Ureteral Endometriosis: Proposal for a Diagnostic and Therapeutic Algorithm with a Review of the Literature

Introduction

The involvement of the urinary tract in deep infiltrating endometriosis (DIE) is defined by the implantation of the stroma and/or endometrial glandular epithelium outside the endometrial cavity and the uterine musculature, penetrating into the retroperitoneal space or the wall of the pelvic organs to a depth of at least 5 mm at different urinary sites [1].

The incidence of urinary tract endometriosis (UTE) has increased during the last few years and, nowadays, it ranges from 0.3 to 12% of all women affected by endometriosis (fig. 1) [2–10].

The ureter is the second most common site affected by UTE, showing an increasing incidence in the contemporary literature because of the improvement in diagnostic tools as well as a greater awareness and skill among clinicians to recognize the disease.

Most of the time, this condition is asymptomatic and is diagnosed incidentally at a gynecologic follow-up. However, the late diagnosis and treatment of this condition might lead to the silent loss of renal function. Nowadays, the modalities of diagnosis and treatment are a matter of debate with increasing evidence of the necessity for a close collaboration between the gynecologist and the urologist.

The objective of this study is to define the state of art of the diagnosis and treatment of ureteral endometriosis (UE) and, consequently, to establish a diagnostic and therapeutic algorithm, based on a peer review of the literature.
Materials and Methods

We performed a literature review by searching the MEDLINE database for articles published between 1996 and 2010. The searches were limited to articles written in the English language; key words were: urinary tract endometriosis, ureteral endometriosis, diagnosis and treatment.

Results

Epidemiology

Cullen [4] first reported a case of UE in 1917. Since then, more than 200 cases have been described in the literature, despite the fact that subclinical disease is probably underestimated due to being easily missed even upon surgical inspection, which means the prevalence is actually higher than assumed [11]. Nevertheless, in the contemporary literature, UE has been reported more frequently, reflecting the greater awareness and skill of clinicians to recognize the disease as well as the significant improvement in diagnostic tools.

Nowadays, UE occurs in 0.1–1% of endometriotic cases, with a peak incidence in patients of 30–35 years of age (fig. 1) [8, 9, 12–18]. UE has been described rarely in postmenopausal women, but reported frequently in those with a history of prolonged estrogen therapy or a massive reduction of estrogen via the functioning of the adrenal or pituitary glands [9, 19–22].

Pathogenesis

The disease most commonly affects the distal segment of the ureter, i.e. the pelvic ureter at 3–4 cm above the vesico-ureteric junction, less commonly the mid-ureter and, rarely, the proximal ureter [14–16, 23]. Bilateral involvement is present in approximately 10–20% of cases, whereas it is usually unilateral, with a left predisposition in most of the patients [24–28].

Interestingly, the proportion of left-sided gonadal and ureteral lesions is remarkably similar (63 and 64%, respectively) with ovarian endometriosis being a prerequisite for ureteral involvement [26]. As a matter of fact, the ureter is in anatomic contiguity with the lateral gonadal aspect, which has been indicated as the site of origin of the classic chocolate cyst [29]. Consequently, if UE develops from ovarian implants or if both lesions have a common pathogenesis, asymmetry should be found also in the left- and right-handed distribution of ureteral foci.

The lateral asymmetry in the occurrence of UE is compatible with the menstrual reflux theory and with the anatomical differences of the left and right hemipelvis [26, 29, 30]. The presence of the sigmoid colon creates a hidden microenvironment around the left fallopian tube and ovary. Thus, the endometrial cells regurgitated through the left tube are less exposed to the peritoneal fluid current and may be partly protected from the macrophage disposal system.

The large bowel does not provide the right hemipelvis with this sort of anatomical shelter since the cecum is more cranial [26, 29]. However, this hypothesis fails to explain the cases of proven UE in women who have no evidence of any other focus of peritoneal disease in the pelvis. The second theory on the origin of ureteral involvement is the embryonal one. Support for this hypothesis stems from the pathological findings of hyperplasia of smooth-muscle cells surrounding the affected ureter, with sparse endometriotic glands and scant stroma in surgical specimens of women who had undergone segmental ureteral resection [31]. The histological appearance of ureteral implants resembling that of adenomyosis has led some investigators to introduce the concept of adenomyotic disease of the retroperitoneal space, postulating a primary development of endometriosis in the retroperitoneum from the embryonic remains of the Müllerian duct [31]. The lateral spread of retroperitoneal lesions up to and around the ureter would explain endometriosis localization by proliferation of the smooth muscle surrounding the ureteral wall [30].

There are two major pathological types of UE: intrinsic and extrinsic, occurring with a 1:4 ratio, respectively [14, 15, 26, 32]. The distinction of the extrinsic or intrinsic nature of ureteral involvement may be considered as arbitrary. The depth of invasion in the extrinsic form has to be confirmed by the final histological examination; thus, differentiation cannot be made reliably, either preoperatively or at surgery.
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Table 1. Differential diagnosis in ureteral endometriosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>1. Primary cancer</td>
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<tr>
<td>2. Metastatic cancer</td>
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<tr>
<td>3. Retroperitoneal lymphadenopathy</td>
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<tr>
<td>4. Idiopathic retroperitoneal fibrosis</td>
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Table 2. The most common symptoms of ureteral endometriosis

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>Severe/incapacitating dysmenorrhea</td>
<td>75%</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>70%</td>
</tr>
<tr>
<td>Pelvic pain</td>
<td>60%</td>
</tr>
<tr>
<td>Pelvic mass</td>
<td>14%</td>
</tr>
<tr>
<td>Cyclic gross hematuria</td>
<td>16%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>24%</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>20%</td>
</tr>
<tr>
<td>Nonspecific flank pain associated with hematuria</td>
<td>23%</td>
</tr>
<tr>
<td>Renal colic</td>
<td>23%</td>
</tr>
<tr>
<td>Intermittent dysuria</td>
<td>13%</td>
</tr>
<tr>
<td>Unexplained hypertension</td>
<td>10%</td>
</tr>
<tr>
<td>Anuria and renal failure</td>
<td>10%</td>
</tr>
</tbody>
</table>

In extrinsic disease, the endometrial tissue invades only the ureteral adventitia or surrounding connective tissue and, consequently, it causes ureteral obstruction [9, 12, 13, 33]. This is the most common form of UE and represents 80% of cases [9, 32].

In intrinsic disease (which occurs in only 20% of cases), ectopic endometrial tissue directly infiltrates the muscularis ureteral wall within the muscularis propria, lamina propria or ureteral lumen; it likely arises from lymphatic or venous metastases. The two pathological types may coexist [12, 13, 34, 35].

Malignancy arising in UE has been reported in only a few studies. Nezhat et al. [36] described the first case of pelvic adenocarcinoma arising from UE in a woman who underwent hysterectomy and bilateral salpingo-oophorectomy, without any evidence of endometriosis (table 1).

Symptoms

UE usually presents with nonspecific symptoms owing to a secondary obstruction, i.e. flank or abdominal pain (rarely associated with hematuria), renal colic and unexplained hypertension (table 2) [12, 13, 37–42].

There is only a limited correlation between the severity of symptoms and the level of obstruction, as a severe obstruction may be asymptomatic for long time, therefore posing differential diagnostic problems and leaving a patient at risk of the subsequent loss of renal function (25–43% of cases) [2, 7, 9, 12, 13, 37, 38, 43–45].

Nevertheless, approximately 50% of the women with UE have some symptoms, i.e. dyspareunia, severe or incapacitating dysmenorrhea, pelvic pain and menorrhagia [9, 12, 31, 38].

Among these symptoms, the gravity of dysmenorrhea might directly correlate with the extension of the DIE, which often involves the recto-vaginal septum, the uterosacral ligaments, the broad ligament and the ovaries.

Several authors have observed a positive correlation between having UE and the incapacitating dysmenorrhea and associated lesions of the retrocervical region or the rectum-sigmoid [4, 31].

Conversely, the main location of the DIE is related to the possibility of presenting UE. As a matter of fact, patients with retrocervical endometriosis were found to have a 7-fold greater chance of having UE and for patients with endometriosis of the rectum-sigmoid, this chance was 22-fold greater [23].

Diagnosis

The diagnosis has to be considered as a step-by-step procedure:

(1) Physical examination: This is unhelpful for the diagnosis. However, a strong association has been reported between large endometriotic nodules involving the recto-vaginal septum and UE [31, 46].

(2) Serum exams: All patients should be assessed for anemia and for renal function by blood creatinine measurements.

(3) Urine exams: The urine should be evaluated for evidence of microscopic or macroscopic hematuria and cultured to rule out an infectious etiology. Moreover, urine cytology is warranted, in order to rule out malignancy.

(4) Imaging methods: When considering the absence of specific urological symptoms and the risk of silent renal loss, checking the integrity of the urinary tract of patients with endometriosis, not only before and after surgery but also during medical therapy, is recommended.

However, imaging techniques are of limited value in providing an accurate depiction of the extent of the disease and the infiltration of the ureteral wall.

Abdominal ultrasound is routinely used as a screening tool to rule out urinary tract obstruction in patients with pelvic endometriosis, because of the high rate of silent presentations [25]. The exam is simple and non-invasive, the evaluation requires no intravenous contrast and the
Intravenous pyelography has been the traditional functional imaging modality used to evaluate women suspected of having UTE. Radiological findings, including hydronephrosis, narrowing of the pelvic ureter and, rarely, an intraluminal ureteral mass, are judged to be nonspecific for the condition. However, intravenous pyelography shows some importance in demonstrating the precise location, extent and degree of ureteral stenosis as well as to confirm renal function. Differential diagnosis includes a number of urological causes of intrinsic or extrinsic ureteral stricture (table 1). The history is valuable in differentiating endometriosis from strictures due to previous surgery or to trauma, such as stone extraction. Transitional cell carcinoma can be radiologically indistinguishable from UE, but such tumors are rare in the premenopausal woman and, unlike endometriosis, typically have an irregular mucosal pattern and are associated with dilatation of the ureter below the lesion. Despite inner limitations, intravenous pyelography, coupled with retrograde pyelography, still remains the most common and valuable test used to assess intrinsic UE.

Although computed tomography is able to identify endometriomas, its poor specificity and high radiation dose have limited its use in the evaluation of endometriosis, especially in fertile women [9]. Instead, magnetic resonance imaging (MRI) may reveal direct signs such as a nodule or a mass invading the ureter along its course or at the ureterovesical junction [6, 34]. Nevertheless, the ureter is a hollow organ only 4–5 mm in diameter and sometimes it is difficult to analyze it with MRI as its spatial resolution reaches its limit. Envelopment of the ureter may arise from an isolated laceral pelvic endometriosis or be associated with a posterior location in the recto-vaginal septum that secondarily invades the ureter. An indirect sign of ureteral involvement is the possible presence of ureteropelvic hydronephrosis above the suspected lesion [47, 48]. MRI sequences known as MR urography are heavily T2-weighted sequences taken in the coronal plane in a wide field and may be useful in detecting hydronephrosis and evaluating other pathology in the abdomen and pelvis (figs. 2, 3) [49]. Nowadays, MRI represents the ideal ‘all-in-one’ examination in patients with suspected UTE because it allows the visualization of all components of the urinary system and the possibility of exploring all pelvic locations of endometriosis. The final aim is to address the surgical approach based on the diagnosis of the extrinsic or the intrinsic form of UE [49].

Ureteroscopy has been used to diagnose intrinsic UE [15, 49]. This exam allows for both direct observations of the bladder and/or ureteral lesions and providing biopsy specimens for histology. The macroscopic appearance of the lesions changes with the different phases of the menstrual cycle, with the best characterization obtained before and during menstruation. The endometriotic lesions often appear as edematous and irregular, with different shapes and colors: blue-red, blue-black or blue-brown lesions are the more common findings. Moreover, they might be isolated or multifocal. It is fundamental to ascertain the distance between the lesion and the ureteral orifices, accordingly to the lower endometriotic margin. In addition, if the ectopic tissue does not extend beyond the ureteral adventitial layer, endoscopy might be useless. Thus, negative endoscopic findings do not necessarily imply the absence of urinary endometriosis.

Ureteroscopy biopsy remains a useful minimally invasive option for some patients with localized UE, in order to establish the diagnosis followed by endoscopic ablation [41].

Treatment

The choice of the treatment to be carried out in the case of UE is controversial. The main aims are: (1) the relief of urinary obstruction; (2) the preservation of renal function; (3) the prevention of disease relapse.

Hormonal Therapy

Variable results have been reported with hormonal therapy (HT) alone. Hormone manipulation may shrink the tissues affected by endometriosis, but obstruction secondary to fibrous tissue and adhesions usually does not resolve. HT has to be considered as an option for patients of childbearing age who desire pregnancy, with close follow-up with ultrasound at 6-month intervals to rule out an obstruction [9]. Nevertheless, HT may be a suitable option in patients without significant fibrosis, in combination with surgery [15, 41].

The most common therapies used in the treatment of endometriosis include: gonadotropin-releasing hormone agonists and antagonist, progestins and combined oral contraceptives.

Local progestogens such as an intrauterine device with levonorgestrel may be useful as a conservative medical approach. Although this treatment is normally used in gynecology as a contraceptive or for idiopathic menorr-
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rhagia, it is effective in endometriosis foci in the pelvis and vesicovaginal septum possibly because it provides high concentrations of the drug to the endometrium and adjacent areas despite low plasma concentrations. This offers two important advantages: it is effective for 5 years and it does not affect future fertility after the treatment is discontinued.

Even if all these drugs may alleviate the severity of pelvic pain, dysmenorrhea and dyspareunia, the symptoms often recur when therapy is discontinued [5]. Moreover, they are frequently associated with suboptimal safety and tolerability and they do not improve fertility.

Finally, the relapse rate in DIE is quite high (about 56%), revealing that such treatment only induces a temporary disappearance of the lesions in such patients. All these features strictly impact on long-term use and compliance.

The ideal patients for HT, in particular growth hormone-releasing hormone analogs, are postmenopausal women. Westney et al. [50] reported a partial or complete resolution of symptoms in 12 of their 14 patients at a mean follow-up of 18.6 months. Close follow-up is recommended.

As a matter of fact, medical management appears to have a high recurrence rate after treatment cessation, and is often considered a palliative modality for the treatment of DIE. In addition, some authors have noted that patient response to hormonal manipulation might be poor, due to the desmoplastic reaction within the detrusor, muscle layers and the serosa of the ureters from repetitive bleeding and resorption of menstrual debris.

**Surgical Therapy**

The main indications for surgical treatment of UE are the presence of symptoms and/or the hydroureteronephrosis [7, 51].

Historically, open surgery has been the preferred treatment in cases of extensive disease [5]. The success of surgery has been correlated with the how extreme the exeresis is and because of a high risk of recurrence, estimated at 30%. As a matter of fact, it may well correspond to the actual persistence of DIE lesions that were left in place as the result of an incomplete initial surgical removal [52–54].

Nowadays, laparoscopic interventions such as ureterolysis, ureterostomy and ureteral reimplantation for ureteral stricture disease secondary to endometriosis can be performed by embracing the same principles of traditional urologic surgery, with a magnified view, superior exposure and a greater ability to identify the disease in the pelvis and retroperitoneal space as well as in the lower urinary tract [9, 55–59].

Finally, a current controversy in the treatment of UE is whether segmental resection and anastomosis, ureterolysis or ureterocystoneostomy are indicated as well as whether procedures involving minimal access are as effective as the traditional open techniques [56–57]. Generally, the choice of surgical treatment may change according to the diagnosis of intrinsic or extrinsic UE.

Fig. 2. MR urography for UE. This is a peculiar reconstruction, represented by heavily T2-weighted sequences. It may be useful in detecting hydroureteronephrosis and evaluating other pathologies in the abdomen and pelvis.

Fig. 3. MR diagnosing UE (fat-suppressed T1-weighted after intravenous injection of gadolinium contrast media). The imaging protocol included: (1) T2-weighted sequences in different slice orientations. (2) T1-weighted sequences in an identical imaging plane that best demonstrates the endometriotic localization. (3) Native T1-weighted without fat suppression and fat-suppressed T1-weighted before and after intravenous injection of gadolinium contrast media.
Table 3. Pros and cons regarding preoperative JJ positioning before ureterolysis

<table>
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<tr>
<th>Pros</th>
<th>Cons</th>
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<tbody>
<tr>
<td>Guide of ureterolysis (especially in women with posterior nodules and in the case of partial cystectomy when ureteral meatus are adjacent to the lesion)</td>
<td>Increasing rigidity of the ureter</td>
</tr>
<tr>
<td>Rapid identification of the ureter</td>
<td>Making ureterolysis more difficult</td>
</tr>
<tr>
<td>Prevention of ureteral lesions</td>
<td>Adding costs and time</td>
</tr>
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</table>

Table 4. Indications and time for JJ positioning related to ureterolysis

<table>
<thead>
<tr>
<th>Preoperative positioning</th>
<th>Intraoperative positioning</th>
<th>Postoperative positioning</th>
</tr>
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<tbody>
<tr>
<td>Ureteral lesion during previous surgery</td>
<td>Intraoperative assessment of hydroureteronephrosis</td>
<td>Iatrogenic lesion</td>
</tr>
<tr>
<td>Hydroureteronephrosis</td>
<td>Iatrogenic lesion during surgery</td>
<td></td>
</tr>
<tr>
<td>Laparoscopic approach</td>
<td>Endometriotic lesion located near the trigone</td>
<td></td>
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</table>

Fig. 4. Algorithm of UE surgical treatment.
Preoperative planning has to be rigorous and complete surgical excision of UE should be ensured by a team of experts who are familiar with endometriosis [35].

Moreover, the endometriosis itself increases the risk of ureteral trauma, which mostly occurs during surgery, with a percentage of about 0.2–2% [9, 60, 61]. As more complex procedures are being performed by laparoscopy more often, the potential for operative injury to the ureter will inevitably increase. About 70% of ureteral injuries are diagnosed postoperatively and, in more than two thirds of cases, a laparotomy is the preferred route for repair [60–65].

This underlines the necessity of having the appropriate tools in order to preoperatively prevent and/or identify any potential lesion.

Extrinsic UE

Elective ureterolysis should be indicated only when there is an extrinsic lesion <3 cm and/or nonobstructive ureteral involvement [6, 12, 56].

The preoperative or intraoperative use of the JJ stent, with both the laparotomic and laparoscopic approach, is still controversial [62, 66, 67]. The JJ stent might also be positioned after ureterolysis. Ureterolysis is contraindicated in the case of intrinsic endometriosis due to both the high percentage of recurrence and ureteral stenosis.

Intrinsic UE

Indications for ureteral resection include an intrinsic ureteral lesion and/or lesions longer than 3 cm and the lesion being situated below the level of the iliac vessels [9, 67]. Traditionally, this type of surgery is performed by laparotomy, which associates with a degree of postoperative morbidity. The ureteral resection requires three techniques of ureteral reconstruction, namely:

- ureteral termino-terminal anastomosis;
- ureteral reimplant with an antireflux technique (i.e. Lich-Gregoire or Leadbetter-Politano);
- the psoas hitch technique [25, 35, 68, 69, 70].

A JJ stent may be a useful device as a permanent landmark for the surgeon during his resection/dissection, simplifying all the stages of reanastomosis or reimplantation (tables 3, 4; fig. 4).

Despite all the ureteral surgical techniques, the percentage of deteriorated renal function still remains significant (40%). In these cases, nephrectomy can become necessary, also because sometimes the lesion mimics a urothelial carcinoma [9, 69, 71].

It is also advisable to perform an immunohistochemical examination with estrogen receptor, progesterone receptor, cytokeratin-7, CA125 or CD10, due to the high percentage of evolution in endometrioid carcinoma [72].

Conclusions

The ureteral involvement in deep pelvic endometriosis is usually asymptomatic and might lead to the silent loss of renal function. UE is usually diagnosed incidentally during gynecological follow-up for deep pelvic endometriosis, and the treatment is usually surgical, with the technique chosen according to the type of UE, the site lesion and the distance to the ureteral orifice. The use of the JJ stent remains a matter of debate. A close collaboration between the gynecologist and urologist is advisable, especially in specialist centers. The surgical urological treatment can have good results in terms of both patient compliance and prognosis.

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