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# Ureteral endometriosis in patients with deep infiltrating endometriosis: characteristics and management from a single-center retrospective study

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## Abstract

**Purpose** As a serious type of deep infiltrating endometriosis (DIE), ureteral endometriosis (UE) can result in decreased kidney function. The aims of this study are to investigate risk factors and surgical treatments for UE.

**Methods** The study enrolled 329 patients with deep infiltrating endometriosis, who were treated with laparoscopic surgery between January 2014 to September 2018. All patients were divided into one of two groups: UE or non-UE. Clinical information and other surgery variables of the two groups were examined.

**Result** Out of 329 patients with DIE, 68 (20.67%) cases of UE were diagnosed. Among them, 37 patients also had hydroureteronephrosis. In a multivariate analysis, the variables revised American Fertility Society (rAFS) stage IV, uterosacral ligament (USL) DIE lesion ≥ 3 cm in diameter and previous surgery for endometriosis significantly increased the risk of UE. A total of 27.03% (10/37) of patients with UE and hydroureteronephrosis showed decreased kidney function. Ureterolysis was performed in 59 patients, and an ureteroneocystostomy was performed in 9 patients. A double-J stent was placed in 37 patients with UE. Only 1 patient developed acute pyelonephritis postoperatively. During more than 2 years of follow-up, no patient experienced recurrence.

**Conclusions** The variables of rAFS stage IV, USL DIE lesion ≥ 3 cm in diameter and previous surgery for endometriosis significantly increased the risk of UE. Laparoscopic ureterolysis and ureteroneocystostomy are feasible and safe procedures with low complication and recurrence rates.

**Keywords** Ureteral endometriosis · Ureterolysis · Ureteroneocystostomy · Hydroureteronephrosis · Kidney function

## Introduction

Endometriosis is defined as a condition resulting from the presence of endometrial glands and stroma outside the endometrial cavity [1]. Deep infiltrating endometriosis (DIE) refers to arbitrary subperitoneal invasion by endometriotic tissue at a depth of at least 5 mm [2, 3]. Most patients with DIE experience severe pain. In addition, DIE can result in damage to multiple organs depending on the location involved, including intestinal obstruction, hydroureteronephrosis, or even kidney dysfunction [3-6].

The urinary tract is the second most common extragenital system affected by DIE. Traditionally, urinary tract endometriosis (UTE) constitutes a small proportion (1–5.5%) of the overall incidence of endometriosis [7-10] and most often involves the bladder (incidence, 84%). Less frequently, endometriosis involves a ureter (incidence, 15%), and in extremely rare cases, it can involve the kidneys and urethra [7, 11, 12]. Ureteral endometriosis (UE) occurs when endometriosis or surrounding associated fibrosis causes compression or distortion of the normal ureteral anatomy with or without hydroureteronephrosis [13]. UE can be divided into two types according to the depth of the endometrial glandular and stromal infiltration by pathological examination: the most common type (80%) is extrinsic UE, which involves the adventitia, and intrinsic UE affects the muscularis propria, lamina propria, or ureteral lumen [14, 15]. UE is asymmetric

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with regard to the site of the occurrence, involving the left side in approximately 80% cases and the right side in 20%; the distal third of the ureter is more often affected due to close proximity to the USL [16].

Late diagnosis of UE may result in the silent loss of kidney function, despite its low incidence [17, 18]. In recent years, awareness of the complications associated with UE has increased, leading to a higher diagnosis rate of UE. Alves et al. [19] observed UE in 30.09% of 658 patients with DIE. These results show that the incidence of UE is not actually rare. However, knowledge of UE is still limited, and the current treatment of this condition has yet to be defined.

The purpose of this study was to investigate the risk factors for and disease characteristics of UE and the results of surgical treatment.

## Materials and methods

This retrospective case control enrolled 351 DIE patients who underwent laparoscopic surgery at the Department of Gynecological Oncology at Renji Hospital Affiliated with Shanghai Jiao Tong University School of Medicine from January 2014 to September 2018. Preoperatively, sonography was performed to evaluate the structure of the ovaries, uterus, ureters and kidneys in all patients. For all patients with clinical and sonographic features of DIE, pelvic magnetic resonance imaging (MRI) and computed tomography urography (CTU) were also performed. Patients with hydroureteronephrosis underwent an additional nephrogram examination to assess kidney function. The standards of unilateral kidney function according to the department of nuclear medicine at our hospital are as follows: normal, glomerular filtration rate (GFR) $\geq$ 40 ml/min/1.73 $m^2$; mildly decreased, GFR 30–40 ml/min/1.73 $m^2$; moderately decreased, GFR 20–30 ml/min/1.73 $m^2$; severely decreased, GFR 10–20 ml/min/1.73 $m^2$; and dysfunctional GFR < 10 ml/min/1.73 $m^2$. The exclusion criteria were abdominal surgery, abandoned surgery, or other identified causes of hydroureteronephrosis (i.e., nephrolithiasis, deformity of a ureter). All patients with DIE were divided into two groups according to the presence (UE group) or absence (non-UE group) of UE. Patients with UE were divided into two groups: hydroureteronephrosis and nonhydroureteronephrosis.

The following ureteral surgical procedures were performed:

(a) Ureterolysis: all UE patients underwent ureterolysis first, and then the situation of UE was re-evaluated. Patients with kidney dysfunction underwent ureterolysis alone with nephroureterectomy.
(b) Ureteroneocystostomy or ureteral resection with end-to-end anastomosis: if ureterolysis failed to restore ureteral anatomy, ureteroneocystostomy or ureteral resection with end-to-end anastomosis was performed (depending on the location of the endometriotic implants and length of the remaining ureter).
(c) Ureteral stent placement: to present postoperative ureteral postoperative ureteral obstruction or leakage due to extensive ureterolysis or ureteroneocystostomy and ureteral resection with end-to-end anastomosis, this procedure was performed.

For each patient with DIE, data were collected regarding clinical information (age, body mass index (BMI), fertility, previous relevant surgery, cancer antigen 125 (CA-125) and carbohydrate antigen 19-9 (CA19-9) levels, dysmenorrhea, lumbago, and hematuria) and surgical findings. All surgeries are performed by the same team. Intraoperatively, all patients were classified from stage I to IV according to the revised American Fertility Society (rAFS) classification of endometriosis [20] by two surgeons. Surgeons detached adhesions, recovered the original pelvic anatomy, incised the side peritoneum, freed the ureter, and excised all endometriosis lesions. If the endometriosis lesion infiltrated the mucosa or most muscularis of the bowel or bladder, a segment or disc resection was performed. The anatomic distribution of deep infiltrating lesions was recorded. In addition, the following information was recorded for all patients with UE: the side affected by hydroureteronephrosis, surgical procedure (ureterolysis**,** ureteroneocystostomy, ureteral resection with end-to-end anastomosis, ureteral stent placement), time to diagnosis, nephrogram, postoperative ureteral fistula, stenosis and infection. During more than 2 years of follow-up, any postoperative recurrence in patients with UE who received surgical treatment was recorded.

This study was approved by the institutional review board. The procedures followed the current regulations of the Chinese government as well as the Declaration of Helsinki. All patients recruited in this study signed an informed consent and allowed researchers to use their clinical data.

### Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software version 23.0 (IBM). Continuous data are expressed as the mean ± standard deviation (SD), and categorical variables are reported as absolute values or percentages. Univariate comparisons were performed using Student's *t* test, Pearson's Chi-square test or Fisher's exact test. Statistically significant differences were evaluated as independent risk factors using multivariate analysis with logistic regression. A value of $P < 0.05$ was considered statistically significant (two-sided test).

## Results

### Clinical information and surgical variables in the UE and non-UE groups

We incorporated 329 patients with DIE into the analysis. The mean age of the included patients was 37.67 ± 8.21 years, and the mean BMI was 21.61 ± 2.56 km/m$^2$. A total of 68 UE cases were diagnosed in 329 patients with DIE. The mean age at the time of surgery was 37.28 years in the non-UE group and 39.15 years in the UE group ($P = 0.095$); no difference in age was found between the two groups. In the univariate analysis, the CA-125 and CA19-9 levels in the UE group were higher than those in the non-UE group (159.76 U/ml vs. 80.92 U/ml, $P < 0.001$; 41.06 U/ml vs. 26.68 U/ml, $P = 0.004$). Severe endometriosis (rAFS stage IV) was more common in the UE group than in the non-UE group (55/68 vs. 168/261, $P < 0.001$). USL DIE lesions ≥ 3 cm in diameter were more frequently identified in the UE group (52/68 vs. 110/261, $P < 0.001$). Regarding the anatomic distribution of deep infiltrating lesions, the rectum (22/68 vs. 29/261, $P < 0.001$) and obliteration of the cul-de-sac (43/68 vs. 88/261, $P < 0.001$) were more frequently identified in the UE group than in the non-UE group. Among the symptoms, patients in the UE group showed more dysmenorrhea, lumbago and hematuria ($P < 0.05$). Previous surgery for endometriosis was more often performed in patients in the UE group than in those in the non-UE group ($P < 0.001$). No significant differences in BMI, parity, or distribution of the ovaries or parametrium were observed between the two groups (Table 1).

To better understand the risk factors for UE, a multivariate analysis was also performed. In accordance with the previous literature, we adjusted for age, BMI and parity. Patients with UE were more likely to have rAFS stage IV (odds ratio (OR) 5.077, 95% confidence interval (CI) 2.056–12.537, $P < 0.001$), USL DIE lesions ≥ 3 cm in diameter (OR 4.264, 95% CI 2.043–8.902, $P < 0.001$) and previous surgery for endometriosis (OR 2.417, 95% CI 1.119–5.217, $P = 0.025$) (Table 2).

### Clinical information and surgical variables in the hydroureteronephrosis and nonhydroureteronephrosis groups

Among the 68 UE cases, 57 (83.82%) involved the unilateral ureter, including 32 (47.06%) on the left side and 25 (36.76%) on the right side; 11 UE cases involved (16.18%) both ureters. According to imaging examination findings or surgical findings, 37 patients (54.41%) showed hydroureteronephrosis preoperatively. The CA19-9 levels in the hydroureteronephrosis group were higher than those

**Table 1** Preoperative and intraoperative characteristics between the UE group and the non-UE group

| | UE group ($N = 68$) | Non-UE group ($N = 261$) | $P$ value |
|---|---|---|---|
| Age (years) | 39.15 ± 6.62 | 37.28 ± 8.55 | 0.095 |
| BMI | 21.20 ± 2.28 | 21.71 ± 2.62 | 0.145 |
| CA-125 (U/ml) | 159.76 ± 211.05 | 80.92 ± 116.66 | < 0.001 |
| CA19-9 (U/ml) | 41.06 ± 47.14 | 26.68 ± 33.09 | 0.004 |
| Dysmenorrhea | 60/68 | 168/261 | < 0.001 |
| Lumbago | 15/68 | 18/261 | < 0.001 |
| Hematuria | 2/68 | 0/261 | 0.042 |
| Parity | | | 0.809 |
| ≥ 1 | 26/68 | 104/261 | |
| 0 | 42/68 | 157/261 | |
| Previous surgery for endometriosis | 20/68 | 31/261 | < 0.001 |
| rAFS stage | | | < 0.001 |
| 1–3 | 13/68 | 172/261 | |
| 4 | 55/68 | 89/261 | |
| Other endometriosis locations | | | |
| Ovary | | | 0.693 |
| USL | 45/68 | 166/261 | < 0.001 |
| ≥ 30 mm | 52/68 | 110/261 | |
| < 30 mm | 16/68 | 151/261 | < 0.001 |
| Rectum | 22/68 | 29/261 | 0.150 |
| Parametrium | 52/68 | 176/261 | < 0.001 |
| Obliteration of the cul-de-sac | 43/68 | 88/261 | |

**Table 2** Logistic regression analysis of factors associated with UE

| | Odds ratio | 95% CI | *P* value |
|---|---|---|---|
| Age (years) | 1.299 | 0.607–2.782 | 0.501 |
| BMI | 0.713 | 0.229–2.214 | 0.558 |
| CA-125 | 1.076 | 0.439–2.634 | 0.873 |
| CA19-9 | 1.721 | 0.803–3.692 | 0.163 |
| Dysmenorrhea | 1.172 | 0.448–3.063 | 0.746 |
| Lumbago | 2.752 | 0.998–7.588 | 0.050 |
| Hematuria | 3.400 E+9 | 0.000–0.000 | 0.999 |
| Parity ≥ 1 | 0.910 | 0.418–1.980 | 0.811 |
| Previous surgery for endometriosis | 2.417 | 1.119–5.217 | 0.025* |
| rAFS stage | 5.077 | 2.056–12.537 | < 0.001* |
| Ovary | 0.855 | 0.394–1.855 | 0.692 |
| USL DIE lesion ≥ 30 mm | 4.264 | 2.043–8.902 | < 0.001* |
| Rectum | 2.166 | 0.992–4.732 | 0.053 |
| Parametrium | 1.759 | 0.834–3.713 | 0.138 |
| Obliteration of the cul-de-sac | 0.978 | 0.414–2.311 | 0.960 |

*$P < 0.05$

in the nonhydroureteronephrosis group (51.33 U/ml vs. 28.81 U/ml; $P = 0.049$). Patients with hydroureteronephrosis more often presented with lumbago symptoms (14/37 vs. 1/31; $P = 0.002$). Previous surgery for endometriosis was more common in the hydroureteronephrosis group (15/37 vs. 5/31; $P = 0.028$). Other symptoms, the rAFS stage and the anatomic distribution of deep infiltrating lesions were not significantly different between the two groups ($P > 0.05$) (Table 3).

### Kidney function, surgery and follow-up in the hydroureteronephrosis and nonhydroureteronephrosis groups

A total of 27.03% (10/37) of patients with UE and hydroureteronephrosis showed decreased kidney function, ranked by nephrogram results as follows: mildly decreased, 8.11%; moderately decreased, 0.00%; severely decreased, 10.81%; and dysfunctional, 8.11% (Table 4).

In 68 cases of UE, 59 patients underwent ureterolysis (29, hydroureteronephrosis group; 30, nonhydroureteronephrosis group), and 9 underwent ureteroneocystostomy (8, hydroureteronephrosis group; 1, nonhydroureteronephrosis group). A double-J stent was placed in 37 patients with UE and in 30 patients in the hydroureteronephrosis group (Tables 3, 5). Only 1 patient experienced acute pyelonephritis postoperatively. During the more than 2-year follow-up period, no patient showed recurrence (Table 5).

## Discussion

To our knowledge, this is the first study to examine the risk factors for UE in DIE. This study revealed that rAFS stage IV, USL DIE lesions ≥ 3 cm in diameter and previous surgery for endometriosis are independent risk factors for UE. It is safe and feasible to treat UE with laparoscopic surgery.

The occurrence of UE has been increasingly reported in recent years, accounting for up to 49.77% of cases of DIE [21] and 20.67% in this study. Nevertheless, UE is not associated with very specific symptoms, such as lumbago, dysuria, and hematuria but has nonspecific symptoms, such as dysmenorrhea [19, 21-23]. Only 22.06% (15/68) of patients with UE reported lumbago, and 2.94% (2/68) experienced dyspareunia. Furthermore, 88.24% (60/68) of patients had dysmenorrhea and exhibited high CA-125 levels. Our results are in agreement with the literature. It is difficult to diagnose UE correctly when specific symptoms are lacking [24]. We calculated that the mean time to diagnosis of UE was 4.6 years, which was similar to that in a previous literature report [25, 26]. Furthermore, 29.41% of UE patients underwent more than one previous surgery for endometriosis in this study, and more than 55% of patients in a previous study underwent more than one previous surgery [22, 24]. Delayed diagnosis of UE can lead to significantly decreased kidney function or even loss of obstruction of ureteral and hydroureteronephrosis [8]. Our analysis revealed that 27.03% of patients with hydroureteronephrosis showed decreased kidney function, and 4.41% patients had kidney dysfunction. However, only limited research has noted that a 3-cm diameter of rectovaginal endometriosis may be related to UE [21]. Among the preoperative and surgical characteristics evaluated, USL DIE lesions ≥ 3 cm in diameter, rAFS stage IV and previous surgery for endometriosis were independent risk factors for UE in this study and also indicated the severity of DIE. Therefore, we infer that severe DIE, especially with USL endometriosis, should be given more attention to avoid missing UE during surgery.

Early and timely diagnosis of UE is important to reduce the occurrence of decreased kidney function. The severity of endometriosis should be evaluated during surgery and should be identified by careful preoperative physical examination and auxiliary examinations. In their study, William Kondo et al. [27] reported that women with retrocervical DIE lesions ≥ 30 mm had a 13.3-fold greater likelihood of having ureteral involvement than those with retrocervical DIE lesions < 30 mm, which demonstrates the importance of preoperative physical exams. Ultrasound is a sensitive modality for diagnosing ovarian endometriosis and adenomyosis but not for evaluating other pelvic

**Table 3** Preoperative and intraoperative characteristics of the hydroureteronephrosis and nonhydroureteronephrosis groups

| | Hydroureteronephrosis group ($N=37$) | Nonhydroureteronephrosis group ($N=31$) | $P$ value |
|---|---|---|---|
| Laterality of UE | | | 0.693 |
| Unilateral | | | |
| Left side | 19/37 | 13/31 | |
| Right side | 12/37 | 13/31 | |
| Bilateral | 6/37 | 5/31 | |
| Age (years) | 39.00 ± 5.63 | 39.32 ± 7.73 | 0.843 |
| BMI | 21.26 ± 2.50 | 21.13 ± 2.03 | 0.822 |
| CA-125 (U/ml) | 189.02 ± 254.44 | 124.83 ± 139.54 | 0.214 |
| CA19-9 (U/ml) | 51.33 ± 54.96 | 28.81 ± 32.46 | 0.049 |
| Dysmenorrhea | 34/37 | 26/31 | 0.307 |
| Lumbago | 14/37 | 1/31 | 0.002 |
| Hematuria | 2/37 | 0/31 | 0.496 |
| Parity | | | 0.054 |
| ≥ 1 | 18/37 | 8/31 | |
| 0 | 19/37 | 23/31 | |
| rAFS stage | | | 0.506 |
| 1–3 | 6/37 | 7/31 | |
| 4 | 31/37 | 24/31 | |
| Previous surgery for endometriosis | 15/37 | 5/31 | 0.028 |
| Time to diagnosis (years) | 3.98 ± 4.10 | 5.36 ± 6.23 | 0.065 |
| Other endometriosis localizations | | | |
| Ovary | 24/37 | 21/31 | 0.803 |
| USL | | | 0.866 |
| ≥ 30 mm | 9/37 | 7/31 | |
| < 30 mm | 28/37 | 24/31 | |
| Rectum | 14/37 | 8/31 | 0.291 |
| Parametrium | 31/37 | 21/31 | 0.120 |
| Obliteration of the cul-de-sac | 23/37 | 20/31 | 0.841 |
| Type of surgical intervention to treat UE | | | 0.061 |
| Ureterolysis | 29/37 | 30/31 | |
| Ureteroneocystostomy | 8/37 | 1/31 | |
| Ureteral stent placement | 30/37 | 7/31 | < 0.001 |

**Table 4** Kidney function of UE with hydroureteronephrosis

| | $N$ | Percent (%) |
|---|---|---|
| Kidney function by nephrography | | |
| Mildly decreased | 3/37 | 8.11 |
| Moderately decreased | 0/37 | 0.00 |
| Severely decreased | 4/37 | 10.81 |
| Dysfunctional | 3/37 | 8.11 |
| Total | | 27.03 |

**Table 5** Comparison between patients treated with ureteral ureteroneocystostomy and ureterolysis

| Treatment (N1, N2) | Recurrence | Complications |
|---|---|---|
| Ureterolysis (N1 = 34, N2 = 59) | 0/34 | 0/59 |
| Ureteroneocystostomy (N1 = 6, N2 = 9) | 0/6 | 1/9 |

*N1* follow-up duration, more than 2 years, *N2* patients with corresponding surgical treatment

locations, such as the bladder, peritoneal or bowel. MRI is the best noninvasive method to evaluate the location of endometriosis [28, 29] and to distinguish endometriosis from cancer. Chamie et al. [30] found that the accuracy of MRI for predicting the location of DIE was up to 90%. Additionally, ureteral hydronephrosis should first be evaluated with renal ultrasound. For suspicious UE or hydronephrosis, CTU [31], as the optimal imaging modality for the kidneys, ureters and bladder, can help to determine the relationship between the lesion and the ureter or bladder and exclude tumors. Despite the fact that hematuria is

less common in UE [13, 19], for patients with hematuria and distinct ureterostenosis, ureteroscopy can help to identify tumors or polyps as part of differential diagnosis. In addition to these diagnostic tools, nephrography should be used to evaluate kidney function on the affected side to formulate a surgical strategy when hydronephrosis is detected by MRI, CTU or another examination.

The choice of UE treatment should aim to relieve ureteral obstruction, preserve renal function and prevent disease relapse [32, 33]. Finding the best treatment for UE is difficult without any relevant randomized controlled trials. Hormone therapy may shrink endometriosis lesions but may not help to resolve fibrous tissue and adhesions, which could result in obstruction or even hydroureteronephrosis. Surgery has become the first choice for treating UE. Methods of surgical intervention depend on the anatomic location of the disease, extent of the surrounding tissue involvement, level of hydroureteronephrosis and surgeon skill. The primary types of surgeries used to treat UE are ureterolysis, ureteroneocystostomy or ureteral resection with end-to-end anastomosis. Buttice et al. [34] suggested that the best choice of surgery depends on whether hydroureteronephrosis has occurred. In this study, ureterolysis was performed in patients who did not have apparent stiffness in the ureter, which allowed for the ureter to be dissociated and the surrounding tissue removed. Our results of no recurrence in 59 patients who underwent ureterolysis show that this surgery is feasible, as confirmed by the results of previous studies [13, 31]. Another nine patients underwent ureteroneocystostomy, where the ureter was obviously stiff and narrow or could not be separated from the surrounding tissues or when lesions were involved in the lower third of the ureter. In addition, a double-J stent was placed to prevent ureteral obstruction or leakage for extensive ureterolysis and all cases of ureteroneocystostomy. No ureteral resection with end-to-end anastomosis performed as the lesions in all nine patients were near the bladder. One patient experienced acute pyelonephritis perhaps due to urine reflux through the anastomotic mouth after ureteroneocystostomy. The surgical treatment outcomes were good, with low recurrence and no serious complications, ureteral leakage, bladder leakage or vesicovaginal fistula formation. Thus, laparoscopic ureterolysis and ureteroneocystostomy are feasible, effective and safe [33-36]. In particular, three patients with kidney dysfunction underwent ureterolysis rather than ureteronephrectomy. All three of these patients had hydronephrosis, and no patient had persistence renal pain or recurrence of renal infection. As there is limited space around the hydronephrotic kidney, laparoscopic ureteronephrectomy increases the transfusion requirements and complications during surgery and postoperatively [37, 38]. Additionally, awareness of the disease should be strengthened and include multidisciplinary cooperation with related departments, such as urinary surgery and general surgery departments, particularly for patients with DIE that involve multiple organs.

Nevertheless, this study was limited by its small sample size and short follow-up period. In the future, large-scale, multicenter randomized studies are needed to confirm the standard treatment and management of UE.

## Conclusion

The incidence of UE is not as rare as originally reported. We found that patients with rAFS stage IV, USL DIE lesions $\geq 3$ cm in diameter and previous surgery for endometriosis had a significantly increased risk of UE. Laparoscopic ureterolysis and ureteroneocystostomy are feasible and safe procedures for treating UE.

**Author contributions** ZJH: protocol development, data collection and management, data analysis, manuscript writing, responsible surgeon. PQL: protocol development, data collection and management, data analysis, manuscript writing, responsible surgeon. QL: data collection, data analysis, responsible surgeon. HZ: data collection, data analysis, responsible surgeon, YXS: data collection, responsible surgeon, XXZ: data collection, responsible surgeon, LX: data collection, responsible surgeon, KJL: protocol development, data management, data analysis, manuscript editing, responsible surgeon.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflicts of interest.

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