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# The Importance of Urethrocystoscopy and Bladder Biopsy in Gynecologic Patients

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## 1. Introduction

Some gynecological dysfunctions, but especially the urogynecological ones, require an endoscopic study and in the presence of structural changes, a biopsy.

The main purpose of this chapter is to feel the close relationship between the female genital tract and the lower urinary tract (LUT) that leads to clinical dysfunctions that can impact either one and cause symptoms with increased severity or significance than the initially affected. A representative example of this would be the Painful Urethral Syndrome, which can cause severe dyspareunia that affects in a significant degree the couple's relationship. In the pelvic compartment, pelvic organ prolapse may cause symptoms of the lower urinary tract both in the filling and emptying phases. In many of these diseases the study of the lower urinary tract symptoms (LUTS) makes it necessary to evaluate the urethra and bladder endoscopically and perform a biopsy when an organic disease is found.

This chapter will focus on those conditions, that according to our experience justifies the expressed above.

### 1.1 Historical perspective

The practice of bladder biopsy is intimately related to the history of urethrocystoscopy that Puigvert narrated (1939). Bozzini in 1805 described the first cystoscope consisting of a metal tube which on the extravescical end applied a spark plug through which the visual field was illuminated and limited at the other end of the tube. Then Desormeaux (1853) submitted to the Paris Academy of Medicine a cystoscope made by him, which consisted of the urethral tube and a lighting apparatus provider of a lamp which burnt a mixture of alcohol and turpentine, whose light reflected, by mirror lit by the tube, the bladder's cavity. Thirteen years later he published the first book on the subject "Treaty of Urinary Endoscopy and its Applications to the Diagnosis and Treatment of Urethrovesical Conditions". In 1886, Max Nitze built a cystoscope with an optical system almost identical to that used today, equipped with an incandescent Edison lighting system.

Howard A. Kelly was appointed the first professor of gynecology at the John Hopkins Medical School. Kelly (1893) believed that gynecology and urology were so closely related

that one could not be trained in either field and ignore the other. Kelly invented in 1914 the urethroscope and emphasized the importance to explore endoscopically not only the bladder but also and principally the female urethra.

Jack R. Robertson (1973) returned to Kelly's concepts and applied modern technology updating Kelly's urethroscope by providing it with a gas source and a recording equipment, calling it "Gynecologic urethroscope". Robertson emphasized the dynamic study of the urethra, asking the patient to strain, contract the pelvic floor and to cough, in order to assess the neuromuscular physiological response.

His concepts, strictly followed by us, strongly influenced the International gynecological environment which favored the creation of the American Urogynecological Society. Robertson was its first President in 1979.

Suprapubic telescoping described by Timmons (1990), has been a significant progress. He placed special emphasis in the intraoperative diagnosis of ureteral injury, assessing the elimination of indigo carmine through the ureteral meatus after the introduction of the cystoscope through a small hole in the extraperitoneal bladder wall.

Interestingly a variant of suprapubic telescoping was already practiced by French urologists (1920), under the title "hypogastric cystoscopy", among them Kraske, who used a special cystoscope equipped with a tip ending in a sharp point. The technique was refined by Katz and Kolisher who performed a suprapubic fistula and used the ordinary cystoscope.

Endoscopy of the LUT in women has been a remarkable progress for the gynecologist and for the development of Urogynecology.

## **2. Bladder biopsy**

The first bladder biopsy forceps were independently described by Young and Marion in 1929, by which it was possible to extract portions of tumor tissue, according to the description of Puigvert (1939).

Currently the general criterion is to perform a bladder biopsy when there is tumor formation or epithelial change that may represent suspicious malignant lesions. In cases where there is no tumor but an epithelial disruption exists, the indication of biopsy is priority if a urinary cytology is positive.

Bladder cancers are classified as being non-muscle-invasive or muscle invasive according to their histological appearance. Non-muscle-invasive bladder cancers account for about 70 to 80% of all bladder cancers (Abel 1988; VanDer Meijde et al. 1999). The primary approach for Ta and T1 tumors is transurethral resection of bladder tumor. The main problem after the initial treatment of non-muscle-invasive cancers is the high recurrence rate (40 to 80%) Gogus et al. (2002). Many prognostic factors, such as tumor stage, tumor grade, multiplicity, concomitant carcinoma in situ and tumor size have been proposed to affect tumor recurrence of non-muscle-invasive bladder carcinoma (May et al. 2003) (Kiemeny et al. (1994).

Additionally, bladder biopsy is also used in patients previously treated for bladder cancer as a method of detection and control. In these cases the criteria for performing biopsy include

suspicious lesions or areas of red urothelium (Lee et al. 2009), but some authors advocate biopsy even in the absence of epithelial disruption. This approach is controversial and it is not in accordance with international guidelines (Matsuchima et al. 2010).

The indication of cystoscopy is controversial. If the object is only the detection of neoplasms of the LUT, a generalized concept is to practice it in the presence of macro or microscopic hematuria or in the presence of a positive urinary cytology with cells suspicious of malignancy. Nevertheless, microscopic hematuria is not a predictive factor for cancer, several authors confirm this. Wu et al. (2006) of 735 patients with irritative symptoms, only 35.9% of the cancers had hematuria. Goldberg et al. (2008) reported that only 40% of cancer patients present hematuria. Flores-Carreras et al. (2010) evaluated 331 women with LUTS of which 62.8% had symptoms of overactive bladder and 31.4% had hematuria. Bladder cancer was diagnosed in two cases (0.6%), similar percentage than that reported by others authors, (0.2% to 3.9%) (Lee et al. 2009; Borden et al. 2003; Sokol et al. 2005). None of the cancer cases had hematuria. They also detected three cases of Cystitis Glandularis of which two had no history of hematuria and two cases of papillomatous tumor, both positive for hematuria. The clinical morphologic and histopathologic diagnosis is showed in Table1.

Diagnosis	with hematuria		without hematuria	
	N	%	N	%
INTERSTITIAL CYSTITIS	5	14.3	10	28.6
BLADDER PAPILOMA	2	5.7	----	----
CHRONIC CYSTITIS	1	2.9	3	8.6
CYSTITIS FOLLICULARIS	1	2.9	3	8.6
BLADDER CANCER	----	----	1	2.9
CYSTITIS GLANDULARIS	1	2.9	2	5.7
ACUTE CYSTITIS	----	----	1	2.9
ANGIOMATOSE POLYP	----	----	1	2.9
POLIPOID CYSTITIS	----	----	1	2.9
MICROPAPILLOMATOSIS	----	----	1	2.9
IN SITU BLADDER CANCER			1	2.9
SQUAMOUS METAPLASIA			1	2.9
TOTAL	10	28.6	25	71.4

Table 1. Clinical, morphologic and histopathology diagnosis in 35 bladder biopsies. Comparative results in patients with and without hematuria.

It is a comparative pathologic result between hematuria and not hematuria cases. As it is possible to see, the most frequent diagnosis was Interstitial Cystitis in both groups (42.9%) of the total cases.

Smoking has been considered a major risk factor for bladder cancer and is responsible for almost half the deaths from bladder cancer in men (48%), and less than a third among women (Pashos et al. 2002). This was the reason why we investigated it and were able to detect 10 patients who smoked (28.6%). One of the two bladder cancer patients was a smoker.

## 2.1 Background

A characteristic of urogynecologic patients with regards to their symptoms is that such symptoms are non-specific. Thus one commonly sees symptoms in patients with stress or urge incontinence similar to the ones in patients with a local irritation due to infection, distal stenosis or a neoplastic process.

## 2.2 Technique

For the urethrocystoscopy, patients were placed in lithotomy position, followed by cleansing the introitus with an antiseptic solution. The order of the endoscopy is to start with the urethroscopy followed by the cystoscopy. For distention in both cases sterile saline solution at room temperature is used.

For the urethroscopy we use the Robertson monitor which is proved for a 0-degree telescope and as mentioned before, perform the dynamic urethroscopy and also visualize the color, the presence of inflammatory signs or any structural lesion as stenosis, fistula or diverticulum. Our particular point of view is that urethroscopy is the best and most practical diagnostic method to detect the presence of diverticulum and obviously, of urethral tumors and urethritis. For the cystoscopy, we use Karl Storz 70° lenses with a 18Fr sheath for exploring, or 22Fr sheath in case of operatory endoscopy. In case of biopsy, flexible 7Fr caliber forceps (Karl Storz) are used. For distention in both cases we used sterile saline solution at room temperature.

In the first ten biopsies we applied xylocaine gel as a local anesthetic, but when the product disappeared from the local market, the biopsy on the rest of the patients was performed without anesthesia. This procedure is well tolerated by the patient if we previously inform of it. This procedure is carried out in the office with the inherent advantages this entails, in terms of the risks and financial expenses brought about by a hospital procedure (Flores Carreras et al. 2010).

## 2.3 Overviewing

There are many pelvic conditions that affect the LUT: chronic pelvic pain, pelvic organ prolapse, postmenopausal hormonal deprivation, vulvar-vaginal infectious processes, lesions of the LUT and pelvic surgery for benign and malignant tumors of the female genital tract. Also urinary problems that affect the gynecological function and well being for example: urinary incontinence, voiding dysfunction, postoperative vulvar-vaginal stenosis, overactive bladder, urethral pain syndrome, Bladder Pain Syndrome/Interstitial Cystitis

(BPS/IC). In some of these conditions, bladder biopsy is advisable; in this chapter we'll discuss pros and cons of this procedure.

Specialized medical literature contains conflicting positions regarding the systematic use of urethroscopy in female patients with LUTS. There are those who recommend the procedure (Lee et al. 2009; Goldberg et al 2008; Cundiff & Bent 1996) and others who restrict it to patients with irritability symptoms together with macro or micro hematuria. In any event, the general consensus is to consider urethral cystoscopy the "gold standard" method to diagnose bladder cancer (Abel 1988; VanDer Meijde et al. 1999). In our opinion, we must incorporate urethroscopy into our protocol to examine patients suffering from: 1) mixed urinary incontinence, 2) hyperactive bladder, 3) macro or micro hematuria, 4) bladder or pelvic pain related with LUTS, 5) recurrent urinary tract infection, 6) urinary symptoms related with pelvic surgery, 7) bladder or urethral tenderness, 8) during pelvic surgery to exclude bladder or ureteral lesion.

About the different points of view Lee et al. (2009) expressed the following concepts: "There are many different points of view related to the practice of cystoscopy between urologists and urogynecologists. For the first one, hematuria is the single most common indication; in contrast, urogynecologists not only perform cystoscopy but also urethroscopy and they visualize the lower urinary tract more thoroughly for a broad range of indications, most commonly for exclusion of intravesical lesions in women with LUTS or recurrent urinary tract infection (RUTI), suspected foreign body and diagnosis of urethral diverticulum".

## 2.4 Urinary incontinence

In this chapter our position is to practice urethroscopy in patients who accuse mixed incontinence (stress and urgency), recurrent or continuous or pure urgency. It is not necessary an endoscopic study of patients with only stress incontinence, not previously treated surgically, and when bladder neck prolapse is demonstrated. It is especially important to perform endoscopic evaluation in patients with recurrent incontinence because you can find in them, a number of surgical sequels of injury of pelvic structures whose non-detection should be classified as a professional negligence. Continuous incontinence mostly preceded by surgery and urgency incontinence, usually accompanied by symptoms of bladder irritability, requires endoscopic study, from our point of view.

## 2.5 Overactive bladder

The International Continence Society (Abrams et al. 2002) defines the overactive bladder (OAB) as "urgency, with or without urge incontinence, usually with frequency and nocturia...if there is not proven infection or other etiology."

The overall prevalence of OAB in United States was 16.9% in women and 16.0% in men, increasing with age. The overall prevalence of OAB dry and OAB wet was 7.6% and 9.3% in women respectively, and 13.6% and 2.6% respectively in men (Noble Program) (Stewart et al. 2003). Although the prevalence of this condition increases with advancing age, having overactive bladder is abnormal at any age. Overall, it is estimated that 17% of the general population over 40 years of age suffers from overactive bladder. Similar prevalence is reported in Europe.

The cause of OAB is unknown in the vast majority of patients. In a few rare cases, it may develop secondary to neurologic disorders, such as stroke, multiple sclerosis or spinal cord injuries. Other causes have been described such as: bladder outlet obstruction, pelvic organ prolapse, impaired detrusor contraction, diabetes, between others. Shaw et al., and Ikeda et al., have reported as risk factors: Caucasian race, insulin-dependent diabetes, alcohol intake and history of depression (Shaw et al. 2011; Ikeda et al. 2011).

Most authors recommend basic evaluations that consist of a focused history and examination, bladder diary and urinalysis. A more detailed diagnostic evaluation is only recommended after treatment failure, if there is micro hematuria or elevated residual urine.

From our point of view, we should perform, in addition to medical history, urinary diary, urine culture, uroflowmetry, investigation of residual urine and urethroscopy. This attitude, which might be considered radical for some physicians, represents for us a complete and secure exploratory approach. Detection of the above-mentioned four tumors would not been possible with a more conservative behavior.

## 2.6 Chronic pelvic pain

Chronic pelvic pain is a typical example of possible indication of endoscopic study of the LUT, especially when the pain is topographically expressed in the suprapubic region, vaginal canal or vulvar area and/or accompanied by urinary increased disorders such as frequency, nocturia and urgency.

The typical bladder pain is felt suprapubically and generally increases with bladder filling and may persist after voiding. Painful bladder syndrome is defined by the International Continence Society (ICS) as suprapubic pain that is related to bladder filling in the absence of proven urinary tract disorders such as infection or other pathology and is often associated with increased frequency and nocturia (Abrams et al. 2002).

Painful bladder syndrome is frequently associated with Interstitial Cystitis that is why denomination PBS/IC was established by the ICS.

The exact prevalence of Painful Bladder Syndrome/Interstitial Cystitis is unknown. Clemens et al., (2005) estimated that in United States of America, one million people suffer IC of which 90% are women. In the last 20 years several epidemiological studies have noted an increase in frequency with values of 25.1, 36.6, 76.3, per 100,000 habitants (Curhan et al. 1999). A relatively recent study reported a prevalence of 0.51% in USA (Jone et al. 1994). In our private urogynecology unit (Urodifem de Occidente S.C.) of a total of 331 female patients studied, the diagnosis of BPS/IC was established in 18 cases (3/15) (Flores Carreras et al. 2010), representing a rate of 5.4% for a unit specializing in urogynecology problems. Biopsy was taken in 14 cases and their histological finding was consistent with those described for IC: lymphoplasmacytic infiltration, fibrosis reaction and in some cases, increase in the number of mast cells. In any case were noted signs of malignancy. The thirty-three of patients with BPS/IC had hematuria.

## 2.7 Urethral painful syndrome

The urethral painful syndrome (UPS) is a condition very common in women. In some patients the onset is at an early age even in nubile women with "nonbacterial cystitis"

expressed in dehydrated patients or coinciding with menses. Often the first expression of this condition is the initiation of sexual activity and therefore has acquired the name of "honeymoon cystitis".

In 2002 the I.C.S defined it as "Occurrence of persistent or recurrent episodic of urethral pain usually on voiding with daytime frequency and nocturia in the absence of proven infection or other obvious pathology". The diagnosis implies longevity symptoms of at least 6 months of duration. The incidence and prevalence of this condition is not known due to the lack of consensus about this condition. Some authors have reported that 15-30% of women who presented with lower urinary tract symptoms were diagnosed as urethral pain syndrome. The prevalence in our casuistic was of 31.4%.

This condition is usually inflammatory in nature. Frequently there are lumps of pus through the periurethral glands seen at urethroscopy, especially when simultaneous urethral massage is performed, however microbiological studies are generally negative. We feel that urethroscopy is very important in these cases to confirm the state of inflammation of the urethra and to detect underlying pathology such as a narrow meatus, urethral diverticulum, suburethral cyst, among other conditions. Many of these patients have been treated with antibiotics with poor results.

In our experience UPS is one of the conditions that mostly affects the couple's sexual identification because it causes dyspareunia or vulvar-vaginal pain after intercourse and occur during the beginning of sexual life. Management is difficult, based on antimicrobial, urethral dilatations, urethral massage, anti-cholinergics, anti-inflammatory drugs, smooth muscle relaxants, precoital lubricants and even emotional and technical support to the couple. We should always rule out the presence of chlamydia and ureaplasma.

## **2.8 Recurrent urinary tract infection (RUTI)**

For definitional purposes RUTI refers to more than three infections in one year (Nickel et al. 1991). The current incidence of urinary infection among premenopausal, sexual active women is 0.5-0.7 infections/person year. Furthermore, 20% of women will have a urinary tract infection (UTI) in their lifetime with 3% having RUTI. Recurrent infections are due to either reinfection or bacterial persistent. Reinfection is recurrent infection with different bacteria. The majority of infections are asymptomatic and clear spontaneously (Lawrentschuk et al. 2006). In symptomatic patients the most common symptoms are dysuria, frequency, urgency, nocturia and suprapubic discomfort. Occasionally mild incontinence and hematuria may occur.

Gram-negative bacilli of the family Enterobacteriaceae are responsible for 90% of infections. *E. Coli* is the single most important organism and accounts for 80 to 90% of uncomplicated infections.

The value of routine cystoscopy investigation has not been clearly defined; there are different opinions such as Fowler and Pulanski (1981), who noted that in young patients the only abnormality that altered treatment was a urethral diverticulum. However, the published literature is in favor of cystoscopy in women with RUTI, principally in patients of more than 50 years old (Lawrentschuk et al. 2006; Van Haarst et al. 2001).

There are certain risk factors for developing urinary infections: hematuria, pyelonephritis, calculi, diabetes, in the elderly patients, urethral obstruction, pelvic surgery and urethral diverticulum (Lawrentschuk et al. 2006). The majority of urinary tract infections are ascending infections from the fecal flora which colonize the vaginal introitus, then the periurethral tissues, and eventually gain entry to the bladder.

### 3. Conclusions

Urethrocystoscopy and eventual bladder biopsy are an integral tool for the evaluation of lower urinary tract symptoms, to make possible the detection of structural lesions, benign or malignant tumors and exclude injuries of the urinary tract between other problems. Almost all of the urogynecologists support the indication of urethrocystoscopy in patients with dysfunction of the lower urinary tract. Urethrocystoscopy provides an anatomical assessment of the urethra and bladder that is not accomplished with urodynamics or other types of tests. If we think only in order of detection of malignant tumors, younger women (less than 50 years) are less likely to have pathology; this condition must be factored into decision to perform or not endoscopy. However, bladder cancer is an important reason to keep in mind for women with abnormal voiding symptoms even in the presence of a normal urinalysis. The rate of detection of cancer in women with LUTS goes from 0.2 to 3.9% (in our casuistic 0.6%). The majority of the cases were discovered in patients presenting without hematuria.

Finally, we consider that a physician who treats women with lower urinary tract symptoms is obligated to provide reasonable assurance that the patient's urinary system is otherwise normal.

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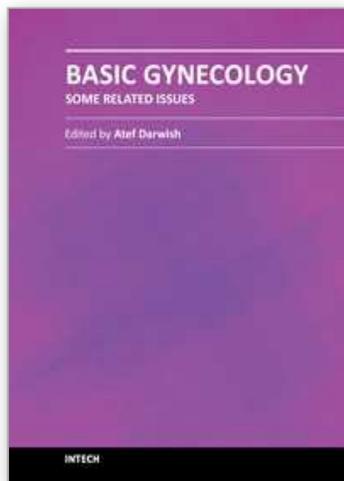
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Edited by Prof. Atef Darwish

ISBN 978-953-51-0166-6

Hard cover, 156 pages

**Publisher** InTech

**Published online** 29, February, 2012

**Published in print edition** February, 2012

This small-sized book concentrates on highlighting some basic sciences mainly related to infertility and menstruation. The readers will find detailed answers to many controversial issues.

#### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Oscar Flores-Carreras, María Isabel González Ruiz and Claudia Josefina Martínez Espinoza (2012). The Importance of Urethroscopy and Bladder Biopsy in Gynecologic Patients, Basic Gynecology - Some Related Issues, Prof. Atef Darwish (Ed.), ISBN: 978-953-51-0166-6, InTech, Available from: <http://www.intechopen.com/books/basic-gynecology-some-related-issues/the-importance-of-urethroscopy-and-bladder-biopsy-in-gynecologic-patients>

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