Urinary Tract Endometriosis

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Recently, occurrence of urinary tract endometriosis (UTE) is more frequently diagnosed. According to literature, it refers to approximately 0.3 to even 12% of all women with endometriosis. The pathogenesis of UTE has not been clearly explained so far. The actually proposed hypotheses include embryonic, migration, transplantation, and iatrogenic theory. Most frequently UTE affects bladder, less often ureters and kidneys. One-third of patients remains asymptomatic or exhibits only minor manifestations. In symptomatic patients main complaints include dysuria, urinary urgency, and/or frequency, painful micturition, and burning sensation in the urethra and discomfort in the retropubic area. Treatment of UTE is challenging and can be pharmacological, surgical or can be a combination of both methods. In this paper we present a review of the literature concerning the UTE, its diagnosis and treatment.

Keywords: endometriosis; complications; diagnosis; urinary bladder; ureter.

INTRODUCTION

Indometriosis, the presence of endometrial tissue outside the uterine cavity, affects 5-15% of premenopausal females. (1) It is usually classified, according to the depth of invasion and anatomic location. One of the divisions differs 3 categories: peritoneal, ovarian, and deep infiltrating endometriosis. (2) Deep infiltrating endometriosis (DIE) is defined as the implantation of endometrial glandular epithelium, and/or stroma and smooth muscle, penetrating walls of any pelvic organs or/and the retroperitoneal space to a depth of at least 5 mm. (1) Recent studies have reported that foci of endometriosis may be supplied by nerves, lymphatic vessels, and blood vessels.^(3,4) In recent years occurrence of urinary tract endometriosis (UTE) has been more frequently diagnosed. (5) According to literature, UTE refers to approximately 0.3 to 12% of all women with endometriosis. (6-9) Most frequently UTE affects bladder (80% of cases), less often ureters (14%) and kidneys (4%). (10) It is shown that in patients with DIE, involvement of the urinary tract can reach more than 52% of patients. (11) UTE generally affects women of childbearing age. Due to the regression of estrogen-dependent endometrial tissue, postmenopausal endometriosis is extremely rare. Endometriosis during premenarchal period is occasional and only several cases have been documented in literature. (12,13) UTE may be primary or secondary. The primary appears spontaneously in urinary tract and pertains to about 11% of women with DIE. The secondary occurs after pelvis surgeries such as caesarean section or hysterectomy. (14-16) Approximately 50% of patients with endometriosis of the bladder or ureter underwent pelvis surgeries in the past. UTE is often multifocal, and usually develops from the outer layer of bladder or ureter, penetrating deeper toward the mucosa. Bladder trigone and bladder apex are the most often affected locations.

The pathogenesis of UTE has not been clearly explained so far. The actually proposed hypotheses include embryonic, migration, transplantation, and iatrogenic theory. The first one is associated with the presence of remnants of the Mullerian ducts, located mainly in the vesicouterine and vesicovaginal septum. (8,15)

The migration theory, called also the reflux theory, claims the existence of menstrual blood regurgitation through the Fallopian tubes into the pelvis and implantation of endometrial cells in the urinary system. This phenomenon is facilitated by the position of vesicouterine pouch. (17,18) At present, the most accepted is the theory of transplantation, according to which, endometrium cells are displaced through the lymphatic and circulatory system and implanted in the urinary system. (17,18) Intraoperative iatrogenic spread of endometrial cells during operations is the basis of the last, the iatrogenic theory. (6,15) Recently the case of scar related abdominal endometriosis in patient after bladder exstrophy reconstruction was reported. (19)

URINARY BLADDER ENDOMETRIOSIS

Endometrial lesions affect mainly detrusor muscle in bladder trigone and bladder apex. Symptoms depend on the location and size of changes. (15,20,21) One-third of patients remains asymptomatic or exhibits only minor complaints. Diagnosis is made incidentally during periodic inspections or during the investigation into causes of infertility. In these asymptomatic cases, endometrial changes in bladder usually do not exceed 1-2 cm. In symptomatic patients main complaints include dysuria, urinary urgency, and/or frequency, painful micturition, and burning sensation in the urethra and discomfort in the retropubic area. These symptoms are recurrent in 40% of patients, usually occur in pre-menstruation period, and are often confused with symptoms of urinary tract infections. Hematuria, which is widely regarded as the dominant symptom of UTE, in fact concerns only 20-30% of patients. It is due to the fact, that endometriosis rarely infiltrates deep enough to cause ulceration of the urothelial mucosa. (22,23) Differential diagnosis

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includes chronic inflammation of bladder and overactive bladder. It is also vital to involve urinary bladder malignancies in differential diagnosis. Bladder cancer can mimic endometriosis symptoms and may lead to therapeutic errors.⁽²⁴⁾

Bimanual examination may reveal large foci of DIE. Transabdominal, transvaginal, and transrectal ultrasonography (USG) might be useful in detecting smaller lesions and additionally hydroureteronephrosis can be shown. The specificity of well-performed USG is high and reaches almost 100%. Unfortunately, detection of lesions smaller than 3 cm is often difficult, especially if the patient has undergone surgical procedures and sensitivity does not exceed 50%. Cystoscopy is a mandatory test in suspected UTE, although the cystoscopy may not be able to reveal shallow penetrating endometriosis. Magnetic resonance imaging (MRI) is considered to be the "gold standard" in UTE diagnosis. According to the latest reports, if examination is performed on 3-Tesla MRI system, the sensitivity reaches 88% and specificity is higher than 98%. (25-28) Urine examination performed to disclose possible hematuria is also recommended. Recent study comparing three-dimensional color Doppler USG with magnetic resonance imaging and cystoscopy in the diagnosis of bladder endometriosis showed that USG seems to be superior to cystoscopy and is at least as effective as MRI in diagnosing and planning the surgery for bladder endometriosis.(29)

Morphology of endometrial changes can vary depending on phase of menstrual cycle. The most characteristic changes, observed just before and during menstruation, have irregular, nodal shape of different color (bluish-red, bluish-black or/and bluish-brown). During cystoscopy it is necessary to determinate distance between endometrial lesions and ureters openings. Pathological changes situated closer than 2 cm from ureters openings may require replantation of ureter. It is also obligatory to perform biopsy, normally by transurethral resection of the bladder (TURB), to exclude presence of bladder carcinoma, mesenchymal bladder tumor or/and uterine fibroids.

Treatment of Bladder Endometriosis

There are no substantial guidelines for the treatment of UTE due to the rarity of the disease, and the inability to conduct randomized trials. Isolated reports of case series treatment are not entirely reliable, because of the different therapeutic success criteria adopted by the authors. Treatment of UTE depends on many factors, such as age of patients, extent of the disease, the severity of urinary tract symptoms and presence of other foci of endometriosis in the abdomen. In some cases fertility preferences should be taken into consideration.

Treatment of bladder UTE can be pharmacological, surgical or can be a combination of both methods. Pharmacological therapy of bladder UTE is in fact designed to achieve regression of endometrial tissue. The ideal candidate for this procedure is menopausal female with single, small (less than 5 mm) endometrial focus in the bladder. The most commonly used drugs include gonadotropin releasing hormone (GnRH) analogues, gestagens, and combined oral contraceptive therapy. Unfortunately almost 50% of patients with DIE do not respond to this therapy. Additionally, side effects are frequent during pharmacological treatment. They include hot flashes, sleep disturbance and vaginal dry-

ness when GnRH analogues are used, and breakthrough bleeding, weight gain, fluid retention, skin changes, hot flashes and loss of libido in case of gestagens therapy. Relapses of symptoms are common when pharmacological therapy is discontinued.

Ability of endometric cells to migrate, metastasize, invade, and induce angiogenesis makes them similar to malignant cells. Therefore, various anticancer drugs are being tested in the UTE treatment. So far, only a combination of aromatase inhibitors with gestagens or GnRH analogues has proven its effectiveness, but because of the high complication rates and the large costs, it is not used in clinical practice. (30)

Surgery is the only treatment that gives a chance for a complete cure. There are many possibilities for surgical management of bladder endometriosis, ranging from endoscopic procedures such as TURB and laparoscopic partial resection of the bladder to the total cystectomy. Transurethral resection is contraindicated in DIE, since lesions infiltrate bladder from the outside toward mucosa and cannot be removed through the urethra. It is therefore essential to perform appropriate imaging and endoscopic visualization procedures. Moreover, accurate evaluation of the size and location of endometric lesions in the bladder, including their relation to ureteral openings and the assessment of the upper urinary tract is very important. The most crucial task is to exclude neoplastic lesions. The therapeutic success can be achieved only by radical elimination of endometric tissue. Incomplete removal of lesions is associated with relapses. (15,31,32) Partial resection of the bladder, which is an excision of endometriotic lesions together with the entire thickness of the bladder wall and surrounding margin of normal tissue, is a procedure that allows maintaining the proper function of the bladder. There are several reports of high efficiency of both laparoscopic and classic partial cystectomy in alleviation of symptoms, improving the quality of life and recurrence-free survival. (6,7,15,20,31) The authors emphasize the desirability of double J ureteral catheter implantation preoperatively or intraoperatively if endometrial lesions are situated closer than 2 cm from the opening of the ureter. Reconstruction of bladder in patients with multiple DIE foci in pelvis is very difficult and often requires multidisciplinary team compound of a gynecologist, an urologist, and not infrequently a surgeon of gastro-intestinal tract. Nezhat and colleagues presented experience with robot-assisted laparoscopy in treatment of one patient with bladder endometriosis and two patients with urethral endometriosis. Authors prove that this therapy can be feasible and safe option in patients with UTE.(33)

One of the major risk factors for treatment failure is the age of the patient. The younger is the patient, the greater is the risk of recurrence. Endoscopic procedures (e.g. TURB) associated with hormonal therapy are a satisfactory option in young patients willing to preserve fertility. However, failure indicator reaches 25-35%. (1.6.10) Older patients approaching menopause may also benefit from this minimally invasive treatment option, as endometriosis is often spontaneously regressing after menopause. (12)

URETERAL ENDOMETRIOSIS

Endometriosis of the ureter is second most common manifestation of UTE. Disease most often affects distal

part of left ureter, less commonly middle part and sporadic the proximal segment. Bilateral manifestation of ureters is rare, occurs in 10-20% of patients. (6,8,10,14,15,17,34) Interestingly, the proportion of left-oriented gonadal and ureteral lesions are remarkably similar (63% and 64%, respectively). This asymmetry in the endometriosis appearance seems to be consistent with the reflux theory and with existence of anatomical differences in the left and right sides of the abdomen.

There are two main ureter endometriosis types - the intrinsic and the extrinsic. The second type occurs four times more frequently. In the extrinsic ureter endometriosis, pathological tissue invades only the outer layer of the ureter, and in some cases may lead to obstruction of the ureter. (8,10,14) In case of inner ureter endometriosis lesions invade muscle layer, basement membrane and finally ureter lumen. These two pathological forms may coexist with each other. It is often impossible to determine which form of endometriosis is present in a particular patient before performing surgery. Degree of ureter endometriosis invasion is specified and confirmed by examining histopathological samples. Recently Seracchioli and colleagues tried to evaluate the histological pattern of ureteral endometriosis (endometriotic or fibrotic ureteral endometriosis) on large group of patients. They proved that endometriotic pattern was more often occurring than fibrotic pattern. Additionally, authors showed that endometriotic pattern was significantly more often associated with the presence of hydroureteronephrosis.⁽³⁵⁾

Endometrial tissue located in ureter undergoes the same hormone-dependent periodic changes as normal uterine endometrium. This causes cyclical bleeding, desquamation of a lesion, necrosis, or fibrosis, which are followed by development of ureteral stenosis. Ureter endometriosis usually gives non-specific symptoms associated with obstruction of the ureter, such as renal colic, back pain and in some cases hematuria. More than half of the patients report dyspareunia, dysmenorrhea, and pelvic pain. Seracchioli and colleagues found that only 40% of the endometriotic patients were suspected of having ureteric endometriosis preoperatively based on clinical symptoms, ultrasound, and intravenous urography. Furthermore, exists a big group of completely asymptomatic patients. (11) There is a limited correlation between severity of symptoms and the degree of obstruction of the ureter. High degree of obstruction may proceed for a long time without symptoms (so-called silent obstructive uropathy), consequently leading to deterioration of renal function. Loss of renal function occurs even in 25-45% of cases. Due to lack of specific symptoms for ureter endometriosis and the high risk of silent kidney function loss, ultrasound control is strongly recommended. USG should be performed in all patients with endometriosis, before and after surgery, and during pharmacological therapy. Unfortunately, both ultrasound and other imaging tests (Uro-CT, MRI, intravenous pyelogram, urography) have limited value in providing accurate information about the extent of the disease and the degree of tissue infiltration. Recent study conducted by Sillou and colleagues endometriotic comparing MRI with intraoperative and histological findings showed that MRI may to be an efficient, non-invasive means of investigation for diagnosing urinary tract endometriosis. Authors tried to predict whether the urinary tract lesions are intrinsic or extrinsic basing on MRI imaging. They stand that MRI is more sensitive than surgery (91% vs. 82%), but less specific (59% vs. 67%) in diagnosing intrinsic disease for ureteric sites of disease.⁽³⁷⁾

It should be remembered that endometriosis can mimic other pathologies, what most important, malignancy. (38) Ureterorenoscopy with biopsy remains a most precise diagnostic option for patients with endometrial changes located in the ureter. This procedure allows confirming the diagnosis and often makes the endoscopic ablation of endometrial tissue possible. (39)

Treatment of Ureteral Endometriosis

The choice of treatment for ureter endometriosis is subject of controversy. The main goal of treatment is to remove obstacles and allow free flow of urine through the ureter. Results of the application of only hormonal therapy are often not satisfactory. It causes reduction of endometrial tissue but the existing obstacle, as a result of tissue fibrosis and existing adhesions, rarely disappears. Hormonal therapy as the sole treatment option may be considered in young patients, who wish to become pregnant quickly. During this treatment active ultrasonographic urinary tract surveillance is strongly recommended to prevent appearance of hydroureteronephrosis, obstructive uropathy, and renal function loss. However, hormonal therapy can also be a valuable treatment option in patients with no significant scarring and/or fibrosis of the ureter. For years, surgery has been the preferred treatment form, especially for extensive and advanced ureter endometriosis. Ureterolysis, which consist of exposing the ureter and freeing it from external lesions or adhesions, ureteroneocystostomy or ureterectomy with end-to-end anastomosis are basic methods of ureteric endometriosis treatment. All of those procedures can be successfully performed by laparoscopic way. This is due to the fact, that modern advanced laparoscopes provide very good visibility and allow exposure of endometrial nodules. Additionally, laparoscopic procedures are much less invasive than open surgery. However, it is believed that ureterolysis is effective only when endometrial foci are small (less than 3 cm) and located superficially. (40) In cases of ureter DIE and in lesions closing the ureter lumen treatment failure rates are high. If hydroureteronephrosis maintains despite of performed ureterolysis, stenosis removal and re-anastomosis of ureteral ends is indicated. (40) In some cases it is necessary to perform ureteroneocystostomy, which is reimplantation of ureter into the bladder. It was shown in large retrospective study that ureteral reimplantation is a suitable technique in cases of severe distal ureteral stenosis, extensive ureteral involvement, or when ureterolysis or ureterectomy with end-to-end anastomosis are not feasible. Authors proved that ureteral reimplantation gives good long term results, with no need for repeat surgical treatment. (41) After these procedures insertion of double J ureteral catheter is mandatory. Isolated reports of successful of intrinsic ureteral endometriosis treatment by endoscopic laser ablation are available, however, that method requires confirmation in a larger number of surveys. Relapse rate after non-radical removal of lesions is very high and reaches 30% of patients. (42) Proper preoperative classification, determination of surgery extension, and experience in gynecological and urological laparoscopy is necessary to ensure therapeutic success and avoid complications.

CONFLICT OF INTEREST

None declared.

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