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Urodynamic observations and lower urinary tract symptoms associated with endometriosis: a prospective cross-sectional observational study assessing women with deep infiltrating disease

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Abstract

Introduction and hypothesis The objective was to assess the association between lower urinary tract disease (LUTD) and the presence of endometriosis at different anatomical sites.

Methods Our prospective cross-sectional observational study evaluated 138 women with deep infiltrating endometriosis who had undergone preoperative evaluation of urodynamics and detailed assessment of lower urinary tract symptoms between August 2013 and May 2016. After laparoscopy, the anatomical sites of histologically confirmed endometriosis lesions were mapped.

Results The presence of endometriosis in the bladder demonstrated significant negative angular coefficients for bladder compliance (mL/cmH_2O) ($P = 0.007$; B = −54.65; 95%CI: −93.76 to −15.51) and for maximum cystometric capacity (mL; $P = 0.001$; B = −39.79; 95%CI: −62.51 to −17.06), whereas endometriosis in the parametrium showed significant positive coefficients for opening pressure (cmH_2O) ($P = 0.016$; B = 5.89; 95%CI: 1.10–10.69) and post-void residual (mL) ($P = 0.015$; B = 31.34; 95%CI: 6.14–56.55). The presence of endometriosis in the bladder was a statistically significant independent predictor of low bladder compliance ($P < 0.001$; OR = 30.10; 95%CI: 9.48–95.55), whereas endometriosis in the parametrium was a statistically significant independent predictor of both abnormal residual urine ($P = 0.019$; OR = 5.21; 95%CI: 1.32–20.64) and bladder outlet obstruction ($P = 0.011$; OR = 7.91; 95%CI: 1.61–38.86). Correspondence analysis suggested two possible independent ways through which endometriosis acts on the genesis of urinary dysfunctions.

Conclusions Our findings strongly suggest that endometriosis involving the bladder might disturb storage function, whereas endometriosis in the parametrium disturbs the voiding phase.

Keywords Endometriosis · Lower urinary tract symptoms · Urodynamics · Micturition · Bladder voiding function

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Introduction

Endometriosis is defined as the presence of endometrial glands and stroma in ectopic locations, which affects 6–10% of reproductive age women [1] and up to 50% of women experiencing pain and/or infertility [2]. Deep infiltrating endometriosis (DIE) infiltrates multiple pelvic organs deeper than 5 mm [3] and is considered the most severe form of endometriosis. DIE can present with a confusing array of symptoms that pose diagnostic and therapeutic challenges [4]. Dysmenorrhea, deep dyspareunia, dyschezia, and dysuria are the most frequently reported symptoms [5] and may occur independently [6].

Clinicians are increasingly concerned about endometriosis-related lower urinary tract dysfunctions (LUTDs), which may be subclinical or overlooked by patients focused on more

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distressing non-urinary symptoms, particularly pain. Although the assessment of urodynamics has long been the standard method for evaluating bladder voiding function [7], recommendations to perform urodynamic studies as part of the preoperative evaluation of women with DIE have not been so clear [8]. Moreover, many published studies do not include the preoperative assessment of LUTD [9]. Recent studies with small sample sizes have shown statistically significant associations between endometriosis and LUTD when preoperatively assessing symptomatic [10] or asymptomatic [11] women.

To better understand the association between endometriosis and LUTD, this interdisciplinary study assessed symptomatic and asymptomatic women with DIE to investigate the association between LUTD (including lower urinary tract symptoms [LUTS] and urodynamic observations) and the presence of endometriosis in different anatomical sites.

Materials and methods

Sample enrollment: inclusion and exclusion criteria

In this prospective cross-sectional observational study, we engaged 138 young women at menacme living in the city of Rio de Janeiro, Brazil, with a clinical diagnosis of DIE, which was confirmed histologically after surgery. Consecutive patients (sequential cases) were enrolled from August 2013 to May 2016, while patients were being prepared to undergo laparoscopy for pain relief, fertility improvement or both.

Concerning LUTDs, we included both symptomatic and asymptomatic women, but considered some exclusion criteria. In the cohort, none of subjects had a history of severe disease in the central or peripheral nervous system, pelvic or perineal surgery (except vaginal delivery and uncomplicated cesarean section), pelvic radiotherapy, chronic pelvic pain syndrome from causes other than endometriosis, LUTD before the diagnosis of deep endometriosis, severe urological disease (lithiasis, tumors, etc.), or prolapse of the uterus, bladder, bowel or rectum. Moreover, none of the patients reported any treatment for LUTDs (i.e., α-adrenergic blockers, antimuscarinic or beta-3 agonists). The assessment of urinary tract dysfunction was performed preoperatively in all women only after laboratory confirmation—by a negative urine culture—of the absence of a urinary tract infection.

Mapping endometriosis

Our multidisciplinary endometriosis referral center manages the diagnosis and treatment of DIE following the guidelines of the American Society of Reproductive Medicine [12] and the European Society of Human Reproduction and Embryology [13]. The diagnosis of DIE involved four steps: medical history, physical examination, magnetic resonance imaging (MRI) showing at least one lesion deeper than 5 mm, and histological confirmation after laparoscopy.

In this series, all MRIs were evaluated by the same experienced radiologist; the major anatomical sites were chosen according to the Lasmar's diagram [14]. All laparoscopies were performed by the same multidisciplinary team, which systematically performed ureterolysis identifying and preserving pelvic nerves. Whether identified by the preoperative MRI or encountered during laparoscopic assessment, all suspected deep lesions in the parametrium were carefully explored. Endometriosis was considered histologically confirmed when endometrial glands and stroma were present upon microscopic examination. The same experienced pathologist (LC) was responsible for the histological examination of all specimens.

LUTS assessment and urodynamics

As per our routine, all women with DIE lesions detected by MRI underwent detailed preoperative LUTD assessment. In this series, the same experienced urologist (JADR Jr) performed a standardized investigation, which included a detailed medical history of lower urinary tract symptoms based on the International Prostate Symptom Score (IPSS) using a validated Portuguese version of the instrument, and assessment of urodynamics according the Standardization Subcommittee of the International Continence Society [15–17].

Urodynamic studies were performed using a Dynapack MPX 816 (Dynamed, São Paulo, Brazil). Urodynamic parameters were dichotomized as "normal" or "abnormal/pathological" according to the criteria of the International Consultation on Incontinence-Research Society [18], in addition to its recommendations for future development of contractility and obstruction nomograms for women [19].

Protection of human subjects

This study was approved by the institutional IRB, the Research Ethics Committee (CAAE 0035.0.008.000–11). All patients gave their informed consent before being included in the study.

Statistics

The sample size calculation was performed contemplating bivariate analysis to compare frequencies of a given condition, assuming an equal number of observations in the two groups. Considering that the frequency of LUTD in the group with endometriosis would exceed 60% [10], the proportion of LUTD in the group without endometriosis would be less than 20% [20], a significance level of 5% and 90% power using a two-tailed test, we estimated that 29 individuals in each group would be adequate to identify statistical associations if they

exist. Nonetheless, because the study was observational, we included more cases to account for potential confounding variables.

We standardized the surgical sites as binary variables (normal or endometriosis) to calculate the prevalence of endometriosis at each anatomical site. The data distributions of discrete variables were considered and nonparametric tests used when necessary.

Associations between the presence of endometriosis and LUTD were first assessed by bivariate analysis. Then multiple logistic regression analysis was used to assess the chance of finding every LUTD (binary outcome) and multiple linear regression models was used to assess every urodynamic measurement (dependent discrete variable) as a function of the presence of endometriosis in different anatomical sites (predictors). Finally, we included the principal anatomical sites and the endometriosis-related LUTD in a correspondence analysis to assess interrelationships among the main findings.

Statistical and graphical analyses were performed with IBM® SPSS® Statistics Standard Grad Pack 20 (NY, USA). Statistical results were considered significant when $P < 0.050$ (two-sided), except for multiple regression analysis (backward stepwise), in which the criteria for predictors selection was $P < 0.100$.

Results

The characterization of the sample is summarized in Table 1. A total of 112 women had never been pregnant (81.2%; 95%CI: 74.6–87.7). Of the 26 women with previous pregnancies, 4 reported at least one abortion (2.9%; 95%CI: 0.7–6.5) and only 2 women delivered vaginally (1.4%; 95%CI: 0.0–4.3).

Anatomical sites affected by endometriosis and their relationship with LUTD

The number of anatomical sites affected by endometriosis in individual patients ranged from 1 to 9 (median = 5; 25th percentile = 3; 75th percentile = 6). Ovary, parametrium, round ligament, and uterosacral ligament presented both uni- and bilateral endometriosis. The uterosacral ligament and rectum were the most commonly affected sites; the respective prevalences were 67.4% (95%CI: 59.4–75.4) and 60.9% (95%CI: 52.9–69.5). The bladder was the most frequently affected site of the urinary tract (prevalence: 23.2%; 95%CI: 16.7–30.4). Only one woman had endometriosis involving a ureter (the right). The prevalence of endometriosis in at least one parametrium was 37.0% (95%CI: 29.0–44.9).

In this sample, we found 67 women (48.6%; 95%CI: 41.3–57.2) with at least one LUTS and 83 women (60.1%; 95%CI: 52–2 – 68.1) with at least one urodynamic observation. Regarding the prevalence of LUTD, 104 women had at least one LUTS or at least one urodynamic observation (75.4%; 95%CI: 68.1–82.6), 46 women had at least one LUTS and at least one urodynamic observation (33.3%; 95%CI: 26.1–42.0), 21 women showed at least one LUTS, but with no urodynamic observation (15.2%; 95%CI: 9.4–22.4), and 37 women had no LUTS, but had at least one urodynamic observation (26.8%; 95%CI: 20.3–34.1; Table 2).

An overview of all LUTD and urodynamic measurements is presented in Table 3. Although the three most prevalent LUTS were obstructive (straining to void [31.2%; 95%CI: 23.9–38.4], feeling of incomplete emptying [26.1%; 95%CI: 18.8–33.3], and intermittency (20.3%; 95%CI: 13.8–26.8]), the most prevalent urodynamic observation was low bladder compliance (34.8%; 95%CI: 27.5–42.8), which refers primarily to bladder storage. Only two women—both with endometriosis involving the bladder wall—had a maximum cystometric capacity of <300 mL. One woman reported cyclic hematuria, but no endometriosis was found in her urinary tract.

Preliminary bivariate analysis

To assess the associations between endometriosis and LUTD, we selected six anatomical sites in or proximal to the lower urinary tract or pelvic nerves—vesicouterine pouch, rectum, bladder, uterosacral ligament, round ligament, and parametrium—in which at least 20% of study subjects had confirmed endometriosis lesions (Table 4).

Among the anterior compartment sites, only endometriosis in the bladder demonstrated a statistical association with LUTD. Actually, as endometriosis in the bladder was associated with endometriosis in at least one round ligament ($P < 0.001$; OR = 6.18; 95%CI: 2.5–14.86), we repeated the tests after excluding cases in which the bladder was affected to avoid confounding. The association between endometriosis in the round ligament and low bladder compliance was in fact not significant ($P = 0.270$; OR = 1.83; 95%CI: 0.66–5.03) and nor was its association with bladder compliance ($P = 0.128$ and 0.143 for t test and Mann–Whitney test respectively) and maximum cystometric capacity ($P = 0.844$ and 0.634 for t test and Mann–Whitney test respectively).

Among the posterior compartment sites, the association of endometriosis in the parametrium with obstructive LUTD was the key finding.

Multivariate regression analysis

After the preliminary bivariate analysis, we recognized endometriosis involving the bladder and in the parametrium as the main potential predictors of LUTD, not only because of the significant statistical associations (Table 4), but also because of their strong relationship with pelvic nerves and bladder

Table 1 Characteristics of the sample ($N = 138$ women)

	Minimum	P25	Median	P75	Maximum	*n*	Percentage	95%CI
Age	22	30	33	37	53			
Dysmenorrhea (VAS)	0	5.75	9	10	10			
Dyspareunia (VAS)	0	0.75	3	8	10			
Hypogastric pain (VAS)	0	3	7	8	10			
Menstrual dyschezia (VAS)	0	0	3	9	10			
Nonmenstrual dyschezia (VAS)	0	0	0	4	10			
Height (cm)	143	156	160	165	177			
Weight (kg)	42	62	70	78	131			
BMI ($kg.m^{-2}$)	17	24	27	30	48			
Partner								
Married						101	73.2	65.9–80.4
Divorced						1	0.7	0.0–2.2
Not informed						1	0.7	0.0–2.9
Single						35	25.4	18.8–32.6
Schooling								
<9th grade						37	26.8	19.6–34.1
9th grade						26	18.8	12.3–24.6
12th grade						44	31.9	24.6–40.6
>12th grade						28	20.3	13.8–26.8
Alcohol intake								
Never						113	81.9	75.4–87.7
≤ 2 times/week						23	16.7	10.9–23.2
>2 times/week						2	1.4	0.0–3.6
Smoking								
Never						117	84.8	79.0–90.6
>6 months without						9	6.5	2.9–10.9
Yes						12	8.7	4.3–13.7
Ethnicity								
Asian						2	1.4	0.0–3.6
Caucasian						87	63.0	54.3–70.3
Black						10	7.2	3.6–11.6
Mixed						39	28.3	21.0–36.2
Sex life								
Not sexually active						35	25.4	18.1–32.6
Sexually active						100	72.5	65.2–79.7
Never been sexually active						3	2.2	0.0–5.1
Reproductive life								
Infertility						27	19.6	13–26.8

Infertility indicates failure to achieve pregnancy after 12 months or more of regular unprotected sexual intercourse [20]

BMI (body mass index) body mass divided by the square of the body height, *VAS* visual analog scale, *P25* 25th percentile; *P75* 75th percentile, *95%CI* 95% confidence interval

voiding function. Moreover, the rectum and uterosacral ligament were also selected because they were the anatomical sites most frequently affected by endometriosis (Table 2).

When endometriosis in the bladder, parametrium, rectum, and uterosacral ligament were simultaneously tested as predictors of each urodynamic observation by multiple linear

Table 2 Prevalence of LUTS and urodynamic observations in women with confirmed endometriosis at different anatomical sites

Anatomical site	Confirmed endometriosis *n* (%)	LUTS[a] *n* (%)	Urodynamic observations[a] *n* (%)
Uterosacral ligament[a]	93 (67.4)	45 (48.4)	59 (63.4)
Rectum	84 (60.9)	45 (53.6)	54 (64.3)
Round ligament[a]	54 (39.1)	22 (40.7)	36 (66.7)
Parametrium[a]	51 (37.0)	30 (58.8)	40 (78.4)
Ovary[a]	43 (31.2)	20 (46.5)	28 (65.1)
Bladder	32 (23.2)	18 (56.2)	29 (90.6)
Posterior vaginal wall	30 (21.7)	17 (56.7)	22 (73.3)
Vesicouterine pouch	30 (21.7)	15 (50.0)	20 (66.7)
Appendix	18 (13.0)	7 (38.9)	11 (61.1)
Sigmoid colon	7 (5.1)	4 (57.1)	7 (100.0)
Cecum	3 (2.2)	2 (66.7)	3 (100.0)
Ureter[a]	1 (0.7)	0 (0.0)	0 (0.0)

N = 138 women with confirmed deep endometriosis

LUTS lower urinary tract symptoms

[a] At least one

regression analysis, two tendencies became evident: endometriosis involving the bladder demonstrated statistically significant negative coefficients for bladder compliance and maximum cystometric capacity, whereas endometriosis in the parametrium demonstrated statistically significant positive coefficients for opening pressure and postvoid residual. When the likelihood of finding LUTD was assessed by multiple logistic regression analysis, the presence of endometriosis in the bladder was a statistically significant independent predictor of low bladder compliance and the presence of endometriosis in the parametrium was a statistically significant independent predictor of both abnormal residual urine and bladder outlet obstruction.

Considering the possibility of some association among the predictors assessed in the regression models, there was no significant association among endometriosis in the bladder, parametrium, rectum, and uterosacral ligament (Pearson's Chi-squared test), which excluded collinearity. The results of all regression models are summarized in Table 5.

Bladder and parametrium: putting the main findings together

Regarding the 32 patients with endometriosis involving the bladder, 13 (40.6%) had endometriosis infiltrating at least one parametrium, whereas, of the 51 women with endometriosis in the parametrium, 13 (25.5%) also had endometriosis involving the bladder. The prevalence of endometriosis-related LUTD in women with or without endometriosis involving the bladder were respectively: low bladder compliance (87.5/18.9%), urgency (40.6/9.4%), intermittency (34.4/16.0%), feeling of incomplete emptying (31.2/24.5%), straining to void (31.2/31.1%), strangury (25.0/10.4%), bladder outlet obstruction (9.4/6.6%) and abnormal residual urine (6.2/8.5%).The prevalence of endometriosis-related LUTD in patients with or without endometriosis in the parametrium were: straining to void (45.1/23.0%), intermittency (43.1/6.9%), feeling of incomplete emptying (39.2/18.4%), low bladder compliance (33.3/35.6%), urgency (21.6/13.8%), strangury (21.6/9.2%), bladder outlet obstruction (15.7/2.3%), and abnormal residual urine (15.7/3.4%).

When the recognized endometriosis-related LUTS were assessed in an exploratory multivariate correspondence analysis considering the two key anatomical sites (bladder and parametrium), the two retained components (eigenvalues >1) accounted for 53.7% of the total variance (Fig. 1a). The presence of endometriosis in the parametrium (0.628), feeling of incomplete emptying (0.666), straining to void (0.758), and intermittency (0.762) loaded mainly on the first component (named the voiding axis); strangury (0.397) loaded moderately; urgency (0.134) and endometriosis in the bladder (0.076) showed negligible loads. Otherwise, the second component (named storage axis) was almost exclusively loaded by endometriosis in the bladder (0.788) and urgency (0.770), with some minimal contributions of feeling of incomplete emptying (0.252) and intermittency (0.220), and negligible loads for straining to void (−0.057) and the presence of endometriosis in the parametrium (0.002). Strangury (0.507) loaded moderately on the storage axis too, which suggests a reasonable contribution of strangury to the two retained components.

Finally, we performed another correspondence analysis assessing the three urodynamic observations that were associated with the presence of endometriosis in the bladder and parametrium. In this second approach, there were also only two retained components (eigenvalue >1), which accounted for 61.8% of the total variance. The key variables that loaded

Table 3 Clinical evaluation and assessment of urodynamics in 138 women with confirmed deep endometriosis

	n	Prevalence (%)	95%CI	Minimum	P25	Median	P75	Max
Lower urinary tract symptom								
Straining to void	43	31.2	23.9–38.4					
Feeling of incomplete emptying	36	26.1	18.8–33.3					
Intermittent stream (intermittency)	28	20.3	13.8–26.8					
Urgency	23	16.7	10.9–22.5					
Urinary incontinence (leakage)	22	15.9	10.1–21.7					
Strangury	19	13.8	8.0–19.6					
Recurrent cystitis	7	5.1	1.4–9.4					
Lumbar pain	6	4.3	1.4–8.0					
Flank pain	4	2.9	0.0–5.8					
Hematuria	1	0.7	0.0–2.2					
Urodynamic observations								
Low bladder compliance	48	34.8	27.5–42.8					
Detrusor underactivity	39	28.3	20.3–36.2					
Abnormal bladder sensation	33	23.9	17.4–31.2					
Detrusor overactivity	15	10.9	5.8–16.7					
Abnormal residual urine	11	8.0	3.6–13.0					
Bladder outlet obstruction	10	7.2	2.9–12.3					
Maximum cystometric capacity <300 mL	2	1.4	0.0–3.6					
At least one abnormal finding	83	60.1	52.2–68.1					
Urodynamic measurements								
Bladder compliance (mL/cmH_2O)				6.0	23.0	35.0	50.0	500.0
Maximum cystometric capacity (mL)				250.0	400.0	500.0	500.0	500.0
Opening pressure (cmH_2O)				3.0	24.0	30.0	42.8	73.0
Maximum pressure (cmH_2O)				8.0	35.0	45.5	58.3	168.0
Pressure at maximum flow (cmH_2O)				13.0	28.0	38.0	45.8	111.0
Closing pressure (cmH_2O)				2.0	16.3	24.0	37.8	114.0
Maximum flow rate (mL/s)				5.0	11.3	16.0	19.0	31.0
Voided volume (mL)				150.0	380.0	440.0	480.0	516.0
Post-void residual (mL)				0.0	10.0	28.5	50.0	350.0
Bladder outlet obstruction index				−23.0	−7.0	3.0	17.0	87.0
Bladder contractility index				68.9	98.0	118.0	135.0	188.0

Low bladder compliance when < 30 cmH_2O

Detrusor underactivity when bladder contractility index (pressure at maximum flow +5 x maximum flow rate) ≤100

Abnormal bladder sensation when the first desire to void occurs at cystometry < 80 or >200 mL

Detrusor overactivity: involuntary detrusor contractions during the filling phase

Abnormal residual urine when postvoid residual >100 mL

Bladder outlet obstruction when bladder outlet obstruction index (pressure at maximum flow – 2 x maximum flow rate) ≥40

Both cases with maximum cystometric capacity < 300 mL had endometriosis in the bladder

Table 4 Association between lower urinary tract outcomes and confirmed endometriosis in different anatomical sites ($N = 138$)

	Vesicouterine pouch	Rectum	Bladder	Uterosacral ligament[f]	Round ligament[f]	Parametrium[f]
Lower urinary tract symptom, OR (95%CI)						
Straining to void	0.61 (0.24–1.55)	1.13 (0.54–2.36)	1.01 (0.43–2.36)	0.86 (0.40–1.85)	0.57 (0.27–1.23)	*2.75 (1.31–5.80)***
Feeling of incomplete emptying	0.37 (0.11–1.13)[c]	0.87 (0.40–1.88)	1.40 (0.59–3.33)	1.14 (0.50–2.58)	0.84 (0.38–1.85)	*2.86 (1.31–6.26)***
Intermittent stream (Intermittency)	0.37 (0.10–1.32)	1.20 (0.51–2.84)	*2.74 (1.12–6.71)**	1.03 (0.42–2.50)	0.68 (0.28–1.65)	*1.24 (3.78–27.77)****
Urgency	1.75 (0.65–4.75)	2.67 (0.93–7.70)	*6.57 (2.52–17.16)****	1.45 (0.53–3.98)	1.90 (0.77–4.67)	1.72 (0.70–4.24)
Urinary incontinence (Leakage)	1.07 (0.36–3.19)	1.88 (0.69–5.16)	1.70 (0.63–4.62)	1.04 (0.39–2.77)	1.34 (0.54–3.42)	0.76 (0.29–2.02)
Strangury	0.38 (0.08–1.76)	0.68 (0.26–1.789)	*2.88 (1.04–7.94)**	1.42 (0.48–4.22)	0.89 (0.33–2.43)	*2.72 (1.01–7.29)**
Urodynamic observation, OR (95%CI)						
Low bladder compliance	1.33 (0.58–3.07)	1.11 (0.54–2.28)	*3.10 (9.48–95.55)[c]****	1.49 (0.69–3.21)	*3.45 (1.66–7.17)***	0.90 (0.44–1.87)
Detrusor underactivity	0.72 (0.28–1.85)	1.66 (0.75–3.65)	1.21 (0.51–2.86)	1.59 (0.69–3.63)	0.83 (0.38–1.78)	1.48 (0.69–3.15)
Abnormal bladder sensation	0.96 (0.37–2.49)	0.84 (0.38–1.85)	1.34 (0.55–3.27)	0.48 (0.18–1.29)	0.37 (0.12–1.18)	0.97 (0.43–2.18)
Detrusor overactivity	1.36 (0.40–4.61)	0.96 (0.32–2.87)	0.21 (0.03–1.68)	0.96 (0.31–3.01)	0.35 (0.10–1.32)	0.84 (0.27–2.60)
Abnormal residual urine	1.39 (0.35–5.60)	1.79 (0.45–7.07)	0.72 (0.15–3.51)	5.30 (0.66–42.77)	0.56 (0.14–2.21)	*5.21 (1.32–20.64)***
Bladder outlet obstruction	0.89 (0.18–4.45)	2.74 (0.56–13.41)	1.46 (0.36–6.02)	2.02 (0.41–9.95)	1.61 (0.44–5.86)	*7.91 (1.61–38.86)***
Urodynamic measurements, P value[a]						
Bladder compliance	0.327	0.521	*<0.001*[d]*/<0.001*[e]	0.215[d]	*0.016*[d]*/0.002*[e]	0.302[a]
Maximum cystometric capacity [b]	0.744	0.686	*0.007*[d]*/0.003*[e]	0.799[a]	0.052[a]/0.074[e]	0.161[d]
Opening pressure	0.966	0.389	0.637[a]	0.377[d]	0.289[a]	*0.028*[d]*/0.020*[e]
Maximum pressure	0.931	0.558	0.874[a]	0.997[a]	0.422[d]	0.906[d]
Pressure at maximum flow	0.835	0.311	0.465[a]	0.616[a]	0.989[a]	0.501[a]
Closing pressure	0.668	0.680	0.540[a]	0.206[a]	0.547[d]	0.244[d]
Maximum flow rate	0.955	0.227	0.263[a]	0.293[a]	0.360[a]	0.060[a]
Postvoid residual	0.511	0.582	0.556[a]	0.420[a]	0.381[a]	0.046[d]/0.156[e]

Low bladder compliance when <30 cmH_2O

Detrusor underactivity when bladder contractility index (pressure at maximum flow +5 x maximum flow rate) ≤100

Abnormal bladder sensation when the first desire to void occurs at cystometry < 80 or >200 mL

Detrusor overactivity: involuntary detrusor contractions during the filling phase

Abnormal residual urine when postvoid residual >100 mL

Bladder outlet obstruction when the bladder outlet obstruction index (pressure at maximum flow – 2 x maximum flow rate) ≥40

Cells in italics were statistically significant

OR odds ratio

*$P < 0.050$

**$P < 0.010$

***$P < 0.001$

[a] *t* test (equal variances assumed when performing Levene's test for equality of variances)

[b] There were only two cases with maximum cystometric capacity < 300 mL; both had endometriosis involving the bladder

[c] Fisher's test was used for comparing two groups instead of Pearson's Chi-squared test

[d] *t* test (equal variances not assumed when performing Levene's test for equality of variances)

[e] Independent samples nonparametric Mann–Whitney *U* test

[f] At least one

on the first component (named storage axis) were low bladder compliance (0.897) and endometriosis in the bladder (0.889); there were minimal contributions from bladder outlet obstruction (0.156), abnormal residual urine (−0.071), and endometriosis in the parametrium (−0.023). The variables that mainly loaded on the second component were endometriosis in the parametrium (0.703) and those naturally associated with micturition: bladder outlet obstruction (0.703) and abnormal residual urine (0.688). The variables low compliance (0.044) and endometriosis in the bladder (−0.009) showed loadings close to zero on the second component, which was named voiding axis (Fig. 1b).

Table 5 Regression analysis (backward method) assessing endometriosis in different anatomical sites as predictors ($N = 138$)

	Rectum	Bladder	Uterosacral ligament[b]	Parametrium[b]
Lower urinary tract symptom, *P* value; OR (95%CI)				
Straining to void				0.008; 2.75 (1.31 to 5.80)
Feeling of incomplete emptying				0.008; 2.86 (1.31 to 6.25)
Intermittent stream (intermittency)		0.029; 3.18 (1.12 to 8.97)		<0.001; 10.91 (3.90 to 30.55)
Urgency	0.082; 2.69 (0.88 to 8.22)	<0.001; 6.59 (2.48 to 17.53)		
Urinary incontinence (leakage)				
Strangury		0.048; 2.84 (1.01 to 7.99)		0.054; 2.68 (0.98 to 7.32)
Urodynamic observation, *P* value; OR (95%CI)				
Low bladder compliance		<0.001; 30.10 (9.48 to 95.55)		
Detrusor underactivity				
Abnormal bladder sensation				
Detrusor overactivity				
Abnormal residual urine				0.019; 5.21 (1.32 to 20.64)
Bladder outlet obstruction				0.011; 7.91 (1.61 to 38.86)
Urodynamic measurement, *P* value; B (95%CI) [a]				
Bladder compliance		0.007; −54.64 (−93.76 to −15.51)		
Maximum cystometric capacity		0.001; −39.79 (−62.51 to −17.06)		
Opening pressure				0.016; 5.89 (1.10 to 10.69)
Maximum pressure				
Pressure at maximum flow				
Closing pressure				
Maximum flow rate				0.060; −1.87 (−3.83 to 0.08)
Postvoid residual				0.015; 31.34 (6.14 to 56.55)

Low bladder compliance when < 30 cmH_2O

Detrusor underactivity when bladder contractility index (pressure at maximum flow +5 x maximum flow rate) ≤100

Abnormal bladder sensation when the first desire to void occurs at cystometry < 80 or >200 mL

Detrusor overactivity: involuntary detrusor contractions during the filling phase

Abnormal residual urine when postvoid residual >100 mL

Bladder outlet obstruction when bladder outlet obstruction index (pressure at maximum flow – 2 x maximum flow rate) ≥40

Backward stepwise selection: removal testing was based on the probability of the statistic ($P \geq 0.100$)

Non-statistically significant values were removed from the table and left the cells blank

[a] B indicates the angular coefficient (unstandardized) of the linear regression model

[b] Uterosacral ligament and parametrium were considered abnormal when at least one side was affected by endometriosis

Discussion

This prospective cross-sectional study was carefully planned to explore relationships between endometriosis and LUTD, which were assessed in women with histologically confirmed DIE. After employing different statistical approaches, we found that the bladder and the parametrium are the key anatomical sites at which endometriosis plays an important role in the genesis of both LUTS and abnormal urodynamics. Indeed, we found a clear and statistically significant association between the presence of endometriosis involving the bladder and functional impairments of bladder storage. Similarly, patients with endometriosis in the parametrium had a higher chance of presenting obstructive problems during the voiding phase.

Given the six anatomical sites of endometriosis lesions studied, it is worth considering the functional neuroanatomy of the pelvis that controls bladder voiding. The superior hypogastric plexus—formed by fibers from the para-aortic sympathetic trunk—gives rise to the hypogastric nerves, which carry the sympathetic signals to the internal urethral and bladder, controlling detrusor relaxation and urethral sphincter contraction, thus promoting continence. Sacral nerve roots, which

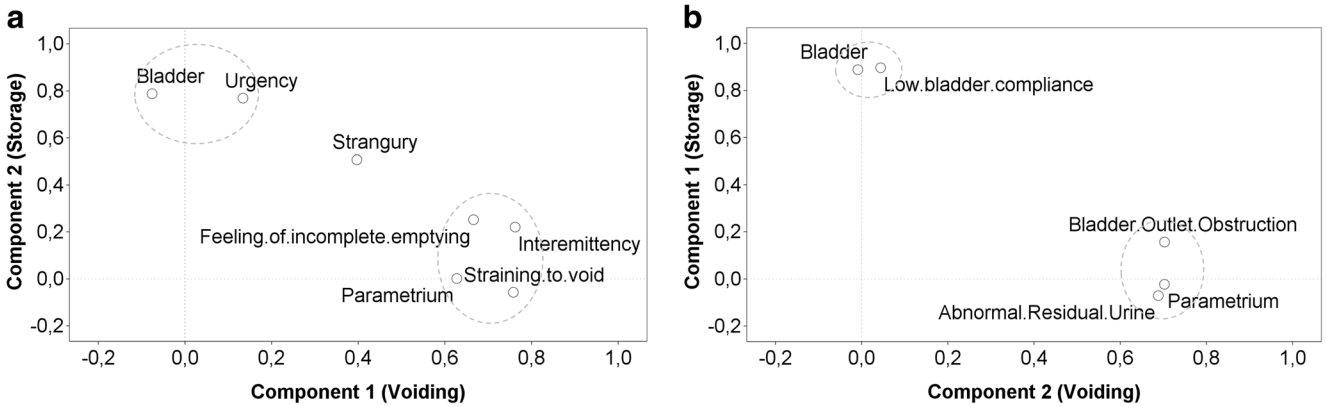

Fig. 1 Multivariate exploratory correspondence analysis assessing **a** the presence of endometriosis in the bladder and in the parametrium besides associated lower urinary tract symptoms and **b** urodynamic observations. Component plots in rotated space: $N = 138$ women. Extraction method: principal component analysis; rotation method: Varimax (orthogonal uncorrelated components) with Kaiser normalization. The Kaiser stopping criterion retained only components with eigenvalues >1, which were named voiding axis and storage axis. The parametrium was considered affected by endometriosis regardless of whether uni- or bilaterally. Postvoid residual urine was considered abnormal when the volume was > 100 mL. Bladder compliance was considered low when <30 cmH_2O. Bladder outlet obstruction when bladder outlet obstruction index (pressure at maximum flow – 2 x maximum flow rate) ≥40. *Grouped circles* denote being related under a multivariate context. The component 1 was switched in the graphic B (represented in the Y axis) to facilitate the visual comparison

course juxta-laterally to the hypogastric fascia (the lateral limit of the presacral space), form the nerves of the sacral plexus and give rise to thin parasympathetic branches called pelvic splanchnic nerves, which promote detrusor contraction and voiding [21, 22]. Our findings suggest that endometriosis lesions involving the bladder and the parametrium somehow differently affect the balance of these two axes.

When a major LUTD is identified after endometriosis surgery, elucidating the etiology of the dysfunction is often contentious [10] because it can also be explained by inflammation or invasion of the pelvic nerves that may have existed before surgery.

We can now hypothesize, for example, that lesions of endometriosis infiltrating the parametrium might stimulate sympathetic fibers of the hypogastric nerve and/or the inferior hypogastric plexus, promoting an increase in urethral sphincter tone and causing different degrees of outlet obstruction. When endometriosis lesions infiltrate the bladder, we can hypothesize that the inflammatory process, in addition to adherence and fibrosis, may compromise bladder elasticity and consequently reduce compliance and the ability to store urine.

The pathophysiology of endometriosis remains poorly understood. Nevertheless, our findings may encourage physicians to consider that LUTD may already be present in women with DIE even before treatment. Awareness of the association between LUTD and DIE may allow a more rational and thorough management, in addition to a more careful treatment for preservation (when possible) and improvement (if possible) of the urinary function rather than the conventional tendency to focus mainly on gynecological and intestinal complaints. As we recently reported [9], the consequences of an inadequate approach in these patients may lead to inadequate surgical procedures with irreversible consequences, which can even be mistaken for preoperative LUTD. Because some urinary conditions are associated with specific anatomical sites of the endometriosis lesions, surgeons and patients could be better prepared to preoperatively consider and discuss the surgery strategy, especially when large resections are contemplated based on imaging studies.

Considering the high prevalence of abnormal urodynamic observations in our sample (60.1%, including symptomatic and asymptomatic women), and that this prevalence may increase according to the anatomical site of the endometriosis (e.g., parametrium 78.4% and bladder 90.6%), we recommend a preoperative functional evaluation of the lower urinary tract, including LUTS investigation and urodynamics, in all patients with DIE.

The strengths of this study included the larger sample size (relative to previous similar studies) and the fact that endometriosis was histologically confirmed and carefully mapped in all cases. Also, despite the possibility of some measurement bias, all cases were managed by the same experienced team (urologist, general surgeon, gynecologist, proctologist, radiologist, pathologist, anesthesiologists, and psychologist), which methodically followed the strategies for diagnosis and treatment. Finally, to reduce confounding, the statistical analyses assessed the data not only using bivariate tests, but also employing multivariate analyses.

Although several patients in the study may already have undergone some previous treatment for endometriosis (i.e., including ongoing hormonal therapy or laparoscopy just for fulguration of superficial implants), this potential covariate was not weighed and may constitute a limitation of this study. Also, although our cohort was drawn from a population of

women with DIE awaiting surgery, readers should interpret these results cautiously because of the possibility of some selection bias.

Conclusion

In summary, our results point to the bladder and the parametrium as being the key sites through which endometriosis impairs bladder voiding function. Our findings strongly suggest that endometriosis in the bladder disturbs storage function and endometriosis in the parametrium disturbs the voiding phase.

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Compliance with ethical standards

Conflicts of interest None.

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