor contractions, but still report urine leakage with the sensation of urgency. Some women with urgency symptoms do not manifest UUI because their urethral sphincter is strong and often able to prevent urine leakage [440].

The role of urodynamics in MUI is unclear, but establishing objective degrees of SUI and DO incontinence may help in counselling patients about the most appropriate initial treatment option.

4.3.2.1 Summary of evidence and recommendations for the diagnosis of mixed urinary incontinence

Summary of evidence	LE
There is no evidence that urodynamics affects outcomes of treatment for MUI.	3

Recommendations	Strength rating
Complete a thorough history and examination as part of the assessment of mixed urinary incontinence (MUI).	Strong
Characterise MUI as either stress-predominant or urgency-predominant where possible.	Weak
Use bladder diaries and urodynamics as part of the multi-modal assessment of patients with MUI to help inform the most appropriate management strategy.	Strong

*4.3.3 **Disease Management***

4.3.3.1 Conservative management

Women with MUI generally have more severe symptoms and respond less well to treatment than women with only SUI or UUI [441]. Clinicians are encouraged to begin treatment for MUI with conservative management directed toward the most bothersome component of the woman's symptom spectrum and to reserve surgery as a last resort [440].

4.3.3.1.1 Pelvic floor muscle training in mixed urinary incontinence

An RCT comparing PFMT with and without an audiotape for 71 women with UI did not find any difference between the two treatment arms [442]. Mean number of incontinent episodes per day decreased from 3.9 overall to 3.2 for participants with MUI. Six months after completing the course of exercises approximately one third of all enrolees reported that they continued to note good or excellent improvement and desired no further treatment.

A small RCT including 34 women with SUI and MUI compared 8 weeks of PFMT with no treatment and found that PFM training significantly increased PFM strength, improved QoL, and reduced the frequency of UI episodes compared to no treatment [443]. Another RCT including SUI and MUI confirmed these results [444].

A multicentre randomised controlled non-inferiority trial on 467 women with MUI was conducted in 10 hospitals. Participants were randomised 1:1 to receive electro-acupuncture (36 sessions over 12 weeks with 24 weeks of follow-up) or PFMT-solifenacin (5 mg/day) over 36 weeks. In women with moderate-to-severe MUI, electro-acupuncture was not inferior to PFMT-solifenacin in decreasing the 72-hour incontinence episodes (between-group difference, -1.34%) [445].

In a comparative study of the effectiveness of behavioural and PFMT (combined with MUS vs. sling alone in women with MUI, 416 (86.7%) had post-baseline outcome data and were included in primary 12-month analyses [446]. The UDI score in both groups significantly decreased (178.0 to 30.7 points in the combined group, 176.8 to 34.5 points in the sling-only group). The model-estimated between-group difference did not meet the minimal clinically important difference threshold. Adherence to the behavioural and PFMT regimes, which is a prerequisite for achieving effect, was not reported in the study.

A Cochrane review comparing PFMT with no or sham treatment included 31 RCTs from 14 countries, but there was only one study including women with MUI and one with UUI and none of them reported data on cure, improvement, or number of episodes of these subgroups [325].

Another Cochrane review comparing different approaches to delivery of PFMT (21 RCTs) concluded that increased intensity of delivery of the therapy improves response and that there is no consistent difference between group therapy and individualised treatment sessions [329]. This concurs with the latest ICI publication [331]. No other consistent differences between techniques were found.

The effect of combining biofeedback with PFMT has already been fully addressed in SUI Section 4.2.4.1.3 - Pelvic floor muscle training and there was no evidence of any additional benefit in a population with predominantly MUI.

4.3.3.1.2 Bladder training

Details on bladder training programs are elucidated in Section 4.2.4 (SUI). The ICI 2017 [331] concluded that for women with UUI or MUI, PFMT and BT are effective first-line conservative therapies. One RCT assigned 108 women with diagnoses of SUI (n = 50), UUI (n = 16), or MUI (n = 42) to six weeks of BT and PFMT or BT alone [447]. The results showed that overall, and in the SUI and MUI subgroups, significantly more patients in the BT and PFMT group reported cure and improved symptoms.

4.3.3.1.3 Electrical stimulation

A Cochrane review on ES for SUI included participants with SUI or stress-predominant MUI. Twenty-five percent of the included trials were deemed to have a high risk of bias due to a variety of factors including baseline differences between groups and industry funding. For subjective cure or improvement of SUI, low-quality evidence indicated that ES was better than no active treatment (RR: 1.73), or sham treatment (RR: 2.03). Electrical stimulation for OAB and SUI is covered in Sections 4.1.4.1.5.4 and 4.2.4.1.3.2, of the respective topics.

4.3.3.2 Summary of evidence and recommendations for conservative management in MUI

Summary of evidence	**LE**
Pelvic floor muscle training appears less effective for MUI than for SUI alone.	2
Pelvic floor muscle training is better than no treatment for improving UI and QoL in women with MUI.	1a
Bladder training, combined with PFMT, may be beneficial in the treatment of MUI.	1b

Recommendations	**Strength rating**
Treat the most bothersome symptom first in patients with mixed urinary incontinence (MUI).	Weak
Offer bladder training as a first-line therapy to adults with MUI.	Strong
Offer supervised intensive pelvic floor muscle training, lasting at least three months, as a first-line therapy to all women with MUI (including elderly and postnatal women).	Strong

4.3.3.3 Pharmacological management

Many RCTs include patients with MUI with predominant symptoms of either SUI or UUI but few report outcomes separately for those with MUI compared to pure SUI or UUI groups.

4.3.3.3.1 Tolterodine

In an RCT of 854 women with MUI, tolterodine ER was effective for improvement of UUI, but not SUI suggesting that the efficacy of tolterodine for UUI was not altered by the presence of SUI [448]. In another study (n = 1,380) tolterodine was equally effective in reducing urgency and UUI symptoms, regardless of whether there was associated SUI [449]. Similar results were found for solifenacin [450, 451].

4.3.3.3.2 Duloxetine

In one RCT of duloxetine vs. placebo in 588 women, subjects were stratified into either stress-predominant, urgency-predominant or balanced MUI groups. Duloxetine was effective for improvement of incontinence and QoL in all subgroups, although results in stress-predominant groups were better [452]. Treatment-emergent adverse event rate in the duloxetine group was high at 61.3% with discontinuation rates of 15.7%. Adverse event rates were higher in those participants taking other concomitant anti-depressant agents.

Duloxetine was also found to have equal efficacy for SUI and MUI from an RCT (n = 553) following secondary analysis of respective subpopulations [453]. No data on adverse events was reported in this study.

4.3.3.3.3 Summary of evidence and recommendations for pharmacological management of MUI

Summary of evidence	LE
Limited evidence suggests that anticholinergic drugs are effective for improvement of the UUI component in patients with MUI.	2
Duloxetine is effective for improvement of both SUI and MUI symptoms, but adverse event rates are high.	1b

Recommendations	Strength rating
Treat the most bothersome symptom first in patients with mixed urinary incontinence (MUI).	Weak
Offer anticholinergic drugs or beta-3 agonists to patients with urgency-predominant MUI.	Strong
Offer duloxetine (where licensed) to selected patients with stress-predominant MUI unresponsive to other conservative treatments and who want to avoid invasive treatment, counselling carefully about the risk of adverse events.	Weak

4.3.3.4 Surgical management

The surgical treatment options for MUI include all the anti-incontinence procedures outlined in the SUI chapter.

Many RCTs include both patients with pure SUI or pure UUI as well as patients with MUI. However, very few RCTs report separate outcomes for MUI subgroups.

Post-hoc analysis of a large RCT showed that in women undergoing either autologous fascial sling or Burch colposuspension, the outcomes were poorer for women with a concomitant complaint of pre-operative urgency [430]. A similar *post-hoc* review of another RCT comparing transobturator and retropubic MUS showed that the greater the severity of pre-operative urgency, the more likely that treatment would fail [99]. However, an earlier study had found that surgery provided similar outcomes, whether or not urgency was present prior to surgery (this study included only a few patients with urodynamic DO). Another RCT including 93 patients with MUI showed a statistical improvement in continence and QoL in the group that had TVT and Botox® rather than with either treatment alone [454].

Case series tend to show poorer results in patients with MUI compared with those with pure SUI. In a case series of 192 women undergoing MUS insertion, overall satisfaction rates were lower for women with mixed symptoms and DO on pre-operative urodynamics compared to those with pure SUI and normal urodynamics (75% vs. 98%, respectively) [455]. A comparison of two parallel cohorts of patients undergoing Burch colposuspension for SUI, with and without DO, found inferior outcomes in women with MUI [456].

One cohort of 450 women, showed that in urgency-predominant MUI, the success rate of TVT fell to 52% compared to 80% in stress-predominant MUI [457]. In a study with 1,113 women treated with TVT-O, SUI was cured equally in stress-predominant MUI or urgency-predominant MUI. However, women with stress-predominant MUI were found to have significantly better overall outcomes than women with urgency predominant MUI [458].

In contrast to studies examining older surgical methods, more recent studies (generally small case series) reported that UUI symptoms improve in 30% to 85% of women with MUI after MUS surgery [459].

In a prospective, multicentre, comparative trial 42 women who had a TVT for MUI had a greater improvement in urgency and QoL scores than 90 women who had a TOT. There were no significant differences in the cure and satisfaction rates between the two groups [460].

In a single-centre prospective study, 86 consecutive women underwent TOT for MUI. At a mean follow-up of 59 months, SUI was cured objectively in 83.7% and subjectively in 87.2% of the patients. The continence rates were 74.4% for UUI and 66.3% for MUI (cure of both components). The patient-reported success rate was 87.2% ('much better' or 'very much better' on Patient Global Impression of Improvement scale). There were statistically significant improvements in all domains except general health. The univariate analysis found no significant risk factor for persistence of SUI. Median age > 60 years and menopause were predictive for persistence of UUI. Median and mean age > 60 years were predictive of persistence of overall incontinence [461]. Overall, the outcome for women with pre-existing UUI remains uncertain.

In a secondary analysis of a study of transobturator TVTs in the treatment of women with urodynamic MUI, no difference in patient-reported success rates was found between the vagina-to-skin (inside-out) and the skin-to-vagina (outside-in) groups (63.2% and 65.5%, respectively; OR: 1.11, 95% CI: 0.33–3.70, p > 0.999) at 9 years follow-up [399].

Analysis of the trial populations included in the meta-analysis on single-incision slings suggests that the evidence is generalisable to women who have predominantly SUI, and no other clinically severe LUT dysfunction. The evidence is not adequate to guide choice of surgical treatment for those women with MUI, severe POP, or a history of previous surgery for SUI.

In general research trials should define accurately what is meant by MUI. There is a need for well-designed trials comparing treatments in populations with MUI, and in which the type of MUI has been accurately defined.

4.3.3.4.1 Summary of evidence and recommendations for surgery in patients with MUI

Summary of evidence	LE
Women with MUI are less likely to be cured of their UI by SUI surgery than women with SUI alone.	1b
The response of pre-existing urgency symptoms to SUI surgery is unpredictable.	3

Recommendations	Strength rating
Treat the most bothersome symptom first in patients with mixed urinary incontinence (MUI).	Weak
Warn women that surgery for MUI is less likely to be successful than surgery for stress urinary incontinence alone.	Strong
Inform women with MUI that one single treatment may not cure urinary incontinence; it may be necessary to treat other components of the incontinence problem as well as the most bothersome symptom.	Strong

4.4 Underactive bladder

Underactive bladder is a common clinical entity, defined by the ICS as *'a symptom complex characterised by a slow urinary stream, hesitancy, and straining to void, with or without a feeling of incomplete bladder emptying sometimes with storage symptoms'* [462]. Diagnosis of UAB is made based on clinical symptoms and can have a highly variable presentation and aetiology.

This differs from DU, which is a diagnosis based on urodynamic studies. Detrusor underactivity is defined by the ICS as *"a detrusor contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span"*[1]. Acontractile detrusor is specified when there is no detrusor contraction.

Female voiding dysfunction is defined by the ICS as a diagnosis based on symptoms and urodynamic investigations characterised by abnormally slow and/or incomplete micturition, based on abnormally slow urine flow rates and/or abnormally high PVR, ideally on repeated measurement to confirm abnormality. Pressure-flow studies can be required to determine the cause of the voiding dysfunction [28].

*4.4.1 **Epidemiology, aetiology, pathophysiology***

4.4.1.1 Epidemiology

Underactive bladder as an entity remains difficult to study in part because its corresponding urodynamic correlate, "detrusor underactivity" remains loosely defined, leading to significant variability in diagnostic criteria across research studies and significant overlap of symptoms with other conditions. As a consequence of the variability in definition, reported prevalence also varies and ranges from 12% to 45% in females with increased prevalence seen with age [76] and in institutionalised elderly women [463].

Several studies have demonstrated similar prevalence rates for DU in the ambulatory setting of around 12%–19.4% [464-466]. As would be expected, voiding symptoms consistent with UAB are slightly higher. A Detroit population study surveyed 291 women with 20% reporting difficulty with emptying their bladder [467]. In a large cross-sectional, population-based internet survey conducted in the USA, UK and Sweden including 15,861 women ≥ 40 years, 20.1% referred to weak flow, 27.4% to incomplete bladder emptying and 38.3% to terminal dribbling [5].

Some studies have identified the coexistence of DO during filling and DU in the voiding phase of urodynamic studies (formerly known as DHIC, "detrusor hyperactivity with impaired contractility") as a common finding in elderly women. Up to 38.1% of incontinent institutionalised women showed DHIC in urodynamic studies [468, 469].

4.4.1.2 Aetiology

The presence of DU in diverse clinical groups suggests a multifactorial aetiology [470]. Idiopathic DU is probably in part an age-dependent decrease in detrusor contractility with no other identifiable causes, but young women can also be identified as having DU. There are many secondary causes of DU including neurogenic (multiple sclerosis, multiple systemic atrophy, spinal cord injury, spina bifida, Parkinson, hydrocephalus, transverse myelitis, stroke, Guillain-Barré syndrome, diabetes mellitus, pelvic nerve injury, etc.), myogenic (acute prolonged bladder overdistension, diabetes mellitus, BOO) and iatrogenic (pelvic surgery) [471].

4.4.1.3 Pathophysiology

There are many pathways involved in normal detrusor contraction, and there are different possible sites of dysfunction [76] with a variety of mechanisms involved in UAB:

- Central circuits and centres (prefrontal cortex, PAG, PMC, hypothalamus): failure of integration or processing;
- Efferent pathways (sacral cord, sacral nerves, pelvic nerves, postganglionic neurons): impaired activation of detrusor;
- Afferent pathways (peripheral afferent nerves, anterolateral white column, posterior column): early termination of voiding reflex;
- Muscle (detrusor myocyte, extracellular matrix): loss of intrinsic contractility.

Different aetiologies can share common pathophysiological mechanisms: for example, diabetes mellitus affects mainly afferent pathways and the detrusor muscle; and neurogenic diseases affect central circuits and efferent-afferent pathways.

One study suggests that in patients with DU, there is significant urothelial dysfunction, increased sub-urothelial inflammation and apoptosis, and altered sensory protein expression [472]. Impaired urothelial signalling and sensory transduction pathways may reflect part of the pathophysiology of DU. Pelvic ischaemia is another proposed mechanism of DU in ageing patients [472]. See Figure 1.

Figure 1: Management and treatment of women presenting with urinary incontinence

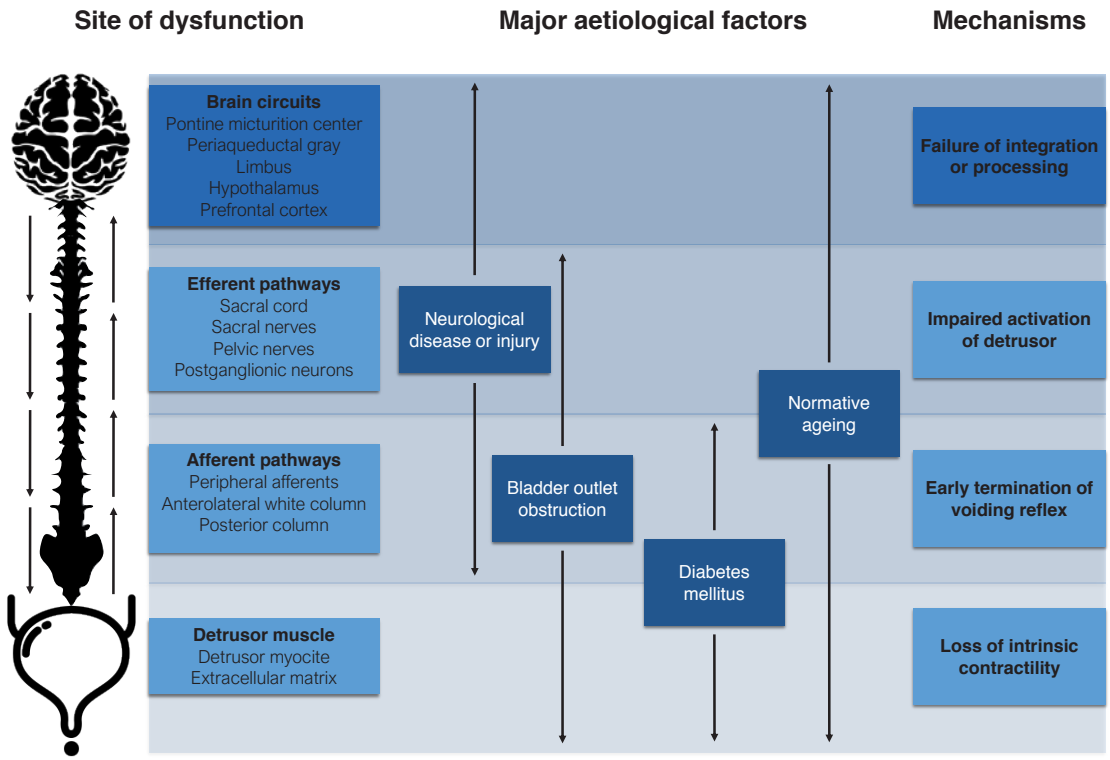

**Figure reproduced with permission from the publisher, from Osman N. et al., [473].*

4.4.2 ***Classification***

There is no current classification system of UAB. Patients can be classified according to presumed aetiology or pathogenic mechanism, but without sufficient longitudinal data or high-level evidence to establish prognostic factors, the classification of UAB patients in terms of relevant clinical characteristics or risk of complications is not possible.

4.4.3 ***Diagnostic evaluation***

4.4.3.1 *Symptoms associated with detrusor underactivity*

A retrospective study correlated LUTS with urodynamic findings in 1,788 patients (1,281 women). In women with DU (defined as $P_{det}Q_{max}$ < 20, Q_{max} <15, BVE% < 90 and excluding obstruction on VUDS), the authors found a statistically higher occurrence of reduced and/or interrupted stream, hesitancy, feeling of incomplete bladder emptying, palpable bladder, and absent and/or decreased sensation compared with women with a normal pressure flow study [474]. A qualitative study on a small sample of male and female patients diagnosed with DU reported a variety of LUT symptoms and associated impact on QoL. Storage symptoms of nocturia, increased daytime frequency, and urgency, and the voiding symptoms of slow stream, hesitancy, and straining were reported by over half of the patients. A sensation of incomplete emptying and post-micturition dribble were also frequently described. The impact of their symptoms on QoL was highly variable, but in general storage symptoms were more bothersome [475].

Based on current data, it is not possible to find a pivotal symptom or collection of symptoms to identify DU patients. The ICI Questionnaire-underactive bladder (ICIQ-UAB) has been developed as a research PROM tool, that needs further validation before use in common clinical practice [476].

4.4.3.2 *Urodynamic studies*

Non-invasive studies like uroflowmetry, PVR measurement and BVE determination are potentially useful to identify women who might have DU. There is considerable symptomatic overlap with BOO and uroflowmetry and PVR findings may also be similar. Only invasive urodynamics with pressure-flow studies can reliably distinguish DU from BOO and these urodynamic diagnoses can co-exist. There is no consensus on the best method to diagnose DU in women. In addition, diagnosis in women is particularly difficult as women can void by relaxing the pelvic floor, that is, without a detectable detrusor contraction during the pressure-flow study and without increased abdominal pressure [477]. The simplest methods to define and diagnose DU are based on the use of cut-off values of Q_{max} and $P_{det}Q_{max}$, possibly combined with cut-off values of PVR and BVE. There is no consensus

on which cut-off values should be used [478]. It is obvious that the prevalence of DU depends on the criteria used. In a retrospective study on 1,015 women, DU was found in 14.9% when using Q_{max} < 12 mL/s or PVR > 150 mL; in 9.6% when using $P_{det}Q_{max}$ < 30 cm H_2O and Q_{max} < 10 mL/s; and in 6.4% when using $P_{det}Q_{max}$ < 20 cm H_2O, Q_{max} < 15 mL/s and BVE < 90% [479].

More elaborate methods combine urodynamic data into an index or a physical quantity that reflects bladder contraction strength. A value below a certain threshold would thus diagnose DU. Again, there is no consensus regarding what is normal and what is abnormal. Table 4 provides an overview of the best-known parameters, their background and typical values. The parameter Watt's factor (WF) estimates the power generated by the detrusor per unit area of bladder surface [480]. Its value varies during voiding. Usually, its maximum value WF_{max} is considered. Alternatively, its value at Q_{max} can be used. Projected isovolumetric pressure (PIP) is a gross simplification of the bladder output relation and estimates the maximum detrusor pressure that can be generated by the bladder when the outlet is closed, the isovolumetric detrusor pressure. The bladder contractility index (BCI) is simply a reduction of PIP to an index [46]. The population in which PIP and BCI were developed mainly consisted of males. Projected isovolumetric pressure (PIP1) also estimates the isovolumetric detrusor pressure, but was developed in an entirely female population via an experimental method [481].

A third method of quantifying bladder contraction strength involves "stop tests". One study compared 3 types of direct measurement of the isovolumetric pressure: (i) the voluntary stop test, in which the patient voluntarily interrupts flow, (ii) the mechanical stop test, in which flow is interrupted by a balloon catheter, and (iii) the continuous occlusion test, in which the subject tries to void against a blocked outlet. The latter had the best reliability and best detected drug-induced changes. The results of the mechanical stop test were however very similar [482].

All parameters discussed above give some information on the strength of the detrusor contraction in a given void. They do not necessarily reflect what the detrusor might potentially achieve under optimum conditions [483]. Also, they give no information on another important aspect of a voiding contraction, namely its duration. No parameters for this are available. Finally, in a given patient an abnormally low bladder contraction strength does not necessarily imply an insufficient bladder contraction strength to achieve optimal voiding. Table 4 summarises different parameters to measure detrusor contraction in female patients.

Table 4: Most used parameters to measure detrusor contraction in female patients

Parameter	Basis	Population	Values
Watt's factor [480]	Hill equation of muscle contraction in a spherical organ, with fixed constants obtained from experimental and clinical studies	8 asymptomatic female volunteers aged 28-45 years (median 34 years)	Ideal voiding (bell-shaped flow curves): WF_{max} 11-24 W/m^2 Non-ideal voiding: WF_{max} 5-10 W/m^2 Normally WF_{max} > 7 W/m^2 (expert opinion, unspecified population) [484]
Projected isovolumetric detrusor pressure (PIP, cm H_2O) and Bladder Contractility Index (BCI, using PIP as an index) [46, 485]	Bladder Output Relation, simplified to a straight line with fixed slope of 5 cm H_2O/mL/sec (Formula: $P_{det}Q_{max} + 5xQ_{max}$)	Unspecified population, mainly men with BPO	Classification based on expert opinion: > 150: strong contraction 100-150: normal contraction 50-100: weak contraction < 50: very weak contraction
Projected isovolumetric detrusor pressure (PIP1, cm H_2O) [481]	Comparison of Q_{max} and $P_{det}Q_{max}$ values with stop test results (Formula: $p_{det}Q_{max} + Q_{max}$)	100 women with UUI aged 53-89 (mean: 70) years	5^{th}-95^{th} percentile: 29-78 cm H_2O Mean: 49 cm H_2O Median: 48 cm H_2O Proposed typical values: 30-75 cm H_2O
Continuous occlusion test [482]	Direct measurement of isovolumetric voiding contraction	70 women with UUI aged 53-89 (mean: 70) years	Mean ± SD: 48.7 ± 24.4 cm H_2O

BPO = benign prostatic obstruction; $P_{det}Q_{max}$ = detrusor pressure at maximum flow rate; PIP = projected isovolumetric pressure; Q_{max} = maximum flow rate; SD = standard deviation; UUI = urgency urinary incontinence; WF = Watt's factor.

*4.4.4 **Disease management***

As there are so many different possible causes and pathogenic mechanisms involved in female UAB, preventive and therapeutic strategies are difficult to define. Among preventive strategies, early recognition after major surgery or labour might prevent long-term problems associated with prolonged bladder over-distension. Nerve-sparing techniques for radical pelvic surgery are more favourable in terms of early recovery of bladder function [486, 487].

Treatment of female DU includes strategies to ensure bladder drainage, increase bladder contraction, decrease urethral resistance or a combination [484]. The goals of management of UAB are to improve symptoms and QoL, to reduce the risk of complications for impaired bladder emptying, but also to identify situations where interventions may not be appropriate.

4.4.4.1 Conservative management

4.4.4.1.1 Behavioural interventions

Regular or timed voiding to avoid bladder over-distension should be encouraged in women with impaired bladder sensations. Assisted voiding by abdominal straining with adequate relaxation of the PFM has been recommended, as well as double or triple voiding in an attempt to improve bladder emptying. None of these manoeuvres have proven their efficacy in a randomised study. There is a possible association between voiding by excessive abdominal straining and the risk of POP development [488]. A small retrospective study in women with neurogenic acontractile detrusor secondary to spina bifida showed that Valsalva voiding may increase the risk of rectal prolapse compared with CISC [489].

4.4.4.1.2 Pelvic floor muscle relaxation training with biofeedback

There are no RCTs on PFM relaxation training in female adults with UAB. Contradictory to common beliefs, one study found significant relaxation of the PFM after a contraction [490] and a second study found that PFMT over time increased the speed of PFM relaxation after a single contraction [491]. However, muscle contraction is known to be followed by relaxation. There is, however, some evidence from the paediatric literature including one randomised study that compared efficacy of PFM relaxation with biofeedback plus a combined therapy (including hydration, scheduled voiding, toilet training and diet) vs. combined therapy alone in children with non-neuropathic UAB and voiding dysfunction. Mean number of voiding episodes was significantly increased in the relaxation training group compared with the group with only combined treatment (6.6 ± 1.6 vs. 4.5 ± 1 times a day, $p < 0.000$). Post-void residual volume and voiding time decreased considerably, whereas maximum urine flow increased significantly in the relaxation group compared with the combined treatment group (17.2 ± 4.7 vs. 12.9 ± 4.6 mL/s, $p < 0.01$) [492].

4.4.4.1.3 Clean intermittent self-catheterisation

See Section 4.1.4.1.3 for details on CISC.

4.4.4.1.4 Indwelling catheter

Indwelling urinary catheter may be an option for some women who have failed all other treatments and are unable to perform CISC. Complications include UTI, stone formation and urethral damage. Suprapubic catheterisation may be preferable over urethral catheterisation to minimise the risk of urethral trauma and pain [493].

4.4.4.1.5 Intravesical electrical stimulation

Intravesical electrical stimulation (IVES) can be used to improve bladder dysfunction by stimulating A-delta mechanoreceptor afferents, but requires preservation of afferent circuit and healthy detrusor muscle. One retrospective study in 16 patients (11 female) found that two-thirds of patients with a weak detrusor after prolonged bladder overdistension regained balanced voiding after IVES due to detrusor reinforcement [494].

4.4.4.1.6 Intraurethral insert

The intraurethral insert is a short silicone catheter containing an internal valve and pump mechanism positioned in the female urethra. See BOO Section 4.5 for more information.

4.4.4.2 Pharmacology management

4.4.4.2.1 Parasympathomimetics

Theoretical approaches to UAB pharmacological treatment include direct stimulation of detrusor cells muscarinic receptors using agonists like carbachol or bethanechol, or inhibiting acetylcholinesterase (enzyme that inhibits the endogenous muscarinic agonist acetylcholine) using agents such as distigmine, pyridostigmine or neostigmine.

A systematic review on the use of parasympathomimetics in patients with UAB included 10 RCTs (controls typically received placebo or no treatment). While three studies reported statistically significant improvements relative to control group, six did not and one even reported significant worsening of symptoms. There was no evidence for differences between individual drugs, specific uses of such drugs, or in outcome measures [495]. The review concluded that the available studies do not support the use of parasympathomimetics for treating UAB, especially when frequent and/or serious possible side-effects (gastrointestinal upset, blurred vision, bronchospasm and bradycardia) are taken into account.

4.4.4.2.2 Alpha-blockers

In order to improve bladder emptying, decreasing outlet resistance through sympathetic blockade at the bladder neck/urethra has been investigated. One prospective study with tamsulosin showed similar improvement in terms of uroflowmetry parameters (specifically in the percentage of patients who had a good therapeutic response) in both women with BOO and women with DU (39.4% and 32.7% respectively) [496]. Another longitudinal study including 14 women with DU showed clinical and urodynamic improvements after tamsulosin [497]. A prospective single-blind randomised study in female patients with DU compared efficacy of alpha-blocker, cholinergic drugs or combination therapy, with the latter exhibiting the best results [498].

4.4.4.2.3 Prostaglandins

Prostaglandins are prokinetic agents that promote smooth muscle contraction. Prostaglandin E2 and F2 have been used intravesically to treat urinary retention after surgery in several studies. A Cochrane systematic review showed a statistically significant association between intravesically administered prostaglandin and successful voiding among post-operative patients with urinary retention (RR: 3.07). However, the success rate is relatively low (32%) compared to placebo. It should also be noted that the 95% CI was very wide, RCTs included in the pooled analysis were underpowered with methodological limitations, and the event rate was very low indicating a very low certainty of the evidence [499]. Intravesical prostaglandin treatment is rarely used and further research is necessary before it can be taken up more widely.

4.4.4.3 Surgical management

4.4.4.3.1 Sacral nerve stimulation

Sacral nerve stimulation is an FDA approved therapy for non-obstructive urinary retention. The mechanism of action has not been fully elucidated, but activation of afferent sensory pathways, modulation-activation of central nervous system and inhibition of inappropriate activation of the guarding reflex are some of the mechanisms proposed.

An RCT included 37 patients in the implantation arm and 31 in the standard medical therapy arm, showing a mean decrease in PVR volume in the implanted group compared with control of 270 mL and a mean increase in voided volume of 104 mL [500]. A meta-analysis of 7 studies showed a mean difference in PVR reduction of 236 mL and a mean voided volume increase of 299 mL [501]. The response rate during the trial phase ranged from 33–90% (mean 54.2) and the success rate of permanent implant ranged from 55–100% (mean 73.9%), highlighting that patient selection is crucial [502]. A subgroup of women with idiopathic urinary retention (Fowler's syndrome) seem to have a higher response rate of 68-77% [503].

In conclusion, SNS is a valid option for female patients with DU, with proper patient selection. Women should have preserved bladder contractility on urodynamic tests and mechanical/anatomical BOO should be excluded. Patients with evidence of anatomical bladder outflow obstruction, suspected loss of intrinsic detrusor contractility or neurogenic bladder dysfunction show lower response rates [504].

4.4.4.3.2 OnabotulinumtoxinA

OnabotulinumtoxinA injections in external striated urethral sphincter may improve voiding in patients with DU by reducing outlet resistance and possibly reducing the guarding reflex. Some retrospective case studies show improvement in voiding symptoms, recovery of spontaneous voiding and improvement in urodynamic parameters (reduction of voiding pressure and/or urethral closure pressures, PVR) [505, 506]. The duration of symptomatic relief is short, typically three months.

4.4.4.3.3 Transurethral incision of the bladder neck

Transurethral incision of the bladder neck has been described in short series of women with refractory DU. In a retrospective case study up to 40/82 (48.8%) of women achieved satisfactory outcomes (spontaneous voiding with voiding efficiency ≥ 50%), but 5 (6.1%) patients developed SUI and 2 (2.4%) developed a vesico-vaginal fistula [507].

4.4.4.3.4 Reduction cystoplasty

This is a very uncommon procedure with a few case reports described only in men [508].

4.4.4.3.5 Myoplasty

One retrospective multicentre study reported the long-term results of *latissimus dorsi* detrusor myoplasty in patients with bladder acontractility, with 71% recovering complete spontaneous voiding, with a mean PVR of 25 mL [509]. No other groups have published their experience to reproduce these findings.

4.4.4.4 Summary of therapeutic evidence on detrusor underactivity

The level of evidence of most of therapeutic interventions on DU is low. Only CISC remains as a gold standard to reduce the adverse consequences of a high PVR and incomplete voiding, in spite of the low level of evidence that supports this statement.

4.4.4.4.1 Summary of evidence and recommendations for underactive bladder

Summary of evidence	**LE**
Clean intermittent self-catheterisation has proven efficacy in patients who are unable to empty their bladder.	3
Indwelling transurethral catheterisation and suprapubic cystostomy are associated with a range of complications as well as an enhanced risk of UTI.	3
Intravesical electrical stimulation may be useful in some patients after prolonged bladder overdistension.	3
Parasympathomimetics do not improve clinical and urodynamic parameters of UAB patients and frequent and/or serious side-effects may arise.	1b
There is limited evidence about effectiveness of alpha-blockers in women with UAB.	2b
Very low certainty evidence indicates that intravesically administered prostaglandins may promote successful voiding in patients with urinary retention after surgery.	1a
Sacral nerve stimulation improves voided volume and decreases PVR in women with DU.	1b
There is limited evidence for the effectiveness of OnabotulinumtoxinA external urethral sphincter injections to improve voiding in women with UAB.	3
Transurethral bladder neck incision may improve voiding in women with DU, but complications (SUI, vesico-vaginal fistulae) may appear.	3
There is very limited evidence for effectiveness of detrusor myoplasty.	3

Recommendations	**Strength rating**
Encourage double voiding in those women who are unable to completely empty their bladder.	Weak
Warn women with underactive bladder (UAB) who use abdominal straining to improve emptying about pelvic organ prolapse risk.	Weak
Use clean intermittent self-catheterisation (CISC) as a standard treatment in patients who are unable to empty their bladder.	Strong
Thoroughly instruct patients in the technique and risks of CISC.	Strong
Offer indwelling transurethral catheterisation and suprapubic cystostomy only when other modalities for urinary drainage have failed or are unsuitable.	Weak
Do not routinely recommend intravesical electrical stimulation in women with UAB.	Weak
Do not routinely recommend parasympathomimetics in the treatment of women with UAB.	Strong
Offer alpha-blockers before more invasive techniques.	Weak
Offer intravesical prostaglandins to women with urinary retention after surgery only in the context of well-regulated clinical trials.	Weak
Offer onabotulinumtoxinA external sphincter injections before more invasive techniques as long as the patient is informed that the evidence to support this treatment is of low quality.	Weak
Offer sacral nerve stimulation to women with UAB refractory to conservative measures	Strong
Do not routinely offer detrusor myoplasty as a treatment for detrusor underactivity.	Weak

*4.4.5 **Follow-up***

Natural history and clinical evolution at long-term follow-up of women with DU is not well known. No longitudinal cohort studies with long-term follow-up are described in the literature. The interval between follow-up visits will depend on patient characteristics, treatments given and the frequency of urinary complications.

4.5 Bladder outlet obstruction

*4.5.1 **Introduction***

Bladder outlet obstruction is defined by the ICS as obstruction during voiding, characterised by increased detrusor pressure and reduced urine flow rate [1]. Its precise diagnosis requires urodynamic evaluation including an assessment of both pressure and flow.

Voiding dysfunction is a broad term which is distinct from BOO and is defined by the ICS as '*a diagnosis made by symptoms and urodynamic investigations characterised by abnormally slow and/or incomplete micturition, based on abnormally slow urine flow rates and or raised PVRs, ideally on repeated measurement to confirm abnormality*' [110]. Pressure-flow studies are required to determine the precise cause of the voiding dysfunction. Bladder outlet obstruction is one possible cause of voiding dysfunction but there are also non-obstructive causes and the two terms should not be used interchangeably. Another term that is to be differentiated from BOO and voiding dysfunction is dysfunctional voiding, which is a specific and discrete form of voiding dysfunction with an intermittent and/or fluctuating flow rate [110].

*4.5.2 **Epidemiology, aetiology, pathophysiology***

4.5.2.1 Epidemiology

Estimates of prevalence of BOO among women vary, with figures of 2.7% to 29% reported in the literature [510]. One large series of women undergoing urodynamic evaluation for LUTS found that around 20% are diagnosed with outlet obstruction. The wide variance between studies is due to several factors, including differences in definitions and diagnostic criteria for female BOO, differences in study populations, and variation in study methodologies. The estimated prevalence rates of LUTS due to BOO in women are lower than those reported in men (18.7–18.9% vs. 24.3–24.7%), respectively [511].

Prevalence of voiding LUTS was found to be associated with age [53, 512, 513], parity [53, 514], prolapse [53, 514] and prior continence surgery [53, 514]. Bladder outlet obstruction has long been postulated to cause mainly voiding symptoms [515] but recent data from a series of 1,142 consecutive women referred for evaluation of LUT symptoms suggest that storage symptoms may be predominant in female patients diagnosed with BOO and excess daytime urinary frequency was the most common symptom reported by 69% [510].

4.5.2.2 Pathophysiology

Bladder outlet obstruction is one of multiple causes of voiding dysfunction in women. The obstruction can be either anatomical (mechanical) or functional. In anatomic BOO, there is a physical or mechanical obstruction to the outflow of urine, whereas in functional BOO there is a non-anatomic, non-neurogenic obstruction of the outlet usually resulting from non-relaxation of bladder neck, sphincter or PFM or increased urethral sphincter tone or PFM contraction during the void, as is observed in patients with dysfunctional voiding.

Mechanisms for anatomic (mechanical) obstruction include external compression, fibrosis, stricture or injury to the urethra and kinking of the urethra due to POP. Progressive fibroblastic reaction around the urethra induced by mesh tapes or slings used in UI surgery may also bring about anatomic (mechanical) obstruction [471]. In a retrospective review of 192 females diagnosed with BOO, 64% had mechanical obstruction [510].

Functional obstruction, on the other hand, may be caused by failure of relaxation, or contraction, of the bladder neck and/or urethral sphincter complex or the PFMs during a sustained detrusor contraction [515]. The exact causes of this lack of relaxation, or contraction, is often elusive but might be due to sympathetic hyperactivity or hypertrophy of the bladder neck smooth muscle for primary bladder neck obstruction [516] or may be mostly behavioural as in dysfunctional voiding [517].

4.5.2.3 Aetiology

Conditions associated with anatomic BOO include POP, incontinence surgery, urethral stricture, urethral stenosis, urethral diverticulum, urethral caruncle, urethral malignancies and para-urethral masses.

Conditions associated with functional BOO include primary bladder neck obstruction, dysfunctional voiding, and idiopathic urinary retention (Fowler's syndrome).

In primary bladder neck obstruction the bladder neck fails to open adequately during voiding in the absence of an anatomical obstruction [518]. It is estimated that 4.6–16% of women presenting with voiding symptoms have primary bladder neck outlet obstruction [516].

Dysfunctional voiding is due to involuntary intermittent contractions of the peri-urethral striated or levator muscles during voiding in a neurologically normal woman, thought to be caused by faulty learned toileting behaviour [471]. There is also some evidence of a link between dysfunctional voiding and a history of sexual abuse [519].

Idiopathic urinary retention, also known as Fowler's syndrome, is a primary disorder of the external urethral sphincter with hypertrophy of the muscle fibres, which fail to relax during micturition. It is associated with decreased detrusor contractility via enhancement of the guarding reflex. It is seen most often, but not exclusively, in young women with urinary retention and is characterised by increased urinary sphincter volume and activity/tone, which may be hormonally triggered [520].

Alpha-adrenergic agonists, such as pseudo-ephedrine commonly contained in decongestants, could lead to some form of functional obstruction due to their stimulatory effects, which may contract the bladder neck and lead to urinary retention [521].

Neurologic conditions can also bring about functional BOO in females. These will not be considered in this Guideline document and are covered elsewhere [9].

*4.5.3 **Classification***

4.5.3.1 Anatomic bladder outlet obstruction

Anatomic BOO involves a physical or mechanical obstruction of the outflow of urine.

4.5.3.2 Functional bladder outlet obstruction

Functional BOO involves a non-anatomic, non-neurogenic obstruction of the outflow of urine resulting from non-relaxation or increased tone in the bladder neck and/or urethral sphincter complex or the PFMs (Table 5). Neurologic causes of functional BOO will not be considered in this Guideline document and are covered elsewhere [9].

Table 5: Main causes of female bladder outlet obstruction

Functional BOO	Anatomical BOO
• Primary bladder neck obstruction • Dysfunctional voiding • Idiopathic urinary retention (Fowler's syndrome)	• Urethral stricture • Anti-incontinence surgery • Pelvic organ prolapse • Urethral diverticulum • Urethral caruncle • Urethral malignancies • Para-urethral masses

4.5.3.3 Recommendation for the classification of bladder outlet obstruction

Recommendation	Strength rating
Use standardised classification of bladder outlet obstruction in women (anatomical or functional) and research populations should be fully characterised using such classification.	Strong

*4.5.4 **Diagnostic evaluation***

The diagnosis of BOO in women, although dependent on formal pressure flow studies, may be suggested by a number of clinical and other non-invasive assessments.

4.5.4.1 Clinical history

In terms of the clinical history a range of LUTS may be elicited and these may not be confined to voiding LUTS. Women may not present until they are suffering with the possible complications of BOO such as recurrent UTI, chronic urinary retention or acute/chronic kidney disease [510]. The evidence regarding clinical utility of symptoms for the diagnosis of BOO is inconclusive. In a single-centre retrospective study involving 587 women, 38 of whom were diagnosed with BOO, the authors concluded that symptom assessment alone was insufficient for the diagnosis and a full urodynamic evaluation was essential [522]. A smaller retrospective study of 57 premenopausal women with bothersome LUTS found a significantly higher proportion of women with bladder dysfunction presenting with the symptom of UUI. Patients with voiding phase dysfunction had

higher total scores and voiding symptom subscores in the American Urological Association Symptom Index (AUASI) [523]. Perhaps some of the difficulty in evaluating the diagnostic accuracy of urinary symptoms comes from the observation that a significant proportion of female patients presenting with obstruction will also have concomitant urodynamic abnormalities. In a large study of over 5,000 women with urinary symptoms identifying 163 with BOO additional urodynamic diagnoses were noted in 54% [524]. Similarly, in a study involving 101 women with a primary diagnosis of SUI, the prevalence of BOO (based on maximum urine flow [Q_{max}] of less than 12 mL per second and maximum detrusor pressure at maximum flow of more than 25 cm H_2O) was 16% [525]. Symptoms alone were not sufficient to discriminate between the various different diagnostic groups of women in these 2 studies. Lower urinary tract symptoms appear to be fairly sensitive to change following intervention for BOO. A prospective study in 53 women with clinically suspected voiding dysfunction describes significant symptom improvement in 12 of 16 patients who underwent surgical intervention [526].

4.5.4.2 Clinical examination

There are no studies evaluating the clinical utility of physical examination in women with suspected BOO. Despite this it is widely considered as a key part of the medical assessment. It allows for visual inspection of the urethra and vagina for possible causes of mechanical obstruction as well as an assessment of the pelvic floor, which may be the cause of functional obstruction.

4.5.4.3 Uroflowmetry and post-void residual volume

Reduced Q_{max} and/or incomplete bladder emptying can result from both a weakness in the contractile strength of the detrusor muscle or the presence of increased outlet resistance due to functional or anatomical/mechanical BOO. The use of a uroflowmetry measurements to differentiate between anatomical and functional BOO was explored in a retrospective study of 157 women [517] which concluded that Q_{max} was statistically significantly lower in those patients with anatomical obstruction but a large degree of overlap was noted. The largest evaluation of the diagnostic utility of urine flow studies and PVR volume estimation derives from a retrospective analysis of over 1,900 patients with symptoms of voiding dysfunction of whom over 800 were diagnosed with BOO based on urodynamic assessment [527]. In this series functional BOO was over 6 times more common than anatomical/mechanical obstruction which is discordant with most of the other epidemiological literature for female BOO. The authors found that although urine flow rate alone was not accurate enough to diagnose BOO, a PVR of 200 mL or more was able to differentiate bladder neck dysfunction from the other causes of BOO, with a receiver-operator characteristics (ROC) AUC of 0.69. Conversely, in a retrospective study involving 101 women primarily presenting with SUI, a good correlation between abnormal uroflowmetry and urodynamic obstruction (phi = 0.718, $p < 0.0001$) was found [525]. In a prospective study of over 50 women with a clinical diagnosis of voiding dysfunction abnormal uroflow curves were observed in around 40% of women, but BOO based on pressure-flow results was confirmed in only 52% of these women [526].

4.5.4.4 Ultrasound

The major utility of US scanning in women with BOO is to detect possible complications such as bladder wall thickening or upper tract dilatation/hydronephrosis. However, the diagnostic capabilities of US have been investigated in a prospective case control study involving 27 patients with cystoscopically confirmed bladder neck obstruction [528]. The value of shear wave elastography (SWE) and acoustic radiation force impulse imaging (ARFI) in the diagnosis of female BOO was compared and the authors concluded that ARFI was more accurate than SWE, but a combination of the two techniques was superior to both in this small study. Ultrasound scanning was further evaluated in a small study of just 15 women with BOO diagnosed urodynamically [529]. The authors proposed that trans-vaginal ultrasonography was able to demonstrate a closed bladder neck during attempts at micturition and concluded that this modality was useful in the evaluation of the possible causal factors of female BOO such as primary bladder neck obstruction.

4.5.4.5 Magnetic resonance imaging

The role of MRI in the diagnostic evaluation of female patients with suspected BOO is poorly defined. Although it allows for the precise anatomical evaluation of pelvic structures there are no reports describing its clinical utility in the diagnosis of female BOO. Magnetic resonance imaging in patients with urethral stricture disease can determine the degree of peri-urethral fibrosis, although the prognostic and clinical significance of such finding has not been established [530].

4.5.4.6 Electromyography

Electromyography (EMG) has been most extensively studied in the subgroup of women with BOO due to idiopathic urinary retention caused by a high-tone non-relaxing sphincter (Fowler's syndrome). Abnormal EMG activity may be associated with non-relaxation of the striated sphincter, abnormally high urethral pressure, and,

through an exaggerated guarding reflex, poor bladder sensation and reduced detrusor contractile strength [519, 531]. Complex repetitive discharges and decelerating bursts are specific EMG abnormalities that have been described in patients with high-tone non-relaxing sphincter although these abnormalities have also been noted in asymptomatic volunteers [532, 533]. A review on the subject of voiding dysfunction in women included 65 studies with only a small number addressing the diagnostic utility of electromyography [471]. The authors commented that increased EMG activity of the PFM can be seen during voiding or non-relaxation and when this is coupled with pressure-flow information from urodynamics may be useful to differentiate between functional and anatomical obstruction. Further evidence for this comes from a retrospective study of 157 women with roughly equal numbers of women with functional and anatomical obstruction concluding that a low level of EMG activity is characteristic of anatomical obstruction [517]. Additional neurophysiological tests such as anal sphincter EMG, bulbocavernosus reflex, and pudendal sensory evoked potentials can assess the integrity of the somatic S2, 3, 4 nerve roots; however, their clinical utility in the context of non-neurogenic female BOO needs to be better defined [519].

4.5.4.7 Cystourethroscopy

Cystourethroscopy can be useful to visualise any anatomical/mechanical obstruction and provide information regarding its nature, location and calibre. Given that pelvic malignancy may cause anatomical BOO, cystourethroscopy is considered an essential part of the diagnostic pathway. Formal urethral calibration may be useful for women with BOO secondary to urethral stricture disease and various different urethral calibre thresholds have been used, from 14Fr to 20Fr [534].

4.5.4.8 Urodynamics and video-urodynamics

Pressure flow studies are the mainstay of BOO diagnosis and the characteristic abnormalities are a combination of low flow and concomitant high detrusor pressure [518]. However, while the general definition of BOO is well-established with some data supporting its clinical validity in male patients [535], the urodynamic definition of female BOO remains a matter of controversy [515]. Several urodynamic criteria have been introduced during the past 20 years but none have been established as a standard due to lack of clinical validation [515, 536]. The Blaivas and Groutz nomogram which plots free Q_{max} and maximum detrusor pressure ($P_{det,max}$) measured during urodynamic studies is one of the most popular [537] but has been suggested to overestimate obstruction [74]. The addition of fluoroscopic imaging suggested by Nitti and colleagues introduces a video-urodynamic criterion for obstruction and has found popularity [77]. However, both methods lack data supporting their clinical validity, especially regarding their predictive value for therapeutic intervention outcomes [75].

In a large retrospective study of 1,914 patients, 810 of whom were diagnosed with BOO, several urodynamic cut-off values were determined by ROC curve analysis to optimise the diagnostic accuracy of video-urodynamic studies [527]:

- $P_{det}Q_{max}$ of 30 cm H_2O or greater for differentiating BOO from bladder dysfunction and normal studies (ROC AUC = 0.78);
- the Abrams-Griffiths number greater than 30 for differentiating anatomic from functional BOO (ROC AUC = 0.66);
- $P_{det}Q_{max}$ of 30 cm H_2O or greater for differentiating dysfunctional voiding from poor relaxation of the external sphincter (ROC AUC = 0.93).

Other smaller studies with a similar methodology of utilising ROC curve analysis have concluded that neither pressure flow data only nor clinical symptoms alone may be sufficient for diagnosing obstruction in women [538], therefore independent validation of any suggested thresholds is necessary.

More recently, Solomon and Greenwell devised a female BOO nomogram which parallels the ICS nomogram used for male BOO [539]. It allows the calculation of an alternative BOO female index (BOOIf), using a formula closely aligned to its male counterpart: $BOOIf = P_{det}Q_{max}\text{-}2.2Q_{max}$.

It is interpreted with a different algorithm however:

- BOOIf < 0: less than 10% probability of obstruction;
- 5 < BOOIf < 18: equivocal, at least 50% likelihood of obstruction;
- BOOIf >18: 90% likelihood of obstruction.

The Solomon-Greenwell nomogram is the first which has been tested for clinical validity. In a recent series of 21 unselected consecutive women treated for BOO, the authors observed significant improvement of all urodynamic parameters (Q_{max}, $P_{det}Q_{max}$, BOOIf) in female patients who became asymptomatic post-operatively [540].

An alternative urodynamic parameter of area under the detrusor pressure curve during voiding (corrected for voided volume) has been proposed following a prospective study involving 103 women [541]. The authors concluded that this variable appears to be the most discriminating urodynamic parameter for the diagnosis of female BOO. This suggested diagnostic method has not been independently validated.

Voiding cystourethrography alone or in conjunction with concomitant pressure flow studies may be useful in delineating the site of obstruction. Characteristic features include:

- radiographic evidence of obstruction between the bladder neck and distal urethra in the presence of a sustained detrusor contraction [77];
- lack of funnelling appearance of the bladder neck/tight bladder neck in primary bladder neck obstruction;
- proximal dilatation of the urethra with distal narrowing in women with urethral stricture disease or pelvic floor hypertonicity.

4.5.4.9 Summary of evidence and recommendations for the diagnosis of bladder outlet obstruction

Summary of evidence	**LE**
The evaluation of LUTS by history and examination alone is insufficient to accurately diagnose female BOO.	3
Urine flow studies cannot diagnose BOO in women with high levels of accuracy.	3
Ultrasound scanning is unable to diagnose BOO in women with high levels of accuracy.	2b
Electromyography alone is unable to diagnose BOO in women with high levels of accuracy although it may be of use both in combination with pressure flow studies and in the differentiation of anatomical vs. functional obstruction.	3
Urodynamics (often combined with videofluoroscopy) is the standard test for evaluating female BOO.	3

Recommendations	**Strength rating**
Take a full clinical history and perform a thorough clinical examination in women with suspected bladder outlet obstruction (BOO).	Strong
Do not rely on measurements from urine flow studies alone to diagnose female BOO.	Strong
Perform cystourethroscopy in women with suspected anatomical BOO.	Strong
Perform urodynamic evaluation in women with suspected BOO.	Strong

4.5.5 ***Disease management***

Therapeutic interventions for BOO aim to decrease outlet resistance in order to increase urinary flow, improve bladder emptying and thus reduce voiding and storage LUT symptoms [75, 515, 536]. Treatment choice is commonly dictated by the nature of the underlying cause of the obstruction.

4.5.5.1 Conservative management

4.5.5.1.1 Behavioural modification

Behavioural modification aims to improve or correct maladaptive voiding patterns through the analysis and alteration of the relationship between the patient's symptoms and her environment, lifestyle and habits. Behavioural modification interventions are often tailored to individual patients' needs, symptoms and circumstances and can include elements such as education regarding normal voiding function, self-monitoring of symptoms, changes in lifestyle factors that may affect symptoms, avoidance of constipation and alteration of voiding technique. Ultimately, techniques aim to improve the coordination between the detrusor and the sphincter resulting in their synergistic action [75, 515, 536].

The vast majority of individual components of self-management have not been critically evaluated and most recommendations are traditionally derived from consensus methodology. General interventions such as those listed above may help with symptoms resulting from BOO but no quantification of their effect is possible.

4.5.5.1.2 Pelvic floor muscle training +/- biofeedback

Pelvic floor muscle training aims to improve pelvic floor function and urethral stability. In the context of BOO, physiotherapy aims to teach patients to relax their PFMs and striated urethral sphincter during voiding. Pelvic floor muscle contraction, particularly in women with pelvic floor dysfunction, has been shown to result in a significant reduction in vaginal resting pressure and surface EMG activity [490]. A 12-week PFMT program in post-menopausal women demonstrated significant improvement in the speed of relaxation after PFM contraction and a decrease in the PFM tone [491].

As mentioned in the section discussing UAB (see Section 4.4.4.1.2 - PFM relaxation training with biofeedback), most of the evidence supporting PFMT in dysfunctional voiding are from studies involving children.

A case-series reported improved PFM relaxation and voiding function following PFMT with biofeedback in 15 women with dysfunctional voiding based on a dilated proximal urethra on voiding cystourethrography (VCUG) and hyperactivity of the pelvic muscles or external urethral sphincter on EMG during voiding. No clinical outcomes were reported by this series [542].

4.5.5.1.3 Electrical stimulation

Application of electrodes that allow for controlled contraction and relaxation of the PFM may theoretically facilitate the relaxation of the external sphincter and pelvic floor but no critical evaluation of this intervention in women with BOO has ever been published.

4.5.5.1.4 Use of vaginal pessary

Intravaginal devices such as pessaries aim to relieve voiding symptoms and improve bladder emptying by the physical correction of the obstruction caused by a prolapsed pelvic organ. In a prospective study of 18 women with grade 3 to 4 cystoceles and diagnosed with BOO by urodynamics (defined as $P_{det}Q_{max}$ > 25 cm H_20, Q_{max} < 15 mL/sec), normal voiding was noted in 17 (94%) immediately after placement of a vaginal pessary. No other outcomes were available in this series [543]. No long-term data are available on the use of vaginal pessary for BOO.

4.5.5.1.5 Urinary containment devices

Urinary containment devices include body-worn absorbent products. Their use in BOO is to achieve social continence in patients with urinary retention and associated overflow UI and they are often only a temporary measure. There are no published studies on the outcomes or adverse events associated with the use of urinary containment devices for the management of female BOO. While there may be no studies exclusively involving women with BOO, there are many involving women with UI who may have BOO as an underlying cause.

4.5.5.1.6 Urinary catheterisation

Significant urinary retention from BOO may be addressed by actively bypassing the obstruction and draining the residual urine. Catheterisation may be used as a treatment itself or as an adjunct to an initial treatment of urethral dilatation or urethrotomy or bladder neck incision. There are two ways of using a catheter: CISC or indwelling catheterisation [115].

Post-UI surgery BOO may be managed by short-term catheterisation for the majority of those who will suffer from transient post-operative voiding difficulty. For a few women who develop chronic urinary retention, CISC or indwelling catheterisation may be offered [471].

A small RCT investigated the effectiveness of CISC to prevent recurrence after internal optical urethrotomy for urethral stricture disease. In the treatment group, CISC was done twice a day for one week, and once a day for 4 weeks, then once weekly for 7 weeks post-urethrotomy. Freedom from stricture recurrence, determined by a urethrogram and uroflowmetry performed 12 weeks post-surgery, was higher in the catheterisation group compared to no catheterisation (78.5% vs. 55.4%) [544]. This finding mirrors the Cochrane systematic review on self-dilatation for urethral stricture among men that showed less recurrence with the performance of self-dilatation [545].

In a series of 20 patients with voiding dysfunction after TVT who were put on a CISC programme, overall cure rate was 59%, with cure defined as consistent residual volume of less than 100 mL. Half of these patients were voiding normally within 12 weeks [546].

A patient satisfaction survey involving 188 patients on CISC/self-dilatation, which included 38 patients with urethral stricture, showed positive (pleased or satisfied) outcomes in 54.3% of all patients, while 28.2% had mixed feelings and 9.6% were unhappy. No rates were given specifically for the BOO group [547].

4.5.5.1.7 Intra-urethral inserts

An intra-urethral insert is a short silicone catheter containing an internal valve and pump mechanism positioned in the female urethra. The valve-pump mechanism is operated by an external control unit, which activates to open the valve and the pump to draw urine from the bladder and allow voiding. At the end of urination the pump ceases to rotate and the valve closes to regain continence. The insert is routinely replaced once a month.

Only one study reported the use of this device in 92 women with voiding dysfunction of various aetiologies including multiple sclerosis, prior pelvic surgery, pelvic radiation, diabetes mellitus, spinal stenosis and injury. The device was removed within 7 days of insertion in 60% of the cases due to discomfort, pericatheter leakage and technical difficulty. An additional 20% of patients had late discontinuations. All those who continued to use the device were satisfied, with PVR volumes remaining at less than 100 mL. Adverse events included migration into the bladder in 6 cases and symptomatic UTI in 4 cases [548, 549]. Extended, long-term data on the use of urethral inserts are not available.

4.5.5.1.8 Extracorporeal magnetic stimulation

Extracorporeal magnetic stimulation involves the patient sitting on a device that induces consistent contraction and relaxation of PFM by repeated magnetic stimulation of motor nerve fibres. Extracorporeal magnetic stimulation contracts and then relaxes the PFM following a set frequency and interval. It is postulated that patients could therefore learn to spontaneously contract or relax the PFM which may enhance their ability to relax their pelvic floor while voiding [550].

In a small (n = 60) prospective non-randomised trial, alfuzosin was compared to EMS and to the combination of alfuzosin + EMS in women with functional BOO. They observed significant increase of Q_{max} and significant decrease of IPSS in all groups and significantly greater improvement in the QoL question of the IPSS in the combination therapy group [550].

4.5.5.1.9 Summary of evidence and recommendations for conservative treatment of bladder outlet obstruction

Summary of evidence	LE
Pelvic floor muscle relaxation training with biofeedback may result in relaxation of the pelvic muscles and external urethra in women with dysfunctional voiding.	3
There is no available evidence in the published literature on the clinical effect of ES for the management of female BOO.	NA
In women with large (grade 3 to 4) cystoceles causing BOO, placement of a vaginal pessary may improve voiding efficiency.	3
Regular CISC after urethrotomy is better than no catheterisation to prevent recurrence of urethral strictures.	1b
A CISC program in women with voiding dysfunction after TVT has a cure rate of 59%.	3
Women who use the intra-urethral device had lower PVR volume but the majority required its removal due to complications.	3
Extracorporeal magnetic stimulation combined with alfuzosin may be more effective than either of these therapies used alone in female patients with functional BOO.	2a

Recommendations	Strength rating
Offer pelvic floor muscle training (PFMT) aimed at pelvic floor muscle relaxation to women with functional bladder outlet obstruction (BOO).	Weak
Prioritise research that will investigate and advance the understanding of the mechanisms and impact of PFMT on the coordinated relaxation of the pelvic floor during voiding.	Strong
Offer the use of a vaginal pessary to women with grade 3 to 4 cystocoeles and BOO who are not eligible/inclined towards other treatment options.	Weak
Offer urinary containment devices to women with BOO to address urinary leakage as a result of BOO, but not as a treatment to correct the condition.	Weak
Offer clean intermittent self-catheterisation to women with urethral strictures or post-urinary incontinence surgery for BOO.	Weak
Do not offer an intraurethral device to women with BOO.	Strong

*4.5.6 **Pharmacologic management***

4.5.6.1 Alpha-adrenergic blockers

Alpha-adrenergic blockers are postulated to relieve LUTS caused by BOO in females via smooth muscle relaxation in the bladder neck thus decreasing bladder outlet resistance [551].

Systematic reviews on the use of alpha-blockers in women generally involve studies with a population that includes females complaining of LUTS and voiding dysfunction. Confirmation of BOO is often not required

in the trials included in these systematic reviews [552, 553]. These reviews showed significant improvements in symptoms and urodynamic parameters associated with their use [552-554]. A meta-analysis of 14 RCTs comparing alpha-blockers and placebo in women with LUTS showed statistically significant symptom relief after alpha-blocker treatment relative to placebo (MD: -1.60, p = 0.004), but no significant difference in Q_{max}, PVR and adverse event rates [552]. This is in contrast with prospective non-comparative trials which consistently show improvements in voiding and storage symptoms, bother scores, and urodynamic parameters (Q_{max}, PVR, $P_{det}Q_{max}$, MUCP) after alpha-blocker use compared to baseline [496, 497, 555-557].

A systematic review performed by the Panel of studies on alpha-blocker used specifically for women with BOO included one placebo-controlled RCT, one RCT comparing two types of alpha-blockers, and 6 prospective non-comparative studies. In the only placebo-controlled RCT reporting subgroup analyses in women with urodynamically proven BOO (based on the Bladder and Groutz nomogram) no statistically significant difference was observed in the changes of IPSS, IPSS sub scores, Q_{max}, PVR and bladder diary after eight weeks of alfuzosin (n = 58) vs. placebo (n = 59). Of note, no EMG and/or voiding cystourethrography was used to distinguish between dysfunctional voiding and primary bladder neck obstruction [558].

Information on the comparative effectiveness of the different types of alpha-blockers is limited to one RCT. A small trial on 37 women with IPSS > 8, Q_{max} < 12 mL/sec and PVR > 50 mL, compared tamsulosin and prazosin over a 3-month treatment period. More patients on tamsulosin were completely satisfied with their treatment (16/20 vs. 9/20, p < 0.05). Both treatment groups showed significant improvement in symptom scores from baseline but no further statistical comparison between the groups was done. However, a larger decrease in AUA symptom score was seen with the tamsulosin group compared to the prazosin group. More adverse events were reported with prazosin group (13 cases vs. 1 case) [559].

A small three-arm non-RCT in women with functional BOO compared alfuzosin monotherapy and EMS. The combination of alfuzosin and EMS showed greater improvement in storage symptoms and QoL with EMS with or without alfuzosin than with alfuzosin monotherapy alone [550].

4.5.6.2 Striated muscle relaxants

Baclofen is a gamma-aminobutyric acid (GABA) agonist that exerts its effect on the GABAergic interneurons in the sacral intermediolateral cell column responsible for the relaxation of the striated urinary sphincter during voiding. Intrathecal administration has been shown to improve voiding in a trial among spinal cord injured patients. Oral baclofen has also been widely studied [536].

A randomised placebo-controlled crossover trial investigated the efficacy and safety of a 4-week course of oral baclofen 10 mg 3 times/day in 60 women diagnosed with BOO, based on an increased EMG activity with a sustained detrusor contraction during voiding. It showed lower number of voids, significant improvements in Q_{max} and $P_{det}Q_{max}$ with baclofen compared with placebo. Post-void residual, maximum cystometric capacity (MCC) and MUCP parameters were not significantly different between groups. Adverse event rates were also similar, with the most common complaints including somnolence, dizziness and nausea. An important limitation of this study was the lack of patient-reported outcomes to assess symptoms and QoL [560].

A small case series reported the outcomes of 20 women with functional BOO who were given oral baclofen 5 mg 3 times/day for 12 weeks. There was significant improvement in the mean voided volume and BVE of the patients. However, Q_{max}, $P_{det}Q_{max}$, PVR and urethral profile pressures did not significantly change. No significant adverse events were noted [561].

4.5.6.3 Oestrogens

The relative reduction in urethral wall compliance seen in atrophic urethritis due to oestrogen deprivation may be responsible for the obstruction in the urethra in post-menopausal women. Oestrogen therapy is thus theoretically expected to improve the condition. There are no published studies on the use of oestrogens specifically for the management of female BOO.

4.5.6.4 Sildenafil

Sildenafil, by inhibiting PDE5, increases the levels of nitric oxide in the female urethral sphincter, thereby promoting urethral relaxation.

A placebo-controlled randomised crossover trial which included 20 females with partial or complete retention or obstructive voiding, with high MUCP and elevated US-estimated sphincter volume (> 1.6 cm) showed that

while there was a significant improvement in symptom scores and urodynamic parameters from baseline with sildenafil treatment, this difference was not significant when compared with placebo [562].

4.5.6.5 Thyrotropin-releasing hormone

Intravenous thyrotropin-releasing hormone has been postulated as a neurotransmitter that induces urethral relaxation [563]. The exact mechanism is unclear.

In a small RCT of 16 women with voiding difficulty, 8 women (3 with BOO) were randomised to receive 200 ug intravenous bolus of TRH, and 8 (3 with BOO) received saline. No difference in the decline in functional profile lengths and maximum urethral closure pressures were noted between treatment groups, despite a significant decline noted from baseline in the treatment group. No subgroup analysis of women with BOO was reported [563].

4.5.6.6 Summary of evidence and recommendations for pharmacologic treatment

Summary of evidence	**LE**
Alpha-blocker use is associated with significant improvement in symptom scores from baseline, but not urodynamic parameters compared with placebo.	1a
Tamsulosin is associated with greater improvement in symptoms score compared with prazosin.	1b
Non-specific alpha-blockers are associated with higher rates of adverse events.	1b
Oral baclofen is better than placebo in improving Q_{max} and $P_{det}Q_{max}$, but not other urodynamic parameters. Its effects on symptoms are not well reported.	1b
Current evidence does not show that sildenafil is superior to placebo in improving symptoms or urodynamic parameters of female patients with BOO.	1b
Trials including women with voiding problems of mixed aetiologies showed no difference in urodynamic outcomes between intravenous thyrotropin-releasing hormone and placebo.	1b

Recommendations	**Strength rating**
Offer uroselective alpha-blockers, as an off-label option, to women with functional bladder outlet obstruction (BOO) following discussion of the potential benefits and adverse events.	Weak
Offer oral baclofen to women with BOO particularly those with increased electromyography activity and a sustained detrusor contraction during voiding.	Weak
Only offer sildenafil to women with BOO as part of a well-regulated clinical trial.	Strong
Do not offer thyrotropin-releasing hormone to women with BOO.	Strong

*4.5.7 **Surgical treatment***

4.5.7.1 Intra-sphincteric botulinum toxin injection

Botulinum toxin inhibits the presynaptic release of acetylcholine, which results in the reduction of the urethral sphincter tone. It is also believed to cause a decrease in the release of norepinephrine in the urethra to counteract external urethral sphincter overactivity [564].

Evidence on the use of botulinum toxin for female BOO is limited to small case series. Most studies included mixed populations without subgroup analyses, or the diagnosis of voiding dysfunction could not be ascertained as solely resulting from BOO. No comparative trial exclusively involving female BOO patients using botulinum toxin has been identified in the literature.

A systematic review including several reports of small case series using variable doses of botulinum toxin A injected peri-urethrally in females with dysfunctional voiding showed improvements in symptoms, reduction in residual volumes and reduction in voiding detrusor pressures. Larger series in adults (both males and females, n > 100) showed success rates of 86–100% [564].

In a randomised, double-blind, placebo-controlled study (n = 73) 100 U onabotulinumtoxinA vs. saline resulted in significantly lower IPSS scores and larger voided volumes compared with placebo in 31 adults (men and women with voiding dysfunction [defined by a spinning top appearance on real-time fluoroscopy, poorly relaxed urethral sphincter on EMG, and a normal-to-high voiding pressure with a low and/or intermittent urinary flow rate, a PVR volume > 300 mL, and a low voiding efficiency]). Other urodynamic parameters were comparable between the groups [565]. A subgroup analysis on the female population of this study was not available.

Two small case series on women with BOO reported the effects of 100 U intra-sphincteric injection of BTA. Both showed improvement in symptom and bother scores and significant reduction in PVR [519, 566]. One study reported increased Q_{max} and improved static urethral pressure profile (UPP) [519]. The average symptom-free duration was noted to be 16.8 weeks in another study [566]. Adverse events included UTI and temporary need for CISC. No SUI was reported.

4.5.7.2 Sacral nerve stimulation

Sacral nerve stimulation is a type of neuromodulation that allows continuous ES from an electrode placed alongside a sacral nerve via a surgically implanted pulse generator. The ES is postulated to decrease the urethral tone. In addition, SNS is also postulated to work by blockage of the inhibitory urethral afferent impulses, which cause inhibition of normal bladder contraction.

No comparative trial has been identified in the literature on the use of neuromodulation for female BOO.

The majority of the publications on neuromodulation for voiding dysfunction are retrospective reviews of cases, involving a mix of patient populations who underwent the procedure for different indications. In studies that indicated a subgroup of patients with urinary retention, there was either no urodynamic confirmation of the nature of the retention or separate outcomes were not reported for participants with retention.

A review of 60 women who underwent sacral nerve stimulation for urinary retention associated with outlet obstruction (defined as UPP > 100 cm H_2O, increased urethral sphincter volume > 1.8 mL, and abnormal EMG with repetitive discharges and decelerating bursts) showed an overall spontaneous voiding rate of 72% over a mean follow up of 4 years. Of those who continued to require CISC up to twice/day post-operatively, the frequency was less than prior to surgery (degree not specified). There were 99 adverse events and 63 surgical revisions. In this series, half of the patients underwent a one-stage SNS procedure and the other half a two-stage procedure. The proportion of patients who required CISC-assisted voiding was higher in the two-stage group (27% vs. 17%). More serious adverse events (defined as 'events requiring admission or surgical revision to resolve issues such as loss of response, lead migration and surgical revisions') were associated with the one-stage procedure [562].

A single-centre series in a subgroup of 32 patients diagnosed with idiopathic urinary retention (Fowler's syndrome) who underwent SNS, 62.5% achieved a > 50% reduction in the CISC rate [567].

4.5.7.3 Pelvic organ prolapse surgery

Pelvic organ prolapse surgery may relieve BOO by correcting the urethral kinking caused by the prolapse or by relieving the urethral compression brought about by the prolapsing organ [75, 515, 536]. No comparative studies on prolapse surgery for female BOO have been published.

Bladder outlet obstruction due to POP may be addressed by corrective surgery. Based on reviews, the majority of patients who had BOO caused by POP who had a repair of their cystocoele demonstrated improvement of their voiding difficulties [471, 568].

A multicentre prospective study involving 277 women with at least grade 2 symptomatic POP who underwent surgery demonstrated a significant reduction in voiding symptoms and PVR volume one year post-operatively [569].

A retrospective study of 50 women who underwent laparoscopic sacrocolpopexy for POP showed a significant increase in the mean post-operative Q_{max} and a decrease in the $P_{det}Q_{max}$ and PVR in those ≥ 65 years old. The OAB symptom score (OABSS) improved but there was no significant difference in the ICIQ-SF score post-operatively [570].

In a case series of 35 females with stage 3-4 POP presenting with a pre-operative PVR > 100 mL (mean 226 mL), 89% had PVR volumes of < 100 mL post-surgery [571]. In another case series of 39 patients with cystocoeles who complained of voiding symptoms pre-operatively, 30 (79%) achieved normal voiding, defined as no obstructive symptoms and a PVR below 50 mL, after bladder neck suspension with anterior colporrhaphy [572].

4.5.7.4 Urethral dilatation

Urethral dilation involves the passage of sequentially greater diameter dilators into the urethra, causing the obstructing fibrotic tissue to break open and thereby widening the lumen. It is considered the primary

procedure of choice for women suspected of urethral stricture disease [534]. Dilation of up to 30-40Fr has been done. There is no standard dilatation technique; dilatation of up to 43F has been described, although other authors suggest dilating to 30Fr or 35Fr.

A systematic review on female urethral stricture management included 3 trials involving urethral dilatation. Pooled analysis from these studies with data from 93 females showed a mean success rate of 49% after urethral dilation to 41Fr with a mean follow up of 46 months. Mean time to failure was 12 months. In treatment-naïve patients, success rate (as defined by trialists) was 58% while in patients who had undergone previous dilatation, success rate was 27.2% [530].

An RCT of 50 women with OAB syndrome and associated urodynamically-confirmed BOO (defined as a Q_{max} of less than 15 mL/sec with a voided volume of 100 mL or above and/or PVR volume over 200 mL, not due to a urethral stricture) compared the effect of cystoscopy and bladder distension with urethral dilatation (22) and cystoscopy only (28) after 6 week follow-up. Significantly more patients who had cystoscopy only had persistent urgency at 6 weeks and 6 months post-operatively. Urodynamic parameters did not significantly change pre- and post-operatively in both groups. The greater improvement in QoL scores based on the King's Health Questionnaire (KHQ) domain scores seen in the non-urethral dilatation group in this trial should be interpreted cautiously because of the higher baseline scores in this group. Of note, there were no significant changes in Q_{max}, PVR, voided volume or $P_{det}Q_{max}$ in any of the two groups at 6 weeks questioning the role of any of these two options for the therapeutic management of BOO. Also, six patients (12%) developed post-operative SUI [573].

A prospective trial of 86 women with primary urethral stricture compared on-demand vs. intermittent urethral dilatation to 24Fr (dilate every 2 months). It showed an overall increase in Q_{max} and decrease in PVR post-dilatation. Significantly greater improvements were seen in the intermittent urethral dilatation group [574].

Three small case series showed improvements in symptoms with relief of urgency and/or UUI but inconsistent results in terms of significant improvement in Q_{max}, PVR and $P_{det}Q_{max}$. Benefits were poorly sustained, with the majority of patients requiring additional or repeat intervention in the long-term [575-577].

Worsening or new-onset SUI is a concern with urethral dilatation but it is less of a concern than after urethrotomy or surgical reconstruction. Patients have also reported frequency and urgency post-dilatation [577].

4.5.7.5 Urethrotomy

Urethrotomy involves the incision of the urethra endoscopically or using a urethrotome. It addresses the urethral narrowing by cutting open the scar tissue which is causing the obstruction [75, 515, 536]. No comparative study has investigated the effectiveness of urethrotomy in female BOO.

A prospective study of 10 females with urethral strictures investigated the effect of Otis urethrotomy to 40Fr followed by 6 weekly dilatations. There was significant improvement in IPSS, QoL, voided volume, Q_{max} and PVR at 6 months. Only the improvements in PVR and QoL were maintained on long-term follow-up (mean 82 months) [575].

4.5.7.6 Bladder neck incision/resection

Transurethral bladder neck incision decreases the resistance at the bladder neck by cutting open the hypertrophic bladder neck smooth muscle in patients with primary bladder neck obstruction. Transurethral incision of the bladder neck may be performed with a unilateral incision at 12 o'clock or with bilateral incisions placed at the 5 and 7 o'clock or at 2 and 10 o'clock or at 3 and 9 o'clock positions, or 4 incisions at 3, 6, 9 and 12 o'clock. This may be done using a resectoscope with a Collin's knife, a cold knife, or using laser energy. Some authors report additional resection of the bladder neck between the 5 and 7 o'clock positions during the procedure.

Evidence on bladder neck incision or resection for female BOO is limited to non-comparative trials. A review of studies on bladder neck incision for the treatment of bladder neck obstruction in women reports success rates between 76–100% [518].

Bladder neck incision was compared with V-Y-reconstruction using Nesbit's technique in a retrospective study of 17 females with BOO, diagnosed by various uroradiological, endoscopic and urodynamic investigations. The results showed similar symptomatic improvement rates and post-operative PVRs between the two groups. V-Y plasty was noted to have a longer operative- and catheter time, lower uroradiological improvement rate, higher transfusion rate, and higher adverse event rate [578].

Several prospective case series consistently reported significant improvements in IPSS, QoL, Q_{max}, $P_{det}Q_{max}$ and PVR after treatment compared to baseline, regardless of the site of the incision, type of energy used or the length of follow up [579-582].

The largest case series with 84 patients diagnosed with primary bladder neck obstruction (based on the lack of funnel shape of the bladder neck during voiding on voiding cystourethrogram, a P_{det} > 20 cm H_20 and a Q_{max} < 12 mL/sec) showed success in 84.5% of patients with improvement in IPSS, QoL, Q_{max} and $P_{det}Q_{max}$ after a mean follow up of 27.4 months (6–78 months). Complications included vesico-vaginal fistula (VVF) (3.6%), SUI (4.7%) and urethral stricture (3.6%) [579].

No comparisons have been made between the different incision techniques (location of incision, length, depth, implement used – cold knife vs. hot knife vs. laser, with or without resection). However, in a case series of 84 patients, complications of VVF and SUI were noted in the cohort of patients who had their incisions at 5 & 7 o'clock, and not in those who had their incisions at 2 & 10 o'clock [579].

Adverse events include SUI, requirement for re-operation and recurrence. Post-operative SUI was reported in 3-33% [518].

4.5.7.7 Urethroplasty/urethral reconstruction

The surgical reconstruction of the female urethra has been used in the management of extensive female urethral stricture. Several urethroplasty techniques have been reported including the use of vaginal or labial flaps, as well as vaginal and buccal grafts after cutting open the fibrotic tissue causing the urethral obstruction [583]. The use of bladder flaps has also been reported [584]. Recently laboratory-engineered tissue grafts have also been used [585].

The surgical approaches have been described based on the position relative to the urethra; dorsal, ventral or circumferential. The dorsal approach is believed to provide better mechanical support and a more vascularised bed for a graft or flap. However, there is greater risk of damage to the sphincter and clitoral bodies with this approach. The ventral approach is more familiar to most surgeons and requires less urethral mobilisation. However, it is reported as being more prone to urethra-vaginal fistulae, although it is not clear to what extent [534].

Reviews of studies reporting outcomes of urethroplasties state success rates ranging from 57–100% [534, 586]. Pooled analysis from 6 studies using vaginal or labial flaps showed a mean success rate of 91% with a mean follow-up of 32 months. Vaginal or labial graft urethroplasty was reported to have an 80% success rate with a mean follow-up of 22 months.

Oral mucosal grafts, reported in 7 studies, had a mean success of 94% after a mean 15-month follow up [534]. A later review of studies on dorsal buccal mucosal reported graft success rates of 62-100%, pooled success rate 86% [587]. Stricture recurrence rate in a long-term study with a mean follow-up of 32 months showed a stricture recurrence rate of 23.1% [586].

A retrospective comparative study on 10 females who underwent urethral dilatation and 12 who underwent dorsal onlay pedicled labium flap urethroplasty, reported both groups with significant improvements from baseline in terms of QoL, AUA symptom score, PVR and Q_{max}. The urethroplasty group had significantly better QoL scores and Q_{max} (17.0 vs. 12) on follow-up as compared to the dilatation group [588]. Adverse events associated with urethroplasties include new-onset SUI and urgency and worsening of UUI.

4.5.7.8 Urethrolysis

Bladder outlet obstruction in females occurring as a complication of surgical procedures for SUI may be managed surgically by lysis of the urethra aiming to regain urethral mobility. Urethrolysis may involve removal of peri-urethral anti-incontinence sutures, scar tissue and fibrosis.

No comparative trials have been published on urethrolysis. Case series showed success rates measured as improved voiding and lower residual volumes, improvement or resolution of symptoms and QoL and improvement of urodynamic parameters post treatment [589-591]. *De novo* SUI was reported in 39% in one study [591].

A study on 21 patients who underwent urethrolysis suggested an association of persistent post-operative bladder symptoms with greater delay in doing urethrolysis. Patients who presented with post-operative storage and voiding symptoms after a mean of 17 months follow-up had a longer time to urethrolysis compared to those who had no complaints (31 vs. 9 months) [592].

4.5.7.9 Removal/excision/section/loosening of mid-urethral sling

In women who develop BOO after placement of a mid-urethral sling, surgical management may include tape loosening, incision or division, and excision and/or removal of the tape [471].

Several small retrospective reviews of cases using different techniques of sling revision (incision, partial excision, excision) showed good success rates in terms of symptom reduction, resumption of voiding with significant reduction in PVRs and improvement of urodynamic parameters. Stress UI recurs in a very small proportion of patients and often to a lesser degree than prior to the sling procedure. Studies show long-term efficacy, including preservation of continence.

In a series of 63 females who presented with voiding dysfunction and persistent PVR > 100 mL after tape surgery for UI, different techniques were compared. Comparisons involved sling revision (sling division (n = 46) vs. partial sling excision (n = 13) vs. sling revision (division or excision) with an additional anti-SUI procedure (n = 4). The authors reported an overall success rate of 87% (success defined as PVR < 150 mL). No statistically significant difference in success rates was demonstrated across the different revision techniques. There was a higher need for surgery for recurrent SUI in the partial sling excision group without an anti-SUI procedure (23% vs. 2.2 and 0) [593].

4.5.7.9.1 Timing of sling revision

One study showed that patients who underwent surgical release more than 180 days after initial anti-UI surgery had significantly less recurrent SUI as compared to patients who underwent the release sooner (15% vs. 46%, p = 0.0008) [594].

4.5.7.10 Summary of evidence and recommendations for surgical management of BOO

Summary of evidence	**LE**
Intrasphincteric injection of botulinum toxin results in the improvement of symptoms and urodynamic parameters.	2
Sacral nerve stimulation results in spontaneous voiding and a reduction in CISC rate in the majority of female BOO patients in idiopathic urinary retention.	3
More serious adverse events and surgical revisions were associated with the one-stage neuromodulator implantation procedure.	3
Repair of pelvic organ prolapse improved PVR volume and voiding symptoms.	3
Urethral dilatation in women with BOO results in significant improvement in OAB symptoms, but improvements in urodynamic parameters of voiding are inconsistent.	1b
Programmed intermittent urethral dilatation results in better outcomes compared with on demand dilatation.	3
Effects of urethral dilation are poorly sustained, requiring repeat intervention in the long term.	3
Internal urethrotomy followed by regular dilatations resulted in significant improvement in symptoms and urodynamic parameters in women with BOO.	3
Bladder neck incision in females with BOO results in improvements in symptoms and urodynamic parameters.	3
Complications of bladder neck incision are not common, but include vesico-vaginal fistula, SUI, and urethral stricture.	3
Urethroplasty using grafts or flaps in women with BOO due to urethral stricture have good success rates with significant improvements of symptoms, QoL scores and urodynamic parameters compared to baseline.	3
Urethroplasty results in better QoL and Q_{max} compared to urethral dilatation.	2
Long-term results showed significant stricture recurrence rate after urethroplasty.	3
Urethrolysis performed on women with voiding problems after anti-UI surgery resulted in improvements in symptoms, QoL and urodynamic parameters post-operatively.	3
Delayed urethrolysis was associated with persistent post-operative bladder symptoms.	3
Sling revision in women who presented with urinary retention or voiding problems and significant PVRs after sling surgery for UI resulted in improvements in symptoms and urodynamic parameters, resumption of voiding and reductions in PVRs.	3
Sling revision is associated with the risk of recurrent SUI.	3

Recommendations	Strength rating
Offer intrasphincteric injection of botulinum toxin to women with functional bladder outlet obstruction (BOO).	Weak
Offer sacral nerve stimulation to women with functional BOO.	Weak
Advise women with voiding symptoms associated with pelvic organ prolapse (POP) that symptoms may improve after POP surgery.	Weak
Offer urethral dilatation to women with urethral stenosis causing BOO, but advise on the likely need for repeated intervention.	Weak
Offer internal urethrotomy with post-operative urethral self-dilatation to women with BOO due to urethral stricture disease but advise on its limited long-term improvement and the risk of post-operative urinary incontinence (UI).	Weak
Do not offer urethral dilatation or urethrotomy as a treatment for BOO to women who have previously undergone mid-urethral synthetic tape insertion due to the theoretical risk of causing urethral mesh extrusion.	Weak
Inform women of limited long-term improvement (only in terms of post-void residual and quality of life) after internal urethrotomy.	Weak
Offer bladder neck incision to women with BOO secondary to primary bladder neck obstruction.	Weak
Advise women who will undergo bladder neck incision on the small risk of developing stress urinary incontinence (SUI), vesico-vaginal fistula or urethral stricture post-operatively.	Strong
Offer urethroplasty to females with BOO due to recurrent urethral stricture after failed primary treatment.	Weak
Caution women on the possible recurrence of strictures on long-term follow-up after urethroplasty.	Weak
Offer urethrolysis to women who have voiding difficulties after anti-UI surgery.	Weak
Offer sling revision (release, incision, partial excision, excision) to women who develop urinary retention or significant voiding difficulty post tape surgery for UI.	Strong
Caution women about the risk for recurrent SUI and the need for a repeat/concurrent anti-UI surgery after sling revision.	Strong

*4.5.8 **Follow up***

Women with BOO should be followed up and monitored regularly due to the risk of further deterioration of voiding or renal function in case of persistence and progression of the obstruction. For those who received treatment, monitoring must be done for the recurrence of the BOO. In particular, women who underwent urethral dilation, urethrotomy or urethroplasty for urethral stricture need to be monitored for the recurrence of the stricture.

4.6 Nocturia

Nocturia was defined by the ICS in 2002 as *'the complaint that the individual has to wake at night one or more times to void'* and quantified in an updated document in 2019 as *'the number of times an individual passes urine during their main sleep period, from the time they have fallen asleep up to the intention to rise from that period'* [595]. A systematic review of the literature in this topic area has been conducted by the EAU Guidelines Panel on Urinary Incontinence covering publications up to and including 2017 [596]. This was supplemented with a scoping search in 2020 covering more recent publications.

4.6.1 Epidemiology, aetiology, pathophysiology

The prevalence of nocturia varies according to age with around 4–18% of women aged 20-40 experiencing 2 or more episodes per night, compared to 28–62% of women aged 70 or older [597]. In a study of 1,000 community-dwelling older adults, nocturia in females was associated with older age, African-American race, a history of UI, swelling of the lower limbs and hypertension [598]. A report on over 5,000 adults aged 30–79 years identified around 28% with nocturia and found additional correlates with increased BMI, cardiac disease, type 2 diabetes and diuretic use [599]. A recent systematic review and meta-analysis has concluded that nocturia is probably associated with an approximate 1.3 fold increased risk of death [600].

The aetiology of nocturia is multifactorial and can include both urological and non-urological causes. Urological conditions which may exhibit nocturia as a significant symptom include OAB syndrome, BOO, DU and dysfunctional voiding. Non-urological causes include 24 hour polyuria (which includes nocturnal polyuria), congestive heart failure, sleep apnoea, restless leg syndrome, peripheral vascular disease, sleep disorders, night-time food ingestion, dependent oedema and excessive fluid intake [601]. Given the varied aetiology of

this symptom there are a range of possible pathophysiological mechanisms. These include: (1) 24 hour polyuria (e.g. diabetes mellitus, primary polydipsia, and diabetes insipidus); (2) nocturnal polyuria (e.g. behavioural, peripheral oedema, obstructive sleep apnoea, glycosuria, hormonal abnormalities and cardiac dysfunction); (3) diminished bladder capacity (e.g. OAB syndrome/DO, pelvic floor dysfunction, BOO, pharmaceuticals, LUT calculi or tumours and neurological bladder dysfunction); and (4) primary or secondary sleep disorders [602].

*4.6.2 **Classification***

Classification of nocturia is dependent on bladder diary analysis and several parameters have been defined as important [603]:

- Nocturnal urine volume - total volume of urine passed during the night (this includes the 1st morning void but does not include the last void prior to sleep);
- Maximum voided volume - the largest single voided volume in 24 hours;
- Nocturia index - the nocturnal urine volume divided by the maximum voided volume;
- Nocturnal polyuria index - the nocturnal urine volume divided by the 24 hour urine volume;
- Nocturnal urine production - the nocturnal urine volume divided by the duration of sleep in hours.

The analysis of these parameters will allow the clinical classification of nocturia based on the physiological abnormalities that can cause nocturia:

- 24 hour polyuria;
- nocturnal polyuria;
- diminished bladder capacity;
- sleep disorders.

*4.6.3 **Diagnostic evaluation***

The evaluation of nocturia should include a thorough medical history and physical examination with particular reference made to a history of sleep disorders, fluid balance, associated LUTS, cardiovascular and endocrine comorbidities, renal disease, current medications and previous urological history [603]. Several nocturia-specific symptom scores exist such as the ICI Questionnaire-nocturia, the Nocturia Quality of Life Questionnaire (N-QoL) and the Nocturia Impact Diary, some of which were developed in men. A further screening tool is also available which aims to identify causes of nocturia; the Targeting the individual's Aetiology of Nocturia to Guide Outcomes (TANGO) assessment tool [604-606].

A bladder diary is a vital initial investigation in any patient that is complaining of nocturia and further supplementary investigations are guided by any abnormalities identified. Bladder diary analysis can allow for the calculations of the parameters detailed in Section 4.6.2. A low nocturnal bladder capacity or global bladder capacity will be highlighted by reduced voided volumes either during nocturnal hours or both night and day. This may suggest an underlying urological condition such as OAB syndrome, BOO or DU. Global polyuria is defined as a 24-hour urine production of more than 40 mL/kg [607] and may be present in conditions such as diabetes mellitus or diabetes insipidus. The definition of nocturnal polyuria is age dependent and the thresholds for this diagnosis range from 20% (in younger persons) to 33% (in those over 65) of the 24 hour urine volume being produced during sleeping hours. This may also be observed in patients with loss of circadian rhythm, cardiovascular disease, sleep apnoea or sleep disorders [603]. A large study conducted across European and American centres involving almost 2,000 patients has identified nocturnal polyuria as a contributory cause of nocturia in 89% of patients who were being treated for LUT abnormalities such as OAB syndrome or benign prostatic enlargement [608].

As an alternative to a three, or more, day bladder diary a nocturnal-only diary has been investigated in men [609]. Overall, results showed acceptable sensitivity and specificity from the nocturnal bladder diary in comparison with the standard bladder diary for the majority of parameters. The nocturnal-only diary was obviously not able to diagnose 24 hour polyuria and has not yet been validated for use in women.

4.6.3.1 Summary of evidence and recommendations for the diagnosis of nocturia

Summary of evidence	**LE**
A thorough medical history is an integral part of the evaluation of women presenting with nocturia.	4
Nocturia-specific questionnaires are sensitive to symptom changes.	3
A bladder diary allows for calculation of important indices and can identify potential causes of nocturia.	3
Nocturnal-only bladder diaries have been evaluated in men only.	3

Recommendations	Strength rating
Take a complete medical history from women with nocturia.	Strong
Use a validated questionnaire during the assessment of women with nocturia and for re-evaluation during and/or after treatment.	Weak
Use a three-day bladder diary to assess nocturia in women.	Strong
Do not use nocturnal-only bladder diaries to evaluate nocturia in women.	Weak

*4.6.4 **Disease management***

When evaluating the results of trials involving treatment strategies for nocturia it is vital to examine for clinical significance as statistical significance can be achieved with very small reductions in nocturia episodes.

4.6.4.1 Conservative management

The individual components of self-management have not been critically evaluated and most recommendations are traditionally derived from consensus methodology. Interventions such as those listed below may help with nocturia but, for the majority, no quantification of their effect is possible:

- reduction of fluid intake at specific times;
- avoidance/moderation of intake of caffeine or alcohol;
- distraction techniques;
- bladder retraining;
- PFMT;
- reviewing medication;
- treatment of constipation.

The available data for conservative treatment of nocturia exhibit significant heterogeneity. In the EAU systematic review [596], three studies [610-612] were favourable for conservative treatment with PFMT, with another failing to confirm benefit [613].

The highest level of evidence comes from a study of 131 patients (as a secondary analysis from a prospective RCT which had urgency-predominant UI as the primary inclusion criterion) and found that training in PFM contraction, which included 4 sessions of biofeedback-assisted PFMT reduced nocturia by a median 0.50 episodes per night and was significantly more effective than anticholinergic drug treatment or placebo [610]. The certainty of evidence associated with this treatment is moderate.

A smaller RCT of 50 women with “urinary complaints”, randomised 1:1 to bladder training and PFMT compared to a control group receiving no treatment, showed a significant decrease in patients’ complaints of nocturia [611]. Another RCT in only 24 women compared PFMT only to transcutaneous electrical nerve stimulation therapy (TENS) plus PFMT [612]. Although the authors did not find significant differences between the groups, the change in nocturia episodes before and after treatment was statistically significant in both groups. This study was underpowered by the authors’ own admission. The level of certainty of the evidence from these two trials is low.

In a secondary analysis from a prospective RCT, 210 women with UUI were evaluated for change from baseline in the number of episodes of nocturia and nocturnal incontinence between groups allocated to medical treatment (tolterodine ER 4 mg) alone vs. medical treatment plus PFMT [613]. No significant difference between the groups was found and the actual difference in nocturia episodes in either treatment arm was small. The level of certainty of the evidence from this trial is low.

A recent RCT has explored both individual and group PFMT with a specific secondary outcome of number of patients with two or more nocturia episodes per night [328]. The authors reported similar reductions with over 30% of patients who had two or more episodes of nocturia at baseline no longer experiencing this level of symptoms at one year following PFMT.

One small, single-centre RCT in which functional magnetic stimulation (FMS) was compared to no treatment in 39 women reported a significant decrease in nocturia (together with voiding frequency and pad use) in the treatment group compared to the control group [614].

In patients with obstructive sleep apnoea who complain of nocturia, treatment with continuous positive airway pressure has been shown to be effective in a systematic review and meta-analysis of 5 RCTs involving both male and female patients [615]. This treatment was associated with an average numerical reduction in nocturia of over two episodes per night.

4.6.4.1.1 Summary of evidence and recommendations for the conservative management of nocturia

Summary of evidence	LE
Individual or group PFMT appear to be equally effective in terms of reduction in nocturia episodes.	1b
The majority of studies evaluating PFMT for nocturia in women with additional urinary symptoms have shown positive results both in comparison to placebo and to anticholinergic drugs.	1b
Treatment of nocturia secondary to obstructive sleep apnoea with continuous positive airway pressure results in reductions in nocturia episodes.	1a

Recommendations	Strength rating
Offer women with lower urinary tract symptoms (LUTS) lifestyle advice prior to, or concurrent with, treatment.	Strong
Offer pelvic floor muscle training for nocturia (either individually or in the group setting) to women with urinary incontinence or other storage LUTS.	Strong
Offer women with nocturia and a history suggestive of obstructive sleep apnoea a referral to a sleep clinic for an assessment of suitability for continuous positive airway pressure treatment.	Strong

4.6.4.2 Pharmacology management

4.6.4.2.1 Desmopressin

Desmopressin is a synthetic analogue of the hormone vasopressin and is most often used for management of nocturia due to nocturnal polyuria. In the recent systematic review [596] 3 trials specifically conducted in women were found but more additional data could be extracted from studies in mixed populations. The earliest evidence comes from a 1982 single-site crossover trial involving 25 women treated with either 20 mcg of desmopressin or placebo revealed a significant decrease in nocturnal urine output at 6 weeks [616]. A more recent multicentre, multinational double-blind RCT involving 141 women used desmopressin in doses 0.1, 0.2, 0.4 mg orally at bedtime after a dose-titration period [617]. This increases the likelihood of a positive outcome because non-responders were excluded at this stage. At 3 weeks significant reductions in nocturnal urinary frequency and nocturnal diuresis were reported. In another multicentre double-blind RCT a total of 58 women were randomised into 5 groups (12 receiving placebo, 12 receiving desmopressin 10 µg, 11 receiving 25 µg, 11 receiving 50 µg and 12 receiving 100 µg) for 4 weeks [618]. A dose-response relationship was observed and female patients appeared more sensitive to desmopressin. Statistically significant changes in nocturnal urine volumes were reported in favour of the higher desmopressin dose. Differences in the nocturnal polyuria index also tended to favour desmopressin over placebo and favoured the higher desmopressin dose. The level of certainty of the evidence from these 3 trials is low.

Desmopressin can be safely combined with anticholinergics with significant benefit in women with OAB and nocturnal polyuria, as shown by a multicentre RCT of 97 patients [619]. A *post-hoc* analysis of data comparing 3-month once-daily combination (desmopressin 25 µg/tolterodine 4 mg, n = 49) or monotherapy (tolterodine 4 mg/placebo, n = 57) revealed a significant reduction in nocturnal void volume and time to first nocturnal void in favour of combination therapy. The level of certainty of the evidence from this trial is moderate.

Pooled data from three RCTs were used to examine the adverse event profile of desmopressin, specifically hyponatraemia [620]. The authors reported that the majority tolerate desmopressin treatment without clinically significant hyponatremia, but risk increased with age and lower baseline serum sodium concentration. They advised that desmopressin treatment in elderly patients should include careful monitoring of the serum sodium concentration and should be avoided in patients with a baseline serum sodium concentration below normal range [620].

4.6.4.2.2 Anticholinergics

The systematic review [596] identified 3 RCTs involving anticholinergics such as oxybutynin 2.5 mg/day [610] and tolterodine 4 mg/day [613, 619]. A secondary analysis from a prospective RCT involving 131 women with nocturia followed up for 8 weeks found that women receiving 2.5 mg once a day immediate-release oxybutynin (with the possibility of self-titration and dose escalation to 5 mg three times a day) had less nocturia episodes than women receiving placebo [610]. Women receiving oxybutynin plus behavioural therapy also exhibited a statistically significant decrease in nocturia episodes compared to both placebo and oxybutynin alone. A multicentre RCT which included 305 women followed up for 8 weeks examined the efficacy of tolterodine tartrate 4 mg alone or in combination with behavioural training [613]. Statistically significant differences

compared to baseline were observed in mean nocturia episodes and nocturnal incontinence episodes in both groups, but no difference was reported between the two treatment groups. The level of certainty of the evidence from this trial is moderate.

In an RCT including 97 women with nocturnal polyuria and OAB syndrome, comparing three months of once-daily combination (desmopressin 25 µg/tolterodine 4 mg, n = 49) or monotherapy (tolterodine 4 mg/placebo, n = 57) a significant reduction in mean number of nocturnal voids compared to baseline was reported in both groups [619]. The level of certainty of the evidence from this trial is moderate.

A well-designed large comparative study followed 407 women with OAB and nocturia for 4 weeks [621]. The patients were given tolterodine as monotherapy in one group, and tolterodine combined with estazolam (a benzodiazepine) in the other group for four weeks. Significant changes from baseline in both groups for the main outcome of number of nocturia episodes were reported. The combination showed a significant benefit for women with OAB and nocturia compared to monotherapy in terms of differences in number of nocturia episodes per night, urgency episodes in 24 hours, UUI episodes in 24 hours, voided volume per micturition. The level of certainty of the evidence from this trial is very low.

4.6.4.2.3 Oestrogens

In the recent systematic review [596] only a single RCT investigating the efficacy of oestrogen for nocturia was identified [622]. This trial compared an oestradiol-releasing vaginal ring with an oestriol vaginal pessary in 251 women followed up for 6 months. There was no difference between the treatment groups in the number of women reporting nocturia though they reported significant change from baseline in both treatment arms with over 50% of subjects responding in each arm. The certainty of evidence for this outcome was low.

4.6.4.2.4 Diuretic treatment

In a randomised placebo-controlled study an afternoon dose of 40 mg of furosemide (taken 6 hours before bedtime) in an attempt to establish and complete a diuresis before bedtime was given to elderly men [623]. In the 43 men who completed the study, night-time frequency in the furosemide group fell by 0.5 compared to placebo, and percentage night-time voided volume fell by 18%. No such study has been carried out in female patients.

4.6.4.3 Surgical management

Surgical treatment is in general reserved for those with underlying correctable LUT disorders. The effect of surgical treatments on symptom of nocturia can be found in the relevant condition-specific sections of this guideline.

4.6.4.4 Summary of evidence and recommendations for the pharmacological management of nocturia

Summary of evidence	**LE**
Desmopressin treatment for nocturia shows significant reductions in nocturnal urine output, nocturnal urinary frequency and nocturnal polyuria index.	1b
The majority of nocturia patients tolerate desmopressin treatment without clinically significant hyponatremia; however, the risk increases with increasing age and decreasing baseline serum sodium concentration.	1a
Treatment of nocturia in OAB patients with anticholinergic drugs shows reduction in nocturia episodes.	1b
Combination of PFMT and pharmacological treatment with anticholinergics does not appear to confer additional benefit over anticholinergics alone.	1b
Combination of anticholinergic and desmopressin treatment appears to reduce nocturnal voided volume and time to 1st nocturnal void in women with nocturnal polyuria.	1b
Vaginal oestrogen may be beneficial in the treatment of nocturia in around 50% of women.	1b
Afternoon (timed) diuretic treatment with furosemide reduces nocturia episodes and nocturnal voided volume in men but no similar studies have been conducted in women.	1b
Examination for clinical significance is important when evaluating the results of trials involving treatment strategies for nocturia as statistical significance can be achieved with very small reductions in nocturia episodes.	3

Recommendations	Strength rating
Offer desmopressin treatment for nocturia secondary to nocturnal polyuria to women following appropriate counselling regarding the potential benefits and associated risks (including hyponatremia).	Strong
Carefully monitor serum sodium concentration in elderly patients treated with desmopressin. Avoid prescribing desmopressin to patients with a baseline serum sodium concentration below normal range.	Strong
Offer a anticholinergic treatment for nocturia to women with urgency incontinence or other storage lower urinary tract symptoms following appropriate counselling regarding the potential benefits and associated risks.	Strong
Inform women with nocturia that the combination treatment with behavioural therapy and anticholinergic drugs is unlikely to provide increased efficacy compared with either modality alone.	Weak
Offer combination treatment with anticholinergics and desmopressin to women with OAB and nocturia secondary to nocturnal polyuria following appropriate counselling regarding the potential benefits and associated risks.	Weak
Offer vaginal oestrogen treatment to women with nocturia following appropriate counselling regarding the potential benefits and associated risks.	Weak
Offer timed diuretic treatment to women with nocturia secondary to polyuria following appropriate counselling regarding the potential benefits and associated risks.	Weak

*4.6.5 **Follow-up***

The follow-up of patients with nocturia will be dependent on both the underlying aetiology of this symptom and the treatment given.

4.7 Pelvic organ prolapse and LUTS

*4.7.1 **Epidemiology, aetiology, pathophysiology***

Pelvic organ prolapse is a common condition in adult women. The prevalence of POP ranges from 3-6% when bothersome symptoms are used to characterise the condition and goes up to as high as 50% when a purely anatomical definition is used [624].

The lifetime risk for POP surgery is an estimated 12.6% [625]. Parity, vaginal delivery, ageing and obesity are the most commonly recognised risk factors [626].

Although the aetiology of POP is not fully understood, birth trauma to the levator ani complex is recognised as central to its development. In normal physiology an intact levator ani complex functionally closes the genital hiatus surrounding the vagina limiting the pressure gradient between the intra-abdominal and intravaginal areas. During physical activities this reduces the stress on the endopelvic fascia and its condensations (e.g. ligaments), which are crucial in securing the bladder, uterus and rectum to their surroundings. Current aetiological concepts include widening of the levator hiatus due to birth trauma, which will create a low-pressure area in the vagina and consequently an increased stress on the ligaments, fascial elements and PFMs during physical activity. When the supporting function of the muscles and connective tissues fail, POP may develop [627]. This concept also explains the time lapse between birth trauma and the occurrence of POP.

Pelvic organ prolapse and LUTS often occur simultaneously in women. Although in isolation both POP and LUTS are already prevalent conditions in women, the prevalence of LUTS in women with POP exceeds that of LUTS in women without POP symptoms [624]. The observation that LUTS symptoms may improve, or worsen, after POP treatment also suggests a link between these two entities [624]. Clinical examples include the occurrence of BOO symptoms in the case of a severe POP, and the disappearance of SUI symptoms with progression of POP (and conversely the occurrence of SUI after treatment of POP) [628].

*4.7.2 **Classification***

Since 1996 POP has been classified according to the Pelvic Organ Prolapse-Quantification (POP-Q) system [629]. For specifics on how to perform the POP-Q measurement and the 9 standard points to be measured, as shown in Figures 2 and 3, we refer to the original publications [629, 630].

The vagina is divided into anterior (bladder), posterior (rectum) and apical (cervix or vaginal vault) compartments. After scoring the position of the 9 POP-Q points, a prolapse of each compartment is graded numerically from stage 0 to 4, with stage 0 being no prolapse and stage 4 being a complete eversion of the uterus/vaginal vault. A crucial landmark in staging of the POP is the hymenal remnant. Any POP with

a maximum descent that is still 1 cm above the hymen (e.g. in the vagina) is considered a stage 1 POP. A maximum descent between 1 cm above and 1 cm below (outside the vagina) the hymen is a stage 2 POP. Any descent beyond 1 cm below the hymen is a stage 3 POP.

The figures below show the POP-Q staging in comparison to the Baden Walker system (and others) used before the international consensus on the POP-Q staging was introduced as the new standard.

Figure 2: Prolapse classification system*

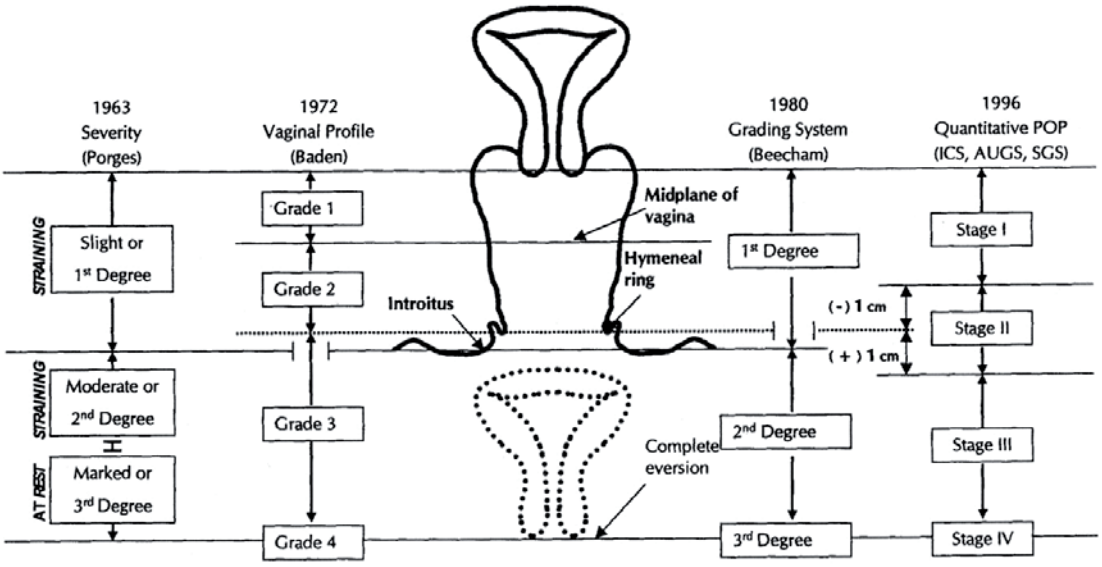

**Figure reproduced with permission from the publisher, from Theofratus JP, et al. [630].*

Figure: 3: Pelvic Organ Prolapse-Quantification staging*

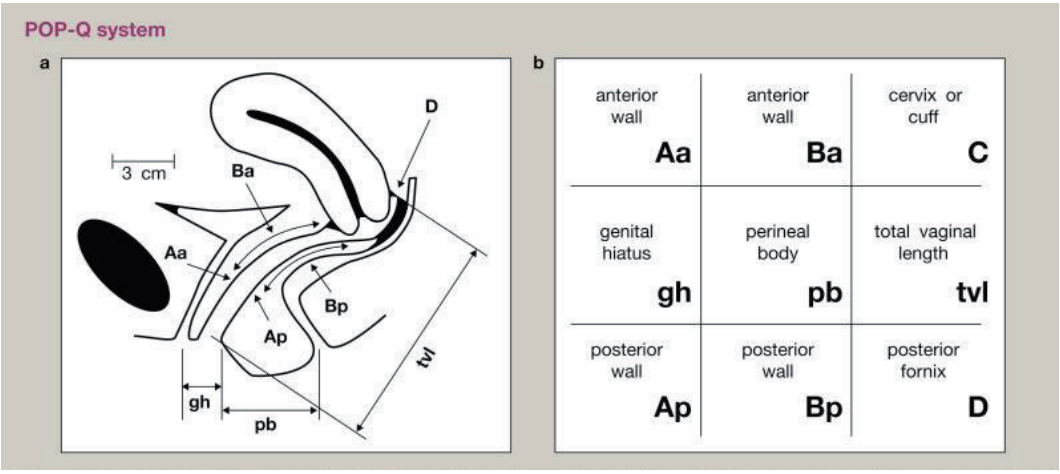

**Figure reproduced with permission from the publisher, from Bump RC, et al, [629]. The standardisation of terminology of female pelvic organ prolapse and pelvic floor dysfunction.*

4.7.3 Diagnostic evaluation

Pelvic organ prolapse is a clinical diagnosis and is staged according to the POP-Q system. In general, a POP that is above the hymen should only produce mild symptoms at most [631]. In cases where there is a discrepancy between the clinical symptoms and POP-Q staging, it is advised to consider performing the POP-Q measurement in a standing position rather than supine, or re-evaluate at a later time in the day. Magnetic resonance imaging assessment demonstrated a marked difference in POP staging between supine and standing position [632]. Additional diagnostic tests for POP are mainly indicated if there are accompanying symptoms like LUTS or bowel dysfunction. Imaging techniques are not advised for the routine diagnostic work-up of patients presenting with POP [67]. The role of urodynamics in the diagnostic work up of SUI has been discussed in the SUI Section of this guideline.

The use of techniques to reduce the POP during urodynamic evaluation in order to diagnose occult SUI is common practice. This information may be used to decide if additional anti-UI surgery should be offered at the time of POP surgery or to counsel patients on the possible after-effects of POP treatment.

There are several POP reduction methods that may be used during physical examination or urodynamic evaluation. In a multicentre observational study, five different cough/stress tests were compared for their ability to detect SUI in women with POP [633]. Stress urinary incontinence during at least one of the five tests occurred in 60/205 (29.2%) of women without SUI symptoms. Looking at single test performance, the detection rate of occult SUI in women without SUI symptoms increases from 4.4% in case of no reduction, to 22% in case of reduction with a pessary.

A large randomised trial which included women with POP without symptoms of SUI, who were randomised to sacrocolpopexy with or without Burch colposuspension [634]. Three hundred and twenty two stress-continent women with stages 2–4 prolapse underwent standardised urodynamic testing, and the protocol included five prolapse reduction methods. Pre-operatively, 12 of 313 (3.7%) women demonstrated urodynamic SUI *without* prolapse reduction. Pre-operative detection of urodynamic SUI *with* prolapse reduction at 300 mL was by pessary, 6% (5 of 88); manual, 16% (19 of 122); forceps, 21% (21 of 98); swab, 20% (32 of 158); and speculum, 30% (35 of 118). Another large trial included women with POP without SUI symptoms randomised to vaginal POP surgery with or without (sham incision) MUS [635]. Before surgery, 33.5% (111/331) of women demonstrated SUI at a prolapse-reduction cough stress test. In an observational study of 172 women with POP without SUI, 19% of women were diagnosed with occult SUI on basic office evaluation (with prolapse reduction with swab on forceps) and 29% on urodynamic evaluation [636].

In summary, SUI can be demonstrated in women with POP without symptoms of SUI after POP reduction in up to 30% of cases. There is no consensus on the best reduction technique.

Although the detection rate of occult SUI increases after reduction of POP in SUI-symptom-negative women, its clinical value is under debate.

In one trial, pre-operative stress continent women were evaluated during urodynamic testing with prolapse reduction to determine if they were more likely to report post-operative SUI, regardless of concomitant colposuspension (controls 58% vs. 38% [p = 0.04] and Burch 32% vs. 21% [p = 0.19]) [634]. In another trial, women with SUI during the cough stress test after POP reduction reported UI at 3 months in 29.6% in the sling group, compared with 71.9% in the sham group (adjusted OR: 0.13) [635]. Women with a positive prolapse-reduction stress test before surgery appeared to receive more benefit from a sling at 3 months, but not at 12 months, than did those with a negative test.

In a large observational study women did not receive additional anti-UI surgery even if they had SUI after POP reduction pre-operatively. In this scenario 9% (16/172) of all women developed post-operative SUI and six women (4%) underwent surgery for *de novo* SUI [636]. Women with demonstrable pre-operative SUI were more at risk of post-operative SUI: 28% vs. 5% (diagnostic OR: 7). Based on urodynamic evaluation only, one more woman was predicted to have post-operative SUI, but all 6 women who underwent treatment for *de novo* SUI showed SUI during basic office evaluation.

In a model developed to predict the risk of *de novo* SUI in women undergoing POP surgery based on findings from two trials, a total of 12 pre-operative predictors were tested [637]. A positive finding of SUI during a pre-operative prolapse reduction test was included in this model, but it failed to be of significant predictive value as a single item. In addition, pre-operative POP stage was not associated with the risk of *de novo* SUI.

4.7.3.1 Summary of evidence and recommendation for the detection of SUI in women with POP

Summary of evidence	**LE**
POP reduction during cough stress test, in office or during UDS, will detect SUI in approximately 30% of continent women.	2a
Women with SUI after POP reduction pre-operatively (occult SUI) are likely to be at increased risk of developing SUI symptoms after POP surgery.	2a

Recommendation	Strength rating
Perform a pelvic organ prolapse (POP) reduction test in continent women to identify those with occult stress urinary incontinence and counsel them about the pros and cons of additional anti-incontinence surgery at the time of POP surgery.	Strong

4.7.3.2 Urodynamics in women with POP and LUTS (without stress urinary incontinence).

The role of urodynamics is less clear in women presenting with POP and concurrent LUTS, other than SUI. Pelvic organ prolapse is a complex condition incorporating not only different compartments of the vagina, but also presenting at different stages in terms of severity. Information about detrusor activity, as assessed with urodynamics, may provide information about the risk of developing DO after surgery, but also on the risk of urinary retention due to DU. An observational study assessed predictors for DO following POP surgery for POP-Q stage 3 or higher in 1,503 women and the authors concluded that a pre-operative maximum urethral closure pressure of ≥ 60 cm H_2O, a Q_{max} of < 15 mL/sec, a maximum detrusor voiding pressure (D_{max}) ≥ 20 cm H_2O and a PVR volume of ≥ 200 mL were independent risk factors for post-operative DO [638]. A small observational study (n = 49) evaluated those with pre-operative DU (detrusor pressure at maximum flow was ≤ 10 cm H_2O and Q_{max} of ≤ 12 mL/s) after POP surgery. Surgery objectively "cured" DU in 47% of women and urodynamic findings normalised after surgery [639]. The 2019 NICE Guidelines do not include a recommendation to perform urodynamics as part of the diagnostic workup of POP, except for the combination with symptomatic SUI [67].

4.7.4 ***Disease management***

Pelvic organ prolapse symptoms can be treated with PFMT, vaginal pessary use, surgery or a combination of these treatments. The scope of this guideline is to focus on LUTS in women and therefore only data on the effect of treatment of urinary symptoms are presented.

4.7.4.1 Conservative treatment of pelvic organ prolapse

The 2013 NICE guideline on Urinary Incontinence and Pelvic Organ Prolapse in Women updated its management section in 2019, including a full evidence review [67]. The overall conclusion with respect to conservative treatment for POP was that the evidence is of low quality. A total of 13 RCT's were identified. Seven studies presented data on changes in urinary symptoms [640-646]. An additional search identified 4 RCT's that addressed the addition of PFMT to POP surgery [647-650], and one that compared combined PFMT/Pilates therapy with lifestyle advice by leaflet [651].

Five studies [641, 643-645, 651] compared PFMT to lifestyle advice/leaflet, one study [642] compared PFMT to PFMT with pessary, one study [646] PFMT to pessary therapy, and five studies compared surgery for POP with or without the addition of PFMT [640, 647-650].

4.7.4.1.1 Pelvic floor muscle training versus lifestyle advice

An RCT (n = 109) reported that at 6 months follow-up the ICIQ-UI-SF scores improved in favour of the PFMT group compared with a control group receiving lifestyle advice only (difference from baseline PFMT 2.40 points and control 0.2 points, p = 0.002) [641]. However, the difference of 2.4 points from baseline, in favour of PFMT, has to be viewed with caution as the mean baseline score in the PFMT group was higher compared to the control group (7.4 vs. 5.9, p = 0.05). Likewise, it has to be noted that the absolute ICIQ-UI-SF values at 6 months follow-up were not significantly different between groups (PFMT 4.8 vs. control 5.2).

Two publications from one RCT reported on the 3, 6 and 12 month results of lifestyle advice only vs. lifestyle advice combined with group PFMT [643, 644]. The UDI-6 and UIQ-7 questionnaires were used to assess urinary symptoms. At 3 months follow-up both groups (53 women in the lifestyle group and 56 in the lifestyle + PFMT cohort) reported significantly improved UDI-6 scores whilst the lifestyle-only group also reported significantly greater improvement on the UIQ-7. Between-group comparison showed no differences in UDI-6 and UIQ-7 scores at 6 months. At 12 months follow-up, the majority of women had sought additional treatment (70% in the lifestyle-only group and 48% in the lifestyle/PFMT group, p = 0.05). The number of patients remaining on the original therapy was too small to reach strong conclusions.

One RCT reported on the 6 and 12 months follow-up of 225 women with POP-Q stage 1–3 randomised to individualised PFMT and 222 women randomised to lifestyle leaflet information only (control) [645]. Urinary symptoms were assessed with a single question on the existence of UI, a single question regarding the need to strain to void and a single question regarding incomplete bladder emptying which were supplemented with the ICIQ-SF questionnaire score. At 6 months, significantly more women in the control group reported UI, the need to strain to empty bladder and the feeling of incomplete emptying compared to the PFMT group. The score on

the ICIQ-SF was also significantly worse in the control group as compared to the PFMT group. However, at 12 months there was no significant difference on these items between groups. It has to be noted that 50% in the control group received additional treatment within the 12-month study period. Twenty-seven percent had additional PFMT, which may have had an effect on the 12-month data.

Another RCT reported on the 24-month follow-up of 414 women with stage 1–3 POP (207 assigned to PFMT/Pilates and 207 to lifestyle advice) [651]. Urinary symptoms were assessed with the ICIQ-UI-SF and a question about UI and difficulty emptying the bladder. At 24 months the ICIQ-UI-SF score was significantly better in the intervention group (mean difference -0.83, p = 0.008). However, the proportion of women reporting any UI did not differ between groups, nor did the number of pads used weekly.

4.7.4.1.2 Pelvic floor muscle training versus pelvic floor muscle training with pessary

One RCT compared PFMT alone to PFMT and pessary therapy for symptomatic POP [642]. Urinary tract symptom changes were assessed using the Urogenital Distress Inventory-6 (UDI-6) and the Urinary Impact Questionnaire (UIQ) at 6 and 12 months follow-up. At 12 months follow-up there was no difference in the between-group comparison. With respect to the UIQ, women in the pessary/PFMT showed a significant improvement from baseline, but the PFMT-only group did not. Women in the pessary/PFMT group reported significantly more frequent *de novo* SUI (48% vs. 22%), and also more improvement of pre-existing voiding difficulty (62.5% vs. 35.5%).

4.7.4.1.3 Pelvic floor muscle training versus pessary only

One RCT reported on the 24-month follow-up of 82 women with symptomatic POP randomised to pessary therapy and 80 women randomised to PFMT [652]. The UDI-6 was used as the outcome measure for urinary symptoms. Both in the ITT and per protocol analyses the UDI score did not differ significantly between groups at 24 months of follow-up.

4.7.4.1.4 Surgery versus surgery with pelvic floor muscle training

An assessor-blinded RCT compared surgery for POP with or without additional pre-and post-operative PFMT. At 12 months after surgery there were no significant differences between groups on the change in scores of the UDI nor the IIQ scores [640].

Another RCT reported on the 6-month follow-up of 57 women (28 surgery/29 surgery with PFMT). The UDI-6 was used to assess urinary symptoms. There was a statistically significant improvement on the UDI-6 score for both groups, but not between groups [648].

Another RCT reported on the results of a 2x2 factorial design in which women were first randomised between two surgical techniques for POP and in addition between additional PFMT (n = 188) or not (n = 186) [649]. The UDI was used to assess urinary symptoms up to 24 months. No significant differences were found between the addition of PFMT to surgery or not. Another study of the same population reported on SUI in particular [650]. and no significant differences were found between women who had additional PFMT and those who had not.

Finally, in 2020 an RCT reported on the 40 and 90 days follow-up of 48 women randomised to supervised PFMT before and after surgery and 40 women having surgery only [647]. The UDI-6 was used to assess urinary symptoms. No statistically significant differences in UDI-6 scores were identified at 40 and 90 days.

The NICE guideline on the management of POP advocates considering supervised PFMT for at least 16 weeks as initial treatment for symptomatic prolapse [67]. The use of pessary is also to be considered, alone or combined with PFMT. It is important to recognise that the benefit is expected on typical POP symptoms, like feeling or seeing a bulge out of the vagina, and not on LUTS, as the reported RCTs show. From a urological perspective, initiating conservative treatment for asymptomatic POP in order to treat UI or bladder emptying problems is not supported by the data.

4.7.4.1.5 Summary of evidence and guidelines for the conservative treatment of pelvic organ prolapse and lower urinary tract symptoms

Summary of evidence	**LE**
Pelvic floor muscle therapy improves LUTS for up to six months in POP patients who do not have additional pessary or surgical treatment.	2a
If pessary therapy or surgical intervention is used for POP, PFMT does not show an additional benefit.	2a

Recommendations	Strength rating
Inform women with pelvic organ prolapse (POP), who do not need a vaginal pessary or surgical intervention, about the potential relief from lower urinary tract symptoms (LUTS) from pelvic floor muscle therapy (PFMT).	Strong
Do not offer pre-operative PFMT in order to improve outcome of LUTS if pessary therapy or surgical intervention is indicated for POP.	Strong

4.7.4.2 Pelvic organ prolapse surgery and overactive bladder

Only a few studies specifically address the effect of POP surgery on OAB symptoms. A systematic review of 12 studies, excluding women with SUI, evaluated OAB symptoms before and after surgery [653]. All but one study reported an improvement of OAB symptoms. The same authors performed a prospective analysis of 505 women who had POP surgery with or without mesh [654]. Symptoms were assessed with UDI questions and each symptom was dichotomised into not bothersome or bothersome. Mean follow-up was 12.7 months. The incidence of bothersome urinary frequency reduced from 36.6% to 14.6%, with *de novo* symptoms occurring in 6.1%. Bothersome urgency symptoms reduced in 36.8% to 12.9% of women, with 5.0% developing *de novo* symptoms. Urgency UI symptoms reduced from 21.2% to 6.1% of women, with 5.3% developing *de novo* symptoms.

One observational study evaluated frequency and urgency symptoms without consideration of bother in 87 women undergoing POP surgery and showed an improvement in frequency by 75%, and in urgency in 83% [655]. The effect of the POP-Q stage did not seem to influence the effect of surgery on OAB symptoms [654, 655].

Another observational study (n = 43) evaluated the effect of posterior repair on OAB/DO and showed a 70–75% improvement rate in both parameters after surgery [656].

4.7.4.3 Pelvic organ prolapse surgery and bladder outlet obstruction

The criteria for BOO are based on urodynamic assessment. Pelvic organ prolapse can be categorised as anatomical BOO which is addressed in Sections 4.5.2.2 and 4.5.3.1.

4.7.4.4 Pelvic organ prolapse surgery and stress urinary incontinence

The aim of this section is to address the options available to women who require surgery for POP and who have associated SUI (either before or after reduction of prolapse), and to assess the value of prophylactic anti-UI surgery in women with no evidence of SUI.

A systematic review and meta-analysis of ten trials on prolapse surgery with or without an anti-incontinence procedure was reported in 2018 [657]. In addition, a Cochrane review including nineteen trials (n = 2,717) evaluating bladder function after surgery for POP presented analyses of women with POP and SUI, women with POP and occult SUI and women with POP who were continent [658].

4.7.4.4.1 Vaginal pelvic organ prolapse surgery in women with stress urinary incontinence

Two trials addressed post-operative SUI in patients who had been diagnosed with SUI pre-operatively and had vaginal POP surgery [659, 660]. Two trials (n = 185 and n = 134) compared the use of MUS at initial POP surgery to POP surgery alone. The RR for post-operative SUI was 0.30 in favour of the combined POP surgery and MUS group. One of these two trials also compared the use of MUS at initial POP surgery and at 3 months if SUI persisted [659]. At 12 months follow-up there was no difference between the groups regarding post-operative UI (RR: 0.41); however, 44% of the women without initial MUS never required surgery and 29% were dry.

4.7.4.4.2 Abdominal pelvic organ prolapse surgery in women with stress urinary incontinence

One RCT randomised 47 women with POP and SUI to an abdominal POP surgical procedure; e.g. sacrocolpopexy with or without Burch colposuspension. Additional SUI surgery did not improve post-operative SUI as compared to sacrocolpopexy alone (RR: 1.38) [661]. This finding remained consistent over 5 years follow-up [662]. Another RCT compared the addition of a MUS or Burch colposuspension to an abdominal sacrocolpopexy in 113 women with POP and SUI [663]. At 2 years follow-up the RR for post-operative SUI was 0.54 in favour of the MUS group.

4.7.4.4.3 Vaginal POP surgery in women with prolapse and occult stress urinary incontinence

Five RCTs including a total of 194 women who had vaginal POP repair alone and 174 women who had an additional MUS at the time of primary surgery were identified [635, 664-667]. The RR of post-operative SUI was 0.38 in favour of the MUS group.

4.7.4.5 Vaginal pelvic organ prolapse surgery in continent women

One RCT comparing vaginal POP surgery alone with concomitant MUS in 220 women found that post-operative SUI occurred in 46/113 (40.7%) women who had POP surgery alone, compared to 30/107 (28.0%) who had additional MUS (RR: 0.69) [658].

4.7.4.5.1 Abdominal pelvic organ prolapse surgery in continent women

Two RCTs, compared abdominal sacrocolpopexy with (n = 189) or without (n = 190) Burch colposuspension with an outcome favouring the addition of Burch colposuspension (RR for *de novo* SUI 0.69) [668, 669].

4.7.4.6 Adverse events associated with combined pelvic organ prolapse and stress urinary incontinence surgery

Data from 6 RCT's on vaginal POP surgery with MUS were pooled to assess adverse events [635, 659, 660, 665-667]. Urgency UI was less frequent after combination surgery as compared to POP surgery alone (28 vs. 42%, RR: 0.7), but there was a tendency towards more voiding problems. Adverse events directly related to surgery occurred more often in the combination group (28% vs. 15%, RR: 1.8), as did serious adverse events such as bladder perforation, urethral injuries, tape exposure (14% vs. 8%, RR: 1.7) [657].

In summary, it is difficult to generalise the results of trials using different procedures to treat both POP and UI. It seems that with a combined procedure the rate of SUI post-operatively is lower but post-operative voiding symptoms and complication rates are higher. Studies using MUS have generally shown more significant differences in UI outcomes with combined procedures than when other types of anti-UI procedure have been used. It must be taken into account that although more women are dry after combined surgery for POP with MUS, there are potential adverse events that should be balanced against potential benefits.

4.7.5 Summary of evidence and recommendations for surgery in women with both pelvic organ prolapse and stress urinary incontinence

Summary of evidence	**LE**
Women with pelvic organ prolapse and urinary incontinence	
Surgery for POP and SUI shows a higher rate of cure of UI in the short-term than POP surgery alone.	1a
There is conflicting evidence on the relative long-term benefit of surgery for POP and SUI vs. POP surgery alone.	1a
Combined surgery for POP + SUI carries a higher risk of adverse events than POP surgery alone.	1a
Continent women with pelvic organ prolapse	
Continent women with pelvic organ prolapse are at risk of developing SUI post-operatively.	1a
The addition of a prophylactic anti-UI procedure reduces the risk of post-operative UI but increases the risk of adverse events.	1a
Women with pelvic organ prolapse and overactive bladder	
There is some low-level inconsistent evidence to suggest that surgical repair of POP can improve symptoms of overactive bladder.	2b

Recommendations for women requiring surgery for bothersome pelvic organ prolapse (POP) who have symptomatic or occult stress urinary incontinence (SUI)	**Strength rating**
Offer simultaneous surgery for POP and SUI only after a full discussion of the potential risks and benefits of combined surgery vs. POP surgery alone.	Strong
Inform women of the increased risk of adverse events with combined prolapse and anti-urinary incontinence surgery compared to prolapse surgery alone.	Strong
Recommendations for women requiring surgery for bothersome POP who do not have symptomatic or occult SUI	
Inform women that there is a risk of developing *de novo* SUI after prolapse surgery.	Strong
Warn women that the benefit of combined surgery for POP and SUI may be outweighed by the increased risk of adverse events compared to prolapse surgery alone.	Strong

4.8 Urinary fistula

The evidence relating to diagnosis and treatment of urinary fistulae is generally of low-level and is largely composed of case series and other consensus statements. In particular, the epidemiology, aetiology, diagnosis, treatment and prevention of obstetric and non-obstetric fistulae have been described in detail during the recent ICI conference [670]. Most non-obstetric fistulae are iatrogenic in origin, with the majority caused by pelvic

surgery (e.g. hysterectomy for benign or malignant conditions, bowel resection, and urological surgery). The risks during pelvic surgery increase relative to the complexity of the resection, the extent of primary disease and the existence of prior radiotherapy (especially for recurrent disease). When a fistula occurs following radiotherapy for primary treatment, this may be an indication of tumour recurrence.

*4.8.1 **Epidemiology, aetiology and pathophysiology***

4.8.1.1 Obstetric fistula

According to the WHO, fistulae affect more than two million women, mostly from sub-Saharan African and Asian countries. The pooled prevalence of fistula from population studies is at 0.29/1000 pregnancies [671]. Poor quality obstetric care, staff unaccountability, late referral and poor nursing standards have been identified as health system causes [671]. However, obstructed labours are poorly documented. The main individual risk factors include age at first marriage, short stature, pregnancy with a male child, failure to attend ante-natal care, low socio-economic status, low social class, lack of employment and illiteracy [672-674]. Obstetric fistulae have detrimental consequences on global and individual health and are associated with malnutrition, sexual dysfunction, anxiety, depression, insomnia, social isolation, worsening poverty and suicide [675, 676].

4.8.1.2 Iatrogenic fistula

Poor obstetric care is usually responsible for VVF in the developing world. By contrast, in the developed world, gynaecological or pelvic surgeries are the main causes of VVF.

4.8.1.2.1 Post-gynaecological surgery

An injury to the urinary tract during hysterectomy for benign conditions (60–75%), hysterectomy for malignant conditions (30%) and caesarean section (6%) are the main causes of post-operative VVF in the developed world [677, 678]. The risk of pelvic organ fistula following hysterectomy ranges from 0.1 to 4% [679]. Furthermore, fistulae may also occur as a result of primary or recurrent malignancy, or as a consequence of cancer treatment by surgery, radiotherapy, and/or chemotherapy.

In a study including 536 women undergoing a radical hysterectomy for invasive cervical cancer, bladder injury occurred in 1.5% with VVF forming in 2.6% and uretero-vaginal fistula (UVF) in 2.4% of cases [680]. Overall, the rate of urogenital fistula appears to be approximately 9 times higher following radical hysterectomy for malignant disease as compared to that following simple hysterectomy (abdominal or vaginal for benign conditions) [681]. Bladder sparing techniques during pelvic exenteration can increase the risk of fistula formation [682].

4.8.1.2.2 Radiation fistula

The risk of fistula seems to be higher for post-operative external radiation (1.9%) compared to intravaginal brachytherapy (0.8%) [683], without any predictive factor being identified [684]. This is most likely due to the heterogeneity of data regarding the tumour type and stage, the form of radiation and the site and dose delivered.

4.8.1.2.3 Rare causes of vesico-vaginal fistula

Foreign bodies such as pessaries, sex toys, cups etc. can be a cause of delayed presentation of VVF [685-687]. Ketamine abuse has also been shown to be responsible for fistula formation [688].

4.8.1.3 Summary of evidence for epidemiology, aetiology and pathophysiology of urinary fistula

Summary of evidence	**LE**
The risk of injury to the urinary tract and subsequent fistula formation is higher in women with malignant disease undergoing radical surgery than in women with benign disease undergoing simple surgical procedures.	2
The rate of fistula formation following radiotherapy for gynaecological cancer appears to be of the same order as that following surgical treatment.	4

*4.8.2 **Classification***

Due to the plethora of VVF classification systems, a consensual classification system needs to be adopted. The Waaldijk and Goh classifications are widely used for diagnosis and follow-up [689-691]. They were originally designed for obstetric fistulae and their use in iatrogenic fistulae is less relevant [692]. Waaldijk's classification is based on the size and site of the fistula and divides them into 3 main categories - type 1 are VVF with no urethral involvement, type 2 fistulae are those which involve the urethra (and are sub-classified into those with

circumferential and non-circumferential urethral involvement) and type 3 are fistula involving other parts of the urinary tract. Goh's classification also uses the presence or absence of urethral involvement to sub-categorise VVF and also takes into account the degrees of fibrosis present. The WHO classification (Table 6) was originally developed for obstetric fistulae and separates fistulae into simple and complex.

Table 6: Adapted WHO Classification of fistulae [671]*

Simple fistula with good prognosis	Complex fistula with uncertain prognosis
• Single fistula < 4 cm	• Fistula > 4 cm
• Vesico-vaginal fistula	• Multiple fistula
• Closing mechanism not involved	• Recto-vaginal mixed fistula, cervical fistula
• No circumferential defect	• Closing mechanism involved
• Minimal tissue loss	• Scarring
• Ureters not involved	• Circumferential defect
• First attempt to repair	• Extensive tissue loss
	• Intravaginal ureters
	• Failed previous repair
	• Radiation fistula

**Although this classification was developed for obstetric fistula initially, it could be relevant for iatrogenic fistula as well.*

4.8.2.1 Recommendation for the classification of urinary fistula

Recommendation	Strength rating
Use a classification system for urinary tract fistulae to try to standardise terminology in this subject area.	Strong

4.8.3 ***Diagnostic evaluation***

Leakage of urine is the hallmark sign of a urogenital fistula. The leakage is usually painless, may be intermittent if it is position dependent, but more usually is constant. Unfortunately, intra-operative diagnosis of a GU or GI injury is made in only about half of all cases [693]. The diagnosis of VVF usually requires clinical assessment often in combination with appropriate imaging or laboratory studies. Direct visual inspection, cystoscopy, retrograde bladder filling with a coloured fluid or placement of a tampon into the vagina to identify staining may facilitate the diagnosis of a VVF. A double-dye test to differentiate between a UVF and VVF may be useful in some cases [678]. Testing the creatinine level in either the extravasated or collected fluid will confirm fluid leakage as urine. Contrast-enhanced CT with late excretory phase reliably diagnoses urinary fistulae and provides information about ureteric integrity and the possible presence of associated urinoma. Magnetic resonance imaging, in particular with T2 weighting, also provides diagnostic information regarding fistulae [694].

4.8.4 ***Management of fistula***

4.8.4.1 Management of vesico-vaginal fistula

4.8.4.1.1 Conservative management

4.8.4.1.1.1 Spontaneous closure

The reported spontaneous closure rate is 13% ± 23% [695], although this applies largely to small fistulae (size < 1 cm) [670, 696]. Hence, immediate management is usually by urinary catheterisation or diversion; however, within the first two weeks following fistula occurrence, surgical exploration and repair can be considered.

4.8.4.1.1.2 Pharmacotherapies

Several case reports describe a successful fistula closure rate following the induction of amenorrhoea by oestrogen, oestrogen/progesterone combinations or luteinising hormone releasing hormone (LHRH) analogues specifically for small (< 7 mm), uretero- or vesico-uterine fistula following caesarean section [697-703]. One RCT comparing the efficacy of using fibrin glue compared to Martius flap inter-positioning (n = 14; < 4 cm and n = 5; > 5 cm) did not report statistically different outcomes between the two types of treatment [704].

4.8.4.1.1.3 Palliation and skin care

During the intervening period between diagnosis and repair, UI pads with the aim of prevention of skin complications related to chronic urinary leakage can be provided and the use of a barrier cream or local oestrogen can also be considered [705, 706].

4.8.4.1.1.4 Nutrition
Nutritional support is essential in patients with fistulae induced by malignant disease or radiotherapy [707], or following diversion surgery [707-709].

4.8.4.1.1.5 Physiotherapy
Early involvement of the physiotherapist in pre-operative management and rehabilitation of fistula patients suffering from limb weakness, foot drop and limb contracture is essential [710, 711].

4.8.4.1.1.6 Antimicrobial therapy
Active infection in the genital or urinary tracts should be treated prior to surgical repair [712].

4.8.4.1.1.7 Counselling
Confident and realistic counselling by the surgeon is essential and the involvement of nursing staff or counsellors with experience of fistula patients is also highly desirable.

4.8.4.1.2 Surgical management
4.8.4.1.2.1 Timing of surgery
Findings from uncontrolled case series suggest no difference in success rates for early (within 3 weeks) or delayed (after 3 months) closure of VVF.

4.8.4.1.2.2 Surgical approaches
Vaginal procedures
There are two main types of closure techniques applied to the repair of urinary fistulae, the classical saucerisation/partial colpocleisis [695] and the more commonly used dissection and repair in layers or 'flap-splitting' technique [713]. There are no data comparing their outcomes.

Abdominal procedures
Repair by the abdominal route is indicated when high fistulae are fixed at the vaginal vault and are inaccessible via a vaginal approach. A transvesical repair has the advantage of being entirely extraperitoneal. A simple transperitoneal repair is used less often although it is favoured by some using the laparoscopic approach. A combined transperitoneal and transvesical procedure may be utilised for fistula repair following Caesarean section. There are no RCTs comparing abdominal and vaginal approaches. Results of secondary and subsequent repairs are not as successful as the initial repair [714].

A single RCT compared trimming of the fistula edge with no trimming and found no difference in success rates but failed repairs in trimmed cases ended up with larger recurrences than untrimmed cases, which were smaller [715].

Laparoscopic and robotic procedures
Very small series (single figures) have been reported using these techniques, but whilst laparoscopic repair is feasible with and without robotic assistance, it is not possible to compare outcomes with alternative surgical approaches.

Tissue interposition
Tissue flaps are often added as an additional layer of repair during VVF surgery. Most commonly, such flaps are utilised in the setting of recurrence after a prior attempt at repair, for VVF related to previous radiotherapy (described later), ischaemic or obstetric fistulae, large fistulae, and finally those associated with a difficult or tenuous closure due to poor tissue quality. However, there is no high-level evidence that the use of such flaps improves outcomes for either complicated or uncomplicated VVF.

Post-operative management
There is no high-level evidence to support any particular practice in post-operative management but most reported series used catheter drainage for at least ten days and longer periods in complex or radiation-associated fistulae (up to three weeks). The performance of post-operative cystogram prior to catheter removal can miss a persistent fistula if not done with a micturition phase or if the fistula is located at the bladder neck.

4.8.4.1.3 Management of complications of vesico-vaginal fistulae
The complications of VVF repair are varied and can include:

- Persistence or recurrence of fistula;
- Persistence or recurrence of UI;

- Persistence of LUT symptoms or occurrence of new LUT symptoms, including *de novo* OAB symptoms and/or SUI;
- Infections: wound and UTIs/urosepsis;
- Ureteric obstruction (ligation, fibrosis, injury);
- Bladder outlet obstruction (meatal stenosis, urethral stricture, bladder neck obstruction);
- Bladder contracture;
- Vaginal stenosis;
- Sexual dysfunction (vaginismus/dyspareunia);
- Rare complications (granulomas/diverticulum formation);
- Neurological complications (foot drop/neurogenic bladder);
- Psychological trauma (social isolation/divorce/mental illness);
- Infertility.

The literature on the treatment and management of complications of fistula repairs is extremely scarce and is mostly experience-based. It is impossible to give any specific evidence-based guidance.

4.8.4.2 Management of radiation fistulae

Modified surgical techniques are often required, and indeed, where the same techniques have been applied to both surgical and post-radiation fistulae, the results from the latter have been consistently poorer [716]. Due to the wide field abnormality surrounding many radiotherapy-associated fistulae, approaches include, on the one hand, permanent urinary and/or faecal diversion [716, 717] or alternatively preliminary urinary and faecal diversion, with later undiversion in selected cases following reconstruction. In cases where life expectancy is deemed to be very short, ureteric occlusion might be more appropriate.

4.8.4.3 Management of ureteric fistulae

4.8.4.3.1 General principles

Patients at higher risk of ureteric injury require experienced surgeons who can identify and protect the ureter and its blood supply to prevent injury and also recognise injury promptly when it occurs. Immediate repair of any intra-operative injury should be performed observing the principles of debridement, adequate blood supply and tension-free anastomosis with internal drainage using stents [718]. Delayed presentation of upper tract injury should be suspected in patients whose recovery after relevant abdominal or pelvic surgery is slower than expected, if there is any fluid leak, and if there is any unexpected dilatation of the pelvicalyceal system. Whilst there is no evidence to support the use of one surgical approach over another, there is consensus that repair should adhere to the standard principles of tissue repair and safe anastomosis, and be undertaken by an experienced team. Conservative management is possible with internal or external drainage, endoluminal management using nephrostomy and stenting where available, and early (< two weeks) or delayed (> three months) surgical repair when required [719]. Functional and anatomical imaging should be used to follow up patients after repair to guard against development of ureteric stricture and deterioration in renal function.

4.8.4.3.2 Uretero-vaginal fistulae

Uretero-vaginal fistula occurring in the early post-operative phase predominantly after hysterectomy is the most frequent presentation of UUT fistulae in urological practice. An RCT in 3,141 women undergoing open- or laparoscopic gynaecological surgery found that prophylactic insertion of ureteric stents made no difference to the low risk (1%) of ureteric injury [720].

Endoscopic management is sometimes possible by retrograde stenting, percutaneous nephrostomy and antegrade stenting if there is pelvicalyceal dilatation, or ureteroscopic realignment [721]. However, the long-term success rate is unknown. If endoluminal techniques fail or result in secondary stricture, the abdominal approach to repair is standard and may require end-to-end anastomosis, re-implantation into the bladder using psoas hitch or Boari flap, or replacement with bowel segments with or without reconfiguration. As a last resort, nephrectomy may be considered, particularly in the context of a poorly functioning kidney and an otherwise normal contralateral kidney [722-726].

4.8.4.3.3 Management of urethrovaginal fistulae

4.8.4.3.3.1 Aetiology

Whilst they are rare, most urethrovaginal fistulae in adults have an iatrogenic aetiology. Causes include surgical treatment of SUI with bulking agents or synthetic slings, surgery for urethral diverticulum and genital reconstruction in adults. Irradiation and even conservative treatment of prolapse with pessaries can lead to the formation of fistulae.

4.8.4.3.3.2 Diagnosis

Clinical vaginal examination, including the three-swab test, is often sufficient to diagnose the presence of a urethrovaginal fistula. Urethroscopy and cystoscopy can be performed to assess the extent and location of the fistulae. In cases of difficult diagnosis, VCUG or US can be useful. 3D-MRI or CT scan is becoming utilised more widely to clarify anatomy [727, 728].

4.8.4.3.3.3 Surgical management

Choice of surgery will depend on the size, localisation and aetiology of the fistula and the amount of tissue loss. Principles of reconstruction include identifying the fistula, creation of a plane between vaginal wall and urethra, watertight closure of urethral wall, eventual interposition of tissue, and closure of the vaginal wall.

One case series reports that a vaginal approach yielded a success rate of 70% at first attempt and 92% at second attempt, and that an abdominal approach only leads to a successful closure in 58% of cases [729]. A vaginal approach required less operating time, had less blood loss and a shorter hospitalisation time.

Most authors describe surgical principles that are identical to those of vesico-vaginal fistula repair: primary closure rates of 53-95.4% have been described. A series of 71 women, treated for urethra-vaginal fistula reports 90.1% of fistulae were closed at the first vaginal intervention. Additionally, 7.4% were closed during a second vaginal intervention. Despite successful closure, SUI developed in 52%. The stress incontinent patients were treated with synthetic or autologous slings and nearly 60% became dry and an additional 32% improved. Urethral obstruction occurred in 5.6% and was managed by urethral dilation or urethrotomy [730].

4.8.4.3.3.4 Flaps and neo-urethra

The simplest flap is a vaginal advancement flap to cover the urethral suture line. Labial tissue can be harvested as a pedicled skin flap. This labial skin can be used as a patch to cover the urethral defect, but can also be used to create a tubular neo-urethra [731, 732]. The construction of a neo-urethra has mostly been described in traumatic aetiologies. In some cases a transpubic approach has been used [733]. The numbers of patients reported are small and there are no data on the long-term outcome of fistula closure and continence rates. The underlying bulbocavernosus tissue can be incorporated in the pedicled flap and probably offers a better vascularisation and more bulking to the repair. This could allow a safer placement of a sling afterwards, in those cases where bothersome SUI would occur post-operatively [734, 735].

4.8.4.3.3.5 Martius flap

While in obstetrical fistula repair it was not found to have any benefit, in a large retrospective study in 440 women the labial bulbocavernosus muscle/fat flap by Martius is still considered by some to be an important adjunctive measure in the treatment of GU fistulae where additional bulking with well-vascularised tissue is needed [736]. The series of non-obstetrical aetiology are small and all of them are retrospective. There are no prospective data, nor randomised studies [737]. The indications for Martius flap in the repair of urethro-vaginal fistulae remain unclear.

4.8.4.3.3.6 Rectus muscle flap

Rectus abdominis muscle flaps have been described by some authors [738, 739].

4.8.4.3.3.7 Alternative approaches

An alternative retropubic retro-urethral technique has been described by Koriatim [740]. This approach allows a urethro-vesical flap tube to be fashioned to form a continent neo-urethra.

4.8.4.4 Summary of evidence and recommendations for the management of urinary fistula

Summary of evidence	**LE**
Spontaneous closure of surgical fistulae does occur, and appears more likely for small fistulae although it is not possible to establish the rate with any certainty.	3
There is no evidence that the timing of repair makes a difference to the chances of successful closure of a fistula.	3
There is no high-quality evidence of differing success rates for repair of vesico-vaginal fistulae by vaginal, abdominal, transvesical and transperitoneal approaches.	3
A period of continuous bladder drainage may be crucial to successful fistula repair but there is no high-level evidence to support one regimen over another.	3
A variety of interpositional grafts can be used in either abdominal or vaginal procedures, although there is little evidence to support their use in any specific setting.	3

Post-radiation fistula	
Successful repair of irradiated fistulae may require prior urinary diversion and the use of non-irradiated tissues to effect repair.	3
Ureteric fistula	
Prophylactic ureteric stent insertion does not reduce risk of ureteric injury during gynaecological surgery.	2
Antegrade endoluminal distal ureteric occlusion combined with nephrostomy tube diversion often palliates urinary leakage due to malignant fistula in the terminal phase.	4
Urethro-vaginal fistula	
Urethro-vaginal fistula repair may be complicated by SUI, urethral stricture and urethral shortening which may necessitate long-term follow-up.	3

Recommendations	Strength rating
General	
When reporting on outcomes after fistula repair, authors should make a clear distinction between fistula closure rates and post-operative urinary incontinence (UI) rates and the time at which the follow-up was organised.	Strong
Do not routinely use ureteric stents as prophylaxis against injury during routine gynaecological surgery.	Strong
Suspect ureteric injury or fistula in patients following pelvic surgery if a fluid leak or pelvicalyceal dilatation occurs post-operatively, or if drainage fluid contains high levels of creatinine.	Strong
Use three-dimensional imaging techniques to diagnose and localise urinary fistulae particularly in cases with negative direct visual inspection or cystoscopy.	Weak
Manage upper urinary tract fistulae initially by conservative or endoluminal techniques where such expertise and facilities exist.	Weak
Surgical principles	
Surgeons involved in fistula surgery should have appropriate training, skills, and experience to select an appropriate procedure for each patient.	Weak
Attention should be given as appropriate to skin care, nutrition, rehabilitation, counselling and support prior to, and following, fistula repair.	Weak
Tailor the timing of fistula repair to the individual patient and surgeon requirements once any oedema, inflammation, tissue necrosis, or infection, are resolved.	Weak
Ensure that the bladder is continuously drained following fistula repair until healing is confirmed (expert opinion suggests: 10–14 days for simple and/or postsurgical fistulae; 14–21 days for complex and/or post-radiation fistulae).	Weak
Where urinary and/or faecal diversions are required, avoid using irradiated tissue for repair.	Weak
Use interposition graft when repair of radiation-associated fistulae is undertaken.	Weak
Repair persistent uretero-vaginal fistulae by an abdominal approach using open, laparoscopic or robotic techniques according to availability and competence.	Weak
Urethro-vaginal fistulae should preferably be repaired by a vaginal approach.	Weak

4.9 Urethral diverticulum

A female urethral diverticulum is a sac-like protrusion composed of the entire urethral wall or only by the urethral mucosa, situated between the peri-urethral tissues and the anterior vaginal wall.

4.9.1 Epidemiology, aetiology, pathophysiology

Urethral diverticulum is an uncommon condition with a prevalence estimated to range between 1 and 6%. Amongst women with LUTS attending a tertiary referral centre one study reported a prevalence of up to 10% [741]. However, as many patients are asymptomatic or misdiagnosed, the true incidence is unknown [742-744]. Given the rarity of the condition, most published series are small and single institutional. Urethral diverticulum are thought to arise from repeated obstruction, infection and subsequent rupture of periurethral glands into the urethral lumen, resulting in an epithelialised cavity that communicates with the urethra [742].

Iatrogenic damage to the urethra may also play a role, as up to 20% of women with urethral diverticula are noted to have a history of prior urethral surgery, dilation, or traumatic delivery [742, 745]. Iatrogenic urethral diverticula formation associated with synthetic suburethral sling has also been reported [746-748].

*4.9.2 **Classification***

Table 7: Classification system for female urethral diverticula based on characteristics*

Localisation	Mid-urethral Distal Proximal Full length
Configuration	Single Multiloculated Saddle shaped
Communication	Mid-urethral No communication visualised Distal Proximal
Continence	Stress urinary incontinence Continent Post-void dribble Mixed incontinence

**Limited LNS C3 classification of urethral diverticula [745, 749, 750].*

*4.9.3 **Diagnosis***

The commonly encountered symptoms for urethral diverticulum such as pain, urgency, frequency, recurrent UTIs, vaginal discharge, dyspareunia, voiding difficulties or UI [751], are common to many other LUT dysfunctions. Consequently, there is no pathognomonic cluster of symptoms to identify urethral diverticula. Many patients with urethral diverticula are asymptomatic. However, urethral diverticulum often presents with a palpable urethral mass. It may be possible to express a purulent exudate from the urethra. Occasionally a stone may develop within the diverticulum.

The diagnosis of a urethral diverticulum may be achieved by physical examination, VCUG and MRI. Other investigations include urethrocystoscopy, endocavitary (often transvaginal or sometimes transurethral) pelvic floor US and double balloon urethrography.

No robust diagnostic accuracy studies address the question of the best test to confirm the diagnosis in a woman with a clinical suspicion of urethral diverticulum. However, a case series of 27 patients concluded that endoluminal (vaginal or rectal) MRI has better diagnostic accuracy than VCUG [752] and determines the size and extent of urethral diverticula more accurately. In a case series of 60 subjects, it was reported that the sensitivity, specificity, positive predictive value and negative predictive value of MRI is 100%, 83%, 92% and 100%, respectively [753]. Another case series reported 100% specificity and sensitivity of MRI in 60 patients [754]. However, in a case series of 41 patients, authors reported a 25% discrepancy between MRI and surgical findings [755]. Endoluminal MRI with either a vaginal or rectal coil may provide even better image quality than simple MRI [756].

Magnetic resonance imaging is the gold standard for the diagnosis and planning surgical repair. Magnetic resonance imaging also proved to be useful in diagnosing inflammation or tumour in the diverticulum [757, 758].

Urethrocystoscopy can be used to visualise the ostia of the diverticulum. Knowledge of the ostia's location and number can assist with surgical planning since each of these ostia need to be closed after diverticulectomy. However, given the challenges of urethroscopy in females the ostia is only seen in 42% of cases [751].

If a VCUG is performed antero-posterior and lateral images are required to optimally characterise the configuration of the diverticulum. There is a high risk of false negatives since the ostia of the diverticulum must be patent and the patient must be able to void during the study. In more complex diverticulum where there is septation, the entire diverticula may not be visualised underestimating its complexity or size [759]. The sensitivity of VCUG is 73.5% which is significantly worse than MRI [751].

Ultrasound can be performed transabdominally, transvaginally or transperineally to identify the diverticulum. In particular the transvaginal approach US allows imaging of the urethra from the meatus to the bladder neck in several planes and can identify the number, size, location and contents of the diverticulum. This technique is

challenging and requires a skilled ultrasonographer. In addition, the probe can compress the urethra, causing distortion [759]. A meta-analysis reported that US of any kind had a sensitivity of 82.0% which was inferior to MRI [759]. However a recent publication on translabial US reported a sensitivity of 95% [760]; therefore, this approach may be explored further by researchers in the future.

For patients who cannot have an MRI and the ostia is not seen on cystoscopy, double balloon urethrography can be an option. Modern series have reported a 94.7% sensitivity which is comparable to that of MRI. The technique uses positive pressure to force contrast into the diverticular sac between two balloons; one placed in the bladder and one outside the ostia of the diverticulum. It is technically difficult to achieve a seal sufficient to create a closed urethral space and avoid contrast leaking around the catheter. The procedure can be painful for the patient and carries a risk of UTI. An experienced radiologist is required as well as specialised equipment. Given the current popularity of other imaging modalities many units may not have access to this technique [759].

4.9.3.1 Associated voiding dysfunction

Although the presentation of urethral diverticulum is often non-specific and variable, urethral diverticula can be associated with voiding dysfunction and SUI or UUI.

One recent series reported SUI occurring in 60% of patients with urethral diverticulum [761]. A urethral diverticulum is most often located at the level of the mid-urethra. This location often overlaps with the external sphincter. However urethral diverticulum may also extend proximally toward the bladder neck in the vicinity of the proximal sphincter mechanism. This morphology may, in part, explain the association between urethral diverticulum and SUI with potentially more proximal lesions at risk for post-operative SUI [762].

Urethral diverticulum may also be associated with BOO due to the mass effect of the urethral diverticulum, urinary retention, or urgency and UUI [763]. Pain and dysuria associated with urethral diverticulum may also result in acquired voiding dysfunction.

Pressure flow studies may have a role in the pre-operative assessment of patients with urethral diverticula and coexisting voiding dysfunction or SUI [744, 764-766]. Indeed, urodynamics may evaluate for coexisting detrusor dysfunction or document the presence or absence of SUI or obstruction prior to repair [767, 768]. Urethral pressure profilometry has also been used in the assessment or diagnosis of urethral diverticulum noting a biphasic pattern, or pressure drop at the level of the lesion during the study [764, 766, 769]. Video-urodynamics may be helpful in differentiating SUI from paradoxical UI due to fluid accumulation in the urethral diverticulum. In addition, resting and straining images obtained during fluoroscopic imaging may document an open bladder neck at rest. This may be a consideration in some patients with an extensive urethral diverticulum at the level of the mid-urethra and potential implications for post-operative UI due to compromise of both sphincter mechanisms.

*4.9.4 **Disease management***

For women with minimal symptoms who would prefer to avoid invasive treatment, conservative management can be considered. Patients should be warned of the small risk of cancer (1–6%) within the diverticulum [770, 771].

4.9.4.1 Surgical treatment

No RCTs were found to inform regarding the relative effectiveness of available surgical treatments in a woman who has a bothersome urethral diverticulum. Thorough evaluation of the anatomy of the diverticulum is essential in planning reconstructive surgery.

There are three surgical approaches to diverticulum: marsupialization, endoscopic incision, and curative treatment with diverticulectomy.

Surgical removal is the most commonly reported treatment in contemporary case series. The principles of successful transvaginal diverticulectomy are to: dissect a well vascularised vaginal flap, preserve the periurethral fascia for closure, remove all the diverticular wall, excise the ostia and close the urethra in a watertight fashion, close the incision in a multi-layered fashion with no overlapping suture lines, and preservation or creation of continence.

The decision to use a labial fat pad flap, commonly known as a Martius flap, is variable and used more frequently in the following situations: recurrent cases, large urethral defects or for deficient vaginal flaps for

closure [745, 749] transection of the urethra required for access to a circumferential diverticulum [758] or in the case of complex configuration [763], and if there is a planned future sling procedure required for UI to facilitate the dissection at that time [745].

Marsupialisation involves incision into the mass on the vaginal side to drain the infected contents. The wall is then sutured open with absorbable suture to allow drainage and prevent reaccumulation of infectious materials. This approach leaves the cystic structure in place and can theoretically cause a urethra-vaginal fistula since there is communication with the diverticular ostia, but it is a rapid procedure with little dissection required. This approach has been advocated in the pregnant patient to decompress the diverticulum to allow safe vaginal delivery. A small case series suggests that 75% pregnant women with urethral diverticula managed expectantly end up requiring postpartum surgery [772].

Endoscopic incision is a rarely reported treatment option [773, 774]. This procedure involves finding the narrow neck of the ostia and incising it with a resectoscope. This unroofing of the diverticulum transforms the narrow communication with the urethra that causes symptoms when it gets obstructed into a wide mouthed sac that drains freely.

4.9.4.2 Management of concomitant stress urinary incontinence

Many women present with concomitant SUI and urethral diverticula, and may request both conditions to be simultaneously treated. A meta-analysis reports that diverticulectomy actually cured the SUI even without a concomitant anti-incontinence procedure, but no data regarding symptom severity was given and it could be assumed that many of these cured patients had more minimal UI before surgery [751]. Therefore, additional surgical corrections may be required [762, 774]. However, there is no consensus on appropriate timing of surgical management of these two conditions. Thus, patients with symptomatic, bothersome SUI in association with urethral diverticulum may be offered simultaneous anti-UI surgery. Although historical series have shown good results with concomitant bladder neck suspension [768], more contemporary series have utilised pubovaginal fascial slings in patients with satisfactory outcomes [775-778]. Mid-urethral synthetic slings are not recommended as a concomitant anti-UI procedure at the time of urethral diverticulectomy [779]. Synthetic material adjacent to a fresh suture line following diverticulectomy in the setting of potentially infected urine may place the patient at higher risk for subsequent urethral erosion and vaginal extrusion of the sling material, as well as urethrovaginal fistula formation and foreign body granuloma formation.

Transvaginal urethral diverticulectomy has a high success rate (defined by being dry) of between 84% and 98%, with a re-operation rate of 2–13% after primary repair during a mean follow-up of 12–50 months [742, 745, 762, 780]. The resolution of symptoms after surgery has been reported to reach 68.8% but less than half of studies comment on symptom improvement [781]. One case series reported rates of storage symptoms decreased significantly post-operatively from 60% to 16% following urethral diverticulum surgery [762]. Other series with long-term follow-up, however, have demonstrated rates of post-operative urgency of 54% [782], and *de novo* UUI in 36% of patients [774]. Such symptoms post-operatively may indicate urethral diverticulum persistence, urethral diverticulum recurrence, or *de novo* OAB syndrome or urethral obstruction.

Early common post-operative complications include: UTI (0–39%), *de novo* SUI (3.8–33%), and *de novo* urinary retention (0–9%), especially in the setting of concomitant placement of an autologous pubovaginal sling [742, 745, 762, 780]. Delayed complications such as urethral stricture are reported in 0–5.2% of cases [742, 745, 774, 780]. Urethrovaginal fistula is a devastating complication presenting in 0.9–8.3% of cases [783]. A distal fistula located beyond the sphincteric mechanism can present with split urinary stream or vaginal voiding and may not require repair. However, a fistula located anywhere from the mid-urethra to the bladder neck may result in UI. These patients should undergo repair with consideration of an adjuvant tissue flap, such as a Martius flap, to aid in closure. The timing of the fistula repair is not well defined, with a delay of 3–6 months after the initial repair generally being a good balance between patient discomfort and optimal tissue quality. Rare complications include: distal urethral necrosis, bladder injury, urethral injury, ureteric injury, and vaginal scarring or narrowing with consequent dyspareunia [783].

One case series reported a recurrence rate of 33% in U-shaped and of 60% in circumferential diverticulum within one year [749], Ingber *et al.* found a 10.7% recurrence rate in 122 women undergoing diverticulectomy, with a higher risk of recurrence in those with proximal or multiple diverticula or after previous pelvic surgery [782] or radiation. A recurrent urethral diverticulum following initial successful urethral diverticulectomy may occur as a result of a new infection or traumatic insult such as childbirth, a new urethral diverticulum, or recurrence of the original lesion. Recurrence of urethral diverticulum may be due to incomplete removal of the urethral diverticulum, inadequate closure of the urethra or residual dead space (circumferential diverticula), or

other technical factors. Repeat urethral diverticulectomy surgery represents a unique challenge due to altered anatomy, scarring, and difficulty identifying proper anatomical planes.

Stress UI can be worsened or occur *de novo* after diverticulectomy. This is most likely due to sphincteric damage from the dissection or scarification preventing urethral closure. *De novo* SUI (10.6% of women) seems to be more common in proximal and in large size (> 30 mm) diverticula [762]. However, Lee *et al.* noted at least some *de novo* SUI in 49% of patients following urethral diverticulectomy, the majority of which was minor and did not require additional therapy [784]. Only 10% of these individuals underwent a subsequent SUI operation. Treatment for SUI after a diverticulectomy is not well described in the literature. The most commonly reported surgery is an autologous pubovaginal sling [773] followed by retropubic suspension [774] however there are two cases reported of synthetic mesh sling to treat the SUI without mesh complications [749, 762], but this is certainly controversial.

4.9.4.3 Pathological findings

Most urethral diverticula are lined with squamous cells, urothelium or columnar epithelium [745, 785, 786]. In this meta-analysis there is a high prevalence of chronic or acute inflammation (68.6%) and the most commonly reported lesions are nephrogenic metaplasia which occurs in 8%. Diverticula may undergo neoplastic alterations (6%) including invasive adenocarcinomas [787], followed by squamous cell carcinoma in 0.7%. It is unknown if the diverticulum forms first and then transforms into a malignancy or if the malignancy develops first. These malignancies are treated in a similar fashion to urethral cancer in the female.

*4.9.5 **Summary of evidence and recommendations for urethral diverticulum***

Summary of evidence	**LE**
Magnetic resonance imaging has the best sensitivity and specificity for the diagnosis of urethral diverticula.	3
Surgical removal of symptomatic urethral diverticula provides good long-term results; however, women should be counselled of the risk of recurrence and *de novo* SUI.	3

Recommendations	**Strength rating**
Offer surgical removal of symptomatic urethral diverticula.	Weak
If conservative treatment is adopted, warn patients of the small (1–6%) risk of cancer developing within the diverticulum.	Weak
Carefully question and investigate patients for co-existing voiding dysfunction and urinary incontinence.	Strong
Following appropriate counselling, address bothersome stress urinary incontinence at the time of urethral diverticulectomy with concomitant non-synthetic sling.	Weak
Counsel patients regarding the possibility of *de novo* or persistent lower urinary tract symptoms including urinary incontinence despite technically successful urethral diverticulectomy.	Strong

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6. CONFLICT OF INTEREST

All members of the Non-neurogenic Female LUTS Panel have provided disclosure statements of all relationships that they have that might be perceived as a potential source of a conflict of interest. This information is publically accessible through the European Association of Urology website: https://uroweb.org/guideline/non-neurogenic-female-luts/.

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