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**ABSTRACT**

*Objectives:* To evaluate urinary tract involvement by deep infiltrating endometriosis (DIE) as well as the surgical treatment and existence of predictive factors for major urologic surgery.

*Methods:* Retrospective analysis of 656 women submitted to surgery for endometriosis, of which 28 patients underwent minor or major surgery for DIE involving the urinary tract, with a mean age of  $38 \pm 6.9$  years (27-50) at diagnosis. Clinical data, surgeries performed and complications were analysed. Minor surgery was defined by endoscopic surgery or insertion of a percutaneous nephrostomy catheter (PCN) and major surgery included open or laparoscopic procedures.

*Results:* Endometriomas affected the ureter in 13 (46.4%), the bladder in 11 (39.3%) and both structures in 4 (14.3%) patients. Twelve (42.9%) patients had decreased renal function, and ureteral involvement was predictive of renal function loss ( $p=0.034$ ). Minor surgeries were performed in most women with isolated bladder involvement and in 12 (42.9%) patients with ureteral infiltration. Patients with ureteric involvement underwent major surgeries more often ( $n=12$  vs  $n=3$ ;  $p=0.025$ ) and had longer hospitalization (8.2 vs 3.1 days,  $p = 0.05$ ). After a mean follow-up of 36.3 (1-102) months, there was no bladder involvement recurrence. The most common complication was ureteral stenosis (Clavien-Dindo grade IIIb), in 3 (10.7%) patients.

*Conclusions:* Surgery is highly successful in most cases. Patients with ureteric involvement are more likely to lose kidney function, undergo major surgery and have longer hospitalization.

## INTRODUCTION

Endometriosis is a benign disease defined as the presence of functional endometrial-like tissue outside the uterus. The main clinical features are chronic pelvic pain, dyspareunia and infertility and it affects primarily women in reproductive age.<sup>1</sup> The exact prevalence of the disease is unknown, but is believed to range from 5% to 10% of general women<sup>2</sup>, but may reach 20% to 50% in infertile female population.<sup>3,4</sup>

Three major phenotypes are described: Ovarian endometrioma (OMA), superficial peritoneal endometriosis (SPE) and deep infiltrating endometriosis (DIE).<sup>5</sup> DIE is defined as endometriosis infiltrating the peritoneum deeper than 5mm<sup>6</sup> and is recognized as the most aggressive clinical form of endometriosis. It may involve the uterosacral ligaments, vagina, bowel, bladder or ureters and the depth of infiltration is related to the severity of symptoms.<sup>6</sup> DIE of the urinary tract is a rare entity, affecting 1-5% of all women with endometriosis. The bladder and ureter are the most affected organs, in approximately 84% and 10% of cases, respectively.<sup>7-9</sup> Ureteral endometriosis has an asymmetric involvement, with the left ureter being more commonly involved than the right, which can be explained by anatomic differences in the pelvis.<sup>10</sup> The ureteral involvement has two major pathological types - extrinsic and intrinsic. The extrinsic type (80%) represents endometrial tissue within

the submucosa and adventitia, whereas intrinsic type (20%) involves the mucosa or muscularis propria of the ureter.<sup>11</sup>

The diagnosis of urinary tract endometriosis (UTE) represents a clinical challenge and requires a high index of suspicion. When the bladder is affected women may complain with lower urinary tract symptoms, namely frequency, urgency, tenesmus, dysuria or haematuria.<sup>12</sup> Flank pain suggests ureteral involvement, but about 50% of patients are asymptomatic.<sup>7</sup> When present, symptoms are often nonspecific and may suggest other conditions (recurrent cystitis, overactive bladder, interstitial cystitis or urothelial carcinoma, ...), potentially leading to delays of several years in diagnosis.<sup>13, 14</sup> This delay is especially harmful when the ureter is involved due to the risk of hydronephrosis and silent loss of renal function.<sup>7</sup>

When UTE is suspected, a pelvic examination is essential. Ultrasonography is usually the first-line investigation test, but pelvic TC, MRI or cystoscopy may be required.<sup>15</sup> However, the definitive diagnosis is based on exploration (preferably laparoscopic) and histopathological study.<sup>15</sup>

The gold-standard treatment for UTE is surgical excision of endometriotic lesions. The indication for surgery is based on symptoms except for silent hydronephrosis which, although rare, needs active treatment to prevent functional exclusion of the kidney.<sup>15,16</sup> For bladder endometriosis, partial cystectomy is preferred over endoscopic resections as these may lead to incomplete removal of the disease due to its full thickness nature.<sup>17</sup> Ureteral

obstruction occurs mainly in the lower third and is usually due to fibrosis, responding poorly to medical treatment.<sup>11</sup> While ureterolysis is indicated for extrinsic, nonobstructive ureteral endometriosis, distal ureterectomy with ureteroneocystostomy may be the best option for intrinsic ureteral lesions.<sup>9</sup>

The aim of our study was to assess the prevalence and severity of involvement of the urinary tract by DIE as well as the surgical treatment and existence of predictive factors for major urologic surgery.

## **MATERIAL AND METHODS**

Retrospective analysis of a population of 656 women undergoing surgery for endometriosis, between January 2005 and August 2016, in a large academic centre. The authors identified a group of 28 patients who underwent minor or major surgery for DIE involving the urinary tract, with a mean age of  $38 \pm 6.9$  (27-50) years at diagnosis.

The prevalence of UTE, clinical symptoms, diagnostic investigation, location and size of the lesions, presence of hydronephrosis and loss of renal function, minor and major surgeries performed, days of hospitalization and complication rates were analysed after review of all clinical, surgical and pathological records.

Patients who had bladder involvement with obstruction of ureteral meatus, without other detectable cause for ureteral obstruction, were considered to have bladder only endometriosis. Minor surgery was defined by any kind of endoscopic surgery or urinary

diversion with percutaneous nephrostomy catheter (PCN). Major surgery included open or laparoscopic procedures. The total hospitalization time was considered the sum of the days of each hospitalization episode. Complications are reported using the Clavien-Dindo grading system.

Statistical analysis was performed using Statistical Package for Social Sciences - IBM SPSS Statistics Data Editor 22.0. Categorical variables are expressed as absolute values and percentages and were compared using the chi-squared test. Continuous data are expressed in terms of mean, standard deviation and range and compared using a t-test. A p-value of <0.05 was considered statistically significant.

## RESULTS

Out of 656 patients, 28 (4.3%) were submitted to surgery due to DIE involving the urinary tract. The most frequent presenting symptoms were lumbar (n=14, 50%) and pelvic pain (n=7, 25%). Six patients (21.4%) had haematuria, 4 (14.3%) lower urinary tract symptoms and 4 (14.3%) dysmenorrhea. Seven women (29.1% of those who were symptomatic) reported more than one symptom at diagnosis. Only 4 (14.3%) patients were asymptomatic, of whom 2 (7.1%) had silent hydronephrosis (Table 1).

Preoperatively, all patients had a renal and bladder ultrasound as initial imaging test, 9 (32.1%) performed abdominopelvic CT and 3 (10.7%) MRI. Fourteen (50%) patients had Tc99m-MAG3 renal scintigraphy and 8 (28.6%) were submitted do cystoscopic evaluation due to suspicion of bladder tumour.

The mean lesions size was  $2.8 \pm 1.7$  cm (0.5-5), and affected the ureter in 17 (60.7%) and the bladder in 15 (53.6%) patients. There were no cases of renal or urethral involvement. Endometriotic lesions affecting other anatomical sites in pelvis further to urinary system involvement were present in 11 (39.3%) women. Regarding just the urinary tract, endometriosis affected only the ureter in 13 (46.4%), only the bladder in 11 (39.3%) and both structures in 4 (14.3%) patients. The left ureter was the most commonly involved ( $n=10$ , 35.7%) followed by the right ( $n=4$ , 14.3%) and both ureters ( $n=3$ , 10.7%) (Table 1).

Radiological evidence of hydronephrosis was detected in 18 (64.3%) patients of whom 12 (42.9%) had renal function impairment. Of these, 7 (25%) had partial loss, and 5 (17.9%) total loss of renal function. Two (7.1%) patients with only bladder involvement had silent hydronephrosis with total loss of renal function at presentation due to obstruction of ureteral meatus. Patients with ureteric involvement were more likely to lose renal function ( $p = 0.034$ ) (Table 2).

There was a preoperative suspicion of bladder tumour, vesical endometriosis and urachal cyst in 7 (25%), 3 (10.7%) and 1 (3.6%) patients with vesical involvement, respectively. In patients with ureteral infiltration, 9 (32.1%) had already a preoperative diagnosis of endometriosis.

All but 3 women with isolated bladder involvement were submitted to minor surgeries only, namely transurethral bladder resection (TURB). One patient previously submitted to TURB had a laparoscopic nephrectomy, with the need of urinary drainage with



PCN prior to surgery due to obstructive pyelonephritis. A woman with concomitant sigmoid endometriosis needed a laparotomy to excise the lesions, and the other was submitted to excision of bladder lesion by laparoscopy.

Concerning ureteral infiltration (with or without bladder involvement), 12 (42.9%) patients underwent minor surgeries (11 urinary diversions with double-J stenting or PCN; 3 ureteroscopies with or without ureteral biopsy and 3 TURB). The patients undergoing TURB had simultaneous bladder involvement. Five (17.9%) patients were treated by endoscopic management only: 2 (7.1%) had undergone TURB only for concomitant bladder disease because no symptoms or radiological evidence of upper urinary tract obstruction were present; the other 3 (10.7%) had urinary diversion with ureteral stenting due to lumbar pain and radiological evidence of hydronephrosis. Major surgeries were performed in 12 (42.9%) patients, the most frequent being distal ureterectomy with reimplantation in 5 (17.9%) women (4 Lich-Gregoir and 1 Lich-Gregoir with psoas hitch). Ureteroureterostomy was performed in 3 (10.7%) and laparoscopic nephrectomy in 2 (7.1%) patients. One (3.6%) patient was submitted to ureterolysis and another woman (3.6%) underwent ureteral and vesical lesion excision by laparotomy to treat concomitant bladder and sigmoid endometriosis. Open surgeries were performed through an infraumbilical and Pfannenstiel incisions in 7 (25%) and 3 (10.7%) patients, respectively.

Eleven (39.3%) patients had more than one surgery, the average number of surgeries performed per patient being  $1.79 \pm 1.3$  (1-6). Total hospitalization time was  $6.3 \pm 7.4$  (1-32) days. Patients with ureteric involvement underwent major surgeries more often ( $n=12$  vs  $n=3$ ,  $p=0.025$ ) and had longer hospital stay ( $8.2$  vs  $3.1$  days,  $p = 0.05$ ) (Table 3).

Histopathological examination confirmed DIE of the bladder in all patients with vesical involvement. Only patients submitted to reimplantation or ureteroureterostomy had histological examination, with 4 (14.3%) having extrinsic and 4 (14.3%) intrinsic involvement. Patients submitted to nephrectomy had no histological evidence of endometriosis.

The mean follow-up was  $36.3 \pm 29.1$  (1-102) months. All patients with only bladder involvement had symptomatic relieve and no evidence of recurrence with a mean follow-up of  $25.9 \pm 17.5$  (1-48) months. Three (10.7%) patients showed ureteral stenosis but had successful resolution after reintervention (Clavien-Dindo grade IIIb): 1 women with ureteral and bladder involvement had stenosis of ureteral meatus secondary to TURB previously performed for bladder disease, and was submitted to a new TURB (the histological examination revealed fibrosis and no evidence of endometriosis); 1 patient previously treated with lesion excision by laparotomy was submitted to ureteroscopy and Lich-Gregoir ureteral reimplantation with psoas hitch; a Boari flap, after urinary diversion with a double-J stent, was performed in a patient who had previously undergone ureteroureterostomy. One (3.6%) patient had double-J stent calcification, which was removed under local anaesthesia (Clavien-Dindo grade IIIa) and 1 (3.6%) woman remained with occasionally lumbar pain, successfully treated with oral analgesics (Clavien-Dindo grade I).

## DISCUSSION

Currently, there is no consensus on the genesis of endometriotic cells. According to the theory of retrograde menstruation, peritoneal endometriosis arises from implantation

of endometrial tissue that refluxes through the fallopian tubes during menstruation.<sup>18</sup> In contrast, the hypothesis of coelomic epithelium metaplasia proposes that the origin of endometriotic lesions within the peritoneal cavity is the differentiation of mesothelial cells into endometrium-like tissue.<sup>19</sup> Another hypothesis argues that endometrial cells travel from the endometrial cavity through lymphatic or blood circulation, like metastasis of cancer cells.<sup>20</sup> A fourth proposal is that endometrial stem cells and bone marrow-derived stem cells can differentiate into endometriotic tissue at various sites.<sup>21</sup> However, it seems that a successful implantation and survival of ectopic endometrial cells onto the peritoneal surface may be explained by molecular abnormalities and/or failure of the immunologic system to clear these implants.<sup>22,23</sup>

The endometriotic implants growth and chronic bleeding provokes a variable extent of inflammation and fibrosis that are responsible for stimulation of nerve endings and impairment of the function of the fallopian tubes, leading to chronic pelvic pain and subfertility.<sup>24</sup>

The prevalence of endometriosis affecting the urinary tract is estimated to be 1-5% of women with the disease and ureteral involvement accounts for only 0.1-0.4% of all cases.<sup>9,25</sup> In our study the prevalence of UTE in patients submitted to surgery for endometriosis was 4.3% but we found a higher prevalence of ureteral involvement (17/656, 2.6%) than classically described. However, ureteral endometriosis is probably underestimated and some authors have reported its occurrence more frequently than expected. Soriano et al <sup>26</sup> observed ureteral involvement in 14.2% of patients treated surgically for endometriosis, and this prevalence may be higher in patients with DIE,

reaching 19.5% and 52.6%, as described by Gabriel et al<sup>27</sup> and Knabben et al<sup>28</sup>, respectively. The growing experience and awareness of physicians and the greater use of laparoscopic techniques may explain the increase prevalence in recent years.<sup>16</sup>

As expected, the left ureter was more often affected. Excluding the 3 cases with bilateral involvement, the left ureter was affected in 10/14 (71.4%) and the right in 4/14 (28.6%). Similar results were reported by Verceliini P et al.<sup>10</sup> This asymmetry is due to anatomical differences in pelvis, once sigmoid colon in left hemipelvis creates an environment that protects endometrial cells that reflux through the left tube and prevents its elimination by peritoneal circulation and macrophages.<sup>10</sup>

In our study, the ureter was more often affected (60.7%) than the bladder (53.6%), which is against literature data. There are two possible explanations for these results. First, most of the times lumbar pain and/or a radiologic evidence of hydronephrosis leads the physicians to act more promptly due to a possibility of loss of renal function. As urinary diversion and investigation of ureteral stenosis is often necessary to prevent kidney loss, it leads to a surgical procedure (the population of our study). Second, in bladder endometriosis the symptoms are often unspecific and may be confused with other pathologies which are medically treated, leading to a delay in diagnosis and surgical treatment.<sup>13,14</sup> In our series, 8 (28.6%) women with isolated bladder involvement treated with TURB were intervened, not because of endometriosis suspicion, but due to a radiological and/or cystoscopic evidence of “bladder tumour” or suspicion of urachal cyst. So it is possible that some women with bladder endometriosis are not receiving surgical treatment, thus not included in this cohort. Although TURB is conceptually wrong for the

treatment of bladder endometriosis, as the vesical lesion is transmural and the complete eradication of the disease would require a bladder perforation<sup>17</sup>, in our study this procedure lead to symptomatic relieve in all patients, with a mean follow-up of  $25.9 \pm 17.5$  (1-48) months. Therefore, TURB may be a viable alternative to partial cystectomy in selected cases.

For ureteral endometriosis an optimal surgical treatment is not defined, as prospective randomized trials are difficult to conduct due to the rarity of the disease.<sup>9</sup> Furthermore, the differentiation between extrinsic and intrinsic disease is impossible clinically or during surgery, as it is a histological diagnosis. Thus a clinical classification is warranted to guide and compare surgical treatments, as proposed recently by Knabben et al.<sup>28</sup> Nevertheless, previous works by Antonelli et al<sup>9,12</sup> reveal that ureterolysis is often not sufficient to treat ureteral endometriosis, being indicated solely for extrinsic, non-obstructive disease. In a recent study, Ucella S et al<sup>29</sup> reports a symptomatic recurrence of 27.5% and the need for second ureteral surgery of 8.6% following ureterolysis, although some authors report higher recurrence rates.<sup>9</sup> The best treatment option for ureteral obstruction is surgical resection, as it removes de lesion and surrounding fibrosis. Ureteroneocystostomy usually has better results than ureteroureterostomy because it removes the distal ureter that has a high risk of recurrence.<sup>9, 12</sup> In our population, 94.1% (16/17) of patients with ureteral involvement had hydronephrosis, of whom 41.2% (7/17) had partial and 17.7% (3/17) had total loss of renal function. Furthermore, histopathological examination reveals that intrinsic ureteral involvement has higher proportion (50%) than was expected (20%). These facts mean that our population had a severe ureteral involvement which probably would not be successfully treated by ureterolysis. This procedure was performed only in one patient who had symptomatic minimal

hydronephrosis without evidence of loss of renal function on renal scintigraphy, with no recurrence after 72 months of follow-up. We performed more often ureteral reimplantations, with no need of re-interventions. The only patient that required a second open ureteral procedure had a previous ureteroureterostomy and also diffuse pelvic endometriosis. A Boari flap was needed to achieve a tension-free anastomosis.

Three patients were successfully treated with ureteral stenting solely because after removing the catheters they had symptomatic relieve and no evidence of loss of renal function during follow-up. In these patients, plus 2 who did not receive any treatment for ureteric involvement, we opted for a close follow-up with ultrasound and renal scintigraphy, as indication for surgery is based on symptoms.<sup>16</sup> We found that ureteric disease was a predictive factor for major surgery probably because these patients had severe ureteral infiltration requiring an ureteroneocystostomy or ureteroureterostomy, while women with bladder endometriosis were mainly submitted to TURB.

The overall rate of laparoscopic nephrectomy was 10.7% (n=3), similar to that reported by other authors<sup>9, 25</sup> and were performed in patients with symptomatic non-functioning kidneys. These patients had no histological evidence of endometriosis probably because the distal ureter, which is usually involved, was not removed for analysis.

## CONCLUSIONS

Despite being a histologically benign disease, DIE can have serious consequences in the urinary tract, often leading to multiple procedures and may result in total loss of kidney

function. Surgery was highly successful in most cases. In our series, endoscopic surgery with TURB revealed to be a good option for patients with bladder endometriosis, as they had symptomatic relieve and no signs of recurrence, with no need to more invasive surgeries. Patients with ureteric involvement were more likely to lose renal function, undergo major surgery and to have longer hospitalization.

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Table 1 – Demographics, clinical data and pre-operative findings

<b>Demographic data</b>	<b>N° patients (%)</b>
Surgery for DIE of the urinary tract	28
Mean age at diagnosis (years $\pm$ SD)	38 $\pm$ 6.9
<b>Presenting symptoms</b>	
- lumbar pain	14 (50)
- pelvic pain	7 (25)
- haematuria	6 (21.4)
- lower urinary tract symptoms	4 (14.3)
- dysmenorrhea	4 (14.3)
- more than one symptom	7 (25)
- asymptomatic	4 (14.3)
- silent hydronephrosis	2 (7.1)
<b>Pre-operative findings</b>	
Mean lesion size (cm $\pm$ SD)	2.8 $\pm$ 1.7
Bladder involvement	15 (53.6)
Ureteric involvement	17 (60.7)
- left	10 (35.7)
- right	4 (14.3)
- bilateral	3 (10.7)
Bladder and ureteric involvement	4 (14.3)
Infiltration of other anatomical sites	11 (39.3)

Table 2 – Hydronephrosis and loss of renal function

	<b>Isolated bladder involvement (n=11)</b>	<b>Ureteral involvement (n=17)</b>	<b>p value</b>
<b>Hydronephrosis (n=18)</b>	2	16	0.001
<b>Loss of renal function (n=12)</b>	2	10	0.034
- Partial loss (n=7)	0	7	
- Total loss (n=5)	2	3	

Table 3 – Minor and major surgical procedures

	<b>Total</b>	<b>Isolated bladder involvement (n=11)</b>	<b>Ureteral involvement (n=17)</b>	<b>p value</b>
<b>Minor surgeries (n° patients)</b>	21	9	12	p=0.5
<b>Procedures</b>				
- TURB	12	9	3	
- PCN / double J stent	12	1	11	
- Ureteroscopy ± ureteral biopsy	3	-	3	
<b>Major surgeries (n° patients)</b>				
<b>Procedures</b>	15	3	12	p=0.025
- Ureterolysis	1	-	1	
- Distal ureterectomy + Lich- Gregoir reimplantation	4	-	4	
- Distal ureterectomy + Lich- Gregoir reimplantation + psoas hitch	1	-	1	
- Ureteroureterostomy	3	-	3	
- Nephrectomy	3	1	2	
- Lesion excision by laparotomy	2	1	1	
- Lesion excision by laparoscopy	1	1	-	
<b>Hospitalization time (days)</b>	6.3 ± 7.4	3.1±2.8	8.2±8.7	p=0.05