Benefits and harms of conservative, pharmacological, and surgical management options for women with bladder outlet obstruction: a systematic review from the European Association of Urology non-neurogenic female LUTS Guidelines Panel

Benoit Peyronnet [1], Marie Carmela Lapitan [2]

Lazaros Tzelves [3], Eabhann O'connor [4], Aisling Nic An Riogh [4], Margarida Manso [5], Cathy Yuhong Yuan [6], Salvador Arlandis [7], Kari Bo [8], Elisabetta Costantini [9], Fawzy Farag [10], Jan Groen [11], Arjun Nambiar [12], Véronique Phé [13], Huub van der Vaart [14], Muhammad Imran Omar [15], Chris Harding [12],

1: Rennes University Hospital, Rennes, France

2: University of the Philippines Manila, Philippines

3: Sismanoglio General Hospital, National and Kapodistrian University of Athens, Greece

4: Beaumont University Hospital, Dublin, Ireland

5: Centro Hospitalar São João, Porto, Portugal

6: Department of medicine, McMaster University, Hamilton, Ontario, Canada

7: Hospital Universitari i Politècnic La Fe, Valencia, Spain

8: Norwegian School of Sport Sciences, Department of Sports Medicine, Oslo and Akershus University Hospital, Lørenskog, Norway

9: Terni Santa Maria Hospital, University of Perugia, Italy

10: Sohag University Hospital, Sohag, Egypt

11: Erasmus Medical Center, Rotterdam, The Netherlands

12: Freeman Hospital, Newcastle-upon-Tyne, UK

13: Sorbonne University, Assistance Publique-Hôpitaux de Paris, Pitié-Salpetrière Academic Hospital, Department of Urology, Paris, France

14: University Medical Centre, Utrecht, The Netherlands

15: University of Aberdeen, Aberdeen, Scotland, UK

Corresponding author

Dr Benoit PEYRONNET

Service d'Urologie, Hopital Pontchaillou

2 rue Henri Le Guilloux, 35000 Rennes, France

mail: peyronnetbenoit@hotmail.fr

This Systematic Review is carried out under the auspices of the European Association of Urology Guidelines Office Board

Word count: 4880

Context: While the management of bladder outlet obstruction (BOO) in men has been a topic of several systematic reviews and meta-analysis, no such evidence base exists for female BOO.

Objective: The aim of this systematic review was to evaluate the benefits and harms of therapeutic interventions for the management of BOO in women.

Evidence acquisition: This systematic review was conducted in accordance with the PRISMA statement. The study protocol was registered with PROSPERO (CRD42020183839). A systematic literature search was performed and updated by a research librarian in May 2021. The study population consisted of adult female patients diagnosed with BOO and who underwent treatment.

Evidence synthesis: Out of 6344 records, we identified 33 studies enrolling 1222 participants, of which only six RCTs were found. One placebo-controlled cross-over randomized trial assessed the role of baclofen in 60 female patients with dysfunctional voiding. The trial met its primary endpoint with a significantly greater decrease in the number of voids/day in the baclofen group (-5.53 vs. -2.70; p=0.001). The adverse events were mild and comparable in both groups (25% vs. 20%). One placebo-controlled cross-over randomized trial assessed the role of sildenafil in 20 women with Fowler's syndrome. There were significant improvements from baseline in Qmax, IPSS, and post-void residual (PVR) but with no statistically significant difference when compared with placebo. In a large RCT including 197 female patients with functional BOO, the alpha-blocker alfusozin significantly improved IPSS, Qmax and PVR compared to baseline but the differences compared to the placebo group were not statistically significant. Several small single arm prospective series reported improvement of BOO related symptoms and voiding parameters with urethroplasty, sling revision, urethral dilation, vaginal pessary and pelvic organ prolapse repair.

Conclusion: Evidence to support the use of conservative, pharmacological and surgical treatments for BOO are scarce.

Patient summary: According to the present systematic review of the literature, evidence to support the use of conservative, pharmacological and surgical treatments for either anatomical or functional BOO are scarce.

Introduction

Bladder outlet obstruction (BOO) is defined by the International Continence Society as the generic term for obstruction during voiding characterized by increased detrusor pressure and reduced urine flow rate [1]. BOO has long been postulated to cause mainly voiding symptoms [2] but recent data suggest that storage symptoms may be predominant in female patients diagnosed with BOO [3]. Owing to the lack of a standardized definition and to its wide spectrum of clinical manifestations, the prevalence of female BOO remains uncertain, postulated to range from 2.7% to 23% of women [5-6]. Pelvic organ prolapse (POP) and previous anti-incontinence surgery are presumed to be the predominant cause of BOO in women [2,5-6]. However, numerous other causes of female BOO do exist and are now well recognized [2,5-6]. The therapeutic management of female BOO is heavily cause-specific and can rely on conservative, pharmacological, and surgical management options [2, 6]. While the outcomes of BOO treatment have been the matter of several systematic reviews and meta-analysis in men [4], no such compilation of evidence exist for female BOO therapeutic management. The aim of this systematic review was to evaluate the benefits and harms of therapeutic interventions for the treatment of bladder outlet obstruction in adult females.

Evidence acquisition

This systematic review was undertaken under the auspices of the EAU. It was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [7] with the principles outlined in the Cochrane Handbook for Systematic Reviews [8] and with the EAU methodology [9]. The study protocol was registered in PROSPERO in May 2020 (CRD42020183839)

Search strategy

A systematic literature search using the Medline, Embase and Cochrane CENTRAL and CDSR, as well as clinicaltrial.gov was performed by a research librarian on May 04 2020 and updated on May 30 2021 from inception of each database. The full search strategy was based on a free text protocol and is presented in Appendix 1. Searches were conducted without language or time restrictions. Cited references from selected studies were also sought. Conference proceedings were excluded.

Inclusion and exclusion criteria

Studies were assessed using the PICOS approach in accordance with the PRISMA guidelines [7]: Patient (P), Intervention (I), Comparator (C), Outcome (O) and Study design (S) (table 1).

Types of patients included

The study population consisted of adult female patients (≥18 years old) diagnosed with BOO. While the definition of BOO is well-established, relatively consensual and with some data supporting its clinical validity in male patients [4], the urodynamic definition of female BOO remains a matter of controversy [2]. Dozens of urodynamic criteria have been introduced during the past 20 years but none have been established as a standard due to lack of clinical validation [2, 5]. As a result, the leading authors devised a list of possible definitions for inclusion. All these definitions were discussed among the panel and the studies which used the following definitions of BOO were considered eligible for inclusion:

- Low flow rate and high detrusor pressure during voiding on pressure-flow studies regardless of the cut-offs/nomogram used

- Evidence of urethral narrowing and/or lack of bladder neck opening during voiding on video cystourethrogaphy or videourodynamic studies
- High activity on sphincter or pelvic floor electromyography during voiding associated with LUTS/voiding difficulty and low maximum urinary flow rate (Qmax)
- Urinary retention or need for extended clean-intermittent self-catheterization in the early post-operative period after anti-incontinence surgery
- LUTS and/or voiding difficulty and/or urinary retention and/or high post-void residual (PVR) with endoscopic diagnosis of fibrotic urethral stricture

The definition of BOO used was recorded. Populations excluded from this systematic review were male patients, paediatric and neurological BOO populations. Studies that included mixed populations were included only if subgroup analysis was provided to allow for extraction of data specific to adult females with non-neurogenic BOO.

Types of interventions and comparators included
Studies which assessed any conservative, pharmacological or surgical intervention in the experimental group were included in the review. Comparator interventions included placebo or sham treatment or any of the above interventions.

Types of outcome measures included
At the time when this systematic review was initiated, no core outcome set had been identified for BOO.

Primary outcomes
The primary benefit outcomes were reduction or cure of the obstruction as defined by the trialist and the reduction of voiding difficulty as measured by questionnaires, bladder diaries, Qmax, PVR or need for catheterization. The primary harm outcome was the occurrence of adverse events associated with any of the BOO treatment.

Secondary outcomes
The secondary outcomes were: improvement of quality of life (QoL), resumption of spontaneous voiding, renal function improvement, resolution of upper urinary tract dilatation, reduction of the number of catheterizations, occurrence of urinary tract infections (UTI), development or worsening of LUTS , development of de novo urinary

incontinence, occurrence of urinary stones.

The following time points were considered for each of the above outcomes: short term (1 to 12 months), medium term (between 1 and 5 years), long term (over 5 years).

All these outcomes at all these time points were included in the summary of findings table if sufficient data were available for each of them.

Types of study designs included

Randomized controlled trials (RCTs) and prospective non-randomized comparative studies were included in this SR. Where no RCTs or prospective non-randomized controlled studies were found, retrospective comparative case series were considered for inclusion. Prospective single arm non-comparative case series were considered for inclusion as a last resort option when no studies of the aforementioned designs were found. Case reports, editorials, letters, review articles and meeting abstracts were excluded from the review process.

Study selection process

After removal of duplicates, four authors (EOC, LT, ANAR, MM) independently screened the titles and abstracts of identified records for eligibility. The full texts of potentially eligible studies were retrieved and screened independently by two authors each, using a standardized form. Any disagreement was resolved by consulting the senior EAU Guidelines Associate (BP).

Data extraction

Data from all selected studies were independently extracted by four reviewers (EOC, LT, ANAR, MM), and were subsequently cross-checked to ensure accuracy. A standardized data extraction form was created and used to collect the data.

Assessment of risk of bias

The risk of bias for each study was independently evaluated by four reviewers (EOC, LT, ANAR, MM) during data collection and according to the principles outlined in the Cochrane Handbook for Systematic Review of Interventions [8, 9]. A risk of bias (RoB) summary (Figure 2) was generated using Cochrane RevMan software v.5.3 (Informatics and Knowledge Management)

Data analysis

For binary/dichotomous/categorical benefit or harm outcomes, risk ratios (RR) were used. For continuous outcomes mean difference (MD) or standardised mean difference (SMD) with corresponding 95% confidence intervals (CIs) were used. The primary analysis was per participant. For studies with more than two intervention groups, only the intervention groups relevant to the review were selected. An intention-to-treat analysis, if data were available; otherwise, an available case analysis was conducted.

We planned to perform meta-analysis if there was more than one randomized controlled trial reporting the same outcome. If meta-analyses were inappropriate, we used the narrative synthesis approach to summarise the results [9].

Descriptive statistics were used to report baseline characteristics. Continuous variables were described using mean and standard deviation (SD), or alternatively, median and interquartile range (IQR). Proportions were used to report categorical variables.

We planned to conduct subgroup analysis to explore potential heterogeneity based on the following:

- type of BOO: anatomical vs. functional obstruction
- basis of BOO diagnosis: based on pressure flow study versus not
- nature of the condition
- Age: elderly patients

Anatomical (mechanical) BOO was defined as evidence of permanent urethral narrowing or obstruction on cystoscopy and/or voiding cystouretrography (VCUG) and/or videourodynamics. Functional BOO was defined as urodynamic evidence of BOO without anatomical BOO.

Quantitative synthesis was not undertaken for non-randomized studies. Instead, we used the narrative synthesis [9] approach to summarize the results.

Assessment of the Certainty of the Evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of the evidence related to the primary outcomes as listed in the Types of Outcomes section above [10].

Evidence synthesis

Out of 4429 abstracts screened, 171 full texts were assessed for eligibility and 33

studies were deemed relevant and included in the present SR [11-40]. A PRISMA flow chart describing the study selection process is presented in Figure 1.

Characteristics of included studies

Overall, the 33 included studies enrolled 1222 patients. The studies and patients' characteristics are summarized in table 2. Only six RCTs were found including a total of 441 participants. There was one prospective non-randomized comparative study and four retrospective comparative studies. All the other included studies were prospective non-comparative series. Two studies evaluated conservative treatments (extracorporeal magnetic stimulation and ring pessary), nine evaluated pharmacological treatments (alpha-blockers, sildenafil and baclofen) and 21 evaluated surgical treatments (urethral dilation, internal urethrotomy, urethroplasty, sling revision and POP repair). We found no study meeting the inclusion criteria for sacral nerve stimulation and intrasphincteric botulinum toxin injections. There were no studies on physiotherapy (pelvic floor muscle relaxation or strength training or electrical stimulation).

Risk of bias and quality assessment of included studies

The RoB and confounding assessment for all included studies is shown in Figure 2. Most included studies carried a high RoB across most fields of the Cochrane Collaboration tool.

Results of interventions

The early (1 to 12 months) and late (>1 to 5 years) functional outcomes are presented in table 3 and table 4 respectively. The adverse events are presented in table 5.

Conservative treatments

<u>Ring pessary</u>

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_2O, $Q_{max} < 15$ mL/sec), "normal voiding" was noted in 17 (94%) immediately after placement of a vaginal pessary [certainty of evidence: very low]. No definition of "normal voiding" was given. No other outcomes were available in this series [31].

Extracorporeal magnetic stimulation

A small prospective non-randomized trial (n=60) compared alfuzosin 10 mg daily alone to extracorporeal magnetic stimulation (EMS) to the combination of alfuzosin 10 mg daily +EMS in women with functional BOO. They observed significant increases in the Qmax and significant decreases of IPSS in all groups compared to baseline [certainty of evidence: low] [16].

Pharmacological treatments

Baclofen

One placebo-controlled cross-over randomized trial assessed the role of baclofen 10 mg three times a day for four weeks in 60 female patients with dysfunctional voiding defined as increased external sphincter activity during voluntary voiding on EMG tracing with a sustained detrusor contraction [12]. The trial met its primary endpoint with a significantly greater decrease in the number of voids/day in the baclofen group (-5.53 vs. -2.70; p=0.001) [certainty of evidence:low]. There was also a greater increase of Qmax (+1.45 vs. +0.33; p=0.001) and a greater decrease in PdetQmax (-2.62 vs. +0.40; p=0.001) [certainty of evidence:low] with no statistically significant difference for other urodynamic parameters associated with the use of baclofen. The adverse events were mild and comparable in both groups (25% vs. 20%) being mostly somnolence (10%) and nausea (10%) in the baclofen group [12].

Sildenafil

One placebo-controlled cross-over randomized trial assessed the role of sildenafil in women with Fowler's syndrome defined as complete or partial urinary retention or obstructed voiding and Qmax<15 ml/s with an elevated maximal urethral closure pressure and sphincter volume [11]. Twenty patients were randomized to receive sildenafil 50 mg twice daily four weeks to cross-over to placebo or the opposite. There were significant improvements from baseline in Qmax (+3.9 ml/s), IPSS (-3.6) and PVR (-42 ml) associated with sildenafil but with no statistically significant difference when compared with placebo [certainty of evidence: low]. The adverse events rates were mild and comparable in both groups [11].

Alpha-blockers

Two RCTs and five prospective non comparative studies evaluated alpha-blockers in female patients with functional BOO.

Lee and coworkers randomized 197 women with voiding dysfunction to receive either alfuzosin 10 mg once daily or placebo for eight weeks [14]. In the subgroup of women with severe BOO (n=58 for alfuzosin and n=59 for placebo), there were statistically significant improvements from baseline in IPSS, IPSS-qol/question 8, PVR and Qmax [certainty of evidence: low] but similar improvements were observed in the placebo group with no statistically significant differences between both groups for any of the study outcomes [14].

One randomized controlled trial of 40 patients compared prazosin to tamsulosin over a 3-month treatment period. More patients on tamsulosin were completely satisfied with treatment (84.2% vs 50%, p<0.05). Both treatment groups showed significant improvement in symptoms score from baseline but no statistical comparison between the groups was done. More adverse events were reported with prazosin (13 cases vs 1 case) [13].

The five prospective non-comparative studies had small sample sizes, ranging from 18 to 33. In all of these studies, at 1 to 12 months, there was a significant increase in Qmax (ranging from +3.6 to + 11 ml/s) and a significant decrease in PVR (ranging from -21 to -80 mL) [18-20, 22-23]. IPSS significantly decreased at six weeks in the only of these studies evaluating IPSS [certainty of evidence: very low]. [20].

Tamsulosin was used in four studies which all reported low rates of adverse events, ranging from 5.3% to 6.2% [certainty of evidence: very low] [13, 18, 20, 22]. The rate of adverse events with other alpha-blockers (prazosin, terazosin and alfuzosin) ranged from 16% to 72.2% [certainty of evidence: very low] [13, 15, 19, 23]. The most common adverse events were dizziness, headache and gastrointestinal discomfort.

Overall, the cure/improvement of BOO as defined by the trialist ranged from 50% to 84.2% with alpha-blockers at 1 to 12 months [certainty of evidence: very low]. No data after 1 year follow-up or more was available for any of the study assessing alpha-blockers.

Surgical treatments

Urethral dilation/Internal urethrotomy
One RCT and one retrospective comparative study were found on urethral dilation and two prospective noncomparative studies assessed internal urethrotomy, (combined with urethral dilation in one of the studies).

Basu *et al* randomized 50 patients with functional BOO (Qmax<15 ml/s and PdetQmax>20 cmH$_2$O without anatomical BOO on cystoscopy) to receive either urethrocystoscopy and bladder distension (N=28) or urethral dilatation (N=22) [14]. At 6 weeks, there were significantly more resolution of urgency in the urethral dilatation group (45.5% vs. 17.9%; p=0.03). Of note, there were no significant change in Qmax, PVR, voided volume or PdetQmax in any of the two groups at 6 weeks questioning the role of any of these two options for the therapeutic management of BOO [certainty of evidence: low]. Also, six patients (12%) developed post-operative stress urinary incontinence [14].

In a retrospective study involving females with urethral stricture Tao *et al* compared the outcomes of repeated urethral dilation (n=10) vs. labium flap dorsal onlay urethroplasty (n=12). They reported significant improvement of Qmax, PVR, IPSS and IPSS qol in both groups although the improvement of Qmax and IPSS-qol was significantly greater in the urethroplasty group [certainty of evidence: low] [29].

The two prospective case series included small numbers of patients [25, 39]. Grivas *et al* reported significant improvements of Qmax, PVR, IPSS and IPSS-qol with urethral dilation combined with internal urethrotomy in 10 women with unspecified functional BOO and reported no de novo SUI [certainty of evidence: very low] [25]. In a series of 23 women with urethral stricture treated with internal urethrotomy, Sharifian et al

observed significant improvements of IPSS and IPSS-qol at 12, 24 and 48 months with 66.7% having reduction or cure of the obstruction and 9.5% of patients developing de novo SUI [certainty of evidence: very low] [39].

Urethroplasty

Eight studies were included: six prospective non comparative studies, one large retrospective comparative study and one small RCT [32, 35-37, 40-43]. The techniques used were very heterogeneous in terms of approach (dorsal vs ventral) and tissue used (local flap vs free graft). The cure or reduction of obstruction rates were 77% and 88% in the two studies reporting it within the first year [32, 40] and 85.7% to 95.5% in the three studies reporting it after a follow-up of 1 to 5 years [35, 37, 43] [certainty of evidence: very low]. Four studies reported the change in Qmax, PVR and IPSS within the first year with significant improvement of all these parameters compared to baseline [certainty of evidence: very low] [32, 36, 40, 42]. The postoperative complication rates ranged from 0% to 14.3%, being mostly de novo/worsened LUTS postoperatively [32, 35-37]. The rates of de novo SUI ranged from 0% to 4.6% [certainty of evidence: very low] [32, 35-37, 40]. The RCT compared dorsal vs. ventral buccal mucosa graft urethroplasty and did not find any significant difference but with only 12 patients in each group [42]. The large multicenter series found a lower rate of success with endoscopic management compared to local flap or free graft urethroplasty (36% vs 66% vs. 64%) with similar morbidities. The techniques used within each of the three groups were very heterogeneous [41].

Transurethral bladder neck incision

Six prospective non comparative studies evaluating transurethral bladder neck incision were found [17, 21, 24, 26, 30, 33]. The rates of cure or reduction of obstruction ranged from 91% to 100% with significant improvement of PVR, Qmax, IPSS and IPSS-qol at 1 to 12 months in all of these five studies [certainty of evidence: very low] [17, 21, 24, 26, 33]. Two studies reported sustained efficacy with significant improvement of PVR, Qmax, IPSS and IPSS-qol after 1 to 5 years [certainty of evidence: very low] [24, 26]. The only complication reported was de novo SUI with rates ranging from 3.3% to 9.1% [certainty of evidence: very low] [17, 21, 24, 26, 33].

<u>Sling revision</u>

In a prospective series including 71 women with voiding dysfunction caused by too tightly positioned tension-free vaginal tape (TVT) and managed by early tape mobilization (median 2 days after TVT insertion) Rautenberg et al reported a resolution of voiding dysfunction/urinary retention in 96.7% of patients and recurrence/persistence of SUI in only 4.9% [certainty of evidence: very low] [34].

<u>Pelvic organ prolapse repair</u>

The only eligible study looking at the role of POP repair in treating BOO was a prospective noncomparative study of 29 women with Qmax<15 ml/s and PdetQmax>20 cmH$_2$O who underwent vaginal mesh or sacrospinous ligament fixation for stage 2 to 4 cystocele. On urodynamics at 6 months, the authors reported resolution of BOO in 100% of patients [certainty of evidence: very low]. No other outcome of interest was reported in this series [38].

Discussion

The therapeutic armamentarium of female BOO is large owing to the numerous possible causes of BOO in women, with many treatments being cause-specific [2,6]. The present systematic review is, to our knowledge, the first aiming to evaluate the evidence supporting all existing treatments for female BOO. We found that the vast majority of the therapeutic options currently used to treat female BOO is supported by scant and poor evidence.

BOO is defined by the International Continence Society as the generic term for obstruction during voiding characterized by increased detrusor pressure and reduced urine flow rate [1]. Hence, its diagnosis implies the need for urodynamics, which is the only test currently available to study the synchronous values of flow rate and detrusor pressure [1]. While the definition of BOO is well-established, relatively consensual and with some data supporting its clinical validity in male patients [4], the urodynamic definition of female BOO remains a matter of controversy [2]. 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 as illustrated by the variety of definitions used for BOO in all included studies [2, 5]. This lack of standardized definition of female

BOO and the absence of consensus on its various entities clearly hamper research in the field.

Although female BOO is certainly underdiagnosed, one should recognize that this remains a relatively uncommon condition. Beyond the lack of consensual definition and diagnostic approach, this scarcity will be the most significant barrier to overcome to build well-designed prospective studies. This also partly explains the paucity of evidence currently available. Future research protocols should favor multicenter settings to allow larger sample size and adequately powered studies

Surprisingly, we did not find any eligible study for several treatments of female BOO. Sacral nerve stimulation (SNS) is a well-recognized treatment option for chronic urinary retention. While often referred to as "non-obstructive" urinary retention, indications of SNM actually encompasses functional BOO as some studies have suggested that SNM may provide better outcomes in women with urodynamically proven BOO [44-45]. No eligible study was found for intrasphincteric botulinum toxin injections, another popular therapeutic option for functional BOO in female patients. A randomized controlled trial does exist including both males and females with no subgroup analysis [46]. While often advocated as the first-line treatment for dysfunctional voiding [47], we could not find any evidence to support the use of pelvic floor physiotherapy in adult patients with functional BOO.

Another point of interest of our study was the comparable efficacy of placebo and pharmacological treatments in almost all placebo-controlled trials available for BOO. The placebo effect has been well documented for lower urinary tract dysfunctions and could be underpinned by numerous mechanisms including the natural history of LUTS or regression to the mean, patients' expectation and the role of the interoceptive network in the neural control of lower urinary tract functioning [48]. This finding underscores the outmost importance of including placebo control arms in future studies evaluating pharmacological treatments of female BOO.

The present systematic review has several limitations that should be acknowledged. The poor diagnostic work-up in many included studies was one of the main shortcomings we observed. One may hypothesize that the lack of characterization of

the BOO etiology and inherent inclusion of heterogeneous group of patients might have undermined the outcomes in those studies. Our systematic review included a wide spectrum of BOO etiologies with heterogeneous definition of BOO which hindered the overall quality of the present work. A global effort is needed to standardize female BOO definition and diagnostic algorithm to enable significant breakthrough in its management. Because some strictures cannot be catheterized, urodynamic is not always feasible in this patient population and though, these patients are unarguably obstructed. However, this definition cannot exclude the coexistence of detrusor underactivity. More globally, the coexistence of detrusor underactivity was not an exclusion criterion in our systematic review which may have impacted our findings. Another important drawback was the relatively small sample size of most included studies and the overall high risk of bias for many studies. The lack of consensual core outcomes for female BOO treatment could be regarded as a significant limitation and may jeopardize future studies in this field. Most studies on surgical treatments did not adhere to current guidelines on complications reporting [49], which prevented proper determination of the relative morbidity of each treatment. Very few studies reported long term outcomes. Finally, the certainty of evidence was low and very low for all included studies

Conclusion

Evidence to support the use of conservative, pharmacological and surgical treatments for BOO are scarce. Baclofen is the only treatment which demonstrated superior efficacy compared to placebo in female patients with functional BOO in a small sample RCT. Alpha-blockers and sildenafil improve voiding parameters in female with functional BOO but did not show superior efficacy when compared to placebo. Urethroplasty, transurethral bladder neck incision, mid-urethral sling revision and urethral dilation are only supported by small sample single arm prospective series. Well-designed prospective studies including well-defined homogeneous groups of patients are needed to build robust therapeutic algorithms for female BOO. In light of the present findings, we suggest that future research protocols should include thorough pretreatment work-up with at least urodynamics and cystoscopy to accurately define the study population. Owing to the relative rarity of many of existing female BOO

causes, multicenter design may be favored to enable larger sample size/adequately powered studies.

Figure Legends

Figure 1: PRISMA Flow Chart

Figure 2: Risk of bias assessment summary

Figure 2a: Risk of bias for comparative studies

Figure 2b: risk of bias for non-comparative studies

References

1. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn. 2002;21(2):167-78

2. Hoffman DS, Nitti VW. Female Bladder Outlet Obstruction. Curr Urol Rep. 2016 ;17(4):31

3. Malde S, Solomon E, Spilotros M, et al. Female bladder outlet obstruction: Common symptoms masking an uncommon cause. Low Urin Tract Symptoms. 2019;11(1):72-77.

4. Rademakers K, Drake MJ, Gammie A, et al. Male bladder outlet obstruction: Time to re-evaluate the definition and reconsider our diagnostic pathway? ICI-RS 2015. Neurourol Urodyn. 2017;36(4):894-901

5. Meier K, Padmanabhan P. Female bladder outlet obstruction: an update on diagnosis and management. Curr Opin Urol. 2016;26(4):334-41.

6. Rademakers K, Apostolidis A, Constantinou C, et al. Recommendations for future development of contractility and obstruction nomograms for women. ICI-RS 2014. Neurourol Urodyn. 2016;35(2):307-11

7. Liberati A, Altman DG, Tetzlaff J & al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions : explanation and elaboration. J Clin Epidemiol 2009 ;62(10):e1-34.

8. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions v.5.0.2. The Cochrane Collaboration, 2011. http://www.cochrane-handbook.org/. Accessed February 2014

9 Knoll T, Omar MI, Maclennan S, Hernandez V, Canfield S, Yuan Y, et al. Key Steps in Conducting Systematic Reviews for Underpinning Clinical Practice Guidelines: Methodology of the European Association of Urology. Eur Urol. 2018; 73(2):290-300

10. Guyatt, G.H., et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ, 2008. 336: 924.

11. Datta SN, Kavia RB, Gonzales G, Fowler CJ. Results of double-blind placebo-controlled crossover study of sildenafil citrate (Viagra) in women suffering from obstructed voiding or retention associated with the primary disorder of sphincter relaxation (Fowler's Syndrome). Eur Urol. 2007;51(2):489-95

12. Xu D, Qu C, Meng H, et al. Dysfunctional voiding confirmed by transdermal perineal electromyography, and its effective treatment with baclofen in women with lower urinary tract symptoms: a randomized double-blind placebo-controlled crossover trial. BJU Int. 2007;100(3):588-92.

13. Hajebrahimi S, Asrbadr YA, Azaripour A, Sadeghi-Bazargani H. Effect of tamsulosin versus prazosin on clinical and urodynamic parameters in women with voiding difficulty: a randomized clinical trial. Int J Gen Med. 2011;4:35-9.

14. Basu M, Khullar V, Duckett J Urethral dilatation: Is there any benefit over cystoscopy and distension? A randomized trial in women with overactive bladder symptoms.Neurourol Urodyn. 2014;33(3):283-8.

15. Lee YS, Lee KS, Choo MS, et al. Efficacy of an Alpha-Blocker for the Treatment of Nonneurogenic Voiding Dysfunction in Women: An 8-Week, Randomized, Double-Blind, Placebo-Controlled Trial. Int Neurourol J. 2018;22(1):30-40.

16. Koh JS, Kim SJ, Kim HS, Kim JC. Comparison of alpha-blocker, extracorporeal magnetic stimulation alone and in combination in the management of female bladder outlet obstruction. Int Urogynecol J. 2011;22(7):849-54.

17. Peng CH, Kuo HC. Transurethral incision of bladder neck in treatment of bladder neckobstruction in women. Urology. 2005;65(2):275-8

18. Pischedda A, Pirozzi Farina F, Madonia M, Cimino S, Morgia G. Use of alpha1-blockers in female functional bladder neck obstruction. Urol Int. 2005;74(3):256-61

19. Kessler TM, Studer UE, Burkhard FC. The effect of terazosin on functional bladder outlet obstruction in women: a pilot study. J Urol. 2006 Oct;176(4 Pt 1):1487-92.

20. Chang SJ, Chiang IN, Yu HJ. The effectiveness of tamsulosin in treating women with voiding difficulty. Int J Urol. 2008 ; 15(11):981-5.

21. Fu Q, Xu YM Transurethral incision of the bladder neck using KTP in the treatment of bladder neck obstruction in women. Urol Int. 2009;82(1):61-4.

22. Costantini E, Lazzeri M, Bini V et al. Open-label, longitudinal study of tamsulosin for functional bladder outlet obstruction in women. Urol Int. 2009;83(3):311-5.

23. Athanasopoulos A, Gyftopoulos K, Giannitsas K, Perimenis P. Effect of alfuzosin on female primary bladder neck obstruction. Int Urogynecol J Pelvic Floor Dysfunct. 2009; 20(2):217-22.

24. Jin XB, Qu HW, Liu H, Li B, Wang J, Zhang YD. Modified transurethral incision for primary bladder neck obstruction in women: a method to improve voiding function without urinary incontinence. Urology. 2012;79(2):310-3.

25. Grivas N, Tsimaris I, Makatsori A, Hastazeris K, Kafarakis V, Stavropoulos NE The effectiveness of otis urethrotomy combined with six weeks urethral dilations until 40 Fr in the treatment of bladder outlet obstruction in women: a prospective study. Urol J. 2014;10(4):1063-6

26. Shen W, Ji H, Yang C, et al. Controlled transurethral resection and incision of the bladder neck to treat female primary bladder neck obstruction: Description of a novel surgical procedure. Int J Urol. 2016;23(6):491-5.

27. Mouracade P, Lang H, Jacqmin D, Saussine C. Transvaginal tape lysis for urinary obstruction after suburethral tape placement. When to do an immediate replacement? Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(9):1271-4

28. Ghoniem G, Abdelwahab H, Elmissiry M, Khater U. Surgical Choices for the Treatment of Bladder Outlet Obstruction After Sling Procedures J Pelvic Med Surg 2008;14:369–374

29. Tao TT, Xu QK, Hu Q, et al. Novel surgical technique for female distal urethral stricture disease: an evaluation of efficacy and safety compared with urethral dilatation. Int J Clin Exp Med 2018;11(11):12002-12007

30. Fenster HN. Female bladder neck incision. Urology. 1990;35(2):109-10

31. Romanzi LJ, Chaikin DC, Blaivas JG. The effect of genital prolapse on voiding. J Urol. 1999;161(2):581-6

32. Montorsi F, Salonia A, Centemero A, et al. Vestibular flap urethroplasty for strictures of the female urethra. Impact on symptoms and flow patterns. Urol Int. 2002;69(1):12-6

33. Sharifiaghdas F, Kardoust Parizi M, Ahadi B. Efficacy of transurethral bladder neck incision with 2-micron continuous wave laser (RevoLix) for the management of bladder outlet stricture in women. Urol J. 2013;10(1):790-4

34. Rautenberg O, Kociszewski J, Welter J, Kuszka A, Eberhard J, Viereck V Ultrasound and early tape mobilization--a practical solution for treating postoperative voiding dysfunction. Neurourol Urodyn. 2014;33(7):1147-51

35. Önol FF, Önol ŞY, Tahra A, Boylu U. Ventral inlay labia minora graft urethroplasty for the management of female urethral strictures. Urology. 2014 ;83(2):460-4.

36. Goel A, Paul S, Dalela D, Sankhwar P, Sankhwar SN, Singh V. Dorsal onlay buccal mucosal graft urethroplasty in female urethral stricturedisease: a single-center experience. Int Urogynecol J. 2014;25(4):525-30

37. Mukhtar BMB, Spilotros M, Malde S, Greenwell TJ. Ventral-onlay buccal mucosa graft substitution urethroplasty for urethral stricture in women. BJU Int. 2017;120(5):710-716

38. Lo TS, Al-Kharabsheh AM, Tan YL, et al. Single incision anterior apical mesh and sacrospinous ligament fixation in pelvic prolapse surgery at 36 months follow-up. Taiwan J Obstet Gynecol. 2017;56(6):793-800

39. Sharifian H, Zargham M, Khorami MH, Mohamadi M, Mazdak H, Mozafarpour S Internal Urethrotomy in Treatment of Female with Anatomical Bladder Outlet Obstruction. Adv Biomed Res. 2019 May 27;8:36

40. Manasa T, Khattar N, Tripathi M, Varshney A, Goel H, Sood R. Dorsal onlay graft urethroplasty for female urethral stricture improves sexual function: Short-term results of a prospective study using vaginal graft. Indian J Urol. 2019;35(4):267-272

41. Lane GI, Smith AL, Stambakio H, et al. Treatment of urethral stricture disease in women: A multi-institutional collaborative project from the SUFU research network. Neurourol Urodyn. 2020;39(8):2433-2441

42. Katiyar VK, Sood R, Sharma U, Goel HK, Gahlawat S, Desai DS. Critical Analysis of Outcome Between Ventral and Dorsal Onlay Urethroplasty in Female Urethral Stricture. Urology 2021 in press. doi: 10.1016/j.urology.2021.05.021

43. Khawaja AR, Dar YA, Bashir F, Wani PM, Bhat AH, Wani MS Outcome of dorsal buccal graft urethroplasty in female urethral stricture disease (FUSD); our institutional experience..Int Urogynecol J. 2021 in press doi: 10.1007/s00192-021-04840-9.

44. De Ridder D, Ost D, Bruyninckx F. The presence of Fowler's syndrome predicts successful long-term outcome of sacral nerve stimulation in women with urinary retention. Eur Urol. 2007; 51:229–233; discussion 233-224.

45. Panicker JN, Anding R, Arlandis S, et al. Do we understand voiding dysfunction in women? Current understanding and future perspectives: ICI-RS 2017. NeuroUrol Urodyn. 2018;37(S4):S75-S85.

46. Jiang YH, Wang CC, Kuo HC. OnabotulinumtoxinA Urethral Sphincter Injection as Treatment for Non-neurogenic Voiding Dysfunction - A Randomized, Double-Blind, Placebo-Controlled Study. Sci Rep. 2016 Dec 13;6:38905.

47. Tarcan T, von Gontard A, Apostolidis A, Mosiello G, Abrams P Can we improve our management of dysfunctional voiding in children and adults: International Consultation on Incontinence Research Society; ICI-RS2018? .Neurourol Urodyn. 2019 Dec;38 Suppl 5:S82-S89.

48. Mostafaei H, Janisch F, Mori K, et al. Placebo Response in Patients with Oral Therapy for Overactive Bladder: A Systematic Review and Meta-analysis. Eur Urol Focus. 2021 Mar 2:S2405-4569(21)00048-1.

49. Mitropoulos D, Artibani W, Graefen M, Remzi M, Rouprêt M, Truss M; European Association of Urology Guidelines Panel. Reporting and grading of complications after urologic surgical procedures: an ad hoc EAU guidelines panel assessment and recommendations. Eur Urol. 2012;61(2):341-9