




Ureteral endometriosis: a systematic review of epidemiology, pathogenesis, diagnosis, treatment, risk of malignant transformation and fertility

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BACKGROUND: The ureter is the second most common site affected by urinary tract endometriosis, after the bladder. Optimal strategies in the diagnosis and treatment of ureteral endometriosis (UE) are not yet well defined.

OBJECTIVE AND RATIONALE: The aim of this study was to systematically review evidence regarding the epidemiology, pathophysiology, diagnosis, medical and surgical treatment, impact on fertility and risk of malignant transformation of UE.

SEARCH METHODS: A systematic literature review, by searching the MEDLINE and PUBMED database until April 2018, 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 CRD42017060065). A total of 67 articles were selected to be included in this review.

OUTCOMES: The involvement of the ureter by endometriosis is often asymptomatic or leads to non-specific symptoms. When the diagnosis is delayed, UE may lead to persistent hydronephrosis and eventually loss of renal function. Ultrasonography is the first-line technique for the assessment of UE; alternatively, magnetic resonance imaging provides an evaluation of ureteral type involvement. The surgical treatment of UE aims to relieve ureteral obstruction and avoid disease recurrence. It includes conservative ureterolysis or radical approaches, such as ureterectomy with end-to-end anastomosis or ureteroneocystostomy performed in relation to the type of ureteral involvement. Fertility and pregnancy outcomes are in line with those observed after surgical treatment of deep infiltrating endometriosis (DIE). Current evidence does not support the potential risk of malignant transformation of UE.

WIDER IMPLICATIONS: In this article, we review available evidence on ureteral endometriosis, providing a useful tool to guide physicians in the management of this disease. Diagnosis and management of UE remain a challenge. In relation to the degree of ureteral involvement and the association with other DIE implants, the surgical approach should be planned and carried out in an interdisciplinary collaboration between gynecologist and urologist.

Key words: ureteral endometriosis / hydronephrosis / ultrasound / ureterolysis / ureterectomy / ureteroneocystostomy / transvaginal ultrasonography / abdominal ultrasonography / magnetic resonance imaging / uro-multislice computed tomography

Introduction

Endometriosis, defined as the presence of endometrial glands and stroma outside the uterus, is classified as superficial or peritoneal, ovarian and deep infiltrating endometriosis (DIE) (Vercellini *et al.*, 2014b). DIE refers to the presence of subperitoneal endometriotic invasion of at least 5 mm in depth (Cornillie *et al.*, 1990) and it includes rectovaginal lesions as well as infiltrating forms that involve abdominal organs (such as the bowel, ureter and bladder detrusor) (Vercellini *et al.*, 2004, 2014b). DIE is the most severe form of endometriosis, with an estimated prevalence of 1% in women of reproductive age and 14–20% in patients with endometriosis (Koninckx *et al.*, 2012). Urinary tract endometriosis (UTE) occurs in ~1–5.5% of women with endometriosis; it involves the bladder in 70–85% of cases and the ureter in 9–23% of the cases (Berlanda *et al.*, 2009). In up to 90% of patients, ureteral endometriosis (UE) is associated with other sites affected by endometriosis (Seracchioli *et al.*, 2015).

The diagnosis of UE is difficult since the disease may be clinically silent in up to 30% of patients, or it may be associated with non-specific symptoms, such as dysmenorrhea, dyspareunia and non-menstrual pelvic pain (Antonelli *et al.*, 2006; Huang *et al.*, 2017). Sometimes progressive upper urinary tract obstruction leads to the silent loss of kidney function (Berlanda *et al.*, 2009). Although many radiological methods have been proposed, currently there is no unanimous consensus on which diagnostic technique should be used to assess UE.

Patients may temporally benefit from medical therapy, but surgery is needed when ureteral obstruction is present (Nezhat *et al.*, 2017). Surgical options are conservative ureterolysis or radical approaches, such as ureterectomy with end-to-end anastomosis or ureteroneocystostomy performed in relation to the type, site and length of ureteral involvement (Berlanda *et al.*, 2009). Finding optimal diagnostic and therapeutic management for UE is difficult owing to the fact that most studies enroll a small number of patients, are uncontrolled and not randomized and have short-term follow-up. The objective of this review is to systematically evaluate evidence regarding pathogenesis, diagnosis and treatment of UE.

Search methods

This review was performed according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement (Moher *et al.*, 2010) and was registered in the PROSPERO register (www.crd.york.ac.uk/PROSPERO CRD42017060065). No institutional review board approval was required 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.

Literature search

A systematic computerized search of the literature, from inception until April 2018 (last research 30 April 2018; the search was run

every month from February 2017 until April 2018) was performed in two electronic databases (PubMed and MEDLINE) in order to identify relevant articles to be included for the purpose of this systematic review. The following keywords and MeSH terms were used: 'ureteral endometriosis' or 'deep infiltrating endometriosis' 'alone' or in combination with 'intrinsic', 'extrinsic', 'pathogenesis', 'diagnosis', 'symptoms', 'treatment', 'clinical examination', 'combined oral contraceptives', 'ultrasound', 'ultrasonography', 'magnetic resonance imaging', 'multislice computed tomography', 'ureteroscopy', 'fertility', 'pregnancy', 'cancer', 'hormonal treatment', 'surgery'.

All pertinent articles were carefully assessed, and their reference lists were evaluated to identify any other study that could be included in this review. The eligibility of the studies was first assessed on titles and abstracts. Full manuscripts were obtained for all selected studies, and the decision for final inclusion was made after a detailed examination of the papers.

Inclusion and exclusion criteria

In this systematic review, only peer-reviewed, English language journal articles concerning DIE, urinary tract endometriosis and ureteral endometriosis were included. In particular, the following topics were covered: epidemiology, pathogenesis, clinic and instrumental diagnosis, medical and surgical treatment, fertility and pregnancy outcomes and the risk of malignant transformation of UE.

Study eligibility

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 screened when available and evaluated only if they contained highly valuable information. Letters to the editor and abstracts accepted at conferences were excluded from the review.

Study selection and data extraction

Two authors (F.B., S.F.) independently screened the titles and abstracts of the studies obtained from the literature search and each author independently assessed the text of the potentially relevant studies for inclusion. To avoid missing any relevant publication, a manual search of the reference lists of the retrieved studies and review articles was performed. The same authors (F.B., S.F.) independently extracted data from the studies as well as characteristics including populations (time when the study was performed, number of participants, and type of ureteral involvement), diagnostic methods (objectives and use of radiological methods), therapeutic methods (medical and conservative or radical surgical treatment), and short and long-term outcomes (symptom improvement and disease recurrence). If the same cohort was used in more than one study with identical end points, the report containing the most comprehensive information was included to avoid overlapping populations. A third author (C.S.) independently reviewed the selection and data extraction processes. The results were then compared and disagreements were discussed and resolved by consensus between the three authors.

Quality assessment

Two authors (V.G.V., E.B.) independently investigated the methodological quality of the studies on diagnostic methods for UE using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool (Supplementary Table 3). In addition, the same reviewers (V.G.V., E.B.) assessed the methodological quality of studies investigating medical and surgical treatment of UE by using the Newcastle-Ottawa Scale (Supplementary Table 4). Discrepancies in an author's judgment were resolved by discussion and consensus.

Levels of recommendations and evidence

Two authors (V.G.V., E.B.) independently assessed the levels of recommendations and the grade of evidence for diagnostic tools and medical and surgical options in the management of UE. The evidence was graded using the CEBM (Centre for Evidence-Based Medicine) criteria (Supplementary Table S1). The GRADE (Grading of Recommendations Assessment Development and Evaluation Working Group) modified criteria were used to assess the grade of evidence (Supplementary Table S2). Disagreements between reviewers were resolved by discussion and consensus.

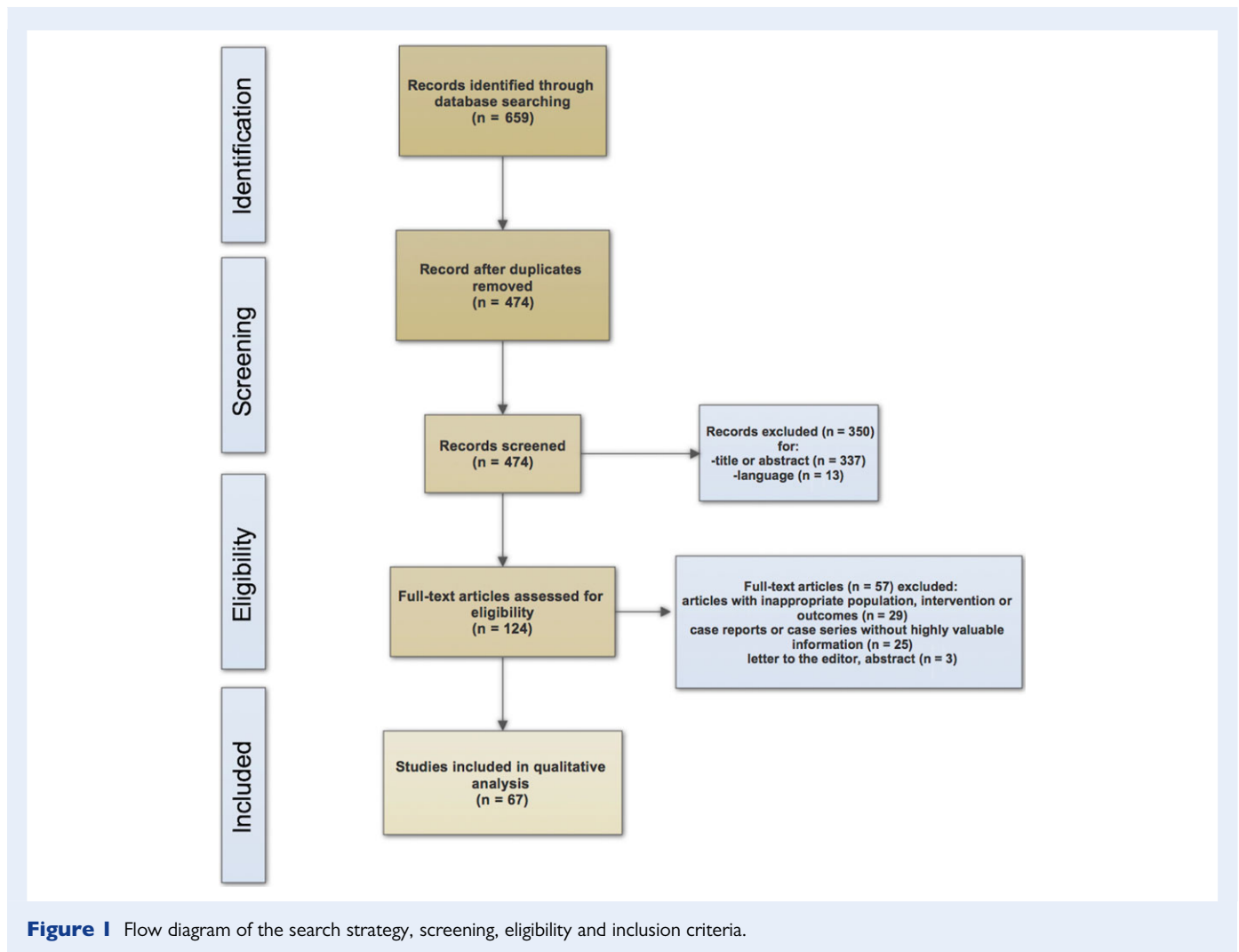
Outcomes

The literature search (Fig. 1), based on our predefined key search items, identified 474 publications after removing duplicates. The titles of these publications were screened and assessed for eligibility, resulting in 124 full-text articles evaluated to be definitively included in the review. Among these, after the evaluation of the full publication text, 57 studies were excluded as they had inappropriate populations, interventions or outcomes ($n = 29$), were case reports or series without highly valuable information ($n = 25$), or were letters to the editor or abstract ($n = 3$). In the end, a total of 67 studies were included in the present systematic review. Given the characteristics of the studies included and the heterogeneity of the available articles in terms of methodology, no meta-analysis was attempted.

Epidemiology of UE

The incidence of UTE ranges from 1% to 5.5% of all women affected by endometriosis (Knabben et al., 2015), and occurs more frequently in patients presenting DIE, reaching 16.4–52.6% (Gabriel et al., 2011; Knabben et al., 2015). The bladder is the most frequently involved organ in UTE, occurring in 70–85% of cases, while ureteral involvement accounts for 9–23%, the kidney for 4%, and the urethra for 2% of the cases (Berlanda et al., 2009).

The prevalence of UE varies considerably from 0.01% to 1.7% in women with endometriosis, according to the different series of cases reported in the literature (Vercellini et al., 2000; Antonelli et al., 2006). UE has a peak incidence in patients aged 30–35 years (Berlanda et al., 2009), and it is mainly encountered incidentally during laparoscopy for extensive endometriosis (Vercellini et al., 2000). The prevalence of the disease is probably imprecise due to the lack of symptomatology in half of the women affected and to the absence of routine urinary tract imaging performed prior to surgery for endometriosis. Moreover, the population selected in clinical studies may



be influenced by the position of institutions as referral centers specialized in the treatment of severe endometriosis.

UE is commonly unilateral, with a left predisposition (Vercellini *et al.*, 2000; Uccella *et al.*, 2016; Alves *et al.*, 2017), but bilateral disease is described in 10–42% of cases (Bosev *et al.*, 2009; Uccella *et al.*, 2014; Alves *et al.*, 2017). It most frequently affects the distal third segment of the ureter at ~3–4 cm above the vesico-ureteric junction (Berlanda *et al.*, 2009).

According to the largest studies available in the literature, it has been demonstrated that UE is frequently associated with ovarian endometriomas in 52–68% of cases (Seracchioli *et al.*, 2015; Gennaro *et al.*, 2017; Raimondo *et al.*, 2018) and with other DIE implants, such as the rectovaginal space, in 47–56% of the patients, uterosacral ligaments in 10–50% and the bowel in 26–39% of patients (Bosev *et al.*, 2009; Uccella *et al.*, 2014; Seracchioli *et al.*, 2015). Isolate UE lesions are rare (Uccella *et al.*, 2014). A recent retrospective study including 697 patients with endometriosis demonstrated that patients with UTE more frequently have advanced stages of endometriosis according to the revised American Fertility Society (rAFS) classification, resulting in the rate of patients with Stage III or IV at 94.6%, compared with 73.3% of patients without UTE ($P < 0.001$) (Knabben

et al., 2015). Moreover, in other studies, 26–62% of patients with UE had at least one previous surgery for endometriosis (Chapron *et al.*, 2010; Seracchioli *et al.*, 2015; Ceccaroni *et al.*, 2018). Raimondo *et al.* (2018) in a large series of 205 patients undergoing laparoscopic surgery for UE observed that women with ureteral compression had lower BMI ($P < 0.001$) than patients without ureteral compression. Although the clinical significance of this finding has to be confirmed, this observation is in line with the trend of inverse association between BMI and the severity of endometriosis reported in the literature (Hediger *et al.*, 2005). Women with rectovaginal endometriosis are at high risk of ureteral involvement: some authors found that the prevalence of UE was significantly higher (12–18%) in patients with rectovaginal nodules with a largest diameter > 3 cm than in those with smaller nodules or without rectovaginal endometriosis (0–1.6%) (Donnez *et al.*, 2002; Kondo *et al.*, 2013). Other authors demonstrated that the presence of a right uterosacral nodule at transvaginal ultrasound (TVS) measuring 1.75 cm has a sensitivity and specificity of 88.2% and 72.3% for estimating the risk of ureteral involvement. Similarly, finding a left uterosacral nodule measuring 1.95 cm has a sensitivity and specificity of 71.4% and 61.4% (Lima *et al.*, 2017). A recent prospective study (Ceccaroni *et al.*, 2018) showed that UE is

strongly associated with wide parametrial involvement arising from a persistent DIE affecting the posterior parametrium (uterosacral ligaments, rectovaginal ligaments, lateral rectal ligaments) and lateral parametrium (cardinal ligaments, vesico-uterine ligaments).

Pathogenesis of UE

As with other DIE locations, the pathogenesis of ureteral involvement by endometriosis remains unclear. The debate between the authors favouring the theory of retrograde menstruation and those supporting the theory of *de-novo* origin from Müllerian remnants is particularly lively in endometriosis (Vercellini et al., 2014b), and thus in UE. The left lateral and third lower predisposition of UE adds support to the hypothesis of retrograde menstruation (Vercellini et al., 2000). Decreased fluid movement in the left hemi pelvis, because of the presence of the sigmoid colon, would favor adhesion and growth of menstrual endometrium regurgitated by tubes on the peritoneal surface of the left pelvic side wall. The generation of an inflammation process and the lateral spread of retroperitoneal lesions up to and around the ureter would explain extrinsic ureteral obstruction. As bladder endometriosis originates from the implantation of endometrial cells on the peritoneum of the anterior pouch, and UE originates from implantation on the posterior pouch, the two forms are not frequently associated (Berlanda et al., 2009). Moreover, UE would be less frequent than bladder endometriosis as the ureters are located laterally, where the effect of gravity in facilitating endometrial cell implantation would be lower compared to the bladder (Abo et al., 2017). Support for retrograde menstruation comes from studies evaluating the frequency of association between different endometriotic implants (Chapron et al., 2010; Uccella et al., 2014). However, this hypothesis cannot completely explain the cases of proven UE in women who have rare isolate ureteral involvement and no evidence of any other implants of endometriotic disease in the pelvis (Vercellini et al., 2014b).

The Müllerian-remnant theory hypothesizes that DIE represents adenomyosis originated in the retroperitoneum from embryonic rests of the Müllerian duct or extension of adenomyotic nodules arising in the myometrium. In fact, the observation that implants of DIE (Anaf et al., 2000), including UE (Donnez et al., 2002), are histologically characterized by fibrotic tissue and smooth muscle cells with islands or strains of glands and stroma, such as uterine adenomyosis, adds credence to this hypothesis. In fact, according to Ferenczy (1998), adenomyosis should refer to endometrial glands and stroma not only located randomly deep within the myometrium but also in extrauterine locations. For this reason, some authors introduced the concept of adenomyotic disease of the retroperitoneal space, in which lateral invasion by adenomyotic nodules includes the rectovaginal space, the vesico-vaginal space and also the area extending laterally in the direction of the cardinal ligaments (Donnez et al., 2002). This theory may explain DIE lesions without concomitant peritoneal involvement (Yates-Bell et al., 1972; Zanetta et al., 1998).

Other authors believe that hematogenic or lymphatic spread of endometrial cells is responsible for distant implants. This theory has often been advocated to explain the pathogenesis of intrinsic UE and the isolated DIE foci (Fujita, 1976).

The iatrogenic theory hypothesizes that a previous pelvic surgery would favor the dissemination of endometrial cells outside the uterus. A cross-sectional study including women with DIE showed that the incidence of UE was similar between patients with (18.7%) or without (10.9%, $P = 0.04$) a history of uterine surgery (Marcellin et al., 2016).

It has been suggested that DIE localizations, including UE, has different pathological characteristics compared to ovarian and peritoneal endometriosis (Nisolle and Donnez, 1997). In DIE, invasive mechanisms (such as matrix metalloproteinase and activins) are more expressed than in the other forms of endometriosis. Moreover, endometriotic cells in DIE implants have decreased apoptosis and increased proliferation because of the abnormal activity of kappa-light-chain-enhancer of activated B cells (NF- κ B) and B-cell lymphoma 2 (Bcl-2), and increased vessel and nerve growth due to the overexpression of neuro-angiogenic proteins, such as nerve growth factor (NGF) and vascular growth factor (VEGF) (Tosti et al., 2015).

Diagnosis of UE

Clinical history and examination

The presence of dysmenorrhea, dyspareunia and non-menstrual pelvic pain in women of reproductive age allows suspicion of DIE; however, while bladder endometriosis is usually symptomatic (Leone Roberti Maggiore et al., 2017), up to 50% of patients with UE do not have specific symptoms. Some authors observed that only 9–16% of the patients with UE present urinary symptoms (Frenna et al., 2007; Soriano et al., 2011; Knabben et al., 2015). In the largest series available, the most common symptoms reported by patients with UE were dysmenorrhea and pelvic pain in 39–79% and in 47–64% of cases, respectively (Uccella et al., 2014; Seracchioli et al., 2015; Ceccaroni et al., 2018). Non-specific symptoms, such as flank or abdominal pain, gross hematuria or a pelvic mass may be present in these patients (Vercellini et al., 2000). Cyclical hematuria, considered highly characteristic of ureteral involvement by endometriosis in the past, is present in <17% of patients with UE (Abrao et al., 2009; Perez-Utrilla Perez et al., 2009). Rare presentations reported in the literature include anuria and renal failure in patients with solitary kidneys (Kyriakidis and Pappas, 1995; Gagnon et al., 2001) or unexplained hypertension (Davis and Schiff, 1988). The degree of symptoms correlates poorly with the degree of obstruction, and a severe ureteral obstruction, not diagnosed for a long time, may lead to the loss of renal function (Vercellini et al., 2000).

Physical examination is often normal in UE, but the palpation of a nodule in the pouch of Douglas or in the uterosacral ligament at rectovaginal examination provides a helpful indication of possible ureteral involvement (Table I) (Knabben et al., 2015). Combined rectovaginal examination could be helpful in case of parametrial involvement, assessing the depth and the extension of lateral infiltration in the involved parametrial ligaments (Ceccaroni et al., 2013, 2018).

In patients with suspected UE, other diagnoses have to be considered, including urologic causes of intrinsic or extrinsic ureteral stenosis, such as stones, primary or metastatic cancer, retroperitoneal lymphadenopathy, idiopathic retroperitoneal fibrosis and infections. The imaging techniques are fundamental for differentiating all of these conditions (Moosavi et al., 2016).

Table I Level of evidence (LE) and grade of recommendations (GR) for the diagnosis of ureteral endometriosis.

Approach	Pros	Cons	Comments	LE	GR
Medical history and physical examination	Noninvasive	Up to 50% of patients with UE are asymptomatic	It can detect rectovaginal nodules or other endometrial implants which may be responsible for ureteral compression	IIb	B
Abdominal Ultrasonography	Noninvasive, cost-effective; it detects hydronephrosis	It does not visualize the whole ureter course	It should be performed as first-line exam suspecting UE. It can indirectly detect ureteral obstruction and evaluate the thickness of the renal parenchyma	Ib	A
TVS	Noninvasive, cost-effective, good diagnostic performance	Experience of the ultrasonographer; it can assess only pelvic ureter	It should be performed as first-line exam suspecting UE. It can detect rectovaginal nodules at the last third of ureter	Ib	B
MRI	Highly accurate to detect and predict the type of UE	Not cost-effective. It overestimates intrinsic ureteral involvement	It should be performed in women with suspicious of UE after ultrasound	Ib	A
MSCT	It visualizes the ureteral obstruction caused by bowel implants if performed with colon distention	Irradiation, discomfort for the eventual enema	It should be used to investigate ureteral involvement associated with bowel endometriosis. Alternative to MRI.	IIb	B
IVP	It detects hydronephrosis	It presents non-specific findings	Alternative to MRI.	IIb	B
Renal scintigraphy	It estimates residual renal function	Not cost-effective. It can not directly detect UE. Irradiation	It should be done in case of signs of significant hydronephrosis at ultrasound or MRI in order to choose the best option between surgical procedures (kidney preservation or nephrectomy)	IIb	B
Ureteroscopy	It directly visualizes the nodules in the ureter wall and it allows to perform biopsy	Invasive. It cannot evaluate extrinsic UE	It should be not performed in clinical practice	IV	D

UE = ureteral endometriosis; TVS = transvaginal ultrasonography; MRI = magnetic resonance imaging; MSCT = multislice computed tomography; IPV = intravenous pyelography; LE = level of evidence; GR = grade of recommendation.

Ultrasonography

Ultrasonography is recommended for the systematic diagnostic assessment of women who are suspected to be suffering from DIE, as it is noninvasive, reproducible and cost effective (Guerrero et al., 2016). Abdominal ultrasonography allows the diagnosis of hydronephrosis, which should be graded on the appearance of the calices and renal pelvis and the thickness of the renal parenchyma. As the entire ureteral course cannot be evaluated by this exam, it may be impossible to directly detect ureteral endometriotic lesions.

The use of TVS to evaluate the pelvis and the periureteral area has been largely overlooked in the literature. Pateman et al. (2013), identifying the pelvic segments of normal ureters and measuring their median diameter in 93% (95% CI, 89.4–96.0%) of 245 women, demonstrated the feasibility of incorporating the assessment of the ureters into the ultrasound examination of women with suspected pelvic endometriosis. At TVS, pelvic ureteral dilation appears as a tubular anechoic image with or without movements in the parametrial tissue, very similar to a blood vessel but with negative color and power Doppler signs. During TVS assessment of ureteral dilatation, the ureteral diameters before and after the stenosis should be measured; furthermore, the location and the distance from the bladder of the endometriotic nodule causing the stenosis should be estimated. In the case of extrinsic UE without evident hydronephrosis, TVS may allow the detection of DIE adjacent to the ureter (Table I) (Exacoustos et al., 2014). Table II reports the main characteristics and findings of studies investigating the performance of TVS for diagnosing UE.

In a prospective observational study enrolling 848 patients with chronic pelvic pain, Pateman et al. (2015) investigated the potential causes of their symptoms by TVS and transabdominal pelvic ultrasonography. The exams had a sensitivity of 92% (95% CI 63.9–99.8) and a specificity of 100% (95% CI 97.6–100) for the diagnosis of UE. Recently, Carfagna et al. (2018) estimated the mean ureteral dilatation, measuring the ureters of 13 women with UE both cranially and caudally to the stenosis at rest and during peristalsis. They found a ureteral diameter ≥ 6 mm (mean diameter: 6.9 mm; range, 6–18 mm) at the peak of distention in patients with histologically confirmed UE (vs. 3.4 mm; range, 2.3–4.5 mm) in patients without UE.

Intraluminal sonography evaluates the ureteral lumen, wall and periureteral tissues using a catheter-based ultrasound probe. One study examined 63 patients with suspected ureteral obstruction by using intraluminal ureteral ultrasonography. In six patients, the exam showed evidence of endometriosis, appearing as blood filled, hyperechoic cystic structures involving the ureteral wall and the periureteral tissue or as polypoid mass lesions obstructing the ureteral lumen (Grasso et al., 1999). However, this exam is invasive and it is not routinely used in clinical practice.

Magnetic resonance imaging

At MRI, the involvement of the ureter appears as a nodule with low-intensity signal associated with hyperintense foci at both T1- and T2-weighted sequences (Table I), while concurrent retractile adhesions appear as periureteral hypointense linear foci with angular deviation,

particularly in long-standing disease. Loss of the fatty interface between the nodule and the ureter suggests ureteral infiltration in cases of extrinsic involvement (Kinkel et al., 2006). Table II reports the main characteristics and findings of the studies investigating the performance of MRI for the diagnosis of UE.

In a cohort of 792 women undergoing MRI for suspected DIE, Balleyguier et al. (2004) correctly identified six cases of UE, describing intrinsic and extrinsic UE types. Whenever MRI diagnosed extrinsic endometriosis, it was indeed present at histologic examination. On the other hand, the prevalence of intrinsic disease was overestimated by MRI; out of four women with intrinsic involvement at MRI, only two had infiltration of the ureteral wall by endometriosis at surgery. In a retrospective study, Sillou et al. (2015) compared MRI to surgery for detecting intrinsic UE. MRI had a sensitivity of 91% (95% CI,

59–99) and a specificity of 59% (95% CI, 39–78), while surgery had a sensitivity of 82% (95% CI, 48–98) and a specificity of 67% (95% CI, 46–83); these results suggest that MRI is more sensitive than surgery in detecting intrinsic involvement, but it is less specific. Also, in this study, MRI overestimated intrinsic disease (21 intrinsic lesions diagnosed by MRI, but only 10 confirmed as intrinsic by histopathology). Moreover, the authors carried out an assessment of the ureteric circumference included in the endometriotic lesion in order to predict whether the lesions were intrinsic. If the ureter was completely surrounded by the lesion (360 degrees), intrinsic disease was confirmed in over 50% of cases, and if it was surrounded by less than 180 degrees, intrinsic disease was present in fewer than 10% of cases. Finally, if the disease surrounded the ureter by less than 360 degrees, extrinsic disease was confirmed in over 80% of the cases.

Table II Results of studies investigating imaging techniques for the diagnosis of ureteral endometriosis.

Study	Type	Instruments type	Population	UE	SE (%)	SP (%)	PPV (%)	NPV (%)	LR+	LR-	ACC (%)
Ultrasonography											
Vimercati et al. (2012)	PS, SI	TVS	90 pts with suspicion for DIE	8	100	100	100	100	INF	INF	100
Exacoustos et al. (2014)	PS, 3I	TVS	104 pts with suspicion for DIE	24	RU: 61.5 LU: 68.7	RU: 97.8 LU: 95.5	RU: 80.0 LU: 73.3	RU: 94.7 LU: 94.4	RU: 28.0 LU: 15.1	RU: 0.4 LU: 0.3	RU: 93.3 LU: 91.3
Pateman et al. (2015)	PS, SI	TVS, AS	848 pts with chronic pelvic pain	14	92	100	100	99.3	NR	0.1	NR
Zannoni et al. (2017)	PS, SI	TVS	45 pts with suspicion for DIE	31	RU: 10 LU: 28.5	RU: 94.8 LU: 96.3	RU: 33 LU: 86	RU: 84 LU: 65	RU: 2.4 LU: 8.1	RU: 0.9 LU: 0.7	RU: 81 LU: 68
Carfagna et al. (2018)	PS, SI	TVS	200 pts with suspicion for DIE	13	100	100	NR	NR	NR	NR	100
MRI											
Balleyguier et al. (2004)	RS, SI	1.5 T MRI	792 pts with suspicion for DIE	6	100	100	NR	NR	NR	NR	100
Chamie et al. (2009)	PS, SI	1.5-T MRI with intravenous injection of contrast	92 pts with suspicion for DIE	9	55.5	100	100	NR	NR	NR	96
Vimercati et al. (2012)	PS, SI	1.5-T MRI with colon water distension and intravenous injection of contrast	90 pts with suspicion for DIE	8	100	100	100	100	INF	INF	100
MSCT											
Biscaldi et al. (2011)	PS, SI	16-MSCT with colon water distension and intravenous injection of iodinated contrast	98 pts with suspicion for bowel endometriosis	34	97.1	98.8	94.4	99.4	83.5	0.03	99.0
Iosca et al. (2013)	RS, SI	64-MSCT with colon water distension and intravenous injection of iodinated contrast	55 pts with suspicion for bowel endometriosis	26	72.2	100	100	87.5	NR	NR	88.8
Zannoni et al. (2017)	PS, SI	64-MSCT with colon air distension and intravenous injection of iodinated contrast	45 pts with suspicion for DIE	31	RU: 60 LU: 57.1	RU: 70.2 LU: 76.9	RU: 33 LU: 63	RU: 90 LU: 71	RU: 2.1 LU: 2.3	RU: 0.5 LU: 0.5	RU: 68 LU: 68

UE = total no of ureters with confirmed surgical and histopathological endometriosis; SE = sensitivity; SP = specificity; PPV = positive predictive value; NPV = negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio; ACC = accuracy RS = retrospective; PS = prospective; SI = single institution; 2I = two institution; 3I = three institution; TVS = transvaginal ultrasonography; AS = abdominal ultrasonography; MRI = magnetic resonance imaging; MSCT = multislice computed tomography; pts = patients; NR = not reported; INF = infinity; RU = right ureter; LU = left ureter.

Multislice computed tomography

Multislice computed tomography (MSCT) was originally used by Donnez *et al.* to estimate the degree of ureteral occlusion in patients with cortical atrophy and decreased renal function (Donnez *et al.*, 2002). More recently, MSCT combined with colon distension with water and intravenous injection of iodinated contrast medium was shown to be accurate in the diagnosis of intestinal endometriosis (Biscaldi *et al.*, 2007a, b). This exam can be performed by using the split-bolus technique and allows detection of ureteral involvement that can be associated with bowel endometriosis (Table 1) (Fig. 2) (Biscaldi *et al.*, 2011). It can directly visualize solid ureteral nodules, which are enhanced by the injection of contrast medium; however, it does not help to clarify whether the nodules are hemorrhagic lesions (Moosavi *et al.*, 2016). An optimal pelvic ureteral opacification is required to diagnose UE, especially when UE does not present with upstream dilatation of the urinary tract (losca *et al.*, 2013). The main limitation of MSCT combined with colon distension with water and intravenous injection of iodinated contrast medium is the radiation dose delivered to each patient, although the dose can be significantly reduced when the exam is performed with the split-bolus technique compared to when it is performed with two post-contrast scans. In any case, this limitation is important considering the young age of the



Figure 2 Multislice computed tomography after colon distension performed with the split-bolus technique. The sagittal reconstruction after split bolus injection shows a stricture (arrow) of distal part of left ureter caused by endometriosis. Proximally to the stenosis the ureter is dilated. B = bladder; C = cecum; U = uterus.

patients and their likely desire for future pregnancies (losca *et al.*, 2013). Table II reports the characteristics and finding of the studies investigating the diagnostic performance of MSCT in the diagnosis of UE. A prospective study (Biscaldi *et al.*, 2011) and a retrospective study (losca *et al.*, 2013) demonstrated that MSCT with colon distension with water and intravenous injection of iodinated contrast medium is a reliable method to investigate ureteral compression in patients with suspicion of bowel endometriosis. Recently, a pilot study compared the diagnostic performance of TVS and MSCT with air-insufflation in the rectum using contrast media and urographic phase. This exam had higher sensitivity (57.1–60%) than TVS (10–28.5%) for the diagnosis of UE, but an inferior specificity (70.2–76.9%) than TVS (94.8–96.3%) (Zannoni *et al.*, 2017).

Other imaging methods

Intravenous pyelography (IVP) and retrograde pyelography have been the traditional imaging methods used to evaluate women suspected of having UTE, but currently, MRI has mainly replaced them (Baileyguier *et al.*, 2004). Although they can demonstrate extension, location and degree of ureteral stenosis, radiologic findings (such as hydronephrosis, narrowing of the pelvic ureter and, rarely, an intraluminal ureteral mass) are non-specific for UE. Moreover, when there is no ureteral obstruction, extrinsic endometriosis cannot be diagnosed by these exams (Pollack and Wills, 1978).

Renal scintigraphy should be performed only in case of signs of significant hydronephrosis at ultrasound or MRI in order to assess residual renal function and to discriminate between surgical procedures with kidney preservation and nephrectomy (Donnez *et al.*, 2002).

Ureteral endoscopy can directly visualize edematous and irregular blue nodules in contact with the ureter wall, and it allows the performance of intraluminal ultrasonography and a biopsy of the lesion. However, as it is invasive and it is not able to detect extrinsic UE, it is not used in clinical practice (Zanetta *et al.*, 1998).

Recently, Knabben *et al.* (2015) proposed a radiological-clinical classification of UE: 'Grade 0, peritoneal endometriosis overlying the ureter; Grade 1, retroperitoneal endometriosis with entanglement of the ureter but no dilatation; Grade 2, dilatation of the ureter and/or hydronephrosis without functional impairment (at urodynamics); Grade 3, urodynamically relevant obstruction with symmetrical renal split clearance in renal furosemide scintigraphy and normal total clearance; Grade 4, urodynamically relevant obstruction with impaired split clearance in renal furosemide scintigraphy or impaired total clearance; Grade 5, silent kidney.'

Histology

The definitive diagnosis of UE is made by histology, as is the case with the other endometriotic implants. The depth of endometriotic invasion in UE has to be assessed by histology because this diagnosis cannot be reliably made by surgery (Seracchioli *et al.*, 2015). Two pathological types of UE, extrinsic and intrinsic are described. In the extrinsic pattern, endometriosis invades only the ureteral adventitia or the surrounding connective tissue being able to cause extrinsic compression of the ureteral wall. In the intrinsic disease, endometrial tissue directly infiltrates the muscularis, submucosa, or mucosa of the ureter (Fig. 3). The two types of UE may sometimes coexist along

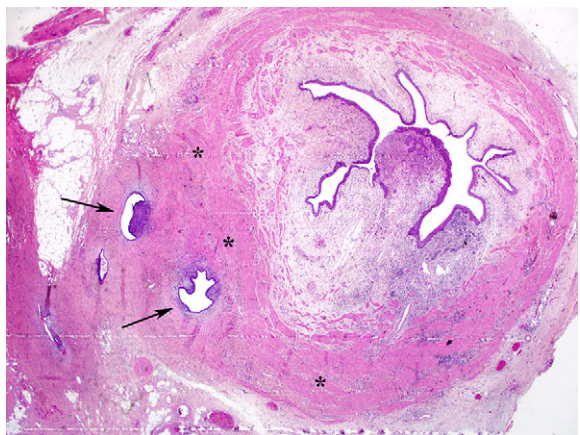


Figure 3 Hematoxylin and eosin staining of intrinsic ureteral endometriosis (x20); endometriosis directly involves the muscularis of the ureter (arrows). The asterisks indicate the ureteral muscularis.

the ureteral course in the same patient (Yohannes, 2003). Accordingly to Lusuardi et al. (2012), peritoneal endometriotic plaques overlying the ureters should not be classified as UE, as they simply require peritoneal excision.

The precise prevalence of intrinsic and extrinsic UE remains unknown because the surgical and histological diagnoses depend on the experience of the gynecologist in performing a complete excision of UE. The rates of intrinsic UE range from 5.1% to 45.6% of the cases in the largest studies available in literature (Alves et al., 2017; Ceccaroni et al., 2018). In presence of ureteral dilatation, the rate of the intrinsic form is higher (Alves et al., 2017). A retrospective study by Chapron et al. (2010) of 29 patients with severe ureteral obstruction found 38.2% of intrinsic lesions and 61.8% of extrinsic lesions, thus demonstrating that also extrinsic lesions may be responsible for ureteral obstruction. This extrinsic ureteral obstruction is often caused by secondary fibrosis originating near the endometriotic implants (Frenna et al., 2007).

In a retrospective observational study, Seracchioli et al. (2015) evaluated the histological pattern of UE by microscopic examination and CD10 immunostaining. Among 77 patients, they proved that the endometriotic pattern (endometrial glands and/or stroma cells seen within the wall of the ureter or within periureteral tissue) was occurring more often than the fibrotic pattern (fibrotic tissue only) (77% versus 23%). Additionally, the authors showed that the endometriotic pattern was significantly more often associated with the presence of hydronephrosis (68% versus 42%, $P = 0.04$), whereas the fibrotic pattern was more often associated with the presence of a rectovaginal nodule (95% versus 45%, $P < 0.001$). This last finding may be linked to the inflammatory process generated by a posterior DIE nodule that extrinsically involves the ureter. A large series of women undergoing laparoscopic surgery for UE confirmed a significant association between endometriotic parametrial infiltration and hydronephrosis ($P < 0.001$) (Raimondo et al., 2018), supporting the idea that endometriotic tissue and surrounding fibrosis seem to follow the course of the blood vessels (such as the uterine artery) and that may be

responsible for ureteral compression, as previously described in literature (Smith and Cooper, 2010).

Treatment

Hormonal therapy

Being safe and effective in long-term administration, hormonal contraceptives and progestogens are first-line therapies to treat pain in patients with DIE (Barra et al., 2018; Ferrero et al., 2018). Gonadotropin-releasing hormone agonists (GnRH-as) are considered a second-line therapy because of the potential adverse effects caused by hypoestrogenism, while aromatase inhibitors can be prescribed to patients refractory to conventional therapies in the setting of scientific research (Ferrero et al., 2015).

Medical therapy is contraindicated as a first line treatment in patients with ureteral obstruction because of the risk of progressive increase in the severity of ureteral stenosis and hydronephrosis which could lead to loss of renal function. However, the role of hormonal therapy in patients with UE without obstruction and suffering pain symptoms has not been established. In these patients, hormonal therapy may be used for controlling symptoms or while planning the surgical approach under renal function control (Table III). After being documented in other DIE lesions (Noel et al., 2010), an immunohistochemical study showed that also endometriotic cells within the ureteral wall express estrogen and progesterone receptors (Al-Khawaja et al., 2008). However, these nodules usually contain extensive fibrosis, poorly responsive to the endocrine therapies (Vercellini et al., 2000; Frenna et al., 2007).

No study with a large sample size has investigated the efficacy of hormonal therapies in treating UE. Only case reports have described the treatment of UE with progestins (Lavelle et al., 1976; Gantt et al., 1981), danazol (Gardner and Whitaker, 1981; Matsuura et al., 1985; Rivlin et al., 1985; Jepsen and Hansen, 1988; Vilos et al., 2015), GnRH-as (Vilos et al., 2015), the levonorgestrel-releasing intrauterine system (Simon et al., 2017) and aromatase inhibitors (Bohrer et al., 2008; Flyckt et al., 2011).

Postoperative medical therapy may be useful in preventing recurrence of endometriosis and associated symptoms, but no study has evaluated its effectiveness in patients with UE (Ferrero et al., 2015).

Surgical therapy

The surgical treatment of UE aims to relieve ureteral obstruction and avoid recurrence (Table III).

In general, the identification of the ureter is critical during surgical excision of pelvic endometriosis in order to avoid iatrogenic ureteral injuries and to evaluate if the disease affects the ureter. Surgical management of UE includes conservative ureterolysis or radical approaches, such as ureterectomy with end-to-end anastomosis, ureteroneocystostomy or nephroureterectomy. The surgical treatment depends on the extension of UE and on the renal function. However, the surgical treatment of UE is not clearly defined because prospective randomized trials are lacking and difficult to conduct because of the rarity of the disease, and most of the available surgical series are retrospective, uncontrolled and include heterogeneous populations.

Table III Level of evidence and grade of recommendation for the medical and surgical treatment of ureteral endometriosis.

Approach	Pros	Cons	Comments	LE	GR
Medical treatment					
Combined hormonal contraceptives and progestins	Cost-effective. They improve pain symptom	They do not resolve the ureteral obstruction	They should not be used instead of a surgical approach They should be considered in women who refuse or are contraindicated for the Surgical approach	III	C
GnRH-as				III	C
Aromatase inhibitors				III	C
Surgical treatment					
Ureterolysis	Lower peri- and post-surgical complication rate	Higher recurrence of the disease	It should be reserved for patients with no or mild obstruction	IIb	B
Partial ureteral wall resection	–	Higher recurrence of the disease	It should be only used in selected patients	IV	C
Ureteral resection with end to end anastomosis	–	Higher recurrence of the disease	It should be used in patients with short length ureteral obstruction not localized near to the vesicoureteral junction	III	C
Ureteroneocystostomy	Lower recurrence of the disease	Higher peri- and post-surgical complication rate	It should be used in patients with moderate-severe obstruction localized in the lower third of the ureter	IIb	B
Nephroureterectomy	Lower recurrence of the disease	It does not preserve kidney	It should be used when small portion of the kidney remains functional (less than 10–15% on scintigraphy)	III	C
Endoscopic excision	Less invasive	Higher recurrence rate of the disease	It should not used in clinical practice	IV	C

GnRH-as = Gonadotropin-releasing hormone-agonists; LE = level of evidence; GR = grade of recommendation.

Table IV shows the studies, including more than 20 cases, that investigate the surgical treatment of UE.

Ureterolysis

Ureterolysis consists of the isolation and mobilization of the ureter, freeing it from the endometriotic and fibrotic lesions to relieve ureteral obstruction (Fig. 4). The laparoscopic approach is currently the most used, as it is considered safe and effective (Elashry *et al.*, 1996; Nezhat *et al.*, 1996). Exposure and isolation of the ureter can be done with dissection methods, such as CO₂ laser, electrocautery, scissors or advanced bipolar or ultrasonic devices, taking into account the heating effect of these new devices.

Ureterolysis is contraindicated in patients who have complete ureteral obstruction, although it is the procedure of choice for minimal, extrinsic and non-obstructive UE. Despite this, there is currently no agreement on the benefit of ureterolysis in patients with mild to severe ureteral obstruction (Vercellini *et al.*, 2000). Ureterolysis should be performed before endometriotic nodule resection in all patients selected for this radical intervention in order to identify the exact position of the ureter, avoiding iatrogenic ureteral injuries during the surgery (Frenna *et al.*, 2007). In their first retrospective studies of laparoscopic ureterolysis, Nezhat *et al.* (1996) and Donnez *et al.* (2002) did not report ureteral recurrences in 39 patients treated for UE or rectovaginal nodules in a follow-up from 3 to 38 months, respectively. Postoperative resolution of ureteral obstruction was observed in all patients and pain relief was reported in 88–95% of cases. Data obtained from more recent series suggest that the recurrence rate after conservative ureterolysis is not negligible, as observed in previous studies. In a multicenter prospective study, Ghezzi *et al.* (2006) showed that among 33 patients with moderate

to severe hydronephrosis on preoperative IPV treated by laparoscopic ureterolysis, four of them (12.1%) required one or more radical operations for disease recurrence at a median follow-up of 16 months. In a prospective study including 52 patients with UE and moderate to severe ureteral dilatation (≥ 1 cm), Mereu *et al.* (2010) performed 35 laparoscopic ureterolysis, but at a 2-month follow-up seven (20%) patients required ureteroneocystostomy because of the persistence of the ureteral stenosis. Camanni *et al.* (2009) showed that among 80 patients with UE, laparoscopic ureterolysis led to the complete removal of the disease in 76 patients (95%) with a high rate of satisfaction after a follow-up of 6, 12 and 24 months. Postoperative complications were more common in patients with more than 4 cm of ureteral length affected by UE (Camanni *et al.*, 2009). In a large retrospective study, Frenna *et al.* (2007) reported no recurrence in the urinary tract among 54 patients with UE treated by laparoscopic ureterolysis, but in this series, obstructive uropathy was present only in three (5.6%) patients. More recently, Uccella *et al.* (2014) retrospectively analyzed the data of 109 patients with UE (hydronephrosis in 61% of cases) treated conservatively. Of the 80 patients with available follow-up data, 22 patients (27.5%) had recurrence of symptoms and secondary ureteral procedures were necessary in five women (6.3%). Interestingly, dividing patients in three groups according to the degree of hydronephrosis, a significant trend was registered toward an increase (20.9%, 26.2% and 54.2%) in the rate of overall adverse outcomes (defined as complications, recurrence of symptoms and reoperations on the ureter, respectively).

Abo *et al.* (2017) used robotic assistance (Da Vinci system, Intuitive Surgical, Inc., Sunnyvale, CA) to perform ureterolysis in 11 patients with UE, resulting in complete freedom of the ureters in all

Table IV Results of studies investigating surgical treatment of ureteral endometriosis.

Study	Type	Pts n	Hydronephrosis n (%)	Treatment n (%)	Complications n (%)	Recurrence n (%)	Follow-up (mo)
Nezhat et al. (1996)	RS	21	21 (100)	Lap ureterolysis: 10 (48) lap ureterectomy with end-to-end anastomosis: 3 (14) lap ureteral partial wall resection: 7 (33) lap ureteroneocystostomy: 1 (5)	Tot procedures = 1 (5)	Tot procedures = 0	Median 22 (range 5–33)
Ghezzi et al. (2006)	PS	33	NR	Lap ureterolysis: 31 (94) lap ureteral partial wall resection: 1 (3) op ureteroneocystostomy: 1 (3)	Tot procedures = 0	Tot procedures = 5 (15)	Median 16 (range 3–53)
Frenna et al. (2007)	RS	54	2 (4)	Lap ureterolysis: 54 (100)	Lap ureterolysis: 4 (8)	Lap ureterolysis: 4 (8)	Median 9 (range 5–12)
Bosev et al. (2009)	RS	96	2 (4)	Lap ureterolysis: 94 (98) lap ureteroneocystostomy: 2 (2)	Lap ureterolysis: 1 (1) lap ureteroneocystostomy: 1 (50)	Tot procedures = 0	Median NR (range 2–50)
Camanni et al. (2009)	RS	80	4 (5)	Lap ureterolysis: 96 (96) lap ureteroneocystostomy: 4 (4)	Lap ureterolysis: 3 (4) lap ureteroneocystostomy: 0	Lap ureterolysis: 2 (3) lap ureteroneocystostomy: 0	Median 22 (range 6–41)
Mereu et al. (2010)	PS	56	NR	Lap ureterolysis: 35 (63) lap ureterectomy with end-to-end anastomosis: 17 (30) op nephrectomy: 2	Lap ureterolysis: 27 (77) lap ureterectomy with end-to-end anastomosis: 6 (35) op nephrectomy: 0	Lap ureterolysis: 3 (9) lap ureterectomy with end-to-end anastomosis: 0 op nephrectomy: 0	Median 21 (range 10–62)
Seracchioli et al. (2010)	PS	30	10 (33)	Lap ureterolysis: 22 (73) lap ureterectomy with end-to-end anastomosis: 5 (17) lap ureteroneocystostomy: 3 (10)	Tot procedures = 16 (53)	Tot procedures = 0	Mean 55±18 (range 4–48)
Soriano et al. (2011)	PS	45	NR	Lap ureterolysis: 41 (91) op/lap ureteroneocystostomy: 4 (9)	NR	Lap ureterolysis: 2 (5) op/lap ureteroneocystostomy: 0	Mean 28.5± 13.3 (range 24–33)
Stepniewska et al. (2011)	RS	20	20 (100)	Lap ureteroneocystostomy: 20 (100)	Lap ureteroneocystostomy: 18 (90)	NR	6*
Uccella et al. (2014)	RS	109	66 (61)	Lap ureterolysis: 108 (99) lap partial wall resection-ureterectomy with end-to-end anastomosis: 1 (1)	Tot procedures = 0	Lap ureterolysis: 8 (6) lap partial wall resection- ureterectomy with end-to-end anastomosis: 0	Median 52 (range 15–109)
Mu et al. (2014)	RS	23	23 (100)	Op ureterolysis: 3 (13) lap ureterolysis: 2 (9) op ureterectomy with end-to-end anastomosis: 12 (52) op ureteroneocystostomy: 6 (26)	Op/lap ureterolysis: 0 op ureterectomy with end-to-end anastomosis: 5 (42) op ureteroneocystostomy: 4 (67)	Tot procedures = 1	Median 41 (range 7–98)
Seracchioli et al. (2015)	RS	77	NR	Lap ureterolysis: 63 (82) lap ureterectomy with end-to-end anastomosis- ureteroneocystostomy: 14 (18)	NR	Tot procedures:0	Median 25 (range 14–36)
Gennaro et al. (2017)	RS	82	18 (22)	No intervention: 9 (11) lap ureterolysis: 63 (77) op/lap/rob ureteroneocystostomy: 10 (12)	NR	Lap ureterolysis: 3 (5) ureteroneocystostomy: 0 lap ureteroneocystostomy: 0 rob ureteroneocystostomy: 0	Mean 7

Alves et al. (2017)	RS	198	28 (14)	Lap ureterolysis: 185 (93) lap ureterectomy with end-to-end anastomosis: 12 (6) lap ureteroneocystostomy: 1 (1)	Tot procedures: 20 (10)	Lap ureterolysis: 33 (19) lap ureterectomy with end-to-end anastomosis/ ureteroneocystostomy: 4 (20)	12*
Huang et al. (2017)	RS	46	46 (100)	Op/lap ureterolysis: 11 (24) op/lap ureterectomy with end-to-end anastomosis: 4 (9) op/lap ureteroneocystostomy: 27 (60) op/lap nephrectomy: 3 (7)	Tot procedures: 9 (20)	Op/lap ureterolysis: 0 op/lap ureterectomy with end-to-end anastomosis: 1 (25) op/lap ureteroneocystostomy: 0 op/lap nephrectomy: 0	24*
Ceccaroni et al. (2018)	PS	160	110 (68.7%)	Lap ureteroneocystostomy: 159 (99) ureterectomy with end-to-end anastomosis 1 (0.5) nephrectomy: 1 (0.5)	Lap ureteroneocystostomy: 27 (17) ureterectomy with end-to-end anastomosis 0 nephrectomy: 0	Lap ureteroneocystostomy: 2 (1) ureterectomy with end-to-end anastomosis 0 nephrectomy: 0	Median (range): 20.5 (1–60)

Only studies with largest sample size (at least 20 patients) were included in the review. Complications of any grade within one month from surgical procedure are reported. Among recurrences, they have included patients having symptoms suggestive of UE and for which the diagnosis of UE cannot be excluded or those with radiological or surgical evidence of UE after primary surgery.

*Only some patients have been followed for the whole follow-up.

Pts = patients; RS = retrospective; PS = prospective; CS = case series; op = open; lap = laparoscopic; rob = robot-assisted; pts = patients NR = not reported; mo = months; tot = total.

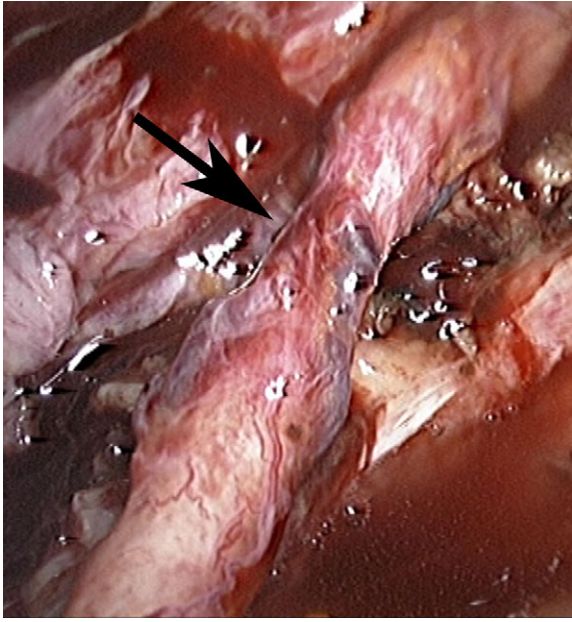


Figure 4 A stricture of the left ureter (arrow) can be observed after laparoscopic ureterolysis.

of them. A major complication occurred in a patient, who 5 days after ureterolysis, presented with a large fistula of the ureter, requiring ureteroneocystostomy. At one-year follow-up, no patient had recurrence of UE.

Partial ureteral wall resection

Nezhat et al. (1996), Ghezzi et al. (2007) performed partial ureteral wall resection in seven (33% of total patients with UE in the study) and one (3%) patients, respectively, reporting no major complication or recurrence. In these studies, the ureter was repaired with three interrupted polydioxanone sutures. The results are too limited for evaluating indications and outcomes of this procedure, and it should not be performed prior to further evaluation.

Ureteral resection with end-to-end anastomosis

Ureteral resection with end-to-end anastomosis provides a more complete excision of endometriosis and surrounded fibrosis from the ureter, but it presents short and long-term complications, such as breakdown or stricture at the anastomosis site. Moreover, as ureteral resection with end-to-end anastomosis preserves the distal tract of the ureter, which crosses the parametrium, there might be a higher risk of UE recurrence (Antonelli, 2012; Freire et al., 2017). Segmental ureteral resection should be reserved for patients with severe or complete ureteral obstruction, with evident stenosis but limited to the upper or middle parts of the ureter (Berlanda et al., 2009).

In their retrospective studies, Nezhat et al. (1996) and Donnez et al. (2002) did not show complications or recurrences in four and two patients, respectively, treated with this laparoscopic procedure. Mereu et al. (2010) reported two cases of persistent ureteral stenosis (12%) which required ureteroneocystostomy in a series of 17 patients who had undergone laparoscopic ureteral resection and end-to-end anastomosis. More recently, Alves et al. (2017) treated

12 women with this procedure and did not find significant differences in recurrences and complications between the group of patients undergoing radical procedures (including segmental ureteral resection) and the group undergoing ureterolysis.

Ureteroneocystostomy

Ureteroneocystostomy consists of the reimplantation of the ureter into a new site in the bladder wall, bypassing the fibrotic and endometriotic area in which the ureter is involved. Laparotomy has long been considered the preferred route of ureterovesical reimplantation, but several studies have demonstrated the feasibility of this procedure by laparoscopy (Nezhat et al., 1996, 2004, 2017; Stepniewska et al., 2011; Ceccaroni et al., 2018).

Ureteral reimplantation should be considered in case of severe ureteral involvement when ureteral lesions are near the bladder insertion, or the lesions involve the ureteral wall along a large extent of the pelvic ureter and thus end-to-end anastomosis is not feasible, or in the case of persistent and recurrent stenosis after a conservative approach (Vercellini et al., 2000). A tension-free direct anastomosis can be performed in the case of short gap due to the ureteral defect, whereas larger distances need a psoas bladder hitch procedure (fixing the posterior bladder wall to the psoas tendon) or a Boari flap (tubularizing a flap of the bladder to substitute the distal ureter) (Stein et al., 2013).

Carmignani et al. (2009) reported a series of 13 patients with UE who underwent laparotomic ureteroneocystostomy with a bladder psoas hitch. The indications were severe hydronephrosis, radiologic evidence of ureteral stricture measuring more than 4 cm and the impossibility of performing ureterolysis due to macroscopic infiltration of endometriosis or secondary atony of the fibrosclerotic ureteral segment. Among 10 patients, they observed no complications or recurrence of ureteral obstruction at the 6-month follow-up. In a retrospective cohort study, Stepniewska et al. (2011) proved the efficacy of laparoscopic ureteral reimplantation with significant symptomatic improvement in all patients during a follow-up of 6 months. Postoperative transient deficit of bladder voiding occurred in five cases (25%), urinary infection in one and postoperative pyrexia in four (20%) patients. Among seven patients evaluated retrospectively, Schonman et al. (2013) demonstrated marked symptomatic improvement in six out of seven (86%) women for three and a half years of follow-up. In their series, three patients were treated laparoscopically, but two cases were converted to laparotomy. In a retrospective study, Chudzinski et al. (2017) reported their experience with 17 patients, who underwent ureteroneocystostomy for severe ureteral endometriotic infiltration, lesion at the ureteral orifice, iatrogenic injury or failure of intraoperative ureterolysis. Ureteral reimplantation was decided before the surgery in 12 (70%), intraoperatively in two (11%) and postoperatively in three (17%) patients. The surgical approach was conventional laparoscopy and robot-assisted laparoscopy for six (35%) and four patients (23%), respectively. Among them, three patients (30%) required conversions to laparotomy. After the surgical procedure, seven (41%) patients had postoperative complications (70% of complication Grade 3A or 3B according the Clavien-Dindo classification) which were most commonly the occurrence of anastomotic leak, ureteral fistula and infection. Subsequently five of them (72%) underwent intervention. Abo et al. (2017) performed robotic-assisted (Da Vinci system) ureteroneocystostomy in two patients with UE; the

authors did not report postoperative complications and recurrences at 1 year of follow-up. A recent study (Ceccaroni *et al.*, 2018) described the largest series of laparoscopic ureteroneocystostomy (Fig. 5A–D), including 160 patients with documented ureteral stricture who underwent radical excision of DIE with ureteroneocystostomy, parametrectomy and, if necessary, segmental bowel resection. The major surgical complication rate was low (seven patients, 4.4%). There was a significant improvement in pain symptoms after surgery and the rate of UE recurrence at 24-month follow was 1.2% (as two patients underwent second opposite side laparoscopic ureteroneocystostomy 36–48 months after the first procedure).

Nephroureterectomy

Severe stenosis of the ureter may lead to hydronephrosis, loss of renal function and end-stage renal disease (ESRD). Moreover, cases of bilateral obstruction, although rare, may lead to chronic renal failure. In some patients, preoperative urinary drainage (nephrostomy or ureteral stenting) may allow the recovery of unilateral renal function (Antonelli *et al.*, 2006). Kidney scintigraphy should be considered in patients with ureteral stenosis and hydronephrosis (Donnez *et al.*, 2002). If only a small portion of the kidney remains functional (less than 10–15% on scintigraphy), nephroureterectomy may be evaluated because the prospects of recovery of renal function following kidney preservation are poor. In fact, Donnez *et al.* (2002) showed that five patients with cortical atrophy at kidney scintigraphy had only slight improvement in parenchymal function after ureterolysis, even if the ureter was completely unobstructed after surgery. No guideline has established the indications for nephroureterectomy in case of ESRD caused by endometriosis. Hydronephrosis and hydronephrosis may be risk factors for renovascular hypertension (Jadoul *et al.*, 2007; Khong *et al.*, 2010). Furthermore, about one-third of patients with hydronephrosis and hydronephrosis suffer superimposed pyelonephritis (Horn *et al.*, 2004; Ponticelli *et al.*, 2010; Huang *et al.*, 2017). Nephrectomy should be performed when renal function is less than 15–10% and the patients suffer flank pain, kidney stones, renovascular hypertension and recurrent urinary tract infections or recurrent pyelonephritis (Langebrenke and Qvigstad, 2011; Nezhat *et al.*, 2012). In contrast, despite the loss of renal function, nephrectomy may not be performed in patients who have no symptom caused by the silent kidney (Langebrenke and Qvigstad, 2011). Notably, in these patients, creatinine levels are usually normal because of the contralateral fully functioning kidney (Nezhat *et al.*, 2012).

When nephrectomy is performed at the same time as laparoscopic removal of pelvic DIE, a transperitoneal approach for nephrectomy may be preferred to the retroperitoneal approach and the vagina can be opened, allowing removal of the both endometriotic nodule and the kidney (Jadoul *et al.*, 2007).

Ureteral stent placement

De Cicco *et al.* (2009) reported ureteral involvement and injury in 1.5% of patients affected by UE without hydronephrosis and in 21% of those with hydronephrosis during laparoscopic gynecologic procedures, concluding the usefulness of the preoperative ureteral stenting to facilitate ureteral identification, to guide ureterolysis and to prevent ureteral injury in these patients. In the largest series available, the use of ureteral double-J (pigtail) stent remains controversial for

ureterolysis, being reported in 4–33% of patients (Ghezzi *et al.*, 2006; Frenna *et al.*, 2007), while, in radical procedures it is a useful tool, reported in 82–100% of patients (Azioni *et al.*, 2010; Stepniewska *et al.*, 2011; Chudzinski *et al.*, 2017). Some authors consider the postoperative placement of an ureteral stent to prevent its obstruction caused by local edema and inflammation after surgery or in presence of a dilated ureter not picked up preoperatively (De Cicco *et al.*, 2011). The main indication for the placement of ureteral double-J stent before surgery is to recover from obstructive uropathy and to improve renal function.

Endoscopic excision

The endoscopic treatment of UE by retrograde ureteroscopy is fascinating because of the minimal invasiveness of the procedure, but it may be effective only in a small percentage of patients with intrinsic UE. In fact, as ureteral involvement is often due to endometriosis and fibrosis present in the deep ureteral wall layers and in the periureteral connective tissue, there is a high rate of obstruction recurrence. Few cases of polypoid endometriotic lesions obstructing the ureteral lumen treated by endoscopic excision have been described. Yamada *et al.* (1995) showed a successful treatment of two patients with ureteral stricture due to endometriosis by ureteroscopic ureterotomy with cold knife assisted by prior balloon dilatation. In a retrospective study, Castaneda *et al.* (2013) treated five patients with hydronephrosis at presentation or severely impaired renal function by ureteroscopic ablation with laser. Among these, three patients were successfully treated with a single ablative procedure, whereas two had persistent symptomatic obstruction, requiring a new endoscopic treatment. During follow-up, three patients developed ureteral strictures, requiring balloon dilation and serial stent exchanges. At a median follow-up of 35 months (16–84), the overall success rate of the procedure was 80% (4 out of 5 patients). In a retrospective study, Buttice *et al.* (2016) used endoureterotomy with laser in 10 women with intrinsic UE, reporting high rates of failure, resulting in the procedure being effective in only four patients (40%).

Impact on fertility

As UE is often associated with other DIE localizations (Seracchioli *et al.*, 2015), it is difficult to evaluate its independent effect on fertility. There is no strong rationale for hypothesizing a detrimental impact of UE *per se* on fertility, as also the effect of DIE on fertility has never been completely demonstrated and remains debatable (Somigliana and Garcia-Velasco, 2015). Moreover, the benefit of surgical treatment of UE on fertility is difficult to evaluate, as frequently concomitant surgical procedures are performed to treat other endometriotic implants. In a retrospective analysis, Uccella *et al.* (2016) evaluated fertility rates, course of pregnancy and perinatal outcomes of 36 women after laparoscopic ureterolysis for UE. In this study, 20 women (56% of patients who wished to conceive after surgery) became pregnant, but six (30%) of them underwent assisted reproductive technologies. The study demonstrated that the pregnancy rates (~56%) were lower than the healthy female population but almost in line with previous reports (42–44%) (Busacca *et al.*, 1999; Vercellini *et al.*, 2014a) after surgical treatment of DIE. Once gestation was established, only the risk of preterm birth (22.6% before 37

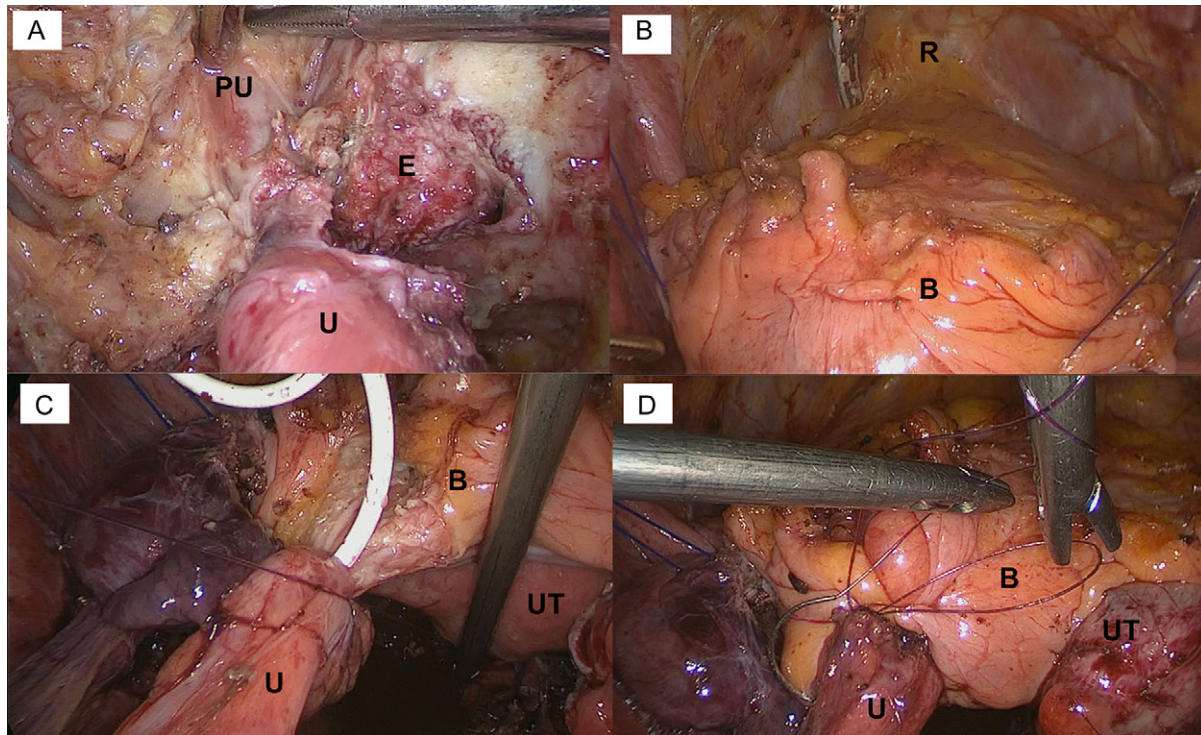


Figure 5 **A:** Laparoscopic surgical field showing an example of ureteral endometriosis arising from a deeply infiltrating endometriotic nodule of the left postero-lateral parametrium, with the detection of a complete stricture after ureterolysis and a caudad pre-vesical healthy ureteral portion. **B:** Laparoscopic dissection of the retropubic Retzius' space, with complete bladder mobilization. **C:** One step of laparoscopic ureteroneocystostomy. **D:** final overview of a ureteroneocystostomy according to the Lich-Gregoir technique. U = ureter, PU = pre-vesical ureter, E = endometriosis of the left postero-lateral parametrium, UA = umbilical artery, B = bladder, R = Retzius Space, UT = uterus.

weeks) or cesarean delivery (40.9%) appeared slightly higher than in the general population, whereas the rate of miscarriage (15.4%), other obstetrical complications and maternal/neonatal outcomes was similar to the rest of pregnant women (Uccella et al., 2016).

Complications of endometriosis during pregnancy mostly have to be attributed to the presence of adhesions that creates traction on surrounding structures when the uterus is enlarged during pregnancy and to decidualization that makes tissues and vessels more friable (Leone Roberti Maggiore et al., 2016). These changes have been involved in the pathogenesis of hemoperitoneum and bowel perforation in pregnant women with endometriosis (Glavind et al., 2018). Endometriotic nodules may also undergo hypertrophic changes under the influence of pregnancy-related endocrine changes (Chertin et al., 2007). Two cases of pregnancy complicated by uroperitoneum or hydronephrosis due to the presence of UE have been reported (Chiodo et al., 2008; Pezzuto et al., 2009).

Malignant transformation of UE

Malignant transformation of endometriosis has been described in the literature, and specific criteria define its development (Vigano et al., 2006). Only two case reports have described malignant tumors that may have arisen from UE. The first case reported that a woman, 5 years after supracervical hysterectomy and bilateral salpingo-

oophorectomy for endometriotic cyst and following 4 years of estrogen replacement therapy, presented a retroperitoneal tumor. At surgical inspection, the right ureter grossly appeared involved by a tumor. Pathologic examination revealed a adenosquamous endometrioid carcinoma (Jimenez et al., 2000). In the second case, a 54-year old patient, pluriparous, with previous history of endometriosis, after undergoing the same surgical treatment due to bilateral ovarian benign cysts and uterine fibroids, received hormonal treatment. After several years, the patient presented a fixed mass encasing the right ureter and expanding its upper part. After the mass was partially removed and a ureteric stent was placed, histologic findings demonstrated ureteral infiltration of well-differentiated endometrioid adenocarcinoma (Salerno et al., 2005). In both cases, it was not possible to exactly define the origin of the tumor, as both the ureter and retroperitoneal structures were involved. Thus, current evidence does not support the potential risk of a malignant transformation of UE.

Discussion

UE may be asymptomatic or associated with non-specific disease symptoms, which, if not correctly diagnosed, can lead to persistent hydronephrosis and ultimately renal failure. Women of reproductive age, especially those presenting a history of pelvic pain and infertility as well as other symptoms suggestive for UE, should be assessed as

first-line approach by TVS, as this exam is noninvasive, reproducible and cost-effective (Guerrero *et al.*, 2016). It has been demonstrated that TVS can examine the bilateral pelvic ureters in more than 90% of cases (Pateman *et al.*, 2015). However, only experienced examiners can evaluate the pelvic ureters by TVS; furthermore, TVS can only detect pelvic UE, and it fails to distinguish extrinsic and intrinsic ureteral involvement. To complete the first-line ultrasonographic evaluation of patients with clinical suspicion of UE, an abdominal ultrasound should be performed in order to estimate the presence and the degree of ureteral hydronephrosis and the kidneys thickness (Fig. 6). In any case, in clinical practice, taking into account the difficulty of performing an accurate ureteral evaluation by TVS, the finding of hydronephrosis at abdominal ultrasound should suggest a more accurate investigation of patients by second-line radiologic methods. Among these, MRI has a pivotal role for the second diagnostic level of patients with suspicious of UE and the previous detection of hydronephrosis at ultrasonography. In fact, it allows a precise identification of the different sites of the DIE, including rectovaginal nodules (Donnez *et al.*, 2002; Kondo *et al.*, 2013). Moreover, MRI should be employed in patients with suspicion of colorectal endometriosis, in which the eventual presence of rectovaginal nodules may increase the risk of subsequent ureteral involvement. Data from several radiologic studies (Table II) suggest that MRI is a sufficiently accurate method for the identification of UE, although an important limitation is that the majority of these studies have included only a small number of cases of UE (6–8 patients) (Balleyguier *et al.*, 2004; Chamie *et al.*, 2009; Vimercati *et al.*, 2012). Unfortunately, the surgical studies with a relatively larger number of cases of patients (Alves *et al.*, 2017; Ceccaroni *et al.*, 2018) did not report the accuracy of MRI for diagnosing of UE. It has been reported also that MRI is able to predict the distinction between intrinsic and extrinsic disease by evaluating the degree of ureteral circumferential involvement, even if tends to overestimate the frequency of intrinsic disease. Overall, an accurate presurgical staging of DIE, and in particular UE, by performing MRI ensures the best treatment planning and permits counseling of patients on the potential complications of surgery (Fig. 6). MSCT with colon distension with water or air and intravenous contrast (in particular with urographic phases) should be considered an alternative second-line exam for women with suspected bowel endometriosis, as it helps to detect the ureteral compression caused by endometriotic implants (Biscaldi *et al.*, 2011), but on the other hand is limited by both the discomfort caused by the rectal enema and the radiation dose delivered to each patient. IVP and retrograde pyelography have been considered the second-line traditional imaging methods used to evaluate women suspected of having UE. However, using these two exams, a filling defect associated with intrinsic UE can sometimes be difficult to distinguish from other urological conditions. Furthermore, when there is no ureteral obstruction, extrinsic involvement cannot be accurately diagnosed.

However, the definitive diagnosis of UE and the assessment of the type of ureteral involvement are based on surgery (preferably laparoscopy) and histopathologic evaluation (Ceccaroni *et al.*, 2018) (Fig. 6). A preoperative renal scintigraphy may be considered whenever hydronephrosis or the hydroureter is present in order to estimate the glomerular filtration rate and to help to predict the efficacy of surgical decompression of ureteral obstruction for ameliorating kidney function (Fig. 7).

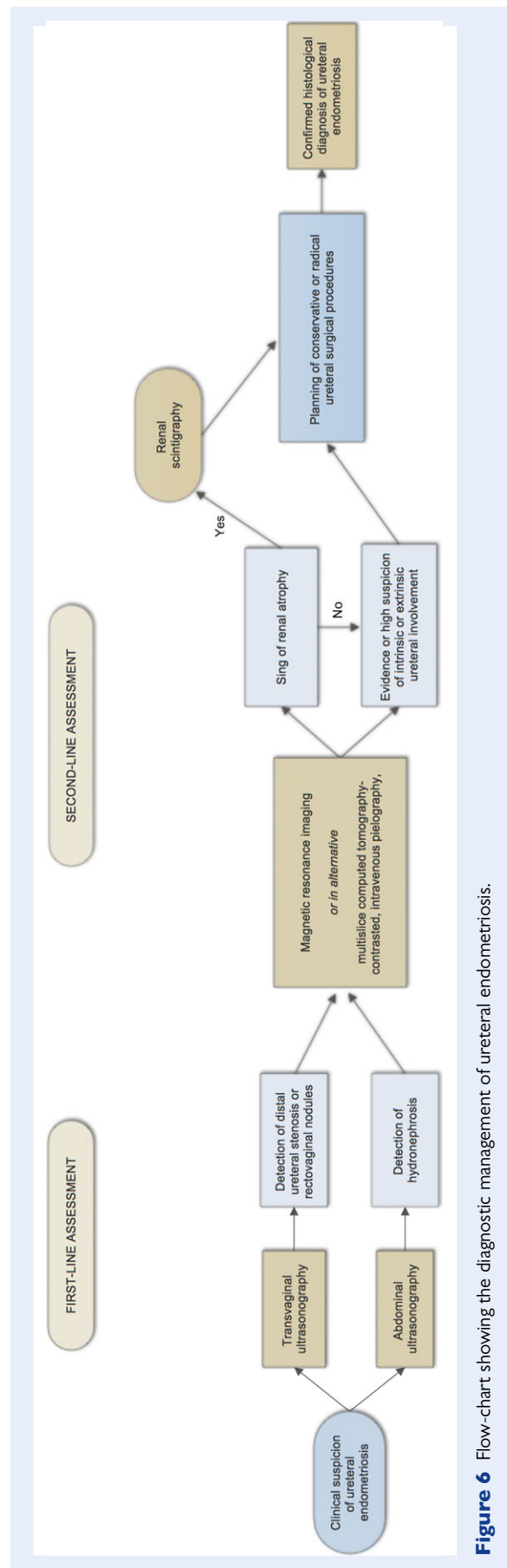


Figure 6 Flow-chart showing the diagnostic management of ureteral endometriosis.

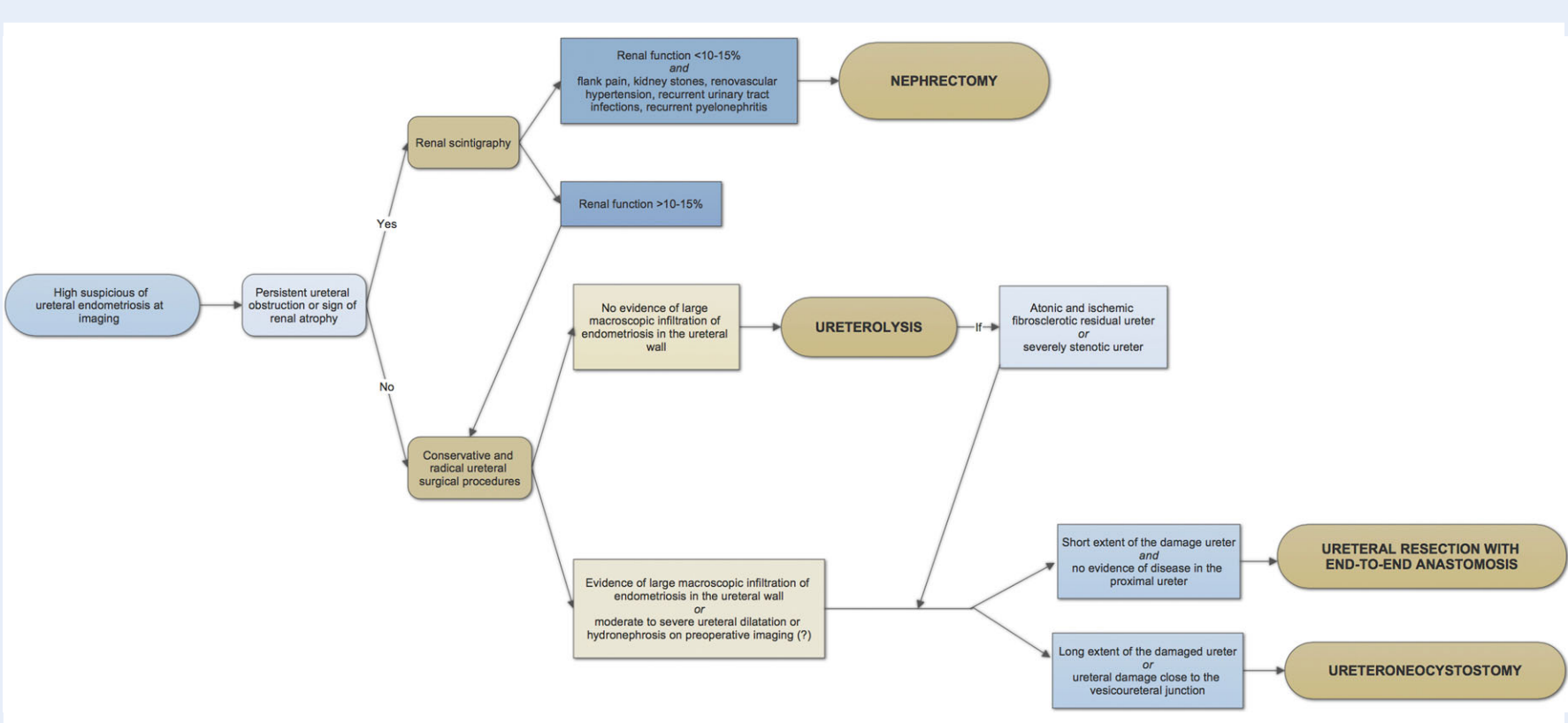


Figure 7 Flow-chart showing the surgical treatment of ureteral endometriosis.

Medical therapy is contraindicated in women with ureteral obstruction, although it can be administered postoperatively to decrease the risk of recurrence of pain symptoms.

To determine the appropriate surgical treatment for UE, the severity of symptoms, the presence of hydronephrosis, the kind of ureteral involvement and the extent and distribution of other endometriotic implants need to be considered. Due to its low prevalence, there have been no RCT comparing the outcomes between conservative and more extensive surgical treatment of UE. Therefore, it is difficult to provide evidence-based recommendations for the surgical treatment of UE. However, it is of pivotal importance that the surgical approach is carried out by gynecologists with experience in the treatment of severe endometriosis, in collaboration with urologists. During surgery, ureteral stenting can help to avoid ureteral injury and help the surgeon to perform the suture on the ureter. There is now good evidence that the surgical treatment of UE can be safely performed by laparoscopy (Alves *et al.*, 2017; Cavaco-Gomes *et al.*, 2017; Darwish *et al.*, 2017; Nezhat *et al.*, 2017; Ceccaroni *et al.*, 2018). Ureterolysis should be the routine procedure to remove UE when there is no evidence of large macroscopic infiltration of endometriosis in the ureteral muscularis, followed by intraoperative evaluation of the ureter to decide if further radical procedures (segmental resection and end-to-end anastomosis or ureteroneocystostomy) are needed. Ureterolysis should be carried out starting proximal to the diseased area, at a level of healthy tissue unaffected by endometriosis. During ureterolysis, the ureter should be carefully dissected until it appears to be healthy and not surrounded by endometriosis or until its insertion into the bladder to ensure that it is completely mobilized. After ureterolysis, the ureteral course, caliber and peristalsis and its residual vascularization must be carefully evaluated in order to decide if ureteral resection with end-to-end anastomosis or ureteroneocystostomy should be performed (Ceccaroni *et al.*, 2018). When the length of the damaged ureter is small and the distal ureter can be preserved, ureteral resection and end-to-end anastomosis can be performed over a ureteral stent. In contrast, when the ureteral damage is close to the vesicoureteral junction and/or it is extensive (>3–4 cm) ureteroneocystostomy should be performed (Carmignani *et al.*, 2009; Maccagnano *et al.*, 2013) (Fig. 7).

Pioneer studies suggested that ureterolysis is associated with a minimal risk of complications (<5%) and no recurrences (Nezhat *et al.*, 1996; Donnez and Brosens, 1997). More recent studies reported contradictory results when ureterolysis was performed in patients with moderate to severe ureteral dilatation or hydronephrosis on preoperative imaging. Among surgical studies enrolling only this group of patients, the recurrence rate after ureterolysis ranges from 9% to 15% (Ghezzi *et al.*, 2006; Mereu *et al.*, 2010). Moreover, the role of preoperatively diagnosed moderate to severe ureteral dilatation or hydronephrosis in choosing the surgical technique remains to be established. In the main surgical studies, it is difficult to accurately extract data regarding disease recurrence, since some of them report only the recurrence of symptoms (which may be due to different anatomic localizations of endometriosis) and others report the specific recurrence at a ureteral site (detected at imaging and confirmed at second surgery).

A considerable rate of postoperative complications have been reported after laparoscopic ureterocystostomy including reoperation for bladder suture leakage (2%), anastomosis leakage requiring to maintain the bladder catheter for another 7–10 days (8%),

transient deficit in bladder voiding (16–25%; median time to resume bladder function, 3 days, range 1–20 days), postoperative fever (5–20%), transient hematuria (1.2%) and vesico-ureteral reflux (16–30%) (Stepniowska *et al.*, 2011; Ceccaroni *et al.*, 2018). Thus, some authors suggest that ureterolysis should be limited to women having minimal ureteral involvement, with no urinary obstruction, and recommend radical resection as the preferred method of treatment in case of obstructive ureteral disease to reduce the risk of recurrence (Chapron *et al.*, 2010). On the contrary, other authors suggest reserving radical surgery only for selected cases and believe that conservative surgery is the treatment of choice in relieving ureteral obstruction and removing UE, even in patients with moderate or severe renal pelvis dilatation (Donnez *et al.*, 2002; Seracchioli *et al.*, 2010; Darwish *et al.*, 2017). In general, the recurrence rate is determined not only by the choice of the surgical procedures, but also by the removal of any other endometriotic implants, especially DIE lesions, such as rectovaginal nodules, often associated with UE (Vercellini *et al.*, 2004; Ceccaroni *et al.*, 2018). No guideline has established the indications for nephroureterectomy in case of ESRD caused by endometriosis because this is a rare condition. However, there is consensus that nephrectomy should be performed when renal function is less than 10–15% and the patients suffer flank pain, kidney stones, renovascular hypertension and recurrent urinary tract infections or recurrent pyelonephritis (Langebrekke and Qvigstad, 2011; Nezhat *et al.*, 2012).

Data regarding the reproductive and obstetrical outcomes of women with implants around or infiltrating the ureter are inconclusive, as often these women have concomitant other localization of DIE and undergo extensive surgical procedure. However, fertility and pregnancy outcomes after ureterolysis are in line with those after surgical treatment of DIE.

Current evidence does not support the potential risk of a malignant transformation of UE.

Conclusion

Overall, patients with a suspicion of DIE and those under long-term hormonal treatment for DIE should be investigated to timely detect ureteral dilatation and/or hydronephrosis, thus preventing the loss of renal function. In general, hormonal therapies are contraindicated when ureteral obstruction is diagnosed because of the potential progression of the UE. The surgical management of UE should be tailor-made, from ureterolysis to ureteroneocystostomy or ureteral resection with end-to-end anastomosis, depending on the extent of the ureteral infiltration, the location of the lesion and on the conditions of the ureter after ureterolysis. In any case, a standardized presurgical radiological classification of UE, as that proposed by Knabben *et al.* (2015), is required to define the type of ureteral involvement or, in general, to predict which patients will probably need a conservative or radical surgical management. The absence of homogenous criteria in the surgical studies for selecting patients for radical procedures (sometimes based on the preoperative evidence of moderate to severe hydronephrosis and others on the radiological or surgical evidence of ureteral infiltration) does not allow a systematic comparative evaluation on the different surgical options for UE. In more detail, dealing with the subgroup of women with moderate ureteral

hydronephrosis on preoperative imaging, where the current surgical results are still controversial, it could be advisable to perform well-powered RCTs in order to investigate more accurately the optimal management and outcomes. In conclusion, a close follow-up with regularly scheduled clinical evaluation and imaging should be suggested in order to compare the risks of persistent and recurrent disease between the surgical procedures.

Supplementary data

Supplementary data are available at *Human Reproduction Update online*.

Authors' roles

S.F. conceived and designed the study, performed the interpretation of data, and drafted and revised the manuscript. F.B. developed the search strategy for the identification of articles, acquired and analyzed the data, and drafted the manuscript. C.S. acquired and analyzed the data. V.G.V and E.B. analyzed the data and revised the manuscript. M.C. and C.T. revised the manuscript. All authors approved the final version of the manuscript.

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