Bladder Endometriosis: A Systematic Review of Pathogenesis, Diagnosis, Treatment, Impact on Fertility, and Risk of Malignant Transformation

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Abstract

\textbf{Context:} The bladder is the most common site affected in urinary tract endometriosis. There is controversy regarding the pathogenesis, clinical management (diagnosis and treatment), impact on fertility, and risk of malignant transformation of bladder endometriosis (BE).

\textbf{Objective:} To systematically evaluate evidence regarding the pathogenesis, diagnosis, medical and surgical treatment, impact on female fertility, and risk of malignant transformation of BE.

\textbf{Evidence acquisition:} A systematic review of PubMed/Medline from inception until October 2016 was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement and was registered in the PROSPERO registry (www.crd.york.ac.uk/prospero; CRD42016039281). Eighty-seven articles were selected for inclusion in this analysis.

\textbf{Evidence synthesis:} BE is defined as the presence of endometrial glands and stroma in the detrusor muscle. Ultrasonography is the first-line technique for assessment of BE owing to its accuracy, safety, and cost. Clinical management can be conservative, using hormonal therapies, or surgical. When conservative treatment is preferred, estrogen-progestogen combinations and progestogens should be chosen because of their favorable profile that allows long-term therapy. Surgery should guarantee complete removal of the bladder nodule to minimize recurrence, thus transurethral surgery alone should be avoided in favor of segmental bladder resection. There is not a strong rationale for hypothesizing a detrimental impact of BE per se on fertility. Furthermore, current evidence does not support the removal of bladder endometriotic lesions because of the potential risk of malignant transformation since this phenomenon is exceedingly rare.

\textbf{Conclusions:} BE is a challenging condition, and the common coexistence of other types of endometriosis means that clinical management of BE should involve collaboration between gynecologists and urologists.

\textbf{Patient summary:} In this article we review available knowledge on bladder endometriosis. The review provides a useful tool to guide physicians in the management of this complex condition.

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1. Introduction

Endometriosis is traditionally classified as one of three main forms: ovarian endometriosis, superficial peritoneal endometriosis, and deep infiltrating endometriosis (DIE). DIE is the most severe type, with an estimated prevalence of 1% among women of reproductive age [1], and is defined as endometriosis infiltrating the peritoneum by >5 mm. More frequently, these lesions are located in the most cul-de-sac part of the pelvis (including the pouch of Douglas, the anterior aspect of the sigma, the uterosacral ligaments, the broad ligaments, the ureter, and the bladder), while other locations (such as other sites in the abdomen, the external genitalia, and distant sites) are less common. Urinary tract endometriosis (UTE) involves the bladder and/or the ureters. UTE is present in approximately 1% of women with endometriosis [2], but its prevalence increases to 19–53% among patients with DIE [3–5]. Bladder involvement is the most frequent type of UTE, occurring in 70–85% of cases, while ureteral involvement accounts for 9–23% of UTE cases [3,6]. Bladder endometriosis (BE) is defined as the presence of endometrial glands and stroma in the detrusor muscle; the base and the dome are the most frequently affected sites. According to its origin, BE may be classified as primary BE when it occurs spontaneously, or as secondary BE when it is related to an iatrogenic lesion occurring after pelvic surgery, such as cesarean delivery or hysterectomy. Endometriotic nodules of the bladder are frequently associated with other forms of pelvic endometriosis, supporting the notion that BE should be considered an independent form of the disease. The presence of at least one other site involved (superficial peritoneal implants, ovarian endometriomas, adhesions, and extravesical deep peritoneal endometriosis) has been documented in approximately 90% of cases [7]. In most cases, BE is associated with lower urinary tract symptoms such as frequency, dysuria, haematuria, and, less frequently, bladder pain and urgency [4,8]. These symptoms may worsen during menstruation, or may have a noncyclical presentation. Depending on the clinical manifestation, both urologists and gynecologists may deal with BE, and their collaboration may be required for clinical management.

To provide more information on this rare and challenging condition, we conducted a systematic review to summarize available knowledge on BE and to identify research needs. The main objective of the review was to systematically evaluate evidence regarding the pathogenesis, diagnosis, medical and surgical treatment, impact on women’s fertility, and risk of malignant transformation of BE.

2. Evidence acquisition

This review was performed according to the Preferred Reporting Items for Systematic Review and Meta-analysis statement [9] and was registered in the PROSPERO register (www.crd.york.ac.uk/prospero; CRD42016039281). No institutional review board approval was needed because only published, de-identified data were analyzed. All authors participated in the design of the search strategy and of the inclusion and exclusion criteria.

2.1. Search strategy

PubMed/Medline was systematically searched from inception until October 2016 (last research October 21, 2016; the search was run every month from March 2016 until October 2016) using the following keywords and MeSH terms: “bladder endometriosis” alone or in combination with “aromatase inhibitors”, “ART”, “assisted reproductive techniques”, “cancer”, “clinical examination”, “combined oral contraceptives”, “cystoscopy”, “diagnosis”, “dienogest”, “fertility”, “hormonal treatment”, “ICSI”, “infertility”, “in vitro fertilization”, “intrauterine insemination”, “IVF”, “IU1”, “magnetic resonance imaging”, “norethindrone acetate”, “painful bladder syndrome”, “pathogenesis”, “pregnancy”, “progestogen”, “questionnaire”, “segmental resection”, “surgery”, “symptoms”, “transurethral surgery”, “treatment”, “ultrasonography”, “ultrasound”, “urodynamics”. All pertinent articles were carefully assessed and their reference lists were evaluated to identify any other study that could be included in this review. All the authors reviewed the articles, and discrepancies were resolved by consensus. The reviewers were not blinded to the names of the investigators or the sources of publication. The eligibility of the studies was first based on titles and abstracts. Full manuscripts were obtained for all selected papers, and the decision for final inclusion was made after detailed evaluation of the articles.

2.2. Inclusion and exclusion criteria

In this systematic review, only peer-reviewed, English-language journal articles concerning BE were included. In particular, the following topics were covered: pathogenesis, diagnosis, medical and surgical treatment, BE in women wishing to conceive, and the risk of malignant transformation. As described later, medical management of BE should be considered as an alternative to surgery, and thus only long-term therapies are included in this review.

2.3. Study eligibility and quality assessment

This review included randomized controlled trials (RCTs), prospective controlled studies, prospective cohort studies or retrospective studies, reviews, case series, and case reports. Case reports and small case series (<10 cases) were considered only if they provided highly valuable information. Letters to the editor and abstracts accepted at conferences were excluded from the review. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool was used to assess the methodological quality of studies investigating diagnostic techniques for BE included in the review (Supplementary Tables 1 and 2) [10,11]. In addition, the Newcastle-Ottawa Scale was used to assess the methodological quality of studies investigating medical and surgical treatment of BE (Supplementary Tables 3 and 4) [12].
3. Evidence synthesis

The search revealed 116 studies eligible for inclusion in the review. Of these, 93 were finally included (Fig. 1). Given the characteristics of the studies included and the heterogeneity of the available articles in terms of methodology, no meta-analysis was attempted.

3.1. Pathogenesis of BE

3.1.1. Anatomic arguments and studies on the frequency of association of the different forms

As a general overview, it has to be mentioned that on one hand, DIE nodules are thought to originate as the natural evolution of superficial peritoneal endometriosis infiltrating behind the peritoneum, while on the other, they are thought to be adenomyotic nodules originating via a process of metaplasia [13]. Specifically for the bladder, the distribution of lesions in relation to factors influencing the spreading of endometrial cells supports the pathogenetic theory of spontaneous BE on the basis of implantation of transtubally regurgitated menstrual endometrium on peritoneal surfaces. Owing to gravity, the anterior cul-de-sac where the bladder is located represents the most frequent site. After implantation, the underlying inflammatory process favors the development of adhesions between the contiguous organs and the formation of a fibrotic nodule, apparently of the vesicovaginal septum, that is buried under the peritoneum [14,15]. Anatomic observations strongly supporting this theory include the absence of BE in women with a retroverted uterus, in whom an anterior cul-de-sac is not present, and the location of most nodules adherent to the uterine body well above the uterine isthmus, adherent to the anterior uterine wall, if not the fundus [15]. Support for this theory comes from studies evaluating the frequency of association between the different forms of the disease, on the assumption that if a peculiar pathogenetic mechanism leading to a specific form of the disease exists, the frequency of other forms of endometriosis in patients affected by the peculiar form should be similar to the frequency observed in the general population (prevalence ~4% [16]). Among cases affected by BE, the incidence observed was 58.6% (95% confidence interval [CI] 45.2–71.2) for superficial peritoneal implants, 44.8% (95% CI 32.2–58.2) for ovarian endometriomas, 81.0% (95% CI 68.4–89.6) for adhesions, and 27.6% (95% CI...
16.7–40.8) for extravasical deep peritoneal endometriosis. The presence of at least one of these was documented in 87.9% of cases (95% CI 76.7–94.3), supporting the notion that BE nodules should not be considered an independent form of the disease, but rather another manifestation of endometrial cell dissemination in the pelvis [7].

The basis for considering BE as an independent pathogenetic form of the disease arises from the idea that it indeed represents adenomyosis originating from metaplasia of Müllerian remnants and/or extension of adenomyotic lesions arising in the myometrium. The observation that these lesions are histologically characterized by dense tissue composed of fibrous and smooth muscle cells with islands or strands of glands and stroma supports this view [17,18]. On anatomopathologic grounds, these nodules are thus more reminiscent of adenomyosis than of endometriosis. However, there are some converse arguments to this theory: (1) histologic evidence documenting the presence of embryologic remnants within the uterine-vesical area has never been provided; (2) it has been shown that smooth muscle cells are present in all endometriotic lesion types [19]; (3) in most series published, no adenomyotic nodules of the uterine wall were found in association with BE [15,18], making the uterine adenomyosis extension theory unlikely. Thus, while the metaplasia theory has lost reliability over time, it should be noted that of the 11 cases of male endometriosis reported in the literature [20–30], four developed endometriosis of the bladder concomitant with high estrogen exposure [26–28,30]. Müllerian duct remnant metaplasia may consistently apply to these cases, with the location of the nodules along the route of the Müllerian ducts, namely the verumontanum, trigone, ureterovesical junction, lateral wall of the bladder, and paratesticular region. Interestingly, probably because of its rarity compared to other forms of the disease, no studies have addressed pathogenetic features of BE, including proliferation activity, apoptosis status, inflammatory characteristics, and neuroangiogenesis capacity.

### 3.1.2. Association with surgical procedures

An iatrogenic form of BE has long been proposed [6] and it has been suggested that it arises from intraoperative dissemination of endometrial cells, as well as disruption of the ureteral incision, even after many years. As early as 1960, Abeshouse and Abeshouse [6] pointed out that 39 out of 56 patients affected by bladder endometriosis had undergone a gynecologic or surgical procedure, which underlined the importance of an accurate operative technique to avoid iatrogenic dissemination. The frequency of caesarean section among women with BE has been reported as 15% (95% CI 8.3–26.9) [7], but the association between BE and the surgical procedure is not consistently recognized [8]. In particular, a very recent cross-sectional study including a consistent number of BE women found that the incidence of isolated BE was similar between patients with (37.5%) and without (41.7%; p = 0.6) a history of uterine surgery. In addition, BE severity and the anatomic distribution of associated DIE lesions, including vaginal, intestinal, and ureteral involvements, did not differ between the two study groups [31]. Overall, these observations indicate that there is still a need for further clarification of the existence of two BE entities after prior uterine surgery.

### 3.2. Diagnosis of BE

#### 3.2.1. Clinical history and examination

A woman of reproductive age complaining of pain symptoms (dysmenorrhea, dyspareunia, and nonmenstrual pelvic pain) is at risk of DIE [32–34]. Some studies reported that DIE is associated with lower urinary symptoms (LUTS); however, the prevalence of this association is unclear ranging between 2% and 77% [35–37]. According to the findings of a recent research, no difference was reported in the rate of urgency, urinary frequency, voiding symptoms and bladder pain between patient with posterior endometriosis plus BE compared with those with posterior endometriosis only [37]. Dysuria, frequency, bladder pain, and, less commonly, hematuria, urgency, and urinary incontinence are symptoms related to the presence of BE [3,4,18,38,39]. Dysuria has been reported in 21–69% of patients with BE [3,4,18,38] and positive correlation was observed between severity and lesion diameter [38]. Hematuria is a less frequent symptom, reported in 0–35% of the cases [3,4,8]; this is explained by the fact that the bladder lesion rarely infiltrates the mucosal layer.

Vaginal examination is a critical part of the evaluation of women with suspected DIE, and is highly reliable [40–43], particularly in detecting BE, for which the accuracy is nearly 100% [41,42]. Physical examination allows identification of a palpable nodule or a thickened area along the anterior vaginal wall that may be painful in 35.7–100% of patients [6,14,18,44] (Table 1).

Symptoms related to BE are common to several urologic conditions such as recurrent cystitis—overactive bladder, bladder carcinoma, interstitial cystitis/bladder pain syndrome, and chronic urethral syndrome. Women of reproductive age complaining of LUTS, particularly in combination with pain symptoms and/or positive anterior vaginal examination, should be always considered for a diagnosis of BE and further investigated via imaging techniques (ultrasonography and magnetic resonance imaging [MRI]).

#### 3.2.2. Endometriosis and interstitial cystitis/bladder pain syndrome

Interstitial cystitis/bladder pain syndrome (BPS) is defined as symptoms of chronic pelvic pain (CPP), pressure, or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom such as a persistent urge to void or frequency in the absence of any identifiable pathology or infection [45,46]. Endometriosis (including BE) and BPS share similar symptoms, and are both causes of CPP. Several studies have shown coexistence (16–78%) of these two conditions [47], defined by Chung et al [48,49] as “evil twin syndrome”. Panel et al [37] investigated the characteristics of LUTS and urodynamic findings for patients with posterior endometriosis versus those with a posterior location and BE. Interestingly, the
study revealed that two urodynamic signs commonly reported by patients with BPS (increased bladder sensation and painful bladder filling) were more frequent among patients with BE than in those with a posterior location only. Furthermore, most of the patients with BE experienced urgency and/or urinary frequency associated with complaints of bladder pain or bladder pain provoked during bladder filling, suggesting a direct role of the endometriotic nodule in the onset of these symptoms/signs. Conversely, it has been proposed that the presence of BPS in patients with DIE but without BE is due to modulation of pain responses by visceral inputs not related to the inflamed site (ie, by bladder filling when an endometriotic implant is located in a small part of the bladder wall) as a result of sensitization [37].

3.2.3. Questionnaires
In 1992, Barry et al [50] developed a seven-item questionnaire, the American Urologic Association Symptom Index (AUASI) (known worldwide as the International Prostate
Symptom Score [IPPS]) to assess the severity of benign prostatic hyperplasia. It was subsequently demonstrated that this questionnaire is accurate in describing LUTS in women [51]. Fedele et al [44] modified the AUASI/IPPS, replacing three questions concerning obstructive symptoms with three questions concerning irritative symptoms, especially during the perimenstrual period; this modified questionnaire allows evaluation of the presence of specific catamenial symptoms related to BE in patients with high suspicion for this disease. The questionnaire was administered to 154 patients undergoing surgery for CPP. Of the total study population, 127 (82.4%) patients had pelvic endometriosis and 14 (9.0%) had BE. The questionnaire was effective in identifying BE (area under the receiver operating characteristic curve 0.951) [44].

More recently, Ballestre et al conducted two studies investigating the presence of urinary dysfunction in patients with DIE before [36,52] and after surgery [36] using the IPPS [52] and the Bristol Female LUTS (BFLUTS) questionnaire [36,52]. The BFLUTS questionnaire comprises three domains: symptom questions (frequency of micturition, nocturia, urgency, urge incontinence, bladder pain, frequency incontinence, stress incontinence, unpredictable miscellaneous incontinence, volume of leakage, hesitancy, strain to start, intermittency, nocturnal incontinence, reduced stream, acute retention, burning, incomplete emptying, stopping flow, and frequency between voiding) mostly with a corresponding subquestion; sexual function questions (pain due to dry vagina, disturbed sex life, pain during intercourse, and leakage during intercourse); and quality-of-life questions (change of underwear/use of pads, number of changes, change of outer clothing, reduction in fluid intake, affected daily tasks, avoidance of situations where no toilet is available, interference with physical activity, interference with social life, overall interference with life, how long symptoms have been bothering, and notion of spending rest of life with no change).

In conclusion, the use of validated questionnaires may be helpful in the management of BE. In particular, the modified AUASI questionnaire by Fedele et al should be utilized during the diagnostic work-up to improve the detection of BE. The IPPS and the BFLUTS questionnaires are useful in assessing the variegated spectrum of LUTS associated with DIE, including BE, and in monitoring changes in symptoms after treatment. However, administration and answering of these questionnaires are associated with significant time costs in routine clinical practice, so we recommend their use mainly for scientific research purposes (Table 1).

3.2.4. Ultrasonography

Ultrasonography is fundamental in the diagnosis of BE and in planning the most appropriate treatment, since it can be used to evaluate the location and size of the nodule, and to estimate the distance between the lesion borders and the urethral orifices (Table 1) [53]. The first description of the sonographic features of BE was provided in 1980 by Goodman and colleagues [54]. On ultrasonography with the bladder full of anechoic urine, BE appears as a filling defect of the posterior wall with a variable protrusion into the lumen, with an iso/hypoechoic aspect sometimes visible with small transonic formations that are usually not vascularized (Fig. 2). Bladder nodules are usually spherical or comma-shaped with regular contours, but sometimes the lesion borders can be irregular, raising a suspicion of malignancy. However, bladder nodules are usually covered by a small rim of the hyperechogenic layers of the bladder wall (submucosal and serosa), while spiky or papillary projections interrupt the hyperechogenic layers of the bladder wall in cancer. Color Doppler may physicians in establishing a differential diagnosis, since it commonly reveals minimal to moderate internal blood flow in patients with BE [55,56].

In 1997, an Italian study including six patients compared abdominal ultrasonography, transvagal ultrasonography (TVS), and MRI in the preoperative evaluation of BE. All the techniques identified bladder lesions; however, TVS was the most accurate in defining the size of the lesions, infiltration of the detrusor muscle, and continuity with extravasical lesions [57]. Both abdominal ultrasonography and TVS may be used to detect vesical endometriotic lesions; however, in gynecologic clinical practice, TVS is the preferred technique. Table 1 summarizes the results of studies investigating the use of TVS to diagnose BE [40,41,58–64]. A recent systematic review and meta-analysis revealed overall pooled sensitivity of 62% (95% CI, 40–80%), specificity of 100% (95% CI, 97–100%), positive likelihood ratio of 208.4 (95% CI, 21.0–2066.0), and negative likelihood ratio of 0.38 (95%CI, 0.22–0.66) for TVS detection of BE. The study suggests that TVS is a useful first-line method for diagnosing BE in clinical practice. The pretest probability was 5%, which increased to 92% when suspicion of DIE was present after TVS examination, and fell to 2% in the absence of ultrasonographic findings in the bladder [65]. Tammaa et al [64] evaluated interobserver agreement and accuracy for TVS in diagnosing endometriomas and DIE, and also considered BE. Patients were independently examined prospectively by two experienced sonographers who were blinded to the other’s results; Gwet’s first-order agreement coefficient (Gwet’s AC1) was used to calculate interobserver agreement. The study demonstrated that TVS had high accuracy and specificity but fair sensitivity in the diagnosis of BE (Table 2); most importantly, TVS was highly
## Table 2 – Main characteristics and findings of studies investigating transvaginal ultrasonography for the diagnosis of bladder endometriosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Setting</th>
<th>TVS parameter</th>
<th>Patients, n (%)</th>
<th>Reference parameter, % (95% confidence interval)</th>
<th>ACC (%)</th>
</tr>
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<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td>Total</td>
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<td>BE</td>
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<td>NE</td>
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<td>5</td>
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<td>Guerriero 2008</td>
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<td>NE</td>
<td>158</td>
<td>NA</td>
<td>5</td>
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<tr>
<td>Fratelli 2013</td>
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<td>SI</td>
<td>NE</td>
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<tr>
<td>Exacoustos 2014</td>
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<td>SI</td>
<td>NE</td>
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<td>104</td>
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<tr>
<td>León 2014</td>
<td>PS</td>
<td>SI</td>
<td>E</td>
<td>51</td>
<td>39</td>
<td>5</td>
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<tr>
<td>Tommasi 2015</td>
<td>PS</td>
<td>SI</td>
<td>NE</td>
<td>67</td>
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<td>4</td>
</tr>
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</table>

RS = retrospective study; PS = prospective study; SI = single institution; 3I = three institutions; NE = nonenhanced; E = enhanced (gel contrast sonovaginography); BE = bladder endometriosis; PPV = positive predictive value; NPV = negative predictive value; LR+ = positive likelihood ratio; LR− = negative likelihood ratio; ACC = accuracy; DIE = deep infiltrating endometriosis; NA = not available; S + H = surgery and histopathology; BC = Bazot’s criteria; TVS = transvaginal ultrasonography

* Tenderness-guided.
reproducible for detection of DIE and in particular BE (Gwet’s AC1 = 1) [64]. A French study including eight women who reported urinary tract symptoms suggestive of BE assessed the performance of three-dimensional (3D) TVS with color Doppler compared to MRI and cystoscopy in the diagnosis of BE. TVS was superior to cystoscopy and at least as effective as MRI in diagnosing and planning surgery for BE. The authors of this study suggested that 3D acquisition may improve endometriotic nodule localization and evaluation of its size, volume, and infiltration of the bladder wall in comparison to two-dimensional TVS [66].

3.2.5. Magnetic resonance imaging
MRI should be regarded as a second-line imaging technique for assessment of BE. In the case of cancer suspicion, it is thought to be helpful because of higher contrast resolution, better delineation of bladder wall layers, better tissue characterization, and better multiplanar capability in comparison with ultrasonography [67]. The MRI appearance of BE is usually of low signal intensity on T2 weighting with intermediate signal intensity on T1 weighting, and spots of high signal intensity on T1 and T2 weighting [68]. Several studies have investigated the role of MRI in the diagnosis of DIE including bladder localizations (Table 3) [68–74]. Medeiros et al [75] conducted a systematic review and meta-analysis to estimate the accuracy of pelvic MRI in the diagnosis of DIE. A total of 20 studies including 1819 women were analyzed; four of these, involving 494 women, assessed the presence of BE. Pelvic MRI had pooled sensitivity of 0.64 (95% CI 0.48–0.77) and pooled specificity of 0.98 (95% CI 0.96–0.99) for detection of BE. The diagnostic odds ratio was 97.36 (95% CI 34.50–274.76) and the area under the curve was 0.93 [75]. No significant advantage has been reported for 3.0-T MRI [70] or gadolinium-enhanced MRI [71].

Considering that in experienced hands TVS has similar or even superior accuracy to MRI in detecting BE and that the latter is much more expensive, we conclude that MRI should not be routinely performed in clinical practice, in accordance with the emerging concept that it is preferable to reduce the use of low-value care interventions with uncertain benefits [76].

3.2.6. Cystoscopy
Cystoscopy is a diagnostic procedure widely performed in the outpatient setting to assess the interior lining of the urethra and bladder. When a BE lesion is present, the cystoscopic findings are more commonly normal owing to the intraperitoneal origin of the nodule. In fact, an endometriotic lesion progresses from the serosal layer of the bladder towards the mucosa through the bladder wall; a typical adenomatous and nodular red or bluish mass is observed in half of cases, and ulcerations are rare [14,15]. Scheduling of cystoscopy immediately before or during menstruation is recommended, when the nodule is larger and more congested, so characterization is optimal. Cystoscopy allows estimation of the distance between the ureteral orifices and the nodule borders for planning of the most appropriate surgical approach. When the caudal margin of the lesion is far from the ureteral orifices, excision is generally easy and safe, and can be performed by a gynecologist, whereas when the endometriotic lesion is close to or involves the ureteral orifices, ureterovesical reimplantation should be planned with an expert urologist. Furthermore, cystoscopy may be helpful in excluding bladder carcinoma, varices, papillomas or angiomata, and detrusor mesenchymal tumors. However, it should be considered that with the exception of transurethral resection (TUR) procedures, biopsy at cystoscopy is frequently not diagnostic for endometriosis [77]. In conclusion, cystoscopy should not be routinely performed apart from in cases of suspicion of malignancy or if the distance between the nodule and the ureteral orifices is not clearly evaluable using TVS (Table 1).

3.2.7. Urodynamics
The presence of LUTS in patients with DIE is well established; however, little research has been conducted to study the lower urinary tract function of patients affected by DIE using urodynamics [35–37,39,78]. Bonneau et al [35] performed a systematic review to assess the incidence of preoperative and postoperative urinary dysfunction in patients with DIE and evaluate the potential role of urodynamics. Their review revealed that there was at least one abnormal urodynamic finding in 48.0%–83.3% of patients with DIE [36,79], but no patient with BE was included in this analysis. Panel et al [37] studied the characteristics of LUTS and urodynamic findings in 30 patients with DIE to correlate them with the anatomic location of nodules found at surgery. All patients had posterior endometriosis and ten (33.3%) also had BE. Urodynamic examination results showed changes in 29 (96.7%) women, and those with BE had a higher rate of bladder sensation (90.0% vs 45.0%) and painful bladder filling (70.0% vs 30.0%), while voiding symptoms (70.0% vs 55.0%), urgency (80.0% vs 40.0%), frequency (60.0% vs 45.0%), and bladder pain (60.0% vs 25.0%) were similar in the two study groups [37].

In conclusion, there is scanty evidence on the role of urodynamics in the assessment of patients with BE, so this should not be performed in clinical practice, but limited to scientific research trials (Table 1).

3.3. Treatment of BE
3.3.1. Medical therapies for the treatment of BE
Combined hormonal contraceptives and progestogens should be regarded as first-line therapy for patients with DIE, as they are efficacious, safe, and well tolerated [80–82]. However, this is a relatively recent and novel concept, as until a few years ago authoritative surgeons considered hormonal treatment to be ineffective and maintained that radical excision was the only successful modality to deal with these demanding conditions [82]. It has been demonstrated that both combined hormonal contraceptives and progestogens are effective in several formulations (oral, cutaneous, vaginal and oral, subcutaneous/intramuscular, intrauterine device, and implants), showing similar results in the treatment of different DIE
Table 3 – Main characteristics and findings of studies investigating magnetic resonance imaging for the diagnosis of bladder endometriosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Setting</th>
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<th>Reference</th>
<th>Parameter, % (95% confidence interval)</th>
<th>ACC (%)</th>
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<td>Sensitivity, Specificity, PPV, NPV, LR+</td>
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<td>Krüger 2014</td>
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<td>0.81 (0.64–1.0)</td>
<td>0.20 (0.08–0.49)</td>
</tr>
<tr>
<td>Chamie 2009</td>
<td>PS</td>
<td>SI</td>
<td>1.5 T</td>
<td>NA</td>
<td>100, 100, 100, 80.3–94.5</td>
<td>99.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.25 (0.25–0.49)</td>
<td>0.12 (0.05–0.36)</td>
</tr>
<tr>
<td>Hottat 2009</td>
<td>PS</td>
<td>SI</td>
<td>3.0 T, US gel</td>
<td>NA</td>
<td>100, 100, 98.7, 75.0</td>
<td>99.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.25 (0.15–0.36)</td>
<td>0.12 (0.05–0.36)</td>
</tr>
<tr>
<td>Bazot 2011</td>
<td>RS</td>
<td>SI</td>
<td>1.5 T, IV Gd</td>
<td>NA</td>
<td>100, 100, 100, 98.7</td>
<td>99.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.25 (0.15–0.36)</td>
<td>0.12 (0.05–0.36)</td>
</tr>
<tr>
<td>Krüger 2013</td>
<td>RS</td>
<td>SI</td>
<td>1.5 T</td>
<td>NA</td>
<td>100, 100, 99.3, 98.2</td>
<td>99.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.25 (0.15–0.36)</td>
<td>0.12 (0.05–0.36)</td>
</tr>
<tr>
<td>Scardapane 2013</td>
<td>PS</td>
<td>SI</td>
<td>1.5 T</td>
<td>NA</td>
<td>100, 100, 99.3, 98.2</td>
<td>99.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.25 (0.15–0.36)</td>
<td>0.12 (0.05–0.36)</td>
</tr>
<tr>
<td>Di Paola 2015</td>
<td>RS</td>
<td>SI</td>
<td>1.5 T</td>
<td>NA</td>
<td>100, 100, 99.3, 98.2</td>
<td>99.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.25 (0.15–0.36)</td>
<td>0.12 (0.05–0.36)</td>
</tr>
</tbody>
</table>

RS = retrospective study; PS = prospective study; SI = single institution; S + H = surgery and histopathology; PPV = positive predictive value; NPV = negative predictive value; LR+ = positive likelihood ratio; LR− = negative likelihood ratio; ACC = accuracy; IV Gd = intravenous gadolinium; NA = not available; R1, R2, R3 = reader 1, 2, 3; R1GD, R2GD, R3GD = reader 1, 2, 3 with gadolinium; US: ultrasonography.
localizations (rectovaginal, colorectal, and bladder endometriosis) [83–92]. To the best of our knowledge, only one randomized controlled trial compared combined hormonal contraceptives with progestogens [84], while no randomized comparisons have been conducted between different types of estrogen-progestins and progestogens. Hence, it may not be currently possible to identify the best compound for these patients in terms of long-term safety, efficacy, and tolerability. In general, currently available solid evidence demonstrates the efficacy of estrogen-progestins and progestins in patients with DIE [82,93].

However, it has recently been suggested that both the symptoms associated with BE and the lesion itself may respond suboptimally to medical therapies owing to desmoplastic reaction within the detrusor resulting from repetitive bleeding and resorption of menstrual debris [94]. Noël et al [95] analyzed the expression of estrogen and progesterone receptors in the smooth muscle component from 60 patients with deep endometriotic lesions, ten of whom had bladder nodules. Estrogen and progesterone receptors were well represented in all detrusor lesions. In addition, progesterone receptors were more abundant than estrogen receptors [95]. Therefore, these forms could also be potentially responsive to hormonal manipulation.

Over the past 16 yr, a total of 36 cases of women with BE treated medically have been described in nine reports (Table 4). The largest experience regards the use of combined oral contraceptives (COC). Westney et al [91] treated 13 women with low-dose monophasic COC, or a decrease in the estrogen component or addition of progesterone to the current regimen, for a period ranging from 8 to 24 mo (mean 19 mo), and reported partial or complete resolution of symptoms in 12 (92%) patients. Fedele et al [92] conducted a prospective, comparative, 6-mo study among ten patients with BE, five of whom were treated with a COC used continuously, and five with a gonadotropin-releasing hormone (GnRH) agonist. At the end of the therapy, cystoscopy revealed nearly complete disappearance of the characteristic lesion in women treated with the GnRH agonist, whereas marked albeit not complete regression was observed in those who used the COC.

The second most frequently studied medical therapy for BE is dienogest, a 19-nortestosterone derivative with anti-androgenic properties. Takagi et al [96] treated a 39-yr-old woman with a positive histologic diagnosis with oral dienogest (2 mg/d) for 6 mo. Her urologic symptoms were promptly relieved and remarkable lesion reduction was observed. Unexpectedly, the patient was symptom-free at 1 yr after drug discontinuation [96]. Harada et al [97] used the same dose for 11 mo in one patient and observed a similar clinical and anatomical response. No post-treatment follow-up was reported [97]. Agarwal et al [98] observed relief of catamenial dysuria and hematuria and a >50% reduction in lesion size in a woman treated with dienogest for 16 mo for a 3-cm endometriotic bladder nodule. Angioni et al [99] used the same dienogest dose for 1 yr in six women who requested a medical approach for BE. Their pain and urinary symptoms improved very quickly and the nodule decreased remarkably in size in all patients [99]. Leone Roberti Maggiore et al [39] used dienogest 2 mg/d to treat a 34-yr-old nulliparous woman with urgency and stress urinary incontinence associated with BE who refused surgery. After 12 mo of therapy, her symptoms improved and urodynamic findings normalized [39].

Aromatase inhibitors were used in three women, one postmenopausal [100] and two premenopausal [101]. In the former case, oral letrozole (2.5 mg three times/wk for 8 mo) was successfully used alone in a woman with an endometriotic bladder nodule identified after hysterectomy and bilateral salpingo-oophorectomy [100]. In the latter cases, the same drug was used daily (2.5 mg per os) and in combination with oral norethisterone acetate (2.5 mg/d) to avoid ovarian stimulation. The double-drug regimen improved pain and urinary symptoms promptly, but one

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Setting</th>
<th>Patients (n)</th>
<th>Treatment type</th>
<th>Mean FU (mo)</th>
<th>Symptom improvement, n (%)</th>
<th>Lesion regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Westney 2000</td>
<td>RS</td>
<td>SI</td>
<td>13</td>
<td>Low-dose monophasic COC</td>
<td>18.6</td>
<td>12 (92.1)</td>
<td>NR</td>
</tr>
<tr>
<td>Fedele 2008</td>
<td>PS</td>
<td>SI</td>
<td>10</td>
<td>Continuous COC (n = 5)</td>
<td>6</td>
<td>NA</td>
<td>COC group: marked but not complete regression; GnRHa group: nearly complete disappearance</td>
</tr>
<tr>
<td>Takagi 2011</td>
<td>CR</td>
<td>SI</td>
<td>1</td>
<td>Dienogest</td>
<td>6</td>
<td>1 (100)</td>
<td>Remarkable reduction in size</td>
</tr>
<tr>
<td>Harada 2011</td>
<td>CR</td>
<td>SI</td>
<td>1</td>
<td>Dienogest</td>
<td>11</td>
<td>1 (100)</td>
<td>Remarkable reduction in size</td>
</tr>
<tr>
<td>Agarwal 2015</td>
<td>CR</td>
<td>SI</td>
<td>1</td>
<td>Dienogest</td>
<td>16</td>
<td>1 (100)</td>
<td>&gt;50% reduction in size</td>
</tr>
<tr>
<td>Angioni 2015</td>
<td>CS</td>
<td>SI</td>
<td>6</td>
<td>Dienogest</td>
<td>12</td>
<td>6 (100)</td>
<td>Remarkable reduction in size</td>
</tr>
<tr>
<td>Leone Roberti</td>
<td>CR</td>
<td>SI</td>
<td>1</td>
<td>Dienogest</td>
<td>12</td>
<td>1 (100)</td>
<td>22.6% reduction in size</td>
</tr>
<tr>
<td>Maggiore 2015</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mousa 2007</td>
<td>CR</td>
<td>SI</td>
<td>1</td>
<td>Letrozole</td>
<td>8</td>
<td>1 (100)</td>
<td>NR</td>
</tr>
<tr>
<td>Ferrero 2011</td>
<td>CS</td>
<td>SI</td>
<td>2</td>
<td>Letrozole + NETA</td>
<td>10</td>
<td>2 (100)</td>
<td></td>
</tr>
</tbody>
</table>

RS = retrospective study; PS = prospective study; CR = case report; CS = case series; SI = single institution; FU = follow-up; COC = combined oral contraceptive; GnRHa = gonadotropin-releasing hormone agonist; NETA = norethisterone acetate; NR = not reported.

Table 5 – Main characteristics and findings of studies investigating surgical treatment of bladder endometriosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Setting</th>
<th>Patients, n (%)</th>
<th>Treatment type, n</th>
<th>FU (mo)</th>
<th>Symptom improvement, n (%)</th>
<th>Relapse, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antonelli 2006 [108]</td>
<td>RS</td>
<td>SI</td>
<td>31 (45.2)</td>
<td>TUR: 2 PC: 9 LPS: PC: 3</td>
<td>58</td>
<td>TUR: 0 (0) LPS: PC: 3 (100)</td>
<td>TUR: 2 (100) PC: 0 (0)</td>
</tr>
<tr>
<td>Perez-Utrilla 2009 [109]</td>
<td>RS</td>
<td>SI</td>
<td>12 (41.7)</td>
<td>TUR: 3 PC: 1 LPS: PC: 1</td>
<td>65.6</td>
<td>TUR: NR LPS: PC: 3 (100)</td>
<td>TUR: 1 (33.3)</td>
</tr>
<tr>
<td>Fuentes Pastor 2014 [110]</td>
<td>CS</td>
<td>SI</td>
<td>2 (100)</td>
<td>TUR: 2 PC: 1 LPS: PC: 1</td>
<td>11.5</td>
<td>TUR: NR LPS: PC: NR</td>
<td>TUR: 0 (0)</td>
</tr>
<tr>
<td>Nezhat 1994 [102]</td>
<td>RS</td>
<td>SI</td>
<td>17 (35.3)</td>
<td>LPS: PC: 6 NR</td>
<td>11.5</td>
<td>LPS: PC: 6 (100)</td>
<td>LPS: PC: 0 (0)</td>
</tr>
<tr>
<td>Chapron 1999 [103]</td>
<td>RS</td>
<td>SI</td>
<td>1650 (8,0)</td>
<td>LPS: PC: 8</td>
<td>31.6</td>
<td>LPS: PC: 8 (100)</td>
<td>LPS: PC: 0 (0)</td>
</tr>
<tr>
<td>Seracchioni 2010 [104]</td>
<td>PS</td>
<td>SI</td>
<td>56 (73.2)</td>
<td>LPS: PC: 41</td>
<td>55</td>
<td>LPS: PC: NR</td>
<td>LPS: PC: 0 (0)</td>
</tr>
<tr>
<td>Chapron 2010 [105]</td>
<td>PS</td>
<td>SI</td>
<td>627 (12,0)</td>
<td>LPS: PC: 75</td>
<td>50.9</td>
<td>LPS: PC: 75 (100)</td>
<td>LPS: PC: 0 (0)</td>
</tr>
<tr>
<td>Soriano 2016 [106]</td>
<td>RS</td>
<td>SI</td>
<td>69 (100)</td>
<td>LPS: PC: 69</td>
<td>≥36</td>
<td>LPS: PC: 67 (97.1)</td>
<td>LPS: PC: 2/69 (2.9)</td>
</tr>
<tr>
<td>Fedele 2005 [107]</td>
<td>RS</td>
<td>SI</td>
<td>47 (100)</td>
<td>PC: 29 LPS: PC: 18</td>
<td>33.5</td>
<td>PC + LPS PC: 39 (83.0)</td>
<td>PC + LPS PC: 5 (10.6)</td>
</tr>
<tr>
<td>Fleisch 2005 [112]</td>
<td>RS</td>
<td>SI</td>
<td>23 (8.6)</td>
<td>PC: 2</td>
<td>45.2</td>
<td>PC: NR</td>
<td>PC: NR</td>
</tr>
<tr>
<td>Roszynski 2011 [113]</td>
<td>RS</td>
<td>SI</td>
<td>30 (15)</td>
<td>LPS: PC: 15</td>
<td>24.9</td>
<td>LPS: PC: 15 (100)</td>
<td>LPS: PC: 0 (0)</td>
</tr>
<tr>
<td>Kjer 2014 [114]</td>
<td>RS</td>
<td>SI</td>
<td>30 (100)</td>
<td>PC: 13 LPS: PC: 17</td>
<td>44</td>
<td>PC: 13 (100)</td>
<td>PC: 0 (0)</td>
</tr>
<tr>
<td>Nezhat 1996 [115]</td>
<td>RS</td>
<td>SI</td>
<td>28 (725)</td>
<td>LPS: PC: 7</td>
<td>24</td>
<td>LPS: PC: 7 (100)</td>
<td>LPS: PC: 0 (0)</td>
</tr>
<tr>
<td>Nezhat 2002 [116]</td>
<td>PS</td>
<td>SI</td>
<td>15 (100)</td>
<td>LPS: PC: 15</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Seracchioni 2002 [117]</td>
<td>CR</td>
<td>SI</td>
<td>1 (100)</td>
<td>LPS: PC: 1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Salvatore 2007 [118]</td>
<td>CR</td>
<td>SI</td>
<td>21 (100)</td>
<td>LPS: PC: 21</td>
<td>19</td>
<td>LPS: PC: 21 (100)</td>
<td>NR</td>
</tr>
<tr>
<td>Granese 2008 [119]</td>
<td>RS</td>
<td>SI</td>
<td>8 (100)</td>
<td>LPS: PC: 8</td>
<td>33.8</td>
<td>LPS: PC: 5 (62.5)</td>
<td>LPS: PC: 0 (0)</td>
</tr>
<tr>
<td>Walid 2009 [120]</td>
<td>CR</td>
<td>SI</td>
<td>1 (100)</td>
<td>LPS: PC: 1</td>
<td>3</td>
<td>LPS: PC: 1 (100)</td>
<td>NR</td>
</tr>
<tr>
<td>Kovoor 2010 [121]</td>
<td>RS</td>
<td>SI</td>
<td>21 (12,4)</td>
<td>LPS: PC: 21</td>
<td>20</td>
<td>LPS: PC: 18 (85.7)</td>
<td>NR</td>
</tr>
<tr>
<td>Lussardi 2012 [122]</td>
<td>RS</td>
<td>SI</td>
<td>10 (30,0)</td>
<td>LPS: PC: 3</td>
<td>26.5</td>
<td>LPS: PC: 3 (100)</td>
<td>LPS: PC: 0 (0)</td>
</tr>
<tr>
<td>Prager 2012 [123]</td>
<td>CR</td>
<td>SI</td>
<td>1 (100)</td>
<td>LPS: PC: 1</td>
<td>18</td>
<td>LPS: PC: 1 (100)</td>
<td>LPS: PC: 0 (0)</td>
</tr>
<tr>
<td>Nezhat 2014 [124]</td>
<td>RS</td>
<td>SI</td>
<td>134 (1,7)</td>
<td>LPS: PC: 1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Chammamas 2008 [125]</td>
<td>CR</td>
<td>SI</td>
<td>1 (100)</td>
<td>RA: PC: 1</td>
<td>12</td>
<td>RA: PC: 1 (100)</td>
<td>RA: PC: 0 (0)</td>
</tr>
<tr>
<td>Liu 2008 [126]</td>
<td>CR</td>
<td>SI</td>
<td>1 (100)</td>
<td>RA: PC: 1</td>
<td>2 b</td>
<td>RA: PC: 1 (100)</td>
<td>RA: PC: 0 (0)</td>
</tr>
<tr>
<td>Nezhat 2011 [127]</td>
<td>CS</td>
<td>SI</td>
<td>5 (20,0)</td>
<td>RA: PC: 1</td>
<td>12</td>
<td>RA: PC: 1 (100)</td>
<td>NR</td>
</tr>
<tr>
<td>Colliner 2014 [128]</td>
<td>RS</td>
<td>SI</td>
<td>164 (14,0)</td>
<td>RA: PC: 23</td>
<td>9,7</td>
<td>NR</td>
<td>RA: PC: 0 (0)</td>
</tr>
<tr>
<td>Siesto 2014 [129]</td>
<td>CS</td>
<td>SI</td>
<td>318 (1,5)</td>
<td>RA: PC: 5</td>
<td>28</td>
<td>NR</td>
<td>RA: PC: 0 (0)</td>
</tr>
<tr>
<td>Abo 2016 [130]</td>
<td>CR</td>
<td>SI</td>
<td>35 (8,5)</td>
<td>RA: PC: 3</td>
<td>12</td>
<td>NR</td>
<td>RA: PC: 0 (0)</td>
</tr>
<tr>
<td>Sener 2006 [132]</td>
<td>CR</td>
<td>SI</td>
<td>1 (100)</td>
<td>TUR + LPS PC: 1</td>
<td>3</td>
<td>TUR + LPS PC: 1 (100)</td>
<td>NR</td>
</tr>
<tr>
<td>Pang 2008 [133]</td>
<td>CR</td>
<td>SI</td>
<td>1 (100)</td>
<td>TUR + LPS PC: 1</td>
<td>14</td>
<td>TUR + LPS PC: 1 (100)</td>
<td>NR</td>
</tr>
<tr>
<td>Xiomeritis 2011 [134]</td>
<td>CR</td>
<td>SI</td>
<td>1 (100)</td>
<td>TUR + LPS PC: 1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Litta 2012 [135]</td>
<td>PS</td>
<td>SI</td>
<td>12 (100)</td>
<td>TUR + LPS PC: 12</td>
<td>12</td>
<td>TUR + LPS PC: 11 (91,7)</td>
<td>NR</td>
</tr>
<tr>
<td>Cheng 2013 [136]</td>
<td>CR</td>
<td>SI</td>
<td>1 (100)</td>
<td>TUR + LPS PC: 1</td>
<td>6</td>
<td>TUR + LPS PC: 1 (100)</td>
<td>NR</td>
</tr>
<tr>
<td>Roman 2014 [137]</td>
<td>CR</td>
<td>SI</td>
<td>1 (100)</td>
<td>TUR + LPS PC: 1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

RS = retrospective study; PS = prospective study; CR = case report; CS = case series; SI = single institution; 2L 3I, 5I, 8I = two, three, five, eight institutions; FU = mean/median follow-up; LPS PC = laparoscopic partial cystectomy; NR = not reported; RA PC = robot-assisted PC; TUR = transurethral resection.

* The same patient experienced two relapses after two TUR procedures.

b At this follow-up the patient became pregnant.

---

patient interrupted the therapy because of myalgia and severe arthralgia. Bladder symptoms recurred 3 mo after treatment discontinuation [101].

According to the limited evidence available, hormonal treatments are effective in temporarily suppressing, but not curing, BE. Hence, if the decision is taken to medically control the condition and avoid excisional surgery, long-term treatment should be planned. In these selected circumstances, estrogen-progestogen combinations and progestogens should be chosen for their efficacy, safety, and cost-effectiveness that allow prolonged periods of therapy, even up to physiologic menopause [81]. Patients should be informed that the disease may progress under medical treatment, so regular follow-up is advisable.

3.3.2. Surgical treatment of BE

Surgical treatment of BE nodules should be always performed after an accurate diagnostic workup; this is crucial to establish a differential diagnosis with malignant lesions, to define the exact location of the node and its relationship to the ureteral meatuses, and to clarify the ureteral status. Two techniques have been proposed for surgical treatment of BE: TUR surgery and partial cystectomy (alone or in combination). The main objective of each surgical procedure should be to entirely remove the bladder lesion. Significant improvements in pain and urinary symptoms have been observed after excision of the whole bladder lesion [102–106]. Complete surgical excision of nodules also minimizes the risk of recurrence [103,105–109]. Table 1 summarizes the main advantages...
and disadvantages associated with the surgical techniques available.

3.3.2.1. TUR surgery. TUR has been proposed for the treatment of BE even though evidence supporting the efficacy and safety of this procedure is poor (Table 5) [108–110]. In fact, this surgical technique does not properly apply to treatment of this type of lesion from a pathogenic point of view [77]. Since the nodule develops from the outer layer of the bladder wall towards the inner layer, complete excision of the endometriotic lesion is virtually unachievable, exposing the patient to a high risk of bladder perforation and short-term recurrence of both symptoms and disease [107–110]. Therefore, on the basis of the evidence available, TUR should not be performed for the treatment of BE.

3.3.2.2. Segmental bladder resection. Partial cystectomy is a bladder-preserving operation for the treatment of BE that can be performed via laparotomy [107,108,111–114] or laparoscopy [102–109,111–124] without or with robotic assistance (Table 5) [125–130]. This procedure consists of partial bladder resection for detrusor endometriosis with or without preventive cystoscopic catheterization of the ureters. Ureteral cannulation is optional in the case of surgery for primary BE nodules, which are usually located on the posterior bladder wall, well above the trigonal area. The decision to perform ureteral cannulation is mainly based on the surgeon’s preference and on the distance between the caudal margin of the endometriotic lesion and the interureteric ridge (advisable if <2 cm). Conversely, preventive catheterization is mandatory when treating recurrent nodules, which may infiltrate down the bladder, approaching the ureteral meatuses [131]. Partial cystectomy is generally a safe and simple procedure: the bladder contents are sterile, vesical sutures heal easily because of rich vascularization, and prolonged urine drainage (∼10 d) usually prevents fistula formation [77]. Several studies have shown that partial cystectomy is an effective technique with excellent long-term results in terms of symptom relief and recurrence [104,105,107,113,114]. As mentioned earlier, complete removal of the lesion is a mandatory aim of the surgical procedure. Fedele et al. [107] reported long-term outcomes for surgical conservative treatment of BE. Thirty-three patients with BE of the base were included: one group (n = 19) underwent partial cystectomy only, while the second group (n = 14) underwent partial cystectomy plus a 0.5- to 1-cm-deep myometrial resection of the anterior uterine wall adjacent to the vesical nodule to remove any adenomyotic focus lying under the vesical lesion. Symptom recurrence was significantly more frequent among women in the first group (36.8%) than those in the second group (7.1%). The type of surgery was the only prognostic factor associated with a higher risk of BE relapse, and no significant association was observed for age, previous surgery for endometriosis, parity, and pregnancy after operation [107].

3.3.2.3. Combined cystoscopic and open/laparoscopic/robotic approach. Different authors have described a combination of TUR and open/laparoscopic/robotic surgery for BE [109,132–137]. The aim of this double approach is to overcome the limitations of both surgical techniques (Table 5). Open/laparoscopic/robotic excision of endometriotic nodules of the bladder may lead to inadvertent removal of healthy bladder muscle, in particular in the case of large endometriotic lesions. Hence, this surgical approach alone increases the risk of postoperative complications and symptoms due to small bladder volume. Conversely, if nodule resection is performed only by TUR, the risks of incomplete removal, of intraoperative bladder perforation (when attempting to achieve complete nodule removal), and of relapse are high. Thus, a combination of TUR and open/laparoscopic/robotic surgery allows complete removal of the endometriotic nodule while sparing most of the healthy bladder tissue. However, evidence on this topic is scanty and limited to case reports and case series. In fact, well-designed (ideally randomized) studies would be very difficult to perform given the relative rarity of BE and the high number of patients to be included in a randomized trial comparing an experimental with the standard procedure.

3.4. Management of BE in patients wishing to conceive

As mentioned earlier, BE is rarely an isolated condition. In nine out of ten cases, other forms of endometriosis are concomitant [7]. In practice, disentanglement of the independent effect of BE on fertility is challenging, if not impossible. Similarly, evaluation of the benefits of surgical excision is demanding because surgery for BE is generally concomitant with treatment for other forms of the disease, such as adhesions, endometriomas, superficial implants, and other deep localizations of the disease. It is noteworthy that there is no strong rationale for hypothesizing a detrimental impact of BE per se on fertility. Similar to other deep locations, bladder lesions are buried under adhesions and the associated inflammation is not expected to perturb the pelvic milieu. In fact, an independent detrimental effect of deep invasive endometriotic peritoneal lesions on fertility has never been demonstrated and remains debated [138]. Moreover, pelvic steps of the conception process (ovulation, oocyte pick-up by the tubes, fertilization, and tubal transport) occur in the posterior pelvis, and are thus distant from the bladder and BE. However, deep peritoneal endometriosis is associated with adenomyosis [139,140], a condition characterized by infiltration of the endometrium into the adjacent myometrium. Infertility in women with BE may actually be mediated by this association, considering in particular that adenomyosis may interfere with fertility [141,142]. Specific data on fertility treatment in women with BE are extremely scanty and controversial. We identified only two case series specifically reporting on pregnancy rates following surgery for BE [106,121] and failed to identify any data on in vitro fertilization (IVF). Specifically, Kovoor et al. [12] reported that five out of ten (50%) infertile women with BE conceived naturally after the intervention. Soriano et al. [106] observed 16 natural pregnancies out of 42 women (38%) seeking pregnancy after the intervention. Data on
natural pregnancy rates in the subgroup of women who were infertile at the time of the intervention (n = 27) were not reported. Overall, albeit scarce, these results are in line with the pregnancy rates of 42–44% observed after surgery for deep endometriosis [143–145].

On this basis, even if BE may actually be less detrimental than deep endometriosis in general, one may reasonably infer that concepts that are valid for the latter may also be valid for the former.

Three main principles applying to infertility associated with deep endometriosis in general [138] deserve to be outlined here. First, the benefits of surgery are modest. The above-mentioned 42–44% rate of success after intervention is probably an overestimation of the role of surgery because some conceptions may occur regardless of surgery and some published case series included both women who were not infertile at the time of intervention and/or pregnancies obtained with the use of in vitro fertilization [143]. Overall, one may postulate that only 20–25% of women may really benefit from the intervention [143], a rate that is similar to the pregnancy rate achieved with a single IVF cycle [146]. More generally, infertility may play a role in the decision-making process on whether to operate women with BE, but infertility alone as an indication for the intervention is questionable. Pain symptoms and functional disturbances should play the major role.

Second, IVF has to be considered the first-line option for treating infertility. Compared to surgery, IVF appears to be more effective and less risky [138,146]. However, a possible and peculiar concern here is the risk of IVF-mediated progression of endometriosis. It cannot be excluded that deep peritoneal lesions may progress under the influence of the higher levels of peripheral sex steroids that typically occur during ovarian hyperstimulation for IVF [147]. It is noteworthy that ureteral obstruction after IVF has been reported in two cases [148,149]. A precise estimation of the magnitude of this risk is lacking, but it is presumably extremely rare, and thus is not sufficient to claim a preventative role of surgery before IVF. Finally, some authors claim that removal of deep lesions and BE may increase the IVF success rate [106,150]. However, evidence to support this approach is weak and the view lacks a biological rationale.

Third, possible concerns regarding conservative management of BE are the risk of endometriosis progression under the influence of the pregnancy hormonal milieu and the impact of the disease on difficulty in performing cesarean sections in pregnant women. In fact, decidualization of endometriosis may occur at any site, including the bladder [151]. Lesions typically grow rapidly during the first weeks of pregnancy and become highly vascularized, thus mimicking cancer. Five case reports of decidualized BE have been reported in the literature [55,152–155]. Decidualization of BE may pose a diagnostic challenge, and surgery may ultimately be decided to rule out cancer. Moreover, decidualization may in some circumstances cause significant progression of the lesions and possible demanding clinical situations such as severe hemorrhage [151,156]. However, this situation is also extremely rare. A policy of systematic surgery before pregnancy to prevent this complication is not justified. However, clinicians should use extreme caution for pregnant women with BE requiring a cesarean section who were conservatively managed. The uterosacral pouch may be partly or completely obliterated, preventing an easy and safe transverse incision of the lower uterine segment to gain access to the uterine cavity. Caudal reflection of the bladder may become particularly challenging and may cause significant bleeding. In such cases, obstetricians should consider an alternative mode (longitudinally on the uterine body) and/or site (transverse but more cranial than the lower uterine segment) of incision to minimize the risk of bladder injuries. Furthermore, it is advisable to plan delivery for these patients in hospitals where urologists and blood banks are promptly available.

3.5. Malignant transformation of BE

Only eight cases of tumor arising from foci of bladder endometriosis have been reported so far in the English literature [157–164]. It should be considered that although specific criteria have been established to define the development of a malignant tumor from endometriosis [165], not all the reports on this topic seemed to have strictly followed these criteria. The age of the women affected ranged from 35 to 62 yr, and only two had a previous history of endometriosis. None of the cases was on estrogen therapy at the time of tumor diagnosis. Pathologic examination revealed two endometrioid and four clear-cell carcinomas, while one was an endometrioid adenosarcoma. Surgical treatment was generally offered.

Hence, current evidence does not support the removal of bladder endometriotic lesions owing to the potential risk of a malignant transformation because the phenomenon is exceedingly rare, as documented in only a few case reports.

4. Conclusions

BE is rarely an isolated condition, and other forms of endometriosis are frequently concomitant [7]. BE is a challenging condition and the coexistence of other types of endometriosis mean that clinical management of BE should be undertaken at referral centers where collaboration between a dedicated gynecologist and urologist is possible. Women of reproductive age complaining of urinary symptoms, most often during the menstrual cycle, should always be investigated for the presence of BE. Urodynamics has been investigated in the assessment of patients with BE. However, scanty evidence is available and future research should evaluate its clinical usefulness, in particular among patients receiving medical/surgical treatment. Abdominal ultrasonography and TVS should be regarded as first-line techniques for assessment of BE owing to their accuracy, safety, and cost-effectiveness. Once a diagnosis of BE has been established, clinical management can be conservative—using hormonal therapies—or surgical. For patients undergoing medical treatment, estrogen-progestogen combinations and progestogens should be preferred because of their favorable safety, tolerability, and cost profiles that...
allow prolonged periods of therapy [81]. Surgical excision of BE nodules should be performed if pain persists despite medical treatment, when the lesion causes ureteral stricture, and for patients with a contraindication to hormonal therapies or who refuse these drugs. The primary goal of surgery should be complete removal of the bladder nodule; consequently, when surgical treatment is chosen, TUR alone should be avoided.

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**Appendix A. Supplementary data**

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**References**


