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BLADDER ENDOMETRIOSIS – A SHORT REVIEW

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ABSTRACT
BLADDER ENDOMETRIOSIS (BE) IS DEFINED AS THE PRESENCE OF ENDOMETRIAL GLANDS AND STROMA IN THE DETRUSOR MUSCLE, USUALLY LOCATED IN THE TRIGONE AND THE DOME OF THE BLADDER. IT IS A DISEASE WITH AN UNKNOWN PREVALENCE, BEING FREQUENT UNDERDIAGNOSED AND HAVING UNSPECIFIC MANIFESTATION, THAT TENDS TO APPEAR IN A CYCLICAL MANNER. MULTIPLE HYPOTHESES REGARDING BLADDER ENDOMETRIOSIS HAVE BEEN PROPOSED, WITH MIGRATION AND TRANSPLANTATION THEORIES BEING THE MOST ACCEPTED. A THOROUGH EXAMINATION OF THE PATIENT IS RECOMMENDED, AND ONCE THE DIAGNOSIS OF BE HAS BEEN MADE, CLINICAL MANAGEMENT CAN BE CONSERVATIVE, USING HORMONALTHERAPIES, OR SURGICAL.

KEY WORDS: BLADDER ENDOMETRIOSIS, CONSERVATIVE MANAGEMENT

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INTRODUCTION

Endometriosis represents the presence of endometrial glands and stroma outside the uterine cavity[9]. The lesions are usually located in the pelvis, but can occur in other locations such as bowel, ovaries, urinary tract and rarely diaphragm, pleural cavity, lungs and central nervous system. It has been observed that most women suffering from endomestriosis have multiple areas of involvement[10]. The presence of extra-uterine endometrial tissue can cause local inflammation with secondary dysmenorrhea, dyspareunia, chronic pain, and infertility, with symptoms varying from mild to severely debilitating[11].

Due to the fact that endometriosis is a histologic diagnosis and that women have varied presentations, ranging from asymptomatic to non-specific symptoms the real, to determine the real incidence and prevalence of this disease is challenging. In one paper it has been stated that endometriosis affects 5-15% of premenopausal females[12]. Ballard et al in their case control study of more than 5500 women found that the prevalence of endometriosis varied from 1.2-1.5%[13]. Furthermore, a retrospective study on 9500 women undergoing hysterectomy for benign tumors, Mowers et al found that up to 15% of patients were diagnosed with endometriosis[14]. Up to 50 % of women with infertility and 70% of patients with chronic pelvic pain (CPP) have been diagnosed with endometriosis[15].

A series of risk factors have been associated with an increased risk of developing endometriosis: nulliparity, early menarche, late menopause with prolonged exposure to endogenous estrogens, shorter menstrual cycle, obstruction of menstrual outflow, heavy menstrual bleeding, lower body mass index.

According to the depth of invasion and anatomic location, endometriosis is usually classified as: ovarian endometriosis, superficial peritoneal endometriosis and the most severe form of endometriosis, deep infiltrating endometriosis - more than 5 mm deep (DIE).

These ectopic endometrial implants can sometimes affect the urinary tract, with the bladder and ureter being the most commonly affected. The prevalence of disease regarding specific sites,

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among women with urinary tract endometriosis (UTE), is as follows: bladder 85-90%, ureter 10%, kidney 4% and urethra 2%[16]. The incidence of UTE seems to vary from study to study, ranging from around 1% to approximately 12% of women affected by endometriosis[17]. Most of the time, UTE is diagnosed because of the complaint of urinary symptoms during gynecologic follow-up for endometriosis. UTE can be classified as primary, spontaneously appearing in the urinary tract or secondary, after pelvic surgeries, such as hysterectomy or cesarean delivery. Approximately half the patients with UTE underwent a pelvic surgery in the past[18]. The reason why the incidence of UTE varies widely between different studies might be the underdiagnosis of this disease in the preoperative evaluation and during laparoscopic surgery[19].

Bladder endometriosis (BE) is defined as the presence of endometrial glands and stroma in the detrusor muscle. It can affect the full thickness of the bladder muscle or it can be partial. BE usually affects premenopausal women, with an average age of 35 years old, while postmenopausal BE is extremely rare, endometriosis being an estrogen-dependent disease[20]. Typically, BE lesions are located in the trigone and the dome of the bladder and the disease usually spreads from the serosal surface of the bladder towards the mucosa.

PATHOGENESIS

Despite the fact that the pathogenesis of bladder endometriosis is still debated, there are four hypotheses that are generally accepted: embryonic, migration, transplantation, and iatrogenic theories.

The embryonal theory suggests that BE could originate from remnants of the Mullerian ducts, mainly located in the vesicouterine and vesicovaginal septum[21]. Proposed for the first time by Donnez et al[22], this theory could explain the existence of endometriosis in girls prior to

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menstruation, and thus not yet exposed to retrograde menstruation, the mechanism proposed in the migration theory.

The migration theory states that endometrial cells flow retrograde through the fallopian tubes and into the peritoneal cavity during menses, and from here they implant themselves into the bladder wall[23]. This process is facilitated by the presence of the vesico-uterine pouch, which creates a sheltered "pocket" in which endometrial cells are protected from the usual peritoneal clearance, thus allowing endometrial implants to develop[24]. This shelter effect can explain why BE is not usually seen in women having a retroverted uterus and why ureteral endometriosis is seen more frequent on the left, where the sigmoid colon creates a shelter on the left side of the pelvis[25]. Furthermore, it has been observed that women with genital tract obstructions that prevent drainage of menstrual blood through the vagina, thus having an increase tubal reflux, have an increased risk of developing endometriosis, further supporting the migration theory[26]. However, due to the fact that up to 90% of women have retrograde menstruation and most of them do not develop endometriosis, additional factors could be involved[27].

According to the transplantation theory, endometrium cells are displaced through the lymphatic and circulatory system and then implanted into the urinary system[28].

Intraoperative dissemination of endometrial cells following pelvic surgery represents the basis of the iatrogenic theory[29].

Once endometriosis is established, the process appears to cause symptoms through inflammatory changes. The mechanism of endometriosis-related infertility seems to involve anatomic distortion from pelvic adhesions and the production of cytokines, prostanoids and other substances that are "hostile" to normal ovarian function, fertilization and implantation.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Women suffering from bladder endometriosis usually presents with bladder pain, suprapubic discomfort, dysuria, urinary urgency, increased urinary frequency and less frequent, hematuria, with symptoms depending on the location and size of the lesions. Urinary incontinence is a very rare symptom associated with BE[30]. However, approximately one third of women remain

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asymptomatic, or presents minor complaints, making the diagnosis an incidental finding[31]. In most of these asymptomatic cases, the lesions measure approximately 1-2 cm in diameter[32]. In the literature, dysuria has been reported in 21-69% of patients with BE. Hematuria has been described in only 20-30% of women suffering from BE, due to the fact that endometriosis rarely infiltrates the mucosal layer. Furthermore, approximately half the patients with BE have been describing a cyclic manner in which these symptoms tend to occur, with predominanceduring the premenstrual period[33].

Bimanual examination of the patient can reveal a thickened area, a palpable nodule or cystic expansion with topographic-anatomical correlation to uterosacral ligaments, vagina, rectovaginal

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space, pouch of Douglas, the rectosigmoid and the posterior wall of the bladder, findings highly suggestive of endometriotic infiltration of the pelvis[34].

All patients should have their renal function evaluated by blood creatinine levels, as a silent loss of renal function is not so rare[35]. An urine examination should be performed for evidence of hematuria and to rule out an infectious etiology for the irritative voiding symptoms[36]. Urine cytology should be performed because of the necessity of differential diagnosis with bladder cancer[37].

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In terms of imaging studies, ultrasonography (abdominal, transvaginal, or transrectal) is the first line tool in diagnosing BE, mainly due to low cost, ready availability, and lack of radiation exposure[38]. On ultrasonography, with the bladder full of anechoic urine, endometriosis lesions appear as a filling defect on the posterior wall, with variable grades of protrusion, with an iso/hypoechoic aspect. These nodules, usually, are spherical or comma-shaped with regular contours, and they display few blood vessels on Doppler examination[39]. Both abdominal and transvaginal ultrasound can be used to detect BE, with the latter being preffered in the gynecological clinical practice. According to literature, transvaginal ultrasonography has a sensitivity of about 60-70%, with a specificity of 100%[40]. Thonnon et al compared the performance of 3D transvaginal ultrasonography with color Doppler to MRI and cystoscopy in the diagnosis of bladder endometriosis and found that ultrasonography was superior to cystoscopy and at least as effective as MRI in the diagnosing and planning surgery for BE[41].

On the MRI, BE appears to be high signal intensity on T1-weighted images and low signal intensity on T2-weighted images. A conventional MRI protocol for diagnosing BE needs to include sagittal and axial T1 and T2-weighted images, before and after fat supression. MRI seems to have a sensitivity reaching 80-90% with a specificity of up to 98%. Due to the fact that it is more expensive than transvaginal unltrasonography, and that in experienced hands, the latter, has approximately similar accuracy in detecting BE, MRI should not be routinely performed. In case of cancer suspicion and in complex cases of endometriosis with extensive adhesions it is more helpful due to its higher contrast resolution,better delineation of bladder wall layers, better tissue characterization, and better multiplanar capability[42].

Due to the fact that the endometriosis lesions progress from the serosal layer to towards the mucosa, thus having an intraperitoneal origin, cystoscopic findings may be normal. However, it can identify in some cases a nodular mass on the posterior bladder wall or on the dome. Scheduling cystoscopy immediately before or during menstruation is important for a best characterization of the nodule. During this period the nodule is larger and more congested, thus the cystoscopic

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visualization is clearer. Endometriotic lesions appear to be an adenomatous and irregular nodular masses,with different colors, with blue-red, blue-black, or blue-brown being the most frequent types. The bladder mucosa is usually unaffected.

Cytoscopy is a very useful tool, allowing the estimation of the distance between the ureteral orifices and the nodule borders, thus contributing to the decision of the most appropriate surgical approach. Furthermore, cystoscopy is very effective in excluding bladder cancer, but it should be noted that, with the exception of transurethral resection (TUR), a simple biopsy is frequently not diagnostic for endometriosis[43]. Some authors recommend that cystoscopy should not be routinely performed, except in those cases when there is a suspicion of bladder cancer or when the distance from the nodule to the ureteral orifices cannot be clearely evaluable using other imaging techniques[44].

Differential diagnosis should be made with urinary tract infections, interstitial cystitis/bladder pain syndrome, urinary tract stones, bladder cancer[45].

TREATMENT

Treatment of BE can be pharmacological, surgical or a combination of both procedures. Due to the relative rarity of this disease, there are no substantial guidelines regarding the treatment of BE.

The objective of the medical treatment is to cause a regression of the endometrial tissue. The most common medical therapies used in the treatment of BE are: gonadotrophin-releasing hormone (GnRH) agonists and antagonists, progestogenes and combined oral contraceptives.

Some authors recommend the use of medical therapy, such as combined oral contraceptives (COC) or progestogenes, regardless of the method of administration, as a first line treatment for DIE (rectovaginal, colorectal, and bladder endometriosis), being efficacious, safe and well tolerated[46]. Noel et al, in their study on estrogen and progesterone receptors in smooth muscle

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component of deep infiltrating endometriosis, found that these receptors were well represented in the detrusor lesions, with progesterone ones outnumbering the estrogen type, thus these lesions could be responsive to hormonal treatment[47].

Westney et al reported partial or complete resolution of symptoms in 12 out of their 13 women with BE treated with low-dose COC for a period of 8-24 months. In some cases progesterone was added to the current regimen of treatment[48].

In a study comparing gonadotropin-releasing hormone agonist and a continuous oral contraceptive pill in the treatment of BE, Fedele et al, treated five women with a COC used continuously and five patients with a GnRH agonist and stated that, at the end of the treatment, cytoscopy showed nearly complete resolution of the lesions in patients treated with GnRH agonists. The patients treated with a COC had a significant regression of the lesions, but not complete[49].

A frequently studied medical therapy for BE is dienogest, a 19-nortestosterone derivative with anti-androgenic properties. Multiple authors treated women with BE with this agent, all having the same result. Takagi et al managed a remarkable relieve in symptoms and a significant reduction in the size of the lesion after a 6 months treatment with oral dienogest in a 39-yr-old woman with a positive histologic diagnosis of BE. The patient was symptom-free at 1 year after drug discontinuation[50]. The same result was found by Harada et al, after 11 months of treatment[51]. Angioni et al treated 6 women who opted for a medical therapy with dienogest for 1 year and their symptoms improved very quickly and the nodule decreased remarkably in size[52].

Hormonal treatment is very effective in supressing, but not treating BE, thus, if the decision is taken to opt for a medical treatment, long-term therapy should be planned. Patients should be counceled on the risk of progression under medical therapy and that regular follow-up is necessary.

Surgical treatment should be performed after a thorough diagnostic workup to rule out bladder cancer, to define the exact location of the endometriotic nodule and its relationship with the ureteral orifices. Two surgical techniques have been proposed: trans-urethral resection (TUR) or partial cystectomy.

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Even though evidence supporting the efficacy and safety of TUR in the management of BE is scarce, this procedure has been proposed as a method of treatment for this disease. Furthermore, this procedure does not apply as a method of treatment for BE from a pathogenic point of view, since the nodules evolves from the serosa of the bladder towards the mucosa and complete resection of the lesion is not achievable without the risk of perforating the bladder[53].

Partial cystectomy is a bladder-preserving surgical technique for the treatment of BE, that can be performed via laparotomy or laparoscopy (with or without robotic assistance). Concomitant cystoscopy can be performed to for better defining the margins of the endometriotic lesion and, depending on the surgeon experience, cystoscopic catheterizations of the ureters may be advisable. Ureteral stenting is recommended when the distance between the caudal border of the endometriotic lesion and the interureteric ridge is < 2 cm[54]. For women with bladder lesions that are less than 2 cm away from the interureteric ridge some authors recommend ureteroneocystostomy to prevent ureteral obstruction or stricture. Partial cystectomy is generally a safe and simple procedure, vesical sutures heal easily because of rich vascularization, and prolonged urine drainage usually prevents fistula formation[55].

Different surgeons have been proposing a combined TUR and laparoscopic partial cystectomy for BE. The aim of this double approach is to overcome the limitations of both surgical techniques. Stopiglia et al presented their experience with a cystoscopy-assisted laparoscopy for bladder endometriosis, in which a partial videolaparoscopic cystectomy was performed with cystoscopy-assisted vesical reconstruction throughout the entire surgical time. They stated that this technique provides adequate identification of the lesion limits, intra or extravesically and it also allows a safe reconstruction of the organ aiming for its maximum preservation. The median operative time was 138 minutes and patients were evaluated for a period of 12-78 months, with clinical evaluation and a control cystoscopy performed every six months. No relapse was observed during the follow-up period[56].

The main goal of partial cystectomy is to completely remove the endometriotic nodule, thus minimizing the risk of recurrence.

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There are some urogenital malformations that could be associated[57]. For eldery patients we should take care of postoperative dementia[58] and, on certain objective criteria, admission in intensive care units could be salutary[59].

CONCLUSIONS

Bladder endometriosis is frequent in the context of DIE, and usually coexists with other forms of endometriosis. BE has unspecific symptoms, thus a thorough differential diagnosis should be made. Women of reproductive age complaining of urinary symptoms, usually during the menstrual cycle, should always be investigated for the presence of BE. Transvaginal ultrasonography should be considered a first line technique to assess endometriotic nodules, followed by pelvic MRI, if the lesion is not well described on US. Once a diagnosis of BE has been established, clinical management can be conservative (hormone therapy) or surgical. When surgical treatment is chosen, TUR alone should be avoided.

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