Maturitas xxx (xxxx) xxx

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Management of urinary incontinence in postmenopausal women: An EMAS clinical guide

Eleonora Russo [a], Marta Caretto [a], Andrea Giannini [a], Johannes Bitzer [b], Antonio Cano [c], Iuliana Ceausu [d], Peter Chedraui [e], Fatih Durmusoglu [f], Risto Erkkola [g], Dimitrios G. Goulis [h], Ludwig Kiesel [i], Irene Lambrinoudaki [j], Angelica Lindén Hirschberg [k], Patrice Lopes [l], Amos Pines [m], Margaret Rees [n], Mick van Trotsenburg [o], Tommaso Simoncini [a,*]

[a] Department of Clinical and Experimental Medicine, University of Pisa, Via Roma, 67, 56100, Pisa, Italy
[b] Department of Obstetrics and Gynecology, University Hospital, Basel, Switzerland
[c] Department of Pediatrics, Obstetrics and Gynecology, University of Valencia and INCLIVA, Valencia, Spain
[d] Department of Obstetrics and Gynecology I, "Dr. I. Cantacuzino" Hospital, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[e] Institute of Biomedicine, Research Area for Women's Health, Facultad de Ciencias Médicas, Universidad Católica de Santiago de Guayaquil, Guayaquil, Ecuador
[f] İstanbul Medipol International School of Medicine, Istanbul, Turkey
[g] Department of Obstetrics and Gynecology, University Central Hospital, Turku, Finland
[h] Unit of Reproductive Endocrinology, First Department of Obstetrics and Gynecology, Medical School, Aristotle University of Thessaloniki, Greece
[i] Department of Gynecology and Obstetrics, University of Münster, Münster, Germany
[j] Second Department of Obstetrics and Gynecology, National and Kapodistrian University of Athens, Greece
[k] Department of Women's and Children's Health, Karolinska Institutet and Department of Gynecology and Reproductive Medicine, Karolinska University Hospital, Stockholm, Sweden
[l] Nantes, France Polyclinique de l'Atlantique Saint Herblain. F 44819 St Herblain France, Université de Nantes F, 44093, Nantes, Cedex, France
[m] Sackler Faculty of Medicine, Tel-Aviv University, Israel
[n] Women's Centre, John Radcliffe Hospital, Oxford, OX3 9DU, UK
[o] Department of Obstetrics and Gynecology, University Hospital St. Poelten, Lilienfeld, Austria

ARTICLE INFO

Keywords:
Urinary incontinence
Aging
Menopause
Estrogens
Midurethral slings

ABSTRACT

Introduction: The prevalence of urinary incontinence and of other lower urinary tract symptoms increases after the menopause and affects between 38 % and 55 % of women aged over 60 years. While urinary incontinence has a profound impact on quality of life, few affected women seek care.
Aim: The aim of this clinical guide is to provide an evidence-based approach to the management of urinary incontinence in postmenopausal women.
Materials and methods: Literature review and consensus of expert opinion.
Summary recommendations: Healthcare professionals should consider urinary incontinence a clinical priority and develop appropriate diagnostic skills. They should be able to identify and manage any relevant modifiable factors that could alleviate the condition. A wide range of treatment options is available. First-line management includes lifestyle and behavioral modification, pelvic floor exercises and bladder training. Estrogens and other pharmacological interventions are helpful in the treatment of urgency incontinence that does not respond to conservative measures. Third-line therapies (e.g. sacral neuromodulation, intravesical onabotulinum toxin-A injections and posterior tibial nerve stimulation) are useful in selected patients with refractory urge incontinence. Surgery should be considered in postmenopausal women with stress incontinence. Midurethral slings, including retropubic and transobturator approaches, are safe and effective and should be offered.

Abbreviations: UI, urinary incontinence; SUI, stress urinary incontinence; UUI, urge urinary incontinence; MUI, mixed urinary incontinence; VVA, vulvovaginal atrophy; GSM, genitourinary syndrome of menopause.

* Corresponding author at: Department of Clinical and Experimental Medicine, Division of Obstetrics and Gynecology, University of Pisa, Via Roma, 67, 56126, Pisa, Italy.
E-mail address: tommaso.simoncini@med.unipi.it (T. Simoncini).

https://doi.org/10.1016/j.maturitas.2020.09.005
Received 21 September 2020; Received in revised form 21 September 2020; Accepted 21 September 2020

1. Introduction

1.1. Definitions and epidemiology

Urinary incontinence (UI) is defined as a "complaint of involuntary loss of urine" [1]. The prevalence of the condition increases with age, and it is reported to affect 58%–84% of elderly women [2]. The reported prevalence of UI varies widely because of the different definitions and assessment tools for diagnosis employed [3]. The general prevalence is reported to be between 38 % and 55 % in women over 60 years [4]. Despite this high prevalence, UI remains underdiagnosed and undertreated. Up to half of women may not report incontinence to their healthcare provider and this may be due to embarrassment or to the belief that UI is a normal part of aging.

Several types of incontinence exist, and a simplified clinical classification can be found in Table 1. Stress urinary incontinence (SUI) is defined as involuntary loss of urine with increases in abdominal pressure such as during exercise or coughing [1]. The main etiology is a poorly functioning urethral closure mechanism and a loss of anatomic urethral support. Urge urinary incontinence (UUI) is characterized by a sudden compelling desire to pass urine that is difficult to postpone [1]. In neurologically intact women, UUI is an idiopathic condition. However, it is common in women with systemic neurologic disorders (e.g. Parkinson disease, multiple sclerosis, pelvic or spinal nerve injury). UUI is part of a broader entity known as overactive bladder syndrome, which is defined as urinary urgency with or without urgency incontinence, frequently associated with increased daytime frequency and nocturia, in the absence of proven urinary infection or other disease [5]. The symptoms of overactive bladder are due to involuntary contractions of the bladder detrusor muscle during the filling phase of the micturition cycle. These involuntary contractions are indicated as "detrusor overactivity" and are related to acetylcholine-induced stimulation of bladder muscarinic receptors [6]. Notably, while overactive bladder is a clinical diagnosis, detrusor overactivity is identified with urodynamic assessment. Many women with incontinence experience coexisting stress and urgency symptoms, called mixed urinary incontinence (MUI).

The prevalence rates of SUI, UUI and MUI in developed countries are 12.6 %, 5.3 % and 9.1 %, respectively [2]. The prevalence of overactive bladder in women increases with age, from 2% up to 53 %, and has been estimated to be 19.1 % for women over 65 years of age [3]. Age, body mass index, parity and mode of delivery are the only established risk factors for female UI at midlife. The EPINCONT study shows a distinct peak in incontinence around the time of menopause, suggesting that the menopause-associated anatomical and functional changes of the lower genitourinary tract are important contributors to all forms of UI. Thus, menopause specialists should be skilled in identifying these changes so that they are able to enact timely and personalized interventions.

These guidelines are written for healthcare professionals and include clinical, evidence-based recommendations on the care of postmenopausal women with non-neurogenic UI.

Table 1
Urinary incontinence: simplified clinical classification and pathophysiology.

Urinary incontinence type	Clinical definition	Main pathophysiological mechanism
Stress urinary incontinence (SUI)	Involuntary loss of urine with increases in abdominal pressure such as during exercise or coughing	Poorly functioning urethral closure mechanism and a loss of anatomic urethral support
Urge urinary incontinence (UUI)	Urinary incontinence characterized by a sudden compelling desire to pass urine that is difficult to postpone	Involuntary contractions of the bladder detrusor muscle during the filling phase of the micturition cycle
Mixed urinary incontinence	The presence of both stress and urge incontinence	The presence of concomitant defective urethral closure or support mechanisms and of detrusor overactivity

1.2. Age- and menopause-related modifications of the lower genitourinary tract

Menopause and aging are strongly associated with the emergence or worsening of lower urinary tract dysfunction [7,8]. The lower urinary tract shares embryological origins with the female reproductive system and it is thus sensitive to the effects of steroid hormones [9]. Sex steroid hormones have an important role in the regulation of lower urinary tract function and estrogen, androgen and progesterone receptors are expressed throughout the lower urinary tract, in particular in structures directly related to urinary continence such as the urethra, the vagina and the pelvic floor muscles, fascia and ligaments [8,10,11].

The role of menopause can be partially explained by the effect of estrogen withdrawal on collagen remodeling with the consequent negative impact on urethral mobility and urethral closure mechanisms, as well as with an increase of collagen in the detrusor smooth muscle, which may aggravate overactive bladder symptoms [12,13].

The frequent report of lower urinary tract dysfunction at the menopause supports the recent broader definition of the genitourinary syndrome of menopause (GSM). It unifies symptoms and signs associated with vulvovaginal atrophy (VVA) with lower urinary tract dysfunction [14,15].

Despite this, the correlation between sex steroids and UI is controversial. A clear association between postmenopausal estrogen withdrawal and the onset of SUI has not been demonstrated, and high-quality evidence is lacking. Some data suggest a relationship between postmenopausal endogenous sex hormone changes and the presence of SUI in women not taking menopausal hormone therapy [16]. There is more evidence to show an association between estrogen deficiency and overactive bladder after the menopause [17].

On the other hand, it is difficult to differentiate the specific contribution of estrogen withdrawal from that of the aging process *per se*. The role of the natural aging process in the development of lower urinary tract dysfunction is controversial. Whether it is an inevitable part of the aging process or whether it reflects pathology is uncertain [18]. Furthermore, it is unclear what regions of the lower urinary tract are most affected by the aging process: the contracting detrusor, the outflow tract, bladder-filling sensation mechanisms, or the central and peripheral control of lower urinary tract function. The known cumulative changes related to the aging process that can exert a long-term impact on the urinary tract are inflammation and progressive ischemia in the lower urinary tract or in its nerve supply [19–21]. These multiple causes should be considered in postmenopausal women with GSM and lower urinary tract dysfunction, particularly when selecting therapeutic strategies.

1.3. The role of the microbiome in postmenopausal women

Declining estrogen levels at the menopause affects the vaginal microbiome. It is well established that sex hormones play a role in regulating the vaginal and intestinal microbiota and that the microbiota itself may modify mucosal estrogen levels [22]. Estrogen contributes to vaginal epithelium maturation through glycogen deposition. Glycogen is metabolized by resident bacterial communities to produce organic acids (lactate) which are thought to protect the integrity of the genital tract and reduce the risk of infections [23,24]. A recent study on the composition of the vaginal microbiota in pre-, peri- and postmenopausal women found significant associations between vaginal bacterial composition with both menopause stage and signs of vaginal atrophy [25].

However, whether sex hormones affect the urobiome in the same manner as the vaginal microbiome needs further investigation. Results from a recent cross-sectional study support this hypothesis. It found that

urinary microbial diversity was higher in postmenopausal women not taking menopausal hormone therapy than in premenopausal women [26,27]. The inter-relationship between microbial presence in the bladder and lower urinary tract symptoms is unclear [28]. However, growing evidence suggests that urinary microbiota may play a role in certain urinary disorders such as UUI and may alter the efficacy of UUI treatments in women [29–32].

2. Diagnosis and assessment of urinary incontinence

After the menopause, different types of incontinence often coexist. Thus, specific attention should be devoted to characterizing the type of incontinence and the presence of comorbidities. The classification of UI into stress, urgency or mixed is essentially clinical. General history should include questions that can help to establish the predominant type of incontinence and the association with voiding and storage symptoms. Further questioning on frequency and severity of the symptoms is essential for treatment planning and to counsel women. Information on the type and size of diapers along with the frequency of pad replacement is helpful to quantify the leakage. In the presence of MUI, assessment of which component is the most bothersome or occurs more frequently is key to appropriate clinical management.

Potential reversible causes should be assessed and treated. These include urinary tract infections, excessive fluid intake, medications that may worsen UI (such as diuretics, alpha blockers, ACE inhibitors) and voiding dysfunctions. Voiding pattern should be documented. The frequency of urination, both day and night, should be assessed [33]. Urinalysis should be used to identify urinary tract infections, glycosuria or hematuria that may be associated with urinary incontinence. A written voiding diary can provide information about potential modifiable factors associated with incontinence episodes. Post-void urinary residue assessment is recommended when pelvic organ prolapse is present or when the patient reports the sensation of incomplete or unsatisfactory voiding. Assessment of bladder emptying by measuring post-void residual volume is also recommended when SUI surgery is planned: up to one-third of total voided volume is considered normal [34].

Other reversible comorbidities such as obesity, constipation and depression should be evaluated and treated. However, the presence of any of these conditions should not be considered a reason to postpone or avoid incontinence treatment. Pelvic examination should assess the presence of vulvovaginal atrophy (VVA), pelvic floor muscle abnormality and pelvic organ prolapse. Pelvic floor muscle integrity and function should be evaluated to identify women who are unable to correctly contract their pelvic floor muscles. These patients can benefit from supervised pelvic floor muscle training.

The clinical workup of UI should identify women who need specialist referral. When the diagnosis is unclear or when conservative measures fail to improve symptoms, timely referral to a specialist is mandatory so to avoid unwanted delays in treatment. Referrals should be undertaken in accordance with local care pathways. The presence of hematuria, pain, recurrent urinary tract infections, previous oncological or pelvic floor reconstructive surgery or radiotherapy, constant leakage suggesting fistula and detection of clinically relevant voiding dysfunctions are the main reasons for specialist referral [33].

More sophisticated tests such as urodynamic studies or urethrocystoscopy are used when specific information about bladder and urethral physiology are needed to better define the type of UI or to plan treatment. At present urodynamic assessment is not recommended in the evaluation of uncomplicated urinary incontinence or before surgical treatment for uncomplicated SUI [35]. However, after the menopause, urodynamic studies are often required to evaluate bladder or urethral function and to plan treatment options [36].

3. Management of incontinence

Urinary incontinence can be managed successfully in primary care for most women, but there may be significant differences in management and referral care pathways across local healthcare systems. Variables that should be considered in treatment selection include: which type of UI is present, the woman's goals and expectations, and treatment-related risks or adverse effects. It is important that women are fully aware of the benefits and risks and side-effects of all treatment options. Some women prefer to try all conservative options before moving to more invasive treatments. Others may prioritize expediency or efficacy, and so more readily accept the risks of surgery or of other more invasive approaches.

3.1. Conservative management

Conservative interventions include lifestyle interventions, behavioral therapies, including bladder training, physical therapies such as pelvic floor muscle training with or without biofeedback, electrical or magnetic stimulation and voiding pattern modification.

3.1.1. Lifestyle interventions and behavioral therapies

Initial management of urinary incontinence can begin with a non-invasive approach. Lifestyle modifications include smoking cessation, weight loss, management of constipation, timed voiding during the day, fluid intake management, and reduction in consumption of caffeine and alcohol [37–39]. Timed voiding and fluid restriction are effective first-line strategies, especially for women with UUI [40,41].

Bladder training consists of patient education aimed at correcting frequent urination, improving bladder control, prolonging voiding intervals, increasing bladder capacity, reducing the number of incontinence episodes, and ultimately regaining confidence in controlling bladder function. Bladder training aiming to decrease voiding frequency to every two to three hours is useful in women with UUI or MUI; however, its effectiveness diminishes after treatment cessation [42].

3.1.2. Pelvic floor muscle training

Pelvic floor muscle training is a supervised treatment that involves exercises to increase awareness of and strengthen the pelvic floor muscles. The main aim is to improve pelvic floor muscle function in terms of strength, endurance and co-ordination.

Through pelvic floor muscle training, a woman can improve muscular support of the bladder neck and the proximal urethra before and during an increase in intra-abdominal pressure, thus preventing stress-associated urine leakage [43]. In the context of UUI, pelvic floor muscle training can provide the ability to inhibit detrusor contractions by repeated and conscious muscle contractions [44]. However, the timing, number, intensity and duration of pelvic floor muscle contractions considered sufficient to reduce detrusor contraction are undetermined [45].

Other treatments can be used in combination with pelvic floor muscle training. However, a recent review of 13 trials evaluating a combination of pelvic floor muscle training and another active treatment to treat all types of urine leakage concluded that there was insufficient evidence to say whether or not the addition of pelvic floor muscle training to another active treatment improves either UI or quality of life when compared with the same active treatment alone [46].

3.2. Medical interventions

3.2.1. Pharmacological approaches

The main drug strategies for UI consist of menopausal hormone therapy, drugs targeting UUI, drugs targeting SUI and drugs with a balanced activity over SUI and UUI. Healthcare professionals should be familiar with all these options and with their specific benefit/risk profiles, so to be able to personalize their approach.

3.2.1.1. Estrogens and selective estrogen receptor modulators. Estrogens have been used to treat incontinence in postmenopausal women for many years, either alone or in combination with other drugs (such as anticholinergic agents) and there is evidence that urinary incontinence may improve with local estrogen treatment [47–50]. There is insufficient high-quality data to support the use of vaginal estrogens for SUI after the menopause. However, the evidence regarding local estrogens and overactive bladder in postmenopausal women is robust [7]. Local estrogen therapy improves voiding function and decreases the risk of developing overactive bladder symptoms [51]. The most recent meta-analysis supports the use of local estrogen in the treatment of UUI and bladder overactivity with a safe and effective profile [52].

Vaginal estrogens cause changes in autonomic and sensory vaginal innervation and may decrease urothelial damage, inflammatory cell infiltration and muscular atrophy [53]. New non-genomic targets for estrogens are under study. One of the most relevant are the voltage-gated big potassium or BK channels. These channels regulate human detrusor smooth muscle function. Recent data suggest a possible role of estradiol in the activation of BK channels in human detrusor smooth muscle cells whereby it decreases excitability and contractility [54].

A recent meta-analysis on the effect of local estrogen treatment for UI and overactive bladder shows changes in subjective and urodynamic variables in favor of vaginal estrogens compared with placebo. No obvious differences in efficacy were found for the combined use of anticholinergics plus local estrogen [55,56]. Thus, there is robust evidence that urinary incontinence is improved with local estrogen treatment after the menopause.

Surprisingly, systemic menopausal hormone therapy seems to worsen urinary incontinence. However, the evidence base consists mainly of large epidemiological studies primarily investigating the use of systemic menopausal hormone therapy in the prevention of cardiovascular disease and osteoporosis, with UI being investigated as a secondary outcome [57–59]. In the randomized Women's Health Initiative (WHI) trial, continent women receiving estrogen, with or without a progestogen, were approximately twice as likely to have developed SUI at 1 year compared with women receiving placebo [58,60]. However, the data regarding incontinence represents a sub-group post-hoc analysis and the instruments used to diagnose incontinence were not designed to assess urinary incontinence type or severity. Therefore, these data need to be interpreted with caution. To date, there is no evidence for the efficacy of systemic estrogen treatment for any form of incontinence.

Preliminary evidence suggests that the selective estrogen receptor modulator ospemifene may have a role in decreasing bladder overactivity in women with postmenopausal VVA [61,62]. A retrospective series of patients with VVA and concomitant overactive bladder symptoms and a more recent prospective study of postmenopausal women with refractory bladder overactivity suggest that ospemifene may decrease urgency. However, the studies are limited by their small sample sizes and further research is needed [63,64].

3.2.1.2. Non-estrogen targeted pharmacological therapies

3.2.1.2.1. Drug treatments for UUI and overactive bladder. Anticholinergic drugs and mirabegron (a beta-3 agonist) are the core pharmacological treatments of UUI.

Anticholinergics are used as second-line treatment for UUI and bladder overactivity. Anticholinergic drugs differ in muscarinic receptor affinity, pharmacokinetic properties and formulation. There are six FDA-approved medications for UUI (darifenacin, oxybutynin, fesoterodine, solifenacin, tolterodine, trospium). These medications block muscarinic receptors in the smooth muscle of the bladder, thereby inhibiting detrusor contraction. Anticholinergics are associated with a moderate improvement in urgency and frequency in women with UUI. Several studies show superiority compared with placebo but there is limited evidence that any anticholinergic drug is superior to another for cure or improvement of UUI [65,66]. Discontinuation because of adverse effects such as dry mouth, constipation, blurred vision or fatigue is frequent. Contraindications to anticholinergic medications include untreated narrow-angle glaucoma and cardiac arrhythmias. A recent longitudinal cohort study showed a risk of deterioration in cognitive function and brain atrophy with prolonged use of anticholinergics, particularly in the elderly [67].

A beta-3 adrenergic agonist (mirabegron) is also available. Stimulation of beta-3 adrenergic receptors stimulates relaxation of bladder smooth muscle, with a consequent increase in urine storage capacity. Mirabegron has resulted in a significant reduction of UUI episodes compared with placebo in several trials [68,69]. The most common adverse events of mirabegron are hypertension, nasopharyngitis and urinary tract infection. In general, the cardiovascular safety of mirabegron is comparable with that of anticholinergics. However, mirabegron should be not offered to patients with uncontrolled hypertension.

3.2.1.2.2. Combining pharmacological therapies. A tailored approach to optimize the therapeutic widow and to minimize side-effects is often required, particularly in elderly women. Thus, different therapeutic approaches can be combined to decrease the dose of each compound or to achieve a synergistic effect, enhancing efficacy and decreasing adverse effects.

Evidence regarding the synergistic use of vaginal estrogen therapy along with anticholinergics in the management of postmenopausal women with overactive bladder is contradictory [70,71]. The combined use of anticholinergics and mirabegron may provide synergistic effects in women who have an insufficient response to monotherapy. A randomized controlled trial in patients who had inadequate response to anticholinergic monotherapy demonstrated an improvement in UI symptoms with combination treatment with mirabegron as compared with dose escalation of anticholinergics [72].

Pharmacological therapy should be considered in patients with UI for whom conservative management has failed. Combination therapy should be considered for UI that is refractory to initial drug treatment. Extended-release formulations and combination therapy should be considered whenever possible in order to reduce adverse effects.

3.2.1.2.3. Treatment of refractory UUI and overactive bladder. There are 3 FDA-approved treatments for women with persistent urgency incontinence symptoms or intolerance to medications. All of these treatments are based on changes in neural control.

Onabotulinum toxin A (onabotA, 100 UI) blocks the presynaptic release of acetylcholine, thus decreasing muscarinic receptor activation and detrusor contraction. The drug is injected into the bladder through a cystoscope with local anesthetic in an office setting. Onabotulinum toxin A has been licensed in Europe to treat overactive bladder with persistent or refractory UUI since 2011. Treatment is effective in approximately 65 % of patients for approximately 6–12 months [73,74]. The most important adverse events are urinary tract infections and an increase in post-void urinary residue that may require temporary intermittent catheterization. Women selected for this option must therefore be willing and able to perform clean self-catheterization.

Sacral neuromodulation is an outpatient surgical procedure in which sacral nerve stimulation occurs through electrodes placed in the S3 foramen. When a short-term test has proved the treatment to be effective for the individual, a permanent external stimulator can be implanted. After implantation, approximately 60%–90% of women report improvement and 30%–50% report cure [75].

Posterior tibial nerve stimulation is an office procedure consisting of 12 weekly 30-minute sessions. A small acupuncture needle is placed posterior and superior to the medial malleolus to stimulate the posterior tibial nerve peripherally and to modulate the sacral nerve plexus through the S2-S4 nerves. The exact mechanism of action of posterior tibial nerve stimulation on bladder function is unclear but it is likely mediated through the retrograde stimulation of the sacral nerve plexus. Systematic reviews of randomized trials and both retrospective and

prospective observational studies report success rates of 54–93 %, with low rates of transient local adverse events and efficacy similar to that of anticholinergic medications [76,77].

At present, the literature suggests that the main mechanism of action of neuromodulation is the plastic reorganization of the cortical network triggered by peripheral neurostimulation [78,79]. All these treatments are effective for selected patients and should be offered to post-menopausal women with UUI that is refractory to behavioral and pharmacological therapy.

3.2.2. Laser treatment

Laser therapy is approved as a non-invasive treatment for VVA and is currently being tested for its potential role in alleviating the symptoms of mild pelvic organ prolapse and urinary incontinence.

While claims regarding these potential applications of lasers are growing, the histological effects on the vaginal wall remain unclear. Furthermore, no effects on surgical dissection or on reconstructive pelvic or anti-incontinence surgery have been demonstrated so far. Laser energy seems to normalize the cycle of collagen formation and breakdown. The photo-thermal effect of a laser beam causes the shrinkage of mucosal tissues and induces the formation of new collagen fibers [80,81].

The available evidence suggests that laser therapy is an effective non-hormonal option for the treatment of VVA. However, its long-term efficacy and safety need to be established [82–84]. The role of laser therapy in the management of UI remains to be defined. Laser energy has been proposed for the management of mild to moderate SUI. The available data comprise only short-term observational studies without a control or placebo group. In these trials the cure rate of SUI after a laser procedure was reported to be between 62 % and 78 % [85–87]. A recent review summarizing the evidence on the risks and benefits of laser therapy for SUI concluded that, despite the short-term data suggesting a beneficial effect, there is still insufficient evidence to offer it as an alternative over the gold standard approaches (pelvic floor muscle training, midurethral slings) [88].

Thus, laser technology may hold promise for the future treatment of lower urinary tract symptoms in selected women with GSM. However, well-designed randomized trials are needed and data on long-term efficacy and safety should be accrued before this technique is used extensively for the treatment of urinary incontinence or pelvic organ prolapse.

3.2.3. Surgical approaches

Patients whose SUI symptoms persist despite conservative measures may be candidates for surgery. In surgical planning, it is important to consider that postmenopausal women may be at a different baseline compared with their younger counterparts, in that urethral and voiding function may be poorer and concomitant urgency may be more common. Surgical options include mid-urethral slings, urethral bulking injections and retropubic suspensions. Overall, surgery is highly effective, with median cure rates of 84.4 % [89].

3.2.3.1. Mid-urethral slings. The most commonly adopted surgical procedure is the placement of a mid-urethral sling, owing to evidence of good long-term efficacy and the minimally invasive approach used. The synthetic sling is inserted with either a retropubic or a transobturator approach and this is usually performed in an outpatient setting. The documented long-term efficacy ranges between 42 % and 92 %, with low rates of complications [90].

Recently, concerns have been raised about the use of synthetic meshes for the transvaginal treatment of pelvic organ prolapse. This is primarily due to the risk of complications, including mesh exposure/erosion, dyspareunia, infections, and pain. The FDA has issued a series of statements concluding that serious complications associated with transvaginal mesh for pelvic organ prolapse repair are not uncommon. However, the FDA emphasized that there are no data to recommend against using mid-urethral slings to treat SUI.

The Trial of Mid-Urethral Slings, a multicenter randomized trial of 597 women comparing retropubic versus transobturator slings with a medium follow-up of two years, showed equivalent subjective and objective cure rates between the two approaches. A higher rate of bladder perforation and voiding dysfunction was found in the retropubic group and more neurologic symptoms (leg weakness or groin numbness) in the transobturator group [91].

A recent meta-analysis confirmed the superiority of mid-urethral slings over other surgical approaches for the treatment of primary female SUI. The comparison of insertion by the retropubic and transobturator routes showed a higher objective cure rate in favor of the retropubic slings but at the cost of higher risks of intraoperative complications and voiding symptoms [92]. The available long-term longitudinal data show a 90 % objective cure rate and a 77 % subjective cure rate, with no long-term adverse effects after 10 years of follow-up for both approaches [93].

In the interest of minimizing invasiveness and operative time, and because of the potential for fewer complications, single-incision mini-slings have gained popularity. However, preliminary studies suggest that mini-slings have lower subjective and objective cure rates and higher reoperation rates than traditional mid-urethral slings [92]. To date, level 1 data are still needed to compare the efficacy of mini-slings with that of retropubic and transobturator slings.

Given the similar efficacy and safety, the choice of sling can be based on adverse events of concern to the patient. Risks of mid-urethral slings include bleeding, pain, infection, de novo urgency, urinary retention, and failure of treatment.

In postmenopausal women, voiding dysfunction can follow the insertion of a mid-urethral sling, in the form of either persistence of an urgency that preceded sling placement or as a de novo urgency. Causes of de novo urgency include urinary tract infection, obstruction and urinary tract perforation; de novo urgency can also be idiopathic. In patients in whom there is no documented infection or when established treatments for overactive bladder do not alleviate symptoms, obstruction or urinary tract perforation should be investigated.

3.2.3.2. Urethral bulking injections. Women with SUI can undergo injection of urethral bulking agents. This minimally invasive, well-tolerated and simple procedure can be performed in an outpatient setting. The bulking material is injected under the urethral mucosal layer to increase outflow resistance. High-quality multicenter randomized trials are lacking, but systematic reviews suggest lower success rates compared with sling procedures and that benefits are short-term. Cure rates with injectable bulking agents range from 24.8 % to 36.9 % of women at 12-month follow-up [94]. At present, urethral bulking agents should be not offered as first-line treatment, particularly in patients desiring a long-term solution for SUI. Urethral bulking agents could be considered in specific postmenopausal populations such as women with recurrent or persistent SUI or in the elderly, for whom a minimally invasive approach is preferred.

3.2.3.3. Retropubic suspension. Historically, the standard surgery for stress incontinence included retropubic urethropexy (Burch colposuspension) or a pubovaginal sling. The Burch colposuspension involves elevating the anterior vaginal wall to the ileo-pectineal ligament using either laparotomy or laparoscopy [95]. Laparoscopic colposuspension shows comparable subjective and objective outcome to open colposuspension in the short to medium term [96]. Laparoscopic colposuspension can be recommended for the surgical treatment of SUI in women by surgeons with appropriate training and expertise and can be an alternative for those women for whom a mid-urethral sling cannot be used.

The autologous sling procedure requires picking a strip of rectus

fascia, placing it transvaginally through the retropubic space, and securing it superiorly to the rectus fascia.

A multicenter randomized controlled trial of these two procedures in 655 women showed similar success rates (66 % vs 49 %; P < .001), with higher voiding dysfunction rates for the pubovaginal sling compared with the Burch colposuspension [97].

4. Future directions

The prevention of lower urinary tract symptoms, particularly in selected populations such as postmenopausal or elderly women, is an exciting area of research that has the potential to reduce the burden of urinary incontinence. After the menopause, several factors contribute to lower urinary tract symptoms and the therapeutic approach to conditions such as UI is challenging and, in some cases, disappointing. Urinary biomarkers are an ongoing area of research, and several clinical trials are underway to identify the role of urinary nerve growth factor, prostaglandin E2, ATP and others as potential biomarkers for overactive bladder syndrome so as to possibly identify at risk-women or to predict treatment response. New alternatives for treatment of lower urinary tract dysfunction are under study. In particular, potentially useful new therapeutic molecular targets (such as adenosine A1 receptor and transforming growth factor beta pathway modulators) have been identified. They may lead to new drugs affecting different levels of the micturition reflex. These new approaches offer a broader set of molecular targets to increase the therapeutic armamentarium.

5. Conclusions

Urinary incontinence is common in women at midlife and beyond. Incontinence causes embarrassment and depression and limits activities and social interactions. Many effective treatment options exist. Healthcare professionals are in a key position to assess and manage the problem. Successful treatment depends on accurate diagnosis of the type of incontinence, identification and treatment of any modifiable contributing factors and a personalized therapeutic approach. Specialist referral is mandatory for the management of complex cases. Effective and personalized care of urinary incontinence should be a healthcare priority so that women do not suffer unnecessarily from this common debilitating condition.

Contributors

Eleonora Russo, Marta Caretto, Andrea Giannini and Tommaso Simoncini prepared the initial draft, which was circulated to all other named authors – EMAS board members – for comments and approval; production was coordinated by Irene Lambrinoudaki and Margaret Rees.

Conflict of interest

1 Eleonora Russo: None declared.
2 Marta Caretto: None declared
3 Andrea Giannini: None declared.
4 Johannes Bitzer in the past 3 years has served on advisory boards of Bayer AG, Merck, MSD, Teva, Theramex, Mithra, Actavis, Ava, Natural cycles, Böhringer Ingelheim, Effik, Lilly, Exeltis, Vifor, Libbs, Gedeon Richter and HRA; and has given invited lectures and received honoraria by Bayer Pharma AG, Merck, Johnson and Johnson, Teva, Mylan, Allergan, Abbott, Lilly, Pfizer, Exeltis, Libbs, HRA and Pierre Fabre.
5 Antonio Cano has received in the past three years consulting fees from Pierre-Fabre Iberica and Mitsubishi Tanabe Pharma; and speakers' honoraria from Shionogi.
6 Iuliana Ceausu: None declared.
7 Peter Chedraui: None declared.
8 Fatih Durmusoglu: None declared.
9 Risto Erkkola: None declared.
10 Dimitrios G. Goulis: None declared.
11 Ludwig Kiesel has received in the past year consulting fees from AstraZeneca, Novartis, Gedeon Richter, Palleos Healthcare, Roche; and speakers' honoraria from: AstraZeneca, Novartis, Gedeon Richter and Roche.
12 Irene Lambrinoudaki: None declared.
13 Angelica Lindén Hirschberg: None declared.
14 Patrice Lopes: None declared.
15 Amos Pines: None declared.
16 Margaret Rees has received consulting fees in the past three years from Sojournix, Inc..
17 Mick van Trotsenburg: None declared.
18 Tommaso Simoncini: has received in the past three years consulting fees from Mitsubishi Tanabe, Sojournix, Estetra and Actavis and speakers' honoraria from: Shionogi and Intuitive Surgical.

Funding

No funding was received for the preparation of this clinical guide.

Provenance and peer review

This article is an EMAS clinical guide and was not externally peer reviewed.

Acknowledgements

Peter Chedraui is supported by the Sistema de Investigación y Desarrollo (SINDE) and the Vice-Rectorado de Investigación & Postgrado (VRIP) of the Universidad Católica de Santiago de Guayaquil, Guayaquil, Ecuador, through grant No. SIU-318-853-2014 (The Omega II, Women's Health Project). Neither SINDE nor VRIP have had involvement in the writing of this clinical guide.

References

[1] B.T. Haylen, D. de Ridder, R.M. Freeman, S.E. Swift, B. Berghmans, J. Lee, A. Monga, E. Petri, D.E. Rizk, P.K. Sand, G.N. Schaer, An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction, Int. Urogynecol. J. 21 (2010) 5–26, https://doi.org/10.1007/s00192-009-0976-9.
[2] H. Mostafaei, H. Sadeghi-Bazargani, S. Hajebrahimi, H. Salehi-Pourmehr, M. Ghojazadeh, R. Onur, R.T. Al Mousa, M. Oelke, Prevalence of female urinary incontinence in the developing world: a systematic review and meta-analysis—a Report from the Developing World Committee of the International Continence Society and Iranian Research Center for Evidence Based Medicine, Neurourol. Urodyn. 39 (2020) 1063–1086, https://doi.org/10.1002/nau.24342.
[3] I. Milsom, K.S. Coyne, S. Nicholson, M. Kvasz, C.-I. Chen, A.J. Wein, Global prevalence and economic burden of urgency urinary incontinence: a systematic review, Eur. Urol. 65 (2014) 79–95, https://doi.org/10.1016/j.eururo.2013.08.031.
[4] J.M. Wu, C.A. Matthews, M.M. Conover, V. Pate, M. Jonsson Funk, Lifetime risk of stress urinary incontinence or pelvic organ prolapse surgery, Obstet. Gynecol. 123 (2014) 1201–1206, https://doi.org/10.1097/AOG.0000000000000286.
[5] P. Abrams, Describing bladder storage function: overactive bladder syndrome and detrusor overactivity, Urology 62 (2003) 28–37, https://doi.org/10.1016/j.urology.2003.09.050.
[6] P. Abrams, K.-E. Andersson, Muscarinic receptor antagonists for overactive bladder, BJU Int. 100 (2007) 987–1006, https://doi.org/10.1111/j.1464-410X.2007.07205.x.
[7] S.R. Davis, I. Lambrinoudaki, M. Lumsden, G.D. Mishra, L. Pal, M. Rees, N. Santoro, T. Simoncini, Menopause, Nat. Rev. Dis. Prim. 1 (2015) 15004, https://doi.org/10.1038/nrdp.2015.4.
[8] P. Monteleone, G. Mascagni, A. Giannini, A.R. Genazzani, T. Simoncini, Symptoms of menopause - Global prevalence, physiology and implications, Nat. Rev. Endocrinol. (2018), https://doi.org/10.1038/nrendo.2017.180.
[9] D. Robinson, P. Toozs-Hobson, L. Cardozo, The effect of hormones on the lower urinary tract, Menopause Int. (2013), https://doi.org/10.1177/1754045313511398.
[10] C.S. Iosif, S. Batra, A. Ek, B. Åstedt, Estrogen receptors in the human female lower urinary tract, Am. J. Obstet. Gynecol. 141 (1981) 817–820, https://doi.org/10.1016/0002-9378(81)90710-9.

[11] S.C. Batra, C.S. Iosif, Progesterone receptors in the female lower urinary tract, J. Urol. (1987), https://doi.org/10.1016/S0022-5347(17)43588-9.
[12] C. Falconer, B. Blomgren, O. Johansson, U. Ulmsten, A. Malmström, G. Westergren-Thorsson, G. Ekman-Ordeberg, Different organization of collagen fibrils in stress-incontinent women of fertile age, Acta Obstet. Gynecol. Scand. 77 (1998) 87–94, https://doi.org/10.1080/00016349808565819.
[13] P. Radziszewski, A. Borkowski, C. Torz, A. Bossowska, S. Gonkowski, M. Majewski, Distribution of collagen type VII in connective tissues of postmenopausal stress-incontinent women, Gynecol. Endocrinol. 20 (2005) 121–126, https://doi.org/10.1080/09513590400021078.
[14] D.J. Portman, M.L.S. Gass, S. Kingsberg, D. Archer, G. Bachmann, L. Burrows, M. Freedman, A. Goldstein, I. Goldstein, D. Heller, C.B. Iglesia, R. Kagan, S. K. Spadt, M. Krychman, L. Nachtigall, R.E. Nappi, J.V. Pinkerton, J. Shifren, J. Simon, C. Stuenkel, Genitourinary syndrome of menopause: New terminology for vulvovaginal atrophy from the international society for the study of women's sexual health and the North American Menopause Society, Menopause (2014), https://doi.org/10.1097/gme.0000000000000329.
[15] J.L. Shifren, Genitourinary syndrome of menopause, Clin. Obstet. Gynecol. 61 (2018) 508–516, https://doi.org/10.1097/GRF.0000000000000380.
[16] A. Augoulea, D. Sioutis, D. Rizos, C. Panoulis, N. Triantafyllou, E. Armeni, E. Deligeoroglou, C. Chrelias, M. Creatsa, A. Liapis, I. Lambrinoudaki, Stress urinary incontinence and endogenous sex steroids in postmenopausal women, Neurourol. Urodyn. 36 (2017) 121–125, https://doi.org/10.1002/nau.22885.
[17] D. Robinson, L. Cardozo, I. Milsom, M.E. Pons, M. Kirby, H. Koelbl, M. Vierhout, Oestrogens and overactive bladder, Neurourol. Urodyn. 33 (2014) 1086–1091, https://doi.org/10.1002/nau.22464.
[18] W. Gibson, A. Wagg, Incontinence in the elderly, "normal" ageing, or unaddressed pathology? Nat. Rev. Urol. 14 (2017) 440–448, https://doi.org/10.1038/nrurol.2017.53.
[19] K.E. Andersson, D.B. Boedtkjer, A. Forman, The link between vascular dysfunction, bladder ischemia, and aging bladder dysfunction, Ther. Adv. Urol. (2017), https://doi.org/10.1177/1756287216675778.
[20] M. Nomiya, K.-E. Andersson, O. Yamaguchi, Chronic bladder ischemia and oxidative stress: new pharmacotherapeutic targets for lower urinary tract symptoms, Int. J. Urol. 22 (2015) 40–46, https://doi.org/10.1111/iju.12652.
[21] K.-E. Andersson, M. Nomiya, N. Sawada, O. Yamaguchi, Pharmacological treatment of chronic pelvic ischemia, Ther. Adv. Urol. 6 (2014) 105–114, https://doi.org/10.1177/1756287214526768.
[22] P.L. Brubaker, Linking the gut microbiome to metabolism through endocrine hormones, Endocrinology 159 (2018) 2978–2979, https://doi.org/10.1210/en.2018-00577.
[23] R. Cruickshank, The conversion of the glycogen of the vagina into lactic acid, J. Pathol. Bacteriol. 39 (1934) 213–219, https://doi.org/10.1002/path.1700390118.
[24] D.W. Sturdee, N. Panay, Recommendations for the management of postmenopausal vaginal atrophy, Climacteric 13 (2010) 509–522, https://doi.org/10.3109/13697137.2010.522875.
[25] R.M. Brotman, M.D. Shardell, P. Gajer, D. Fadrosh, K. Chang, M.I. Silver, R. P. Viscidi, A.E. Burke, J. Ravel, P.E. Gravitt, Association between the vaginal microbiota, menopause status, and signs of vulvovaginal atrophy, Menopause 21 (2014) 450–458, https://doi.org/10.1097/GME.0b013e3182a4690b.
[26] K.J. Thomas-White, S. Kliethermes, L. Rickey, E.S. Lukacz, H.E. Richter, P. Moalli, P. Zimmern, P. Norton, J.W. Kusek, A.J. Wolfe, L. Brubaker, Evaluation of the urinary microbiota of women with uncomplicated stress urinary incontinence, Am. J. Obstet. Gynecol. 216 (2017) 55.e1–55.e16, https://doi.org/10.1016/j.ajog.2016.07.049.
[27] A.J. Wolfe, L. Brubaker, Urobiome updates: advances in urinary microbiome research, Nat. Rev. Urol. 16 (2019) 73–74, https://doi.org/10.1038/s41585-018-0127-5.
[28] L. Brubaker, A.J. Wolfe, The female urinary Microbiota/Microbiome: clinical and research implications, Rambam Maimonides Med. J. 8 (2017), e0015, https://doi.org/10.5041/RMMJ.10292.
[29] K.J. Thomas-White, E.E. Hilt, C. Fok, M.M. Pearce, E.R. Mueller, S. Kliethermes, K. Jacobs, M.J. Zilliox, C. Brincat, T.K. Price, G. Kuffel, P. Schreckenberger, X. Gai, L. Brubaker, A.J. Wolfe, Incontinence medication response relates to the female urinary microbiota, Int. Urogynecol. J. 27 (2016) 723–733, https://doi.org/10.1007/s00192-015-2847-x.
[30] M.M. Pearce, E.E. Hilt, A.B. Rosenfeld, M.J. Zilliox, K. Thomas-White, C. Fok, S. Kliethermes, P.C. Schreckenberger, L. Brubaker, X. Gai, A.J. Wolfe, The female urinary microbiome: a comparison of women with and without urgency urinary incontinence, MBio (2014), https://doi.org/10.1128/mBio.01283-14.
[31] M.M. Pearce, M.J. Zilliox, A.B. Rosenfeld, K.J. Thomas-White, H.E. Richter, C. W. Nager, A.G. Visco, I.E. Nygaard, M.D. Barber, J. Schaffer, P. Moalli, V.W. Sung, A.L. Smith, R. Rogers, T.L. Nolen, D. Wallace, S.F. Meikle, X. Gai, A.J. Wolfe, L. Brubaker, The female urinary microbiome in urgency urinary incontinence, Am. J. Obstet. Gynecol. 213 (2015) 347.e1–347.e11, https://doi.org/10.1016/j.ajog.2015.07.009.
[32] L. Brubaker, A. Wolfe, M. Pearce, M. Zilliox, A. Rosenfeld, K. Thomas-White, The urinary microbiome of women with urinary urgency incontinence, Neurourol. Urodyn. (2014).
[33] F.C. Burkhard, J.L.H.R. Bosch, F. Cruz, G.E. Lemack, A.K. Nambiar, N. Thiruchelvam, A. Tubaro, EAU guidelines on urinary incontinence in adults, Eur. Assoc. Urol. (2018).
[34] C.S. Elliott, C.V. Comiter, Evaluation and management of urinary retention and voiding dysfunction after sling surgery for female stress urinary incontinence, Curr. Bladder Dysfunct. Rep. 7 (2012) 268–274, https://doi.org/10.1007/s11884-012-0150-y.
[35] C.W. Nager, L. Brubaker, H.J. Litman, H.M. Zyczynski, R.E. Varner, C. Amundsen, L.T. Sirls, P.A. Norton, A.M. Arisco, T.C. Chai, P. Zimmern, M.D. Barber, K. J. Dandreo, S.A. Menefee, K. Kenton, J. Lowder, H.E. Richter, S. Khandwala, I. Nygaard, S.R. Kraus, H.W. Johnson, G.E. Lemack, M. Mihova, M.E. Albo, E. Mueller, G. Sutkin, T.S. Wilson, Y. Hsu, T.A. Rozanski, L.M. Rickey, D. Rahn, S. Tennstedt, J.W. Kusek, E.A. Gormley, A Randomized Trial of Urodynamic Testing before Stress-Incontinence Surgery, N. Engl. J. Med. 366 (2012) 1987–1997, https://doi.org/10.1056/NEJMoa1113595.
[36] C.E. DuBeau, G.A. Kuchel, T. Johnson II, M.H. Palmer, A. Wagg, Incontinence in the frail elderly: report from the 4th international consultation on incontinence, Neurourol. Urodyn. 29 (2010) 165–178, https://doi.org/10.1002/nau.20842.
[37] L.L. Subak, R. Wing, D.S. West, F. Franklin, E. Vittinghoff, J.M. Creasman, H. E. Richter, D. Myers, K.L. Burgio, A.A. Gorin, J. Macer, J.W. Kusek, D. Grady, Weight loss to treat urinary incontinence in overweight and obese women, N. Engl. J. Med. 360 (2009) 481–490, https://doi.org/10.1056/NEJMoa0806375.
[38] K.L. Burgio, S.R. Kraus, S. Menefee, D. Borello-France, M. Corton, H.W. Johnson, V. Mallett, P. Norton, M.P. FitzGerald, K.J. Dandreo, H.E. Richter, T. Rozanski, M. Albo, H.M. Zyczynski, G.E. Lemack, T.C. Chai, S. Khandwala, J. Baker, L. Brubaker, A.M. Stoddard, P.S. Goode, B. Nielsen-Omeis, C.W. Nager, K. Kenton, S.L. Tennstedt, J.W. Kusek, T.D. Chang, L.M. Nyberg, W. Steers, Behavioral therapy to enable women with urge incontinence to discontinue drug treatment: a randomized trial, Ann. Intern. Med. (2008), https://doi.org/10.7326/0003-4819-149-3-200808050-00005.
[39] B.U. Tomlinson, M.C. Dougherty, J.F. Pendergast, A.R. Boyington, M.A. Coffman, S.M. Pickens, Dietary Caffeine, Fluid intake and urinary incontinence in older rural women, Int. Urogynecol. J. 10 (1999) 22–28, https://doi.org/10.1007/PL00004009.
[40] J. Ostaszkiewicz, L. Johnston, B. Roe, Timed voiding for the management of urinary incontinence in adults, Cochrane Database Syst. Rev. (2004), https://doi.org/10.1002/14651858.cd002802.pub2.
[41] P. Zimmern, H.J. Litman, E. Mueller, P. Norton, P. Goode, Effect of fluid management on fluid intake and urge incontinence in a trial for overactive bladder in women, BJU Int. 105 (2009) 1680–1685, https://doi.org/10.1111/j.1464-410X.2009.09055.x.
[42] K. Bo, H.C. Frawley, B.T. Haylen, Y. Abramov, F.G. Almeida, B. Berghmans, M. Bortolini, C. Dumoulin, M. Gomes, D. McClurg, J. Meijlink, E. Shelly, E. Trabuco, C. Walker, A. Wells, An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for the conservative and nonpharmacological management of female pelvic floor dysfunction, Neurourol. Urodyn. 36 (2017) 221–244, https://doi.org/10.1002/nau.23107.
[43] K. Bø, Pelvic floor muscle strength and response to pelvic floor muscle training for stress urinary incontinence, Neurourol. Urodyn. 22 (2003) 654–658, https://doi.org/10.1002/nau.10153.
[44] K. Bø, L.C.M. Berghmans, Nonpharmacologic treatments for overactive bladder - Pelvic floor exercises, Urology (2000), https://doi.org/10.1016/S0090-4295(99)00485-9.
[45] E.J.C. Hay-Smith, R. Herderschee, C. Dumoulin, G.P. Herbison, Comparisons of approaches to pelvic floor muscle training for urinary incontinence in women, Cochrane Database Syst. Rev. (2011), https://doi.org/10.1002/14651858.cd009508.
[46] R.O. Ayeleke, E.J.C. Hay-Smith, M.I. Omar, Pelvic floor muscle training added to another active treatment versus the same active treatment alone for urinary incontinence in women, in: E.J.C. Hay-Smith (Ed.), Cochrane Database Syst. Rev., John Wiley & Sons, Ltd, Chichester, UK, 2013, https://doi.org/10.1002/14651858.CD010551.pub2.
[47] J.D. Cody, M.L. Jacobs, K. Richardson, B. Moehrer, A. Hextall, Oestrogen therapy for urinary incontinence in post-menopausal women, Cochrane Database Syst. Rev. (2012), https://doi.org/10.1002/14651858.cd001405.pub3.
[48] V. Šimunić, I. Banović, S. Ciglar, L. Jeren, D. Pavičić Baldani, M. Šprem, Local estrogen treatment in patients with urogenital symptoms, Int. J. Gynecol. Obstet. 82 (2003) 187–197, https://doi.org/10.1016/S0020-7292(03)00200-5.
[49] L.D. Cardozo, B.G. Wise, C.J. Benness, Vaginal oestradiol for the treatment of lower urinary tract symptoms in postmenopausal women - A double-blind placebo-controlled study, J. Obstet. Gynaecol. (Lahore). (2001), https://doi.org/10.1080/01443610120059941.
[50] D.D. Rahn, C. Carberry, T.V. Sanses, M.M. Mamik, R.M. Ward, K.V. Meriwether, C. K. Olivera, H. Abed, E.M. Balk, M. Murphy, Vaginal estrogen for genitourinary syndrome of menopause, Obstet. Gynecol. 124 (2014) 1147–1156, https://doi.org/10.1097/AOG.0000000000000526.
[51] M. Caretto, A. Giannini, E. Russo, T. Simoncini, Preventing urinary tract infections after menopause without antibiotics, Maturitas 99 (2017), https://doi.org/10.1016/j.maturitas.2017.02.004.
[52] L. Cardozo, G. Lose, D. McClish, E. Versi, A systematic review of the effects of estrogens for symptoms suggestive of overactive bladder, Acta Obstet. Gynecol. Scand. 83 (2004) 892–897, https://doi.org/10.1111/j.0001-6349.2004.00581.x.
[53] Y. Tanidir, F. Ercan, T. Tarcan, Exogenous testosterone and estrogen affect bladder tissue contractility and histomorphology differently in rat ovariectomy model, J. Sex. Med. 8 (2011) 1626–1637, https://doi.org/10.1111/j.1743-6109.2011.02227.x.
[54] G.V. Petkov, Central role of the BK channel in urinary bladder smooth muscle physiology and pathophysiology, Am. J. Physiol. - Regul. Integr. Comp. Physiol. 307 (2014) R571–R584, https://doi.org/10.1152/ajpregu.00142.2014.

[55] G. Capobianco, E. Donolo, G. Borghero, F. Dessole, P.L. Cherchi, S. Dessole, Effects of intravaginal estriol and pelvic floor rehabilitation on urogenital aging in postmenopausal women, Arch. Gynecol. Obstet. 285 (2012) 397–403, https://doi.org/10.1007/s00404-011-1955-1.
[56] M.A. Weber, M.H. Kleijn, M. Langendam, J. Limpens, M.J. Heineman, J.P. Roovers, Local oestrogen for pelvic floor disorders: a systematic review, PLoS One 10 (2015), e0136265, https://doi.org/10.1371/journal.pone.0136265.
[57] S.L. Hendrix, B.B. Cochrane, I.E. Nygaard, V.L. Handa, V.M. Barnabei, C. Iglesia, A. Aragaki, M.J. Naughton, R.B. Wallace, S.G. McNeeley, Effects of estrogen with and without progestin on urinary incontinence, J. Am. Med. Assoc. (2005), https://doi.org/10.1001/jama.293.8.935.
[58] H.D. Nelson, M. Walker, B. Zakher, J. Mitchell, Menopausal hormone therapy for the primary prevention of chronic conditions: a systematic review to update the U. S. Preventive services task force recommendations, Ann. Intern. Med. (2012), https://doi.org/10.7326/0003-4819-157-2-201207170-00466.
[59] E.P. Gurney, M.J. Nachtigall, L.E. Nachtigall, F. Naftolin, The Women's Health Initiative trial and related studies: 10 years later: a clinician's view, J. Steroid Biochem. Mol. Biol. 142 (2014) 4–11, https://doi.org/10.1016/j.jsbmb.2013.10.009.
[60] F. Grodstein, K. Lifford, N.M. Resnick, G.C. Curhan, Postmenopausal hormone therapy and risk of developing urinary incontinence, Obstet. Gynecol. 103 (2004) 254–260, https://doi.org/10.1097/01.AOG.0000107290.33034.6f.
[61] V. Di Donato, M.C. schiavi, V. iacobelli, O. D'oria, E. Kontopantelis, T. Simoncini, L. Muzii, P. Benedetti Panici, Ospemifene for the treatment of vulvar and vaginal atrophy: A meta-analysis of randomized trials. Part I: Evaluation of efficacy, Maturitas (2019), https://doi.org/10.1016/j.maturitas.2018.11.016.
[62] V. Di Donato, M.C. Schiavi, V. Iacobelli, O. D'oria, E. Kontopantelis, T. Simoncini, L. Muzii, P. Benedetti Panici, Ospemifene for the treatment of vulvar and vaginal atrophy: A meta-analysis of randomized trials. Part II: Evaluation of tolerability and safety, Maturitas (2019), https://doi.org/10.1016/j.maturitas.2018.11.017.
[63] M.C. Schiavi, M.A. Zullo, P. Faiano, O. D'Oria, G. Prata, V. Colagiovanni, A. Giannini, C. Di Tucci, G. Perniola, V. Di Donato, M. Monti, L. Muzii, P. Benedetti Panici, Retrospective analysis in 46 women with vulvovaginal atrophy treated with ospemifene for 12 weeks: improvement in overactive bladder symptoms, Gynecol. Endocrinol. (2017), https://doi.org/10.1080/09513590.2017.1323859.
[64] L. Novara, L.G. Sgro, M. Mancarella, R. Capece, E. Canale, N. Biglia, Potential effectiveness of Ospemifene on Detrusor Overactivity in patients with vaginal atrophy, Maturitas (2020), https://doi.org/10.1016/j.maturitas.2020.05.001.
[65] B.P. Rai, J.D. Cody, A. Alhasso, L. Stewart, Anticholinergic drugs versus non-drug active therapies for non-neurogenic overactive bladder syndrome in adults, Cochrane Database Syst. Rev. (2012), https://doi.org/10.1002/14651858.CD003193.pub4.
[66] G. Nabi, J.D. Cody, G. Ellis, J. Hay-Smith, G.P. Herbison, Anticholinergic drugs versus placebo for overactive bladder syndrome in adults, Cochrane Database Syst. Rev. (2006), https://doi.org/10.1002/14651858.cd003781.pub2.
[67] S.L. Risacher, B.C. McDonald, E.F. Tallman, J.D. West, M.R. Farlow, F. W. Unverzagt, S. Gao, M. Boustani, P.K. Crane, R.C. Petersen, C.R. Jack, W. J. Jagust, P.S. Aisen, M.W. Weiner, A.J. Saykin, Association Between Anticholinergic Medication Use and Cognition, Brain Metabolism, and Brain Atrophy in Cognitively Normal Older Adults, JAMA Neurol. 73 (2016) 721, https://doi.org/10.1001/jamaneurol.2016.0580.
[68] C.R. Chapple, L. Cardozo, V.W. Nitti, E. Siddiqui, M.C. Michel, Mirabegron in overactive bladder: a review of efficacy, safety, and tolerability, Neurourol. Urodyn. 33 (2014) 17–30, https://doi.org/10.1002/nau.22505.
[69] Y. Cui, H. Zong, C. Yang, H. Yan, Y. Zhang, The efficacy and safety of mirabegron in treating OAB: a systematic review and meta-analysis of phase III trials, Int. Urol. Nephrol. 46 (2014) 275–284, https://doi.org/10.1007/s11255-013-0509-9.
[70] M. Serati, S. Salvatore, S. Uccella, L. Cardozo, P. Bolis, Is There a Synergistic Effect of Topical Oestrogens When Administered with Antimuscarinics in the Treatment of Symptomatic Detrusor Overactivity? Eur. Urol. 55 (2009) 713–720, https://doi.org/10.1016/j.eururo.2008.06.051.
[71] L.H. Tseng, A.C. Wang, Y.L. Chang, Y.K. Soong, L.K. Lloyd, Y.J. Ko, Randomized comparison of tolterodine with vaginal estrogen cream versus tolterodine alone for the treatment of postmenopausal women with overactive bladder syndrome, Neurourol. Urodyn. (2009), https://doi.org/10.1002/nau.20583.
[72] S. Herschorn, C.R. Chapple, P. Abrams, S. Arlandis, D. Mitcheson, K.S. Lee, A. Ridder, M. Stoelzel, A. Paireddy, R. van Maanen, D. Robinson, Efficacy and safety of combinations of mirabegron and solifenacin compared with monotherapy and placebo in patients with overactive bladder (SYNERGY study), BJU Int. (2017), https://doi.org/10.1111/bju.13882.
[73] J.B. Duthie, M. Vincent, G.P. Herbison, D.I. Wilson, D. Wilson, Botulinum toxin injections for adults with overactive bladder syndrome, Cochrane Database Syst. Rev. (2011), https://doi.org/10.1002/14651858.cd005493.pub3.
[74] J.T. Anger, A. Weinberg, M.J. Suttorp, M.S. Litwin, P.G. Shekelle, Outcomes of intravesical botulinum toxin for idiopathic overactive bladder symptoms: a systematic review of the literature, J. Urol. 183 (2010) 2258–2264, https://doi.org/10.1016/j.juro.2010.02.009.
[75] T. Yamanishi, K. Kaga, M. Fuse, C. Shibata, T. Uchiyama, Neuromodulation for the treatment of lower urinary tract symptoms, LUTS Low. Urin. Tract Symptoms. 7 (2015) 121–132, https://doi.org/10.1111/luts.12087.
[76] P.J. Levin, J.M. Wu, A. Kawasaki, A.C. Weidner, C.L. Amundsen, The efficacy of posterior tibial nerve stimulation for the treatment of overactive bladder in women: a systematic review, Int. Urogynecol. J. 23 (2012) 1591–1597, https://doi.org/10.1007/s00192-012-1712-4.
[77] H.F.A. Moossdorff-Steinhauser, B. Berghmans, Effects of percutaneous tibial nerve stimulation on adult patients with overactive bladder syndrome: a systematic review, Neurourol. Urodyn. 32 (2013) 206–214, https://doi.org/10.1002/nau.22296.
[78] E. Finazzi-Agrò, C. Rocchi, C. Pachatz, F. Petta, E. Spera, F. Mori, F. Sciobica, G. A. Marfia, Percutaneous tibial nerve stimulation produces effects on brain activity: study on the modifications of the long latency somatosensory evoked potentials, Neurourol. Urodyn. 28 (2009) 320–324, https://doi.org/10.1002/nau.20651.
[79] M.S. Elkelini, A. Abuzgaya, M.M. Hassouna, Mechanisms of action of sacral neuromodulation, Int. Urogynecol. J. 21 (2010) 439–446, https://doi.org/10.1007/s00192-010-1273-3.
[80] S. jun Lee, D.H. Suh, J.M. Lee, K.Y. Song, H.J. Ryu, Dermal remodeling of burn scar by fractional CO2 laser, Aesthetic Plast. Surg. (2016), https://doi.org/10.1007/s00266-016-0686-x.
[81] S. Salvatore, U. Leone Roberti Maggiore, S. Athanasiou, M. Origoni, M. Candiani, A. Calligaro, N. Zerbinati, Histological study on the effects of microablative fractional CO2 laser on atrophic vaginal tissue, Menopause 22 (2015) 845–849, https://doi.org/10.1097/GME.0000000000000401.
[82] Y. Tadir, A. Gaspar, A. Lev-Sagie, M. Alexiades, R. Alinsod, A. Bader, A. Calligaro, J.A. Elias, M. Gambaciani, J.E. Gaviria, C.B. Iglesia, K. Selih-Martinec, P. L. Mwesigwa, U.B. Ogrinc, S. Salvatore, P. Scollo, N. Zerbinati, J.S. Nelson, Light and energy based therapeutics for genitourinary syndrome of menopause: consensus and controversies, Lasers Surg. Med. 49 (2017) 137–159, https://doi.org/10.1002/lsm.22637.
[83] D. Elia, M. Gambacciani, N. Berreni, J.M. Bohbot, R. Druckmann, H. Geoffrion, F. Haab, N. Heiss, N. Rygaloff, E. Russo, Genitourinary syndrome of menopause (GSM) and laser VEL: a review, Horm. Mol. Biol. Clin. Investig. 41 (2020), https://doi.org/10.1515/hmbci-2019-0024.
[84] M. Gambacciani, M. Levancini, E. Russo, L. Vacca, T. Simoncini, M. Cervigni, Long-term effects of vaginal erbium laser in the treatment of genitourinary syndrome of menopause, Climacteric 21 (2018) 148–152, https://doi.org/10.1080/13697137.2018.1436538.
[85] N. Fistonić, I. Fistonić, A. Lukanovič, Š.F. Guštek, I.S.B. Turina, D. Franić, First assessment of short-term efficacy of Er:YAG laser treatment on stress urinary incontinence in women: prospective cohort study, Climacteric 18 (2015) 37–42, https://doi.org/10.3109/13697137.2015.1071126.
[86] J.I. Pardo, V.R. Solà, A.A. Morales, Treatment of female stress urinary incontinence with Erbium-YAG laser in non-ablative mode, Eur. J. Obstet. Gynecol. Reprod. Biol. 204 (2016) 1–4, https://doi.org/10.1016/j.ejogrb.2016.06.031.
[87] A. Gaspar, H. Brandi, Non-ablative erbium YAG laser for the treatment of type III stress urinary incontinence (intrinsic sphincter deficiency), Lasers Med. Sci. 32 (2017) 685–691, https://doi.org/10.1007/s10103-017-2170-5.
[88] J.E. Walter, A. Larochelle, No. 358-Intravaginal Laser for Genitourinary Syndrome of Menopause and Stress Urinary Incontinence, J. Obstet. Gynaecol. Can. (2018), https://doi.org/10.1016/j.jogc.2017.11.040.
[89] R. Riemsma, S. Hagen, R. Kirschner-Hermanns, C. Norton, H. Wijk, K.E. Andersson, C. Chapple, J. Spinks, A. Wagg, E. Hutt, K. Misso, S. Deshpande, J. Kleijnen, I. Milsom, Can incontinence be cured? A systematic review of cure rates, BMC Med. (2017), https://doi.org/10.1186/s12916-017-0828-2.
[90] A.A. Ford, L. Rogerson, J.D. Cody, P. Aluko, J.A. Ogah, Mid-urethral sling operations for stress urinary incontinence in women, Cochrane Database Syst. Rev. (2017), https://doi.org/10.1002/14651858.CD006375.pub4.
[91] L. Brubaker, P.A. Norton, M.E. Albo, T.C. Chai, K.J. Dandreo, K.L. Lloyd, J. L. Lowder, L.T. Sirls, G.E. Lemack, A.M. Arisco, Y. Xu, J.W. Kusek, Adverse events over two years after retropubic or transobturator midurethral sling surgery: findings from the Trial of Midurethral Slings (TOMUS) study, Am. J. Obstet. Gynecol. 205 (2011) 498.e1–498.e6, https://doi.org/10.1016/j.ajog.2011.07.011.
[92] F. Fusco, M. Abdel-Fattah, C.R. Chapple, M. Creta, S. La Falce, D. Waltregny, G. Novara, Updated systematic review and meta-analysis of the comparative data on colposuspensions, pubovaginal slings, and midurethral Tapes in the surgical treatment of female stress urinary incontinence, Eur. Urol. (2017), https://doi.org/10.1016/j.eururo.2017.04.026.
[93] C.G. Nilsson, K. Palva, M. Rezapour, C. Falconer, Eleven years prospective follow-up of the tension-free vaginal tape procedure for treatment of stress urinary incontinence, Int. Urogynecol. J. 19 (2008) 1043–1047, https://doi.org/10.1007/s00192-008-0666-z.
[94] V. Kirchin, T. Page, P.E. Keegan, K.O.M. Atiemo, J.D. Cody, S. McClinton, P. Aluko, Urethral injection therapy for urinary incontinence in women, Cochrane Database Syst. Rev. (2017), https://doi.org/10.1002/14651858.CD003881.pub4.
[95] J.C. Burch, Cooper's ligament urethrovesical suspension for stress incontinence. Nine years' experience–results, complications, technique, Am. J. Obstet. Gynecol. (1968), https://doi.org/10.1016/S0002-9378(15)33576-6.
[96] N. Dean, G. Ellis, G.P. Herbison, D. Wilson, A. Mashayekhi, Laparoscopic colposuspension for urinary incontinence in women, Cochrane Database Syst. Rev. (2017), https://doi.org/10.1002/14651858.cd002239.pub3.
[97] M.E. Albo, H.E. Richter, L. Brubaker, P. Norton, S.R. Kraus, P.E. Zimmern, T. C. Chai, H. Zyczynski, A.C. Diokno, S. Tennstedt, C. Nager, L.K. Lloyd, M. FitzGerald, G.E. Lemack, H.W. Johnson, W. Leng, V. Mallett, A.M. Stoddard, S. Menefee, R.E. Varner, K. Kenton, P. Moalli, L. Sirls, K.J. Dandreo, J.W. Kusek, L. M. Nyberg, W. Steers, Burch Colposuspension versus Fascial Sling to Reduce Urinary Stress Incontinence, N. Engl. J. Med. 356 (2007) 2143–2155, https://doi.org/10.1056/NEJMoa070416.