Review – Bladder Outlet Obstructions

Diagnostic Tests for Female Bladder Outlet Obstruction: A Systematic Review from the European Association of Urology Non-neurogenic Female LUTS Guidelines Panel


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1. Introduction

Female bladder outlet obstruction (fBOO) is an uncommon condition that can be caused by anatomical or functional abnormalities [1]. The estimated prevalence is 2–23% depending on diagnostic criteria [2]. The International Continence Society (ICS) defines fBOO as “the generic term for obstruction during voiding, characterised by a reduced urine flow rate (FR) and/or presence of a raised post-void residual (PVR) and an increased detrusor pressure (Pdet)” [3]. Female patients typically present with lower urinary tract symptoms (LUTS), which are rarely isolated voiding symptoms [4]. The urodynamics (UDS) criteria and diagnostic cut-off values for fBOO are not defined, and vary in the literature. This is in stark contrast to bladder outlet obstruction (BOO) in males, which is well defined and has a greater evidence base [5]. The objective of the current systematic review (SR) was to identify and compare different diagnostic tests, which have been proposed for the diagnosis of fBOO.

2. Evidence acquisition

2.1. Review protocol and search strategy

The review followed the methods detailed in the Cochrane Handbook and followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist (Supplementary Table 1), guided by the European Association of Urology (EAU) Guidelines Office Methods Committee [6–8].

Medline, Embase, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials databases were searched without language or other restrictions for all relevant publications up to August 4, 2020. The search strategy is detailed in the Supplementary material. Reference lists of the included studies were screened, and included for full-text screening and data extraction if they fulfilled our a priori inclusion criteria.

Two review authors (K.H.P. and R.C.) screened all abstracts and full-text articles independently. Any
disagreement was discussed and resolved by the senior authors (M.I.O. and C.K.H.). Standardised data extraction was performed by the same two review authors who performed screening. The flowchart depicting the overall review process according to the PRISMA statement is shown in Figure 1.

### 2.2. Eligibility criteria

Eligibility criteria of this SR are the following:

1. **Study design**: All types of studies including at least ten participants assessing the diagnostic accuracy of tests for fBOO.
2. **Participants:** Adult female (≥18 yr) patients with non-neurogenic LUTS suspected of BOO with no established aetiology

3. **Index tests:** Any test used to diagnose BOO (including, but not limited to, uroflowmetry, standard UDS, video-urodynamics [VUDS], voiding fluoroscopy, electromyography, urethral pressure profilometry, Doppler ultrasound, infrared spectroscopy, or endoscopy)

4. **Comparator tests:** Any of the abovementioned diagnostic tests or no control group

5. **Test accuracy measures:** Any metric pertaining to diagnostic accuracy for BOO, including sensitivity, specificity, negative/positive predictive value (NPV/PPV), and overall accuracy

6. **Secondary outcomes**

   - Including the criteria for defining fBOO

### 2.3 Assessment of risk of bias in individual studies

Risk of bias (RoB) assessment within the included studies was performed independently by two authors (K.H.P. and R.C.) according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (Fig. 2 and 3) [9]. This tool provides a measure for RoB and applicability over four domains of interest (patient selection, index test, reference standard, and timing of the index test and the reference standard). A list of the most important potential confounders for outcomes was developed a priori with clinical content experts (EAU Non-neurogenic Female LUTS Guidelines Panel). Confounder assessment included whether each diagnostic confounder was considered and whether, if necessary, it was controlled for in the analysis. Potential confounding factors assessed were the following: (1) whether indices for UDS were determined automatically or manually, and (2) whether the UDS adhered to contemporaneous quality standards (ICS standards for studies from 2002 onwards; for studies before 2002, judgment was made by reviewers). Disagreement was solved by a third review author (M.I.O.).

### 2.4 Data analysis

Owing to the expected heterogeneity in definitions and thresholds of the index tests for diagnosing fBOO, a quantitative analysis and meta-analysis was not feasible, and therefore a qualitative (narrative) synthesis of all included studies was performed. Where elements of diagnostic accuracy were not reported by study authors, we calculated these by using a two-by-two contingency table consisting of true positive, false positive, false negative, and true negative rates based on the data reported by study authors. True positive cases were those diagnosed by VUDS used as the reference standard. Measures of test performance included sensitivity, specificity, PPV, NPV, and overall accuracy.

### 3. Evidence synthesis

#### 3.1 Study selection

The search identified 6344 citations. After duplicate report removal, 4076 were screened by abstract and 79 were assessed for full-text eligibility. Overall, 28 studies fulfilled the inclusion criteria set for this review, and 10 248 patients were included in the qualitative analysis (Fig. 1) [4,10–32].

#### 3.2 Characteristics of the included studies

The characteristics of the 28 included studies are detailed in Table 1 and Supplementary Table 2. Of these, 25 evaluated
the use of UDS ± fluoroscopy [4,10–22,26–36], two of which evaluated pre-existing nomograms [35,36], one evaluated the use of transvaginal ultrason sound scan (TVUS) and voiding UDS [23, and two looked at transperineal Doppler ultrasound scan (TPUS) [24,25]. Five studies defined cut-offs for UDS parameters [17,26,29,31,32], one study described fluoroscopic characteristics for fBOO [20], one study evaluated the area under the curve (AUC) of detrusor pressure [18], and three studies derived a nomogram to diagnose fBOO [10,14,19].

3.3. RoB assessment

The QUADAS-2 tool was used to assess RoB within studies. Results are graphically illustrated in Figures 2 and 3. The proportions of studies with a low RoB in the “patient selection”, “index test”, “reference standard”, and “flow and timing” domains were 75%, 82.1%, 42.9%, and 78.6%, respectively. The domain showing the highest proportion of studies with an “unclear” RoB was the “reference standard” domain (57.1%). Overall, there were low levels of concern about the applicability of the studies’ findings to the review question regarding the “patient selection” and “index test” domains, while there was a high level of concern regarding the “reference standard” domain in more than half of the included studies (54%).

3.4. Results of individual studies: a narrative synthesis

The UDS parameter cut-offs, and nomogram and diagnostic details for each study are summarised in Table 2. The overall ranges of diagnostic performance across all tests were as follows: sensitivity, 54.6–92.5%; specificity, 64.6–93.9%; PPV, 50–95.5%; NPV, 33.3–97.1%; and overall accuracy, 64.1–92.2%.

3.4.1. Defining UDS cut-off values

Massey and Abrams [32] defined cut-offs of Qmax <12 ml/s, Pdet.Qmax >50 cmH2O, and urethral resistance >0.2 to diagnose fBOO. In 5948 consecutive patients presenting with LUTS, 163 (2.74%) were found to have fBOO based on these criteria. Lemack and Zimmern [31] performed receiver-operator characteristic analyses from UDS on female patients with voiding LUTS. All patients had prior voiding cystourethrography, and cut-off values of Qmax ≤11 ml/s and Pdet.Qmax ≥21 cmH2O optimised the diagnostic accuracy for fBOO. These cut-offs provided sensitivity, specificity, and overall accuracy of 91.5%, 73.6%, and 81%, respectively. Defreitas et al [29] found in women with a range of LUTS that the Pdet.Qmax value with high specificity and the greatest sensitivity for detecting fBOO was 25 cmH2O, and the Qmax value resulting in equal sensitivity, specificity, and accuracy (68%) was close to 12 ml/s. Kuo [17] analysed VUDS data from 580 patients with a range of LUTS, and proposed thresholds of Qmax ≤15 ml/s and Pdet.Qmax ≥35 cmH2O improving sensitivity, specificity, and overall accuracy for fBOO to 81.6%, 93.9%, and 92.2%, respectively. Gravina et al [26] found that Qmax ≤15 ml/s was associated with sensitivity of 78.9% and specificity of 85.9% in a cohort of women with a range of LUTS. A Pdet.Qmax of ≥28 cmH2O resulted in poor sensitivity of 64.2% and specificity of 64.6%. However, when using a BOO index (Pdet.Qmax / Qmax of >–8, the sensitivity and specificity increased to 80.8% and 86.1%, respectively. Cormier et al [18] used the previously defined Qmax of <12 ml/s, but evaluated additional UDS parameters: (1) AUC of Pdet during voiding (AUCdet) and (2) AUC of Pdet during voiding adjusted for voided volume (AUCdet/Vol), in a cohort of women with a clinical diagnosis of dysfunctional voiding. Dysfunctional voiding is defined by the ICS as “an intermittent and/or fluctuating flow rate due to involuntary intermittent contractions of the peri-urethral striated or levator muscles during voiding in neurologically normal women” [3]. Using linear discriminant analysis, AUCdet/Vol was confirmed as a relevant parameter to classify patients into obstructed, equivocal, and nonobstructed groups. A cut-off value of 5.83 cmH2O/ml separated obstructed from equivocal cases and 2.56 cmH2O/ml distinguished equivocal from unobstructed cases.

3.4.2. Fluoroscopy

Nitti et al [20] proposed VUDS criteria, based mainly on fluoroscopic appearance, for diagnosing fBOO. In a study of 261 women with “non-neurogenic voiding dysfunction”, BOO was defined as radiographic evidence of obstruction between the bladder neck (BN) and distal urethra in the presence of a sustained detrusor contraction of any magnitude, which was usually associated with a reduced urinary flow rate. Bladder neck obstruction (BNO) was diagnosed when the BN was closed/narrowed during attempted voiding. Radiographic obstruction of the urethra was diagnosed as a discrete area of narrowing with proximal dilatation. Strict pressure-flow criteria were not used to classify cases as obstructed or unobstructed in their study. Overall, 76 (29.1%) patients met the fluoroscopic criteria for
### Table 1 – Overview of the design, patient population, and diagnostic criteria for bladder outlet obstruction among the studies included in the review

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Study design</th>
<th>Country</th>
<th>Clinical presentation</th>
<th>Total no. of patients analysed</th>
<th>BOO, n (%)</th>
<th>Age (yrs), mean (SD or range)</th>
<th>Test evaluated</th>
<th>Reference test</th>
<th>Diagnostic criteria for BOO as reported by authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akikwala (2006)[27]</td>
<td>Prospective—single centre</td>
<td>USA</td>
<td>LUTS</td>
<td>91</td>
<td>40 (44.0)</td>
<td>62.3 (16–90)</td>
<td>VUDS, PF EMG</td>
<td>Fluoroscopy</td>
<td>Five criteria, including (1) fluoroscopy, (2) $Q_{\text{max}} \leq 15 \text{ ml/s}$ and $P_{\text{det}}\cdot Q_{\text{max}} \geq 20 \text{ cmH}<em>2\text{O}$, (3) $Q</em>{\text{max}} \leq 11 \text{ ml/s}$ and $P_{\text{det}}\cdot Q_{\text{max}} \geq 21 \text{ cmH}<em>2\text{O}$, (4) $Q</em>{\text{max}} \leq 12 \text{ ml/s}$ and $P_{\text{det}}\cdot Q_{\text{max}} \geq 25 \text{ cmH}_2\text{O}$, and (5) the Blaivas-Groutz nomogram</td>
</tr>
<tr>
<td>Blaivas (2000)[19]</td>
<td>Retrospective—single centre</td>
<td>USA</td>
<td>LUTS</td>
<td>100</td>
<td>50 (50)</td>
<td>BOO: 64.4 (17.6); unobstructed: mean 64.8 (10.7)</td>
<td>VUDS, EMG, endoscopy</td>
<td>Fluoroscopy</td>
<td>One or more: (1) free $Q_{\text{max}} \leq 12 \text{ ml/s}$ and $P_{\text{det}}\cdot Q_{\text{max}} \geq 20 \text{ cmH}<em>2\text{O}$, (2) radiographic evidence BOO with sustained detrusor contraction $&gt;20 \text{ cmH}<em>2\text{O}$, and poor $Q</em>{\text{max}}$, regardless of free $Q</em>{\text{max}}$, (3) inability to void with transurethral catheter in place despite a sustained detrusor contraction of $&gt;20 \text{ cmH}_2\text{O}$</td>
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<tr>
<td>Chen (2014)[22]</td>
<td>Retrospective—single centre</td>
<td>Taiwan</td>
<td>LUTS</td>
<td>440</td>
<td>168 (38.2)</td>
<td>DV: 67.8 (18.1); control: 58.9 (18.4)</td>
<td>VUDS</td>
<td>Fluoroscopy</td>
<td>DV: high $P_{\text{det}}$, intermittently increased external sphincter EMG activity and a “spinning top” urethral appearance on cinefluoroscopy during voiding</td>
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<tr>
<td>Choi (2013)[11]</td>
<td>Prospective—multicentre</td>
<td>Korea</td>
<td>LUTS</td>
<td>792</td>
<td>89 (11.2)</td>
<td>Voiding difficulty: 61.8 (12.1); LUTS: 62.7 (10.2)</td>
<td>UDS</td>
<td>Clinical assessment</td>
<td>$Q_{\text{max}} &lt; 15 \text{ ml/s}$ and $P_{\text{det}}\cdot Q_{\text{max}} &gt; 20 \text{ cmH}_2\text{O}$</td>
</tr>
<tr>
<td>Chuang (2012)[16]</td>
<td>Retrospective—single centre</td>
<td>Taiwan</td>
<td>LUTS</td>
<td>781</td>
<td>405 (51.9)</td>
<td>NR</td>
<td>VUDS</td>
<td>Fluoroscopy</td>
<td>BND: VUDS revealing narrow BN with high/normal detrusor contractility; DV: high $P_{\text{det}}$ with open BN and narrow mid urethra during voiding; stricture: narrow distal urethra with low FR regardless high/normal VP; PRPF: could not relax their PF muscle with low VP and intermittent flow</td>
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<tr>
<td>Cormier (2002)[18]</td>
<td>Prospective—single centre</td>
<td>France</td>
<td>VD</td>
<td>85</td>
<td>21 (24.7)</td>
<td>55 (18–83)</td>
<td>VUDS, UP</td>
<td>Fluoroscopy</td>
<td>$Q_{\text{max}} \geq 12 \text{ ml/s}$ and $P_{\text{det}}\cdot Q_{\text{max}} &gt; 150 \text{ ml}$</td>
</tr>
<tr>
<td>Defreitas (2004)[29]</td>
<td>Prospective—single centre</td>
<td>USA</td>
<td>LUTS</td>
<td>313</td>
<td>169 (54.0)</td>
<td>BOO: 60 (15); control: 42 (7)</td>
<td>UDS</td>
<td>Clinical assessment</td>
<td>$Q_{\text{max}} \geq 12 \text{ ml/s}$ and $P_{\text{det}}\cdot Q_{\text{max}} &gt; 25 \text{ cmH}_2\text{O}$</td>
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<tr>
<td>Dybowiski (2014)[14]</td>
<td>Retrospective—multicentre</td>
<td>Poland</td>
<td>Voiding LUTS</td>
<td>67</td>
<td>21 (31.3)</td>
<td>Median 53</td>
<td>UDS</td>
<td>Clinical assessment</td>
<td>BOO = $(P_{\text{det}}\cdot Q_{\text{max}} - 1.5 \times Q_{\text{max}}) &gt; 10$</td>
</tr>
<tr>
<td>Galica (2015)[23]</td>
<td>Retrospective—single centre</td>
<td>Italy</td>
<td>BOO symptoms</td>
<td>15</td>
<td>3 (20)</td>
<td>NR</td>
<td>TVUS, VUDS, EMG</td>
<td>Fluoroscopy</td>
<td>$Q_{\text{max}} &lt; 12 \text{ ml/s}$ and $P_{\text{det}}\cdot Q_{\text{max}} &gt; 20 \text{ cmH}_2\text{O}$, no images for urethral stricture at fluoroscopy, silent EMG</td>
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<tr>
<td>Gravina (2007)[26]</td>
<td>Retrospective—single centre</td>
<td>Italy</td>
<td>LUTS</td>
<td>170</td>
<td>133 (78.2)</td>
<td>BOO, median (IQR): UDS 62 (56–69); unobstructed: 57.5 (48.3–63.5)</td>
<td>UDS</td>
<td>Clinical assessment</td>
<td>1. $Q_{\text{max}}$ cut-off $&lt; 15 \text{ ml/s}$</td>
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<td>2. BOOI cut-off $&gt; 8$</td>
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<td>3. $P_{\text{det}}\cdot Q_{\text{max}} \geq 28 \text{ cmH}_2\text{O}$</td>
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<tr>
<td>First author</td>
<td>Study design</td>
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<td>Groutz (2000) [4]</td>
<td>Retrospective—single centre</td>
<td>USA</td>
<td>Voiding LUTS</td>
<td>587</td>
<td>38 (6.5)</td>
<td>63.9 (17.5)</td>
<td>VUDS, EMG, endoscopy</td>
<td>Fluoroscopy</td>
<td>$Q_{\text{max}} &lt; 12 \text{ ml/s}$ and $P_{\text{det,Qmax}} &gt; 20 \text{ cmH}_2\text{O}$; site of obstruction: narrowest point in the urethra during VCUG; urethral obstruction: (1) visible signs of narrowed urethra, analogous to urethral stricture in men; (2) the urethra felt narrow because it &quot;gripped&quot; the cystoscope; or (3) the bladder neck and proximal urethra appeared to be compressed, analogous to benign prostate hyperplasia in men</td>
</tr>
<tr>
<td>Ha (2009) [34]</td>
<td>Retrospective—multicentre</td>
<td>Korea</td>
<td>LUTS</td>
<td>320</td>
<td>39 (12.2)</td>
<td></td>
<td>UDS</td>
<td>Clinical assessment</td>
<td>$Q_{\text{max}} &lt; 12 \text{ ml/s}$ and $P_{\text{det,Qmax}} &gt; 20 \text{ cmH}_2\text{O}$; site of obstruction: narrowest point in the urethra during VCUG; urethral obstruction: (1) visible signs of narrowed urethra, analogous to urethral stricture in men; (2) the urethra felt narrow because it &quot;gripped&quot; the cystoscope; or (3) the bladder neck and proximal urethra appeared to be compressed, analogous to benign prostate hyperplasia in men</td>
</tr>
<tr>
<td>Hsiao (2017) [21]</td>
<td>Retrospective—single centre</td>
<td>Taiwan</td>
<td>VD</td>
<td>1914</td>
<td>1858 (97.1)</td>
<td></td>
<td>Uroflowmetry, UDS, VCUG</td>
<td>Fluoroscopy</td>
<td>$Q_{\text{max}} &lt; 12 \text{ ml/s}$ and $P_{\text{det,Qmax}} &gt; 20 \text{ cmH}_2\text{O}$; site of obstruction: narrowest point in the urethra during VCUG; urethral obstruction: (1) visible signs of narrowed urethra, analogous to urethral stricture in men; (2) the urethra felt narrow because it &quot;gripped&quot; the cystoscope; or (3) the bladder neck and proximal urethra appeared to be compressed, analogous to benign prostate hyperplasia in men</td>
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<tr>
<td>Klijer (2004) [30]</td>
<td>Prospective—single centre</td>
<td>Poland</td>
<td>Chronic bladder symptoms</td>
<td>53</td>
<td>19 (35.9)</td>
<td>Median (range): 37.5 (16–70)</td>
<td>Uroflowmetry, UDS, VCUG</td>
<td>Fluoroscopy</td>
<td>$Q_{\text{max}} &lt; 12 \text{ ml/s}$ and $P_{\text{det,Qmax}} &gt; 20 \text{ cmH}_2\text{O}$; site of obstruction: narrowest point in the urethra during VCUG; urethral obstruction: (1) visible signs of narrowed urethra, analogous to urethral stricture in men; (2) the urethra felt narrow because it &quot;gripped&quot; the cystoscope; or (3) the bladder neck and proximal urethra appeared to be compressed, analogous to benign prostate hyperplasia in men</td>
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<tr>
<td>Kuo (2004) [17]</td>
<td>Retrospective—single centre</td>
<td>Taiwan</td>
<td>LUTS</td>
<td>580</td>
<td>76 (13.1)</td>
<td>BOO: 50.2 (15.1); SUI: 51 (12.7); asymptomatic: 44.6 (16.4)</td>
<td>VUDS</td>
<td>Fluoroscopy</td>
<td>1. Obstructive voiding and irritative symptoms</td>
</tr>
<tr>
<td>Kuo (2005) [12]</td>
<td>Retrospective—single centre</td>
<td>Taiwan</td>
<td>BOO signs and symptoms</td>
<td>207</td>
<td>194 (93.7)</td>
<td>BOO: 50.2 (15.1); SUI: 51 (12.7); asymptomatic: 44.6 (16.4)</td>
<td>VUDS, urethral EMG</td>
<td>Fluoroscopy</td>
<td>2. Sustained detrusor contraction during voiding phase in UDS</td>
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<td>4. DSD: increased sphincter EMG during voiding; PRPF: no concomitant relaxation of EMG activity during micturition</td>
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</table>

<table>
<thead>
<tr>
<th>First author</th>
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<th>Country</th>
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<th>Test evaluated</th>
<th>Reference test</th>
<th>Diagnostic criteria for BOO as reported by authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuo (2012) [15]</td>
<td>Retrospective—single centre</td>
<td>Taiwan</td>
<td>LUTS and pain</td>
<td>1605</td>
<td>314 (19.6)</td>
<td>58 (18–98)</td>
<td>VUDS Fluoroscopy</td>
<td>BND: VUDS revealing narrow BN with high/normal detrusor contractility; DV: high Pdet with open BN and narrow midurethra during voiding; stricture: narrow distal urethra with low FR regardless of high/normal VP; PRPF: could not relax their PF muscle with low VP and intermittent flow</td>
<td></td>
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<tr>
<td>Lemack (2000) [31]</td>
<td>Prospective—single centre</td>
<td>USA</td>
<td>Voiding LUTS</td>
<td>211</td>
<td>87 (41.2)</td>
<td>NR</td>
<td>UDS, PF EMGClinical assessment</td>
<td>Qmax &lt; 11 ml/s and Pdet.Qmax ≥ 21 cmH2O</td>
<td></td>
</tr>
<tr>
<td>Massey (1988) [32]</td>
<td>Retrospective—single centre</td>
<td>UK</td>
<td>LUTS</td>
<td>163</td>
<td>163 (100)</td>
<td>51.6 (8–81)</td>
<td>Uroflowmetry, UDS, UP, EMG Fluoroscopy</td>
<td>Two or more of the following parameters: (1) Qmax &lt; 12 ml/s, (2) Pdet.Qmax &gt; 50 cmH2O, (3) urethral resistance &gt; 0.2 (P/F2), (4) “significant” residual urine in the presence of raised Pdet.Qmax or urethral resistance</td>
<td></td>
</tr>
<tr>
<td>Nitti (1999) [20]</td>
<td>Retrospective—single centre</td>
<td>USA</td>
<td>Non-neurogenic VD</td>
<td>261</td>
<td>76 (29.1)</td>
<td>BOO: 57.5; unobstructed: 55</td>
<td>VUDS Fluoroscopy</td>
<td>BOO: radiographic evidence of obstruction between BN and distal urethra with sustained detrusor contraction of any magnitude, which was usually associated with reduced or delayed urinary flow rate; radiographic obstruction at the BN was diagnosed when BN was closed/narrow during voiding; radiographic obstruction of the urethra was diagnosed as a discrete area of narrowing with proximal dilatation</td>
<td></td>
</tr>
<tr>
<td>Ong (2020) [13]</td>
<td>Retrospective—single centre</td>
<td>Taiwan</td>
<td>LUTS</td>
<td>530</td>
<td>474 (89.4)</td>
<td>BOO: 57.8 (16.7); BND: 63.9 (17.1); DV: 61.1 (16.5); normal VUDS: 54.0 (14.3)</td>
<td>VUDS, EMG, VCUG Fluoroscopy</td>
<td>High voiding pressure: Pdet.Qmax ≥ 35 cmH2O</td>
<td></td>
</tr>
<tr>
<td>Qian (2016) [24]</td>
<td>Retrospective—single centre</td>
<td>China</td>
<td>LUTS</td>
<td>66</td>
<td>36 (54.6)</td>
<td>BNO: 55 (13); control: 50 (14)</td>
<td>TPUS and VirtualTouch tissue quantification UDS</td>
<td>1. Polyuria, urgency, frequency, nocturia, dysuria</td>
<td></td>
</tr>
<tr>
<td>Qian (2019) [25]</td>
<td>Retrospective—single centre</td>
<td>China</td>
<td>LUTS</td>
<td>51</td>
<td>27 (52.9)</td>
<td>FBNO: 56 (10); control: 47 (16)</td>
<td>TPUS UDS</td>
<td>Best ROC cut-off for FBNO: SWV 2.38 m/s</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>First author</th>
<th>Study design</th>
<th>Country</th>
<th>Clinical presentation</th>
<th>Total no. of patients analysed</th>
<th>BOO, n (%)</th>
<th>Age (yr), mean (SD or range)</th>
<th>Test evaluated</th>
<th>Reference test</th>
<th>Diagnostic criteria for BOO as reported by authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenblum (2004) [28]</td>
<td>Retrospective—single centre</td>
<td>USA</td>
<td>LUTS</td>
<td>57</td>
<td>2 (3.5)</td>
<td>30 (19–47)</td>
<td>VUDS, PF EMG, CMG</td>
<td>Fluoroscopy</td>
<td>BOO: fluoroscopy; DV: increased external sphincter activity during voluntary voiding, as evidenced by EMG tracing and/or fluoroscopy, with a sustained detrusor contraction</td>
</tr>
<tr>
<td>Solomon (2018) [10]</td>
<td>Retrospective—single centre</td>
<td>UK</td>
<td>LUTS</td>
<td>535</td>
<td>125 (23.4)</td>
<td>Obstructed: 51.9 (12.3); unobstructed: 49.1 (16.1)</td>
<td>VCMG</td>
<td>Fluoroscopy</td>
<td>BOO likely if Pdet.Qmax &gt; 2.2 × Qmax + 5</td>
</tr>
<tr>
<td>Vírseda Chamorro (1998) [35]</td>
<td>Retrospective—single centre</td>
<td>Spain</td>
<td>LUTS</td>
<td>80</td>
<td>56 (70)</td>
<td>62.19 (13.29); range (18–84)</td>
<td>Standard UDS, urethral resistance</td>
<td>Clinical assessment</td>
<td>Noninvasive Qmax ≤ 10th percentile in Haylen nomogram</td>
</tr>
<tr>
<td>Vírseda Chamorro (2006) [36]</td>
<td>Cross-sectional study</td>
<td>Spain</td>
<td>LUTS</td>
<td>52</td>
<td>25 (48.1)</td>
<td>48.7 (14.4); Range 20–81</td>
<td>VUDS, Blaivas-Groutz nomogram</td>
<td>Fluoroscopy</td>
<td>High Pdet associated with one of the following: (1) absence of BNO, (2) decrease in urethral diameter with proximal dilatation (urethral obstruction)</td>
</tr>
<tr>
<td>Yenilmez (2005) [33]</td>
<td>Retrospective—single centre</td>
<td>Turkey</td>
<td>LUTS</td>
<td>122</td>
<td>39 (32.0)</td>
<td>Group 1 urethral stricture (n = 19); 58.6 ± 10.5; group 2 DV (n = 13); 46.8 ± 15.2; group 3 pelvic prolapse (n = 7); 56.1 ± 9.4; controls (SU1 group; n = 83); 54.1 ± 9.7</td>
<td>UDS, endoscopy</td>
<td>Clinical assessment</td>
<td>Qmax ≤ 15 ml/s and Pdet.Qmax &gt; 20 cmH2O (endoscopice measures and clinical symptoms should also be considered)</td>
</tr>
</tbody>
</table>

BN = bladder neck; BND = bladder neck dysfunction; BNO = bladder neck obstruction; BOO = bladder outlet obstruction; BOOI = BOO index; BOOIf = bladder BOOI female; CMG = cystometrogram; DSD = detrusor sphincter dyssynergia; DV = dysfunctional voiding; EMG = electromyography; FBNO = female BNO; FR = flow rate; IQR = interquartile range; LUTS = lower urinary tract symptoms; NR = not reported; Pdet = detrusor pressure; Pdet.Qmax = detrusor pressure at Qmax; PF = pelvic floor; PRPF = poor relaxation of pelvic floor; PVR = postvoid residual; Qmax = maximum flow rate; ROC = receiver operating characteristic curve; SD = standard deviation; SU1 = stress urinary incontinence; SWV = shear wave velocity; TPUS = transperineal two-dimensional Doppler ultrasound; TVUS = transvaginal ultrasound; UDS = urodynamics; UP = urethral profiling; USS = ultrasound scan; VD = voiding dysfunction; VCMG = video cystometrogram; VCUG = voiding cystourethrography; VP = vesical pressure; VUDS = video urodynamics.
Table 2 - Overview of the accuracy metrics (including sensitivity, specificity, negative predictive value, positive predictive value, and overall accuracy) of different tests used to diagnose bladder outlet obstruction among the studies included in the review

<table>
<thead>
<tr>
<th>First author (Year)</th>
<th>Qmax (ml/s)</th>
<th>P det.Qmax (cmH2O)</th>
<th>Nomogram</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Overall accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qmax: 78.9; BOOI: 80.8; Pdet.Qmax: 64.2</td>
<td>100</td>
<td>64.6</td>
<td>91.5</td>
<td>NA</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Qmax: 85.9; BOOI: 86.1; Pdet.Qmax: 64.6</td>
<td>110</td>
<td>71.6</td>
<td>71.5</td>
<td>NR</td>
<td>NA</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Qmax: 95.4; BOOI: 95.5; Pdet.Qmax: 64.2</td>
<td>120</td>
<td>82.9</td>
<td>91.8</td>
<td>NA</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Qmax: 53.3; BOOI: 56.1; Pdet.Qmax: 33.3</td>
<td>130</td>
<td>60.7</td>
<td>91.5</td>
<td>NA</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Qmax: 80.5; BOOI: 82.3; Pdet.Qmax: 64.1</td>
<td>140</td>
<td>71.5</td>
<td>91.8</td>
<td>NA</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Qmax (ml/s)</th>
<th>Pdet.Qmax (cmH2O)</th>
<th>Nomogram</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Overall accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blavivas (2000)</td>
<td>≤12</td>
<td>≥20</td>
<td>Classify into no, mild, moderate, severe obstruction: (1) between unobstructed and minimally obstructed: a line with slope 1.0 and intercept 7 cmH2O; (2) between minimally and moderately obstructed: a horizontal line at Pdet(<em>{\text{Qmax}}) 57 cmH2O; (3) between moderately and severely obstructed: a horizontal line at Pdet(</em>{\text{Qmax}}) 107 cmH2O</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Dybowski (2014)</td>
<td>≤12</td>
<td>NR</td>
<td>Pdet.Qmax = 1.5 × Qmax + 10; BOO = (Pdet(Qmax) × 1.5 × Qmax) &gt; 10</td>
<td>90.5</td>
<td>65.2</td>
<td>54.3</td>
<td>94</td>
<td>73.1</td>
</tr>
<tr>
<td>Solomon (2018)</td>
<td>NR</td>
<td>NR</td>
<td>If Pdet.Qmax = 2.2 × Qmax + 5 or BOOIf = Pdet.Qmax = 2.2 × Qmax (&lt;0 = &lt;10%, 5 = 50%, &gt;18 = &gt;90% obstructed)</td>
<td>86</td>
<td>93</td>
<td>78.8</td>
<td>95.7</td>
<td>91.4</td>
</tr>
<tr>
<td>Transvaginal USS</td>
<td>≤12</td>
<td>&gt;20</td>
<td>NA</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Transperineal Doppler USS</td>
<td>≤12</td>
<td>&gt;20</td>
<td>NA</td>
<td>ARFI: 88.9; SWE: 81.5; combined: 92.5</td>
<td>ARFI: 79.2; SWE: 81.5; combined: 92.5</td>
<td>ARFI: 82.8; SWE: 81.5; combined: 89.3</td>
<td>ARFI: 86.4; SWE: 79.2; combined: 91.3</td>
<td>ARFI: 84.3; SWE: 80.4; combined: 90.2</td>
</tr>
</tbody>
</table>

ARFI = acoustic radiation force impulse; AUC = area under the curve; BND = bladder neck dysfunction; BOO = bladder outlet obstruction; BOOIf = BOO index female; DV = dysfunctional voiding; NA = not applicable; NPV = negative predictive value; NR = not reported or necessary information required to calculate this test accuracy measure not reported; Pdet\(_{\text{Qmax}}\) = detrusor pressure at Qmax; PPV = positive predictive value; Qmax = maximum flow rate; SWE = shear wave elastography; SWV = shear wave velocity; USS = ultrasound scan.

* Defined Qmax and Pdet.Qmax cut-offs.
obstruction, but diagnostic performance statistics in comparison with pressure-flow thresholds were not reported.

3.4.3. UDS and fluoroscopy

The ranges of diagnostic values for all VUDS studies included were as follows: sensitivity, 54.6–91.5%; specificity, 64.6–93.9%; PPV, 50–95.5%; NPV, 33.3–97.1%; and overall accuracy, 64.1–92.2%. Several studies have used predefined UDS cut-offs to evaluate their cohorts.

Grootz et al [4] used Qmax ≤15 ml/s and Pdet.Qmax >20 cmH2O (Chassagne et al’s [37] criteria) to diagnose BOO in 6.5% of 587 women presenting with voiding symptoms. Kljier et al [30] used a Qmax of <15 ml/s and a Pdet.Qmax of >40 cmH2O, and diagnosed BOO in 18.9% of 53 women with “chronic bladder symptoms”. Choi et al [11] analysed 792 women with a range of LUTS and diagnosed BOO in 11.2%, using Qmax <15 ml/s and Pdet.Qmax >20 cmH2O. Rosenblum et al [28] evaluated voiding dysfunction in 57 nulliparous women with a range of LUTS, and female BNO (BNO) was diagnosed in 3.5% using Nitti et al’s [20] radiological criteria.

Yenilmez et al [33] examined a UDS database of 412 women with various LUTS and analysed 122 with complete data. Testing different Qmax and Pdet.Qmax cut-offs, Qmax ≤15 ml/s and Pdet.Qmax >20 cmH2O gave sensitivity and specificity of 84.6% and 84.3%, respectively.

Ha et al [34] conducted UDS on 320 women with LUTS and diagnosed 39 (12.2%) with BOO using cut-offs of Qmax ≤12 ml/s and Pdet.Qmax >25 cmH2O. They found that the use of a Qmax of ≤15 ml/s resulted in sensitivity and specificity of 83% and 72%, respectively.

Six studies from the same group used VUDS to evaluate females with LUTS [15], voiding dysfunction [13,16,21], dysfunctional voiding [22], and signs and symptoms of BOO [12]. Nitti et al’s [20] criteria were used for the radiological definition of BOO, and the Qmax (<15 ml/s) and Pdet.Qmax (>35 cmH2O) cut-offs were used as pressure-flow thresholds [17]. In another study, VUDS findings from 1914 women with suspected voiding dysfunction were examined and BOO was diagnosed in 42.3%. Using diagnostic thresholds of Pdet.Qmax >30 cmH2O for fBOO, sensitivity, specificity, and overall accuracy of, respectively, 54.6%, 91.8%, and 76% were obtained. Using an Abrams-Griffiths BOO index cut-off of 30 for differentiating anatomic BOO from functional BOO yielded sensitivity of 46.9% and specificity of 76.5% [21]. Ong et al [13] identified bladder neck dysfunction (BND) in 12.3% of 810 women with voiding dysfunction. They further classified BND into high (Pdet.Qmax >35 cmH2O) or low (<35 cmH2O) pressure.

Akikwala et al [27] compared five UDS definitions and determined their correlation in women with a clinical suspicion of fBOO:

1. Nitti et al’s [20] radiological definitions
2. Qmax ≤15 ml/s and Pdet.Qmax ≥20 cmH2O (Chassagne et al’s [37] criteria)
3. Qmax ≤11 ml/s and Pdet.Qmax ≥21 cmH2O (Lemack and Zimmern’s [31] criteria)
4. Qmax ≤12 ml/s and Pdet.Qmax ≥25 cmH2O (Defreitas et al’s [29] cut-offs)

5. Blaivas-Grootz nomogram [19]

A total of 91 women were evaluated and 40 (44%) had fBOO by at least one criterion. Overall, 38 (42%) were diagnosed with fBOO using the Blaivas-Grootz nomogram, 28 (31%) using Chassagne et al’s [37] criteria, 26 (29%) using Nitti et al’s [20] criteria, 18 (20%) using Lemack and Zimmern’s [31] criteria, and 13 (14%) using Defreitas et al’s [29] proposed thresholds. The study concluded that Nitti et al’s [20] radiological criteria and Chassagne et al’s [37] pressure-flow criteria have the highest concordance, the Blaivas-Grootz nomogram overestimated fBOO, whereas Defreitas et al’s [29] cut-offs tended to underestimate it [27].

3.4.4. Nomograms to define fBOO

Nomograms are commonly used for the diagnosis of male BOO and most show good concordance [5]. However, there is greater disparity in diagnostic methods for fBOO. The Blaivas-Grootz nomogram used free Qmax and Pdet.Qmax to define four groups: severe, moderate, mild, and no obstruction. Using this nomogram, 50 obstructed patients (Qmax ≤12 ml/s and Pdet.Qmax ≥20 cmH2O) were reclassified into those with severe (n = 4, 8%), moderate (n = 12, 24%), and mild (n = 34, 68%) BOO. Of the 50 unobstructed controls, 40 (80%) women were classified as those having no obstruction by the nomogram, six (12%) having between no obstruction and mild obstruction, and the remaining four (8%) being mildly obstructed [19]. Virseda Chamorro et al [36] categorised 52 women with LUTS according to the Blaivas-Grootz nomogram and compared the results with VUDS findings. Using the nomogram, the sensitivity for BOO was 100%, but its specificity was 67.5%. In addition, Virseda Chamorro et al [35] also used the Liverpool uroflowmetry nomogram [38] to categorise women with Qmax percentile ≥50 or ≤10, and, using UDS, found that the urethral resistance average was the only significant UDS parameter to diagnose voiding dysfunction in women.

Dybowski et al [14] proposed a new nomogram following the observation that when Qmax and Pdet.Qmax, of individual patients were plotted on a pressure-flow graph, a distinctive distribution of patients with clinical signs and symptoms of BOO was noted, enabling a straight line to be drawn. The straight line separating obstructed women from the rest (described by the equation \( P_{\text{det},Q \text{max}} = 1.5 \times Q_{\text{max}} + 10 \)) was tested on 67 women, and the sensitivity, specificity, PPV, NPV, and overall accuracy were 90.5%, 65.2%, 54.3%, 94%, and 73.1%, respectively.

The Solomon-Greenwell nomogram used Qmax and Pdet.Qmax based on radiographic evidence of increased urethral resistance and a Bayesian approach rather than suggesting discrete pressure-flow thresholds. In a cohort of 535 women with various LUTS, the sensitivity, specificity, PPV, NPV, and overall accuracy were 86%, 93%, 78.8%, 95.7%, and 91.4%, respectively. The authors proposed a female BOO index (BOOIf) calculated using the following formula: \( \text{BOOIf} = P_{\text{det},Q \text{max}} - 2.2x Q_{\text{max}} \). The percentages of fBOO were <10%, 50%, and >90% if the BOOIf values were <0, >5, and >18, respectively [10]. This nomogram was tested for use in women.
correlation with symptoms in 1014 women with LUTS, and the most common symptom in the 19% diagnosed with fBOO was increased daytime urinary frequency [37]. Treatment validation was also examined in a study of 21 women treated at the authors’ own institution [38]. Sensitivity to change was demonstrated with consistent reductions in indices and probability of fBOO after treatment.

3.4.5. Transvaginal ultrasound scan

Galica et al [23] investigated the role of TVUS in women with LUTS suggestive of BOO, and $Q_{\text{max}} < 12$ ml/s and $P_{\text{det}}.Q_{\text{max}} > 20$ cmH$_2$O. A mean distance of 1.3 cm from the BN to the vaginal wall was found in women with BNO (fBNO). The authors concluded that VUDS remains the principal diagnostic method and did not propose a diagnostic method based on ultrasonographic indices.

3.4.6. Transperineal Doppler ultrasound scan

Two separate studies in women with a range of LUTS evaluated TPUS in diagnosing fBNO. In one study, transperineal sonography and Virtual Touch tissue quantification were used. BOO was defined as $Q_{\text{max}} < 12$ ml/s and $P_{\text{det},Q_{\text{max}}} > 20$ cmH$_2$O. The thickness and shear wave velocity (SWV) of the BN were higher in the fBNO group. For the anterior and posterior lips of the BN, SWVs of 2.11 m/s (AUC 0.78; sensitivity 69.4%; specificity 81.5%) and 2.06 m/s (AUC 0.83; sensitivity 66.7%; specificity 85.2%) were the best thresholds for diagnosing fBNO [24]. In another study, fBNO was diagnosed with cystoscopy and/or UDS, and the diagnostic efficacy of shear wave elastography (SWE) and acoustic radiation force impulse imaging (ARFI) was compared. Using both in combination was better than using either ARFI or SWE alone. This provided sensitivity, specificity, PPV, NPV, and overall accuracy of 92.5%, 87.5%, 89.3%, 91.3%, and 90.2%, respectively [25].

3.4.7. Excluded studies

A couple of earlier studies were not included in the current SR because the inclusion criteria were not met. Axelrod and Blaivas [39] in a study of three patients defined fBNO as $Q_{\text{max}} < 12$ ml/s, sustained detrusor contraction $\geq 20$ cmH$_2$O, and radiological evidence of obstruction at the vesical neck. Chassagne et al [37] in a study that was not included, as a proportion of patients had stress urinary incontinence, used thresholds of $Q_{\text{max}} \leq 15$ ml/s and $P_{\text{det},Q_{\text{max}}} > 20$ cmH$_2$O to diagnose fBOO, and reported sensitivity and specificity of 74.3% and 91.1%, respectively. These cut-off values were also used in a number of studies included in this SR.

3.5. Discussion

3.5.1. Principal findings

This is the first SR to summarise evidence from 28 studies involving 10 248 patients comparing the diagnostic measures of different tests used to diagnose fBOO. It is evident that studies within this topic area are difficult to compare for a number of reasons. Firstly, the included studies show considerable variation in inclusion criteria. Some studies have looked at a general population of women with LUTS, whereas others have concentrated on those with predominant voiding symptoms, and some have investigated groups with a poorly defined range of clinical diagnoses such as “voiding dysfunction” or “chronic bladder symptoms”. This results in a wide range of prevalence rates, and consequently the true incidence of fBOO is difficult to define.

Further heterogeneity is encountered due to a lack of consensus and consistency regarding reference UDS criteria used to diagnose fBOO. This variation has ultimately precluded any meta-analysis of these data. Nitti et al’s [20] radiological definition of fBOO and the UDS thresholds of $Q_{\text{max}} < 12$ ml/s and $P_{\text{det},Q_{\text{max}}} > 20$ cmH$_2$O appear to be the most widely used diagnostic cut-offs, indicating that UDS is the current standard investigation for fBOO, which is reflected in the recommendations of contemporary guidelines [1].

Novel diagnostic measurements and parameters have not enjoyed widespread uptake. The AUC/volume method proposed by Cormier et al [18] has not been replicated in larger studies. Similarly, the BOO index cut-off of $> 8$ to diagnose fBOO, proposed by Gravina et al [26], is derived from the work in males by Abrams and Griffiths and may not be applicable in women. Urethral pressure profile studies and surface electromyography are not utilised widely in contemporary clinical practice and considered optional, perhaps due to a poor correlation between results from different centres and continuing scepticism regarding the additional value provided by these tests [1,40].

Three nomograms (Blaivas-Groultz, Dybowski, and Solomon-Greenwell) were identified in this SR, and were based on $Q_{\text{max}}$ and $P_{\text{detmax}}$ or $P_{\text{det},Q_{\text{max}}}$ [10,14,19]. However, there have been no head-to-head studies, and hence strong recommendations cannot be made regarding their comparative utility.

3.5.2. Implications for clinical practice

At present, there are no standardised UDS parameters and hence no widely accepted definition for fBOO. Clinical history, pelvic ultrasound scan, and flow rates provide guidance to decide on more invasive investigations such as endoscopy or (V)UDS. TPUS is as an alternative noninvasive method in diagnosing fBNO [24,25], and the use of TVUS to assess the BN [20] may be more appropriate as adjuncts rather than primary diagnostic modalities.

3.5.3. How the review compares with previous reviews/guidelines

We have highlighted the difficulties in establishing appropriate and accepted criteria to define fBOO. The complexity of the diagnosis of fBOO was highlighted in a meeting of experts, which concluded that the diagnosis should be multifactorial and should include a detailed history, neurological and urogynaecological examination, pressure-flow studies, voiding phase fluoroscopy, urethral pressure profile, ultrasound, and cystoscopy [2].

3.5.4. Strengths and limitations

A major strength of this review is the systematic approach taken to examine the evidence base, including the use of Cochrane methodology, RoB assessment using QUADAS-2 tool, and adherence to the PRISMA checklist.
There are limitations at a review level. Firstly, we included only studies with a minimum sample size (including ten or more patients), potentially limiting the inclusion of promising studies on other diagnostic techniques. However, such smaller series are deemed unlikely to influence practice due to a lack of power and potential for selection bias. Secondly, we intentionally excluded from the final qualitative analysis the studies that included female patients with LUTS for whom a clear aetiological diagnosis was established before undergoing any diagnostic test for suspected BOO. While following this criterion has allowed us to homogenise the final qualitative analysis by focusing only on studies including women with suspected BOO of (predominantly) unknown cause, this choice might have led us to exclude potentially relevant papers describing useful diagnostic tests for fBOO. Thus, our findings should be interpreted carefully in light of the specific research question framework defined for this review.

There are limitations at a study level, including the heterogeneity amongst studies with regard to both definitions and the use of index tests and reference standards, as shown by our RoB assessment (Fig. 2 and 3).

We assumed, based on current guidelines [1] and consensus publications [2], that pressure-flow studies with fluoroscopy was the definitive diagnostic test and reference standard. However, a lot of studies omitted this, or the criteria for index UDS, such as Q_max and Pdet.Q_max, varied. Therefore, for over half of the studies included, test accuracy was either not reported or not possible to calculate. A second key limitation was the heterogeneity across included studies regarding the study design and the patient inclusion/exclusion criteria (Supplementary Table 2), which partly limit the generalisability of this review's findings. Finally, the extent to which the different time periods in which the included studies were performed might have contributed to differences in the diagnostic criteria for fBOO (in light of the changing paradigms to evaluate female patients with LUTS over time) is unknown.

3.5.5. Future research
Larger studies with more stringent methodological standards are required urgently. Future researchers in this topic area are encouraged to study better-defined cohorts and, as a minimum, separate fBOO into its anatomical and functional entities. The evaluation of diagnostic methods should include precise detail of diagnostic parameters, conventional measures of accuracy, assessment of prediction of treatment outcome, and sensitivity to change following treatment. In addition, future research/guidelines should focus on a standardised reporting system for fBOO that may enable a meta-analysis of individual trials, which was not possible in this review.

4. Conclusions
The available evidence on diagnostic tests and definition criteria for fBOO is limited and heterogeneous. Nomograms using pressure-flow measurements have also been proposed, but variation exists between them. Clearly in contemporary practice, appropriate management of patients and diagnosis of fBOO should be based on a careful history, clinical examination, and VUDS, which remains the recommended standard evaluation as it provides objective functional and anatomical data, but agreement regarding diagnostic criteria is needed urgently.

Author contributions: Muhammad Imran Omar had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Omar, Harding.
Acquisition of data: Pang, Campi, Omar, Harding.
Analysis and interpretation of data: Pang, Campi, Omar, Harding.
Drafting of the manuscript: Pang, Campi.
Critical revision of the manuscript for important intellectual content: Omar, Harding, Arlandis, Bo, Chapple, Costantini, Farag, Groen, Karavitakis, Lapitan, Manso, Arteaga, Nambiar, Nic An Riogh, O’Connor, Osman, Peyronnet, Phé, Sakalis, Sihra, Tzelves, van der vaart, Yuan.
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