In this chapter, five urogenital disorders are discussed that occur more often in patients with Sjögren's syndrome than in the general population. These disorders are:

1. overactive bladder syndrome
2. interstitial cystitis/bladder pain syndrome
3. non-bacterial prostatitis
4. vulvodynia
5. dyspareunia

1. OVERACTIVE BLADDER SYNDROME

Overactive bladder (OAB) syndrome is the term used to describe the symptom complex of urinary urgency with or without urge incontinence, usually with frequency and nocturia, in the absence of any sign of infection or other identifiable cause of the symptoms. Symptoms of overactive bladder may also have identifiable causes.

OAB with incontinence is currently referred to as OAB wet, in contrast to OAB dry when there is no incontinence.

The symptoms of OAB are primarily due to involuntary contractions of the detrusor muscle during the filling phase of the micturition cycle. These contractions, when observed during urodynamic studies, are termed detrusor overactivity and are mediated by acetylcholine-induced stimulation of bladder muscarinic receptors.

OAB symptoms have a profound impact on the quality of life and patients may feel a sense of shame and embarrassment, in particular in OAB wet. The diagnosis of OAB is based on symptoms and does not require invasive tests. Careful questioning about symptoms is important in achieving a differential diagnosis (table 12.2). The most common differential diagnosis is a urinary tract infection but in a small number of cases bladder cancer is underlying the symptoms of OAB.

Table 12.1 Examples of causes of overactive bladder symptoms

- detrusor overactivity
  (overactive bladder syndrome, OAB)
- urinary tract infections
- drugs (side-effects)
- bladder cancer; prostate cancer
- benign prostatic hyperplasia
- stones in the bladder
- constipation
- pelvic organ prolapse
- bladder injury
- nerve damage
- neurological diseases (multiple sclerosis, Parkinson's disease, spinal cord lesions, spina bifida, stroke)

Table 12.2 Presenting symptomatology for overactive bladder (OAB), bladder cancer and urinary tract infections (UTIs)

<table>
<thead>
<tr>
<th>presenting symptom</th>
<th>OAB bladder cancer UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>urgency yes</td>
<td>occasionally yes</td>
</tr>
<tr>
<td>frequency yes</td>
<td>occasionally yes</td>
</tr>
<tr>
<td>urgency incontinence yes</td>
<td>occasionally rare</td>
</tr>
<tr>
<td>nocturnal frequency 33% often</td>
<td>occasionally rare</td>
</tr>
<tr>
<td>pain no</td>
<td>occasionally yes</td>
</tr>
<tr>
<td>dysuria no</td>
<td>occasionally yes</td>
</tr>
<tr>
<td>pyuria no</td>
<td>rare</td>
</tr>
<tr>
<td>haematuria no</td>
<td>yes</td>
</tr>
</tbody>
</table>
Treatment of OAB includes bladder training, diet modification, drugs, neuromodulation and in the last resort surgery. Anticholinergic drugs are the mainstay of drug treatment for OAB symptoms but have side-effects such as dry mouth and dry eyes. Intravesical injections of botulinum toxin A (Botox A) into the detrusor muscle and/or bladder sphincter have produced good results for OAB that failed to respond to other treatment.

See box above for various aspects of urinary incontinence.

### OAB and Sjögren’s syndrome

Walker et al 41 found that 61% of patients with primary Sjögren’s syndrome reported severe urological symptoms compared with 40% of control patients with osteoarthritis. This difference was predominantly attributable to bladder irritability associated with urgency and not nocturia (OAB).

### Cause of OAB in Sjögren’s syndrome

Wang et al 40 did an interesting study on the passive transfer of serum IgG from patients with Sjögren’s syndrome. The IgG showed inhibitory anti-muscarinic M3 receptor (M3R) activity but produced a paradoxical increase in contractile responses of detrusor strips to cholinergic stimulation. Cystometry of whole bladders revealed a corresponding decrease in bladder wall compliance and phasic detrusor contractions upon filling, replicating the urodynamic features of overactive bladder. The features of cholinergic hyperresponsiveness were associated with increased post-synaptic M3R expression and were reproduced by injecting mice with a rabbit antibody against the second extracellular loop of M3R. These findings were consistent with the notion that there was initial inhibition of parasympathetic neurotransmission by antagonistic autoantibodies to M3R, which produced a compensatory increase in M3R expression in vivo. The enhanced cholinergic responses during bladder distention resulted in detrusor overactivity.

These data suggest that the overactive bladder associated with Sjögren’s syndrome is an autoantibody-mediated disorder of the autonomic nervous system, which may be part of a wider spectrum of cholinergic hyperresponsiveness.40
2. INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Interstitial cystitis or bladder pain syndrome (IC/BPS) is a chronic bladder disease characterized by symptoms of cystitis. These are pain, pressure or discomfort in or around the bladder, a persistent urge to urinate and frequent urination both in the daytime and at night. The pain usually increases as the bladder fills. However, no urinary tract infection can be found. The symptoms have serious consequences for the social and personal life of the patients. In the case of many patients, it may take many years before the diagnosis of IC/BPS is established.

During the past few years, there has been much international discussion concerning the name and definition of this disease. Other names that are used are painful bladder syndrome (PBS) or hypersensitive bladder, with or without the addition of IC.

Definition of the disease

The name interstitial cystitis suggests that inflammation is present in the interstitium of the bladder. A great problem was that in many patients with varying degrees of chronic urinary symptoms and pelvic pain, no abnormalities could be found by physical, microbiological and histological investigations. The inability to make a classifying diagnosis in these patients necessitated resolving the discrepancies between nomenclature, definitions and clinical practice by introducing other names, definitions and diagnostic criteria.

In 1987, Holm-Bentzen expanded the concept of interstitial cystitis by describing it as a subgroup of painful bladder disease with abnormal findings such as detrusor mastocytosis.

In 1988, the NIDDK (National Institute for Diabetes and Digestive and Kidney Diseases) consensus criteria for the research diagnosis of interstitial cystitis (IC) were published. These so-called NIDDK criteria did not require histological evidence of inflammation. The NIDDK criteria were found to be very specific, but more than 60% of patients regarded by researchers as definitely or likely to have IC did not fulfill the NIDDK criteria.

In 1989, Witherow et al used the name painful bladder syndrome (PBS), defined as a clinical diagnosis in patients with symptoms of varying severity. These symptoms always included frequency and suprapubic pain and occasionally dysuria, nocturia and urgency persisting for more than 3 months with no loss of bladder capacity and no overt infection. The term PBS was used independently of objective bladder pathology.

In 2002, the International Continence Society (ICS) defined PBS as the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology. In a footnote it is stated that “The ICS believes this to be a preferable term to interstitial cystitis. Interstitial cystitis is a specific diagnosis and requires confirmation by typical cystoscopic and histological features. In the investigation of bladder pain it may be necessary to exclude conditions such as carcinoma in situ and endometriosis”.

The Chronic Pelvic Pain Group of the European Association of Urology (EAU) expanded the concept in a classification based on chronic pain, the perceived localization of the pain and possible abnormal findings. Chronic pelvic pain was defined as non-malignant pain perceived in structures related to the pelvis. Chronic pelvic pain syndrome was described as the occurrence of persistent or recurrent episodic pelvic pain associated with symptoms suggestive of lower urinary tract, sexual, bowel or gynaecological dysfunction, without proven infection or other obvious pathology. The EAU definitions use the axial structure of the International Association for the Study of Pain (IASP; www.iasp-pain.org) and as symptoms invariably define the clinical condition, they consider the term painful bladder syndrome or bladder pain syndrome more apposite. The EAU Group clearly distinguishes classic ulcer disease from non-ulcer bladder pain syndrome. They state that these can be discriminated non-invasively and show different clinical presentations, age distributions, histopathology, response to treatment and clinical course. Depending on the level of available evidence, classification of a particular patient may change over time, e.g. from chronic pelvic pain syndrome to bladder pain syndrome or interstitial cystitis.

In 2004, the International Scientific Committee at the 3rd International Consultation on Incontinence (ICI) gave the following recommendation on what kind of patient should be evaluated for PBS/IC: “Men or women with bladder pain, with or without a sensation of urgency, often with urinary frequency and nocturia (especially if drinking a normal amount of fluids) and no abnormal gynecologic findings to explain the symptoms should be evaluated for PBS/IC. Patients with infection should be treated and reassessed. Those with recurrent urinary infection, abnormal urinary cytology, and haematuria are evaluated with appropriate imaging and endoscopic procedures, and only if findings are unable to explain the symptoms are they diagnosed with PBS/IC.”
The European Society for the Study of IC/PBS (ESSIC; www.essic.eu) presented their consensus on definitions, confusable diseases, diagnostic criteria, disease types and a proposal to change the name into bladder pain syndrome (BPS) at a NIDDK meeting in October 2006 (www.niddk.nih.gov/fund/other/niddkfrontiers/frontiers in PBS Summary report.pdf). Their proposed diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis was published in 2008. In short, it was concluded that “the diagnosis will be made on the basis of the symptom of chronic pain related to the urinary bladder, accompanied by at least one other urinary symptom such as daytime and night-time frequency, exclusion of confusable diseases as the cause of the symptoms and cystoscopy with hydrodistension and biopsy if indicated.”

In a reaction to these proposals, the Association of Reproductive Health Professionals (ARHP) held a multidisciplinary meeting of researchers, clinicians and patients in the USA in February 2007. In a majority statement, IC/PBS was defined as follows: “Pelvic pain, pressure, or discomfort related to the bladder, typically associated with persistent urge or urinary frequency, in the absence of infection or other pathology.”

At the 2nd International Consultation on Interstitial Cystitis Japan (ICICJ) in March 2007, Homma proposed the term hypersensitive bladder syndrome (HSB) characterized by increased sensation, usually associated with frequency and urgency, with or without bladder pain. PBS is defined as a symptom syndrome characterized by bladder pain, usually associated with frequency, urgency and increased sensation. IC is defined as a disease name that should not be used as a symptom syndrome. IC is characterized by 1. HSB; 2. no other obvious diseases that explain the HSB, and 3. bladder pathology (histological evidence of inflammation and/or abnormal cystoscopic findings (Hunner’s ulcer or bladder bleeding at hydrodistension). PBS is contained in the HSB, while IC is also contained in HSB, but only partially overlaps PBS and OAB, meaning that some patients with IC have neither urgency nor pain.

It can be concluded that there is strong international support (ICS, EAU, IASP, ICI, ARHP, ESSIC) to consider pain as a key feature of PBS/IC while urgency and frequency are common symptoms but not a prerequisite for a diagnosis (table 12.3).

### Table 12.3 Summary of the mandatory features for the diagnosis of IC/BPS as proposed by various authors and scientific organizations. See the text for explanation of the abbreviations.

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>DISEASE NAME</th>
<th>PAIN</th>
<th>URGENCY</th>
<th>FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holm-Bentzen</td>
<td>IC is subgroup of PB disease</td>
<td>yes?</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>NIDDK</td>
<td>IC</td>
<td>pain or urgency</td>
<td>no</td>
<td>pain or urgency; glomerulations or Hunner’s “ulcer”</td>
</tr>
<tr>
<td>Witherow</td>
<td>PBS</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>ICS</td>
<td>PBS</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>EAU</td>
<td>PBS/BPS</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>ICI</td>
<td>PBS/IC</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>ESSIC</td>
<td>BPS types</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>ARHP</td>
<td>IC/PBS</td>
<td>yes</td>
<td>urgency or frequency</td>
<td></td>
</tr>
<tr>
<td>Homma (ICICJ 2007)</td>
<td>HSB</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>PBS</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>IC</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>
ESSIC has slightly adapted its initial disease description on the basis of the discussions at the ARHP and 2nd ICICJ meetings (see below).

ESSIC diagnostic criteria

The European Society for the Study of IC/PBS (ESSIC) has recently proposed a new definition, new diagnostic criteria and the name bladder pain syndrome (BPS).\textsuperscript{33} ESSIC has defined types of BPS on the basis of findings used to document the diagnosis of BPS.

BPS type indications consist of two symbols: first symbols 1, 2 or 3 indicate increasing grade of abnormal findings at cystoscopy with hydrodistension and second symbols A, B or C indicate increasing grade of abnormality of biopsy findings. X indicates that no cystoscopy with hydrodistension (first symbol) or no biopsy (second symbol) was done (see figure 12.1).

The name IC/BPS will be used here further as a synonym for interstitial cystitis, painful bladder syndrome and bladder pain syndrome.

Pain, pressure and discomfort

Many patients report a sensation of pressure or discomfort in the bladder/pelvic area and do not report this sensation as pain but rather as urgency.

The IASP (International Association for the Study of Pain; www.iasp-pain.org) definition of pain is: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Patients having microwave treatment for benign prostatic obstruction producing tissue damage at the bladder neck report the same sensation of pressure and discomfort in the bladder region. The sensation is therefore by definition a pain sensation, but not described as such by the patient.\textsuperscript{33}

Disease characteristics

Cystoscopy is an essential diagnostic procedure for IC/BPS because it allows the inside of the bladder to be examined and small samples of tissue to be taken. This enables many other diseases such as carcinoma in situ to be excluded as a cause of the symptoms. A number of findings are considered to be hallmarks of IC/BPS, despite not being specific. These are glomerulations (diffuse pinpoint haemorrhages) in the bladder wall when the bladder is filled with water, a bladder capacity of less than 350 ml and so-called Hunner’s "ulcers". None of these characteristics are found in all patients.

The typical histological finding in IC/BPS is submucosal edema, vasodilatation and an inflammatory infiltrate of lymphocytes and mast cells.\textsuperscript{2} The number of mast cells is particularly elevated in the detrusor muscle layer and to a lesser extent in the mucosa and submucosa.\textsuperscript{3} Immunofluorescence may show

\begin{table}
<table>
<thead>
<tr>
<th>BIOPSY</th>
<th>CYSTOSCOPY WITH HYDRODISTENSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>not done</td>
<td>not done</td>
</tr>
<tr>
<td>normal</td>
<td>XX</td>
</tr>
<tr>
<td>inconclusive</td>
<td>XA</td>
</tr>
<tr>
<td>positive</td>
<td>XB</td>
</tr>
<tr>
<td></td>
<td>XC</td>
</tr>
</tbody>
</table>

1 cystoscopy: glomerulations grade II-III
2 with or without glomerulations
3 histology showing inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis.

Figure 12.1 BPS types as proposed by the European Society for the Study of IC/PBS (ESSIC). \textsuperscript{33} BPS type indications consist of two symbols: first symbols 1, 2 or 3 indicate grades of abnormal findings at cystoscopy with hydrodistension and second symbols A, B or C indicate grades of abnormality of biopsy findings.\textsuperscript{34} X indicates that no cystoscopy with hydrodistension (first symbol) or no biopsy (second symbol) was done.
strong diffuse or focal colouring of IgA throughout the urothelium. IgE can sometimes be seen on mast cells.\(^4\) In some patients the bladder is fibrotic.

**Hunner’s lesion (Hunner’s "ulcer")**

Hunner’s lesion or Hunner’s "ulcer" is a distinctive inflammatory lesion presenting a characteristic deep rupture through the mucosa and submucosa provoked by bladder distension. Despite the name, it is not an ulcer. ESSIC, therefore, has decided to use the name **Hunner’s lesion** instead of Hunner’s ulcer.\(^3^3\) The detection of Hunner’s lesions is in general only possible at cystoscopy with hydrodistension under proper anesthesia by an experienced urologist with training to detect them.

**Definition of Hunner's lesion**

The following definition by Magnus Fall was accepted by ESSIC: \(^3^3\)

The Hunner’s lesion typically presents as a circumscript, reddened mucosal area with small vessels radiating towards a central scar, with a fibrin deposit or coagulum attached to this area. This site ruptures with increasing bladder distension, with petechial oozing of blood from the lesion and the mucosal margins in a waterfall manner. A rather typical, slightly bullous edema develops post-distension with varying peripheral extension.

**Classic IC**

IC with Hunner’s lesions is called **classic IC** as opposed to **nonulcer IC** when Hunner’s lesions are not found. Classic IC is the same as BPS type 3A, 3B or 3C depending on whether biopsies were done and, if so, the biopsy findings.

It is not clear to date whether the nonulcer and classic types represent different stages of a single disease, or whether they are different disease entities. Patients with the nonulcer type are 10 years younger on average than those with the classic type but this is compatible with both theories. The lack of data that patients with nonulcer type progress to the classic type is in line with the hypothesis that they represent different diseases. However, several circumstances severely hamper the detection of such transitions in clinical practice. These are:

1. the chance to detect Hunner’s lesions are directly related to the urologists’ experience; these skills are likely to be concentrated in particular urological centres;
2. the detection of Hunner’s lesions usually requires cystoscopy with hydrodistension;
3. Hunner’s lesions tend to recur and have likely been already present before their first detection.

This implies that if an existing Hunner’s lesion is not detected (missed) at the first clinical evaluation, it will not be detected later either. But if the initial evaluation correctly did not reveal a Hunner’s lesion, a newly developed Hunner’s lesion is likely to be missed. This makes it almost impossible to document transitions from nonulcer type into classical type. Future studies, in which patients are evaluated and classified according to the ESSIC guidelines,\(^3^3,3^4\) are needed to clarify this issue. The measurement of the nitric oxide (NO) concentration in the bladder lumen may be an important aid for the early detection of
Hunner’s lesions (see below).

Nitric oxide in the bladder lumen

Logadottir et al found that all their IC/BPS patients with Hunner’s lesions had high levels of luminal nitric oxide (NO) while none of the other patients had any significant increase in NO levels in the bladder. Bacterial cystitis may also increase the NO level and must be excluded. The NO level in patients with Hunner’s lesions was not related to symptoms, but rather to the assignment to this specific subgroup. The excellent correlation between luminal NO and the presence of Hunner’s lesions warrants further evaluation of the value of luminal NO measurement for the diagnosis of IC/BPS and the assessment of disease damage of IC/BPS. Moreover, NO measurement during cystoscopy without hydrodistension could be useful for selection of patients during followup that have developed new Hunner’s lesions and need treatment for them.

Prevalence of Hunner’s lesion

In urologic centers with expert skills to detect Hunner’s lesions, Hunner’s lesions are detected in about 50% of the patients with IC/BPS. The majority of IC/BPS patients with Hunner’s lesions, however, are probably not recognized in centers with less experience. This underdiagnosis is probably due to a combination of factors such as:

1. the confusion caused by the name Hunner’s ulcer while it is not an ulcer: the term Hunner’s ulcer suggests that it can be seen at cystoscopy without hydrodistension;
2. the detection of Hunner’s lesions is almost impossible if cystoscopy is performed without hydrodistension;
3. many urologists suppose that Hunner’s lesions are rare; the fact that they rarely detect them is considered to be in line with this false impression;
4. even when cystoscopy with hydrodistension is performed, Hunner’s lesions are likely to be detected only by experienced urologists; biopsy may be necessary to prove that it is a Hunner’s lesion and/or to exclude a carcinoma in situ.

Treatment of Hunner’s lesion

Bladder pain may improve dramatically when the Hunner’s lesions are treated by electrocoagulation, laser or resection. Unfortunately, Hunner’s lesions tend to recur but the interval may vary between several months and e.g. more than 5 years.

Prevalence of IC/BPS

IC/BPS occurs 5-10 times more frequently in women than in men. Prevalence differs per study, in part due to the use of different definitions. In the Netherlands, prevalence is estimated at 8-16 cases per 100,000 women. Recently, however, far higher figures were found in the USA: varying from 197 cases per 100,000 women and 41 per 100,000 men to 10% of third year women medical students. IC/BPS is also found in children. Due to the fact that the NIDDK criteria (National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health, Bethesda, MD, USA) exclude the diagnosis of IC in persons under the age of 18 years, there are no figures in the literature concerning the prevalence of IC/BPS in children.

Pathogenesis and etiology

There are various theories concerning the cause of IC/BPS, none of which have been scientifically proven. It is consequently often suggested that IC/BPS may be multicausal. A number of these theories will be briefly discussed below.

Increased permeability of the bladder mucosa

The bladder wall is covered with a mucin layer which includes glycosaminoglycans (GAGs). GAGs are hydrophilic and maintain a stable layer of water between the urothelium and bladder lumen. The theory is that a defect in the GAG causes inflammation of the urothelium through contact with bacteria and toxic agents in the urine. This hypothesis is the rationale for treating IC/BPS with drugs aimed at replacing the GAG layer, such as pentosan polysulfate, heparin, hyaluronic acid and glucosamines.

The potassium sensitivity test (PST) is based on the hypothesis that instilled potassium provokes symptoms such as pain and urgency in case of a permeable bladder epithelium. The PST has been found positive in 66-83% of patients with IC/BPS. The PST has been found positive in 66-83% of patients with IC/BPS but also in similar proportions of patients with cystitis due to radiation and other causes, prostatitis, bladder cancer and even in one third of healthy subjects. The low sensitivity and specificity makes the PST unsuitable as a diagnostic tool on the one hand, and contradicts a central role of increased bladder permeability in the pathogenesis of IC/BPS on the other.

Mast cells

Detrusor mastocytosis is defined as more than 28 mast
cells per mm$^2$ tissue; fewer than 20 are considered to be normal.$^6$ While there is no correlation between the number of mast cells and the severity of the symptoms, there is a correlation, however, with the degree of inflammation in the submucosa and the presence of “ulcers”.$^9$ Most of the mast cells are degranulated due to IgE or other isotypes binding to their Fc receptors. The vasoactive and proinflammatory mediators hereby released, such as histamine, prostaglandins, leuko- trienes and tryptases, may possibly play a role in the pathogenesis. The urine may contain elevated concentrations of methylhistamine and tryptase.

Mast cells can also release mediators under degranulation under the influence of anaphylatoxins, neuropeptides and cytokines.$^{11}$ In patients with spina bifida and fibrosis of the bladder, it has been shown that mast cells stimulate the synthesis of collagen, leading to fibrosis.$^{12}$

Mast cells also occur in the bladder wall in healthy people and in people with bacterial cystitis and bladder carcinoma, albeit in lower numbers.$^{13,14}$ There is no consensus concerning the significance of mast cells in the bladder in IC/BPS.

**Neurogenic factors**

The presence of degranulated mast cells at nerve endings has led to the hypothesis of neurogenic inflammation.$^{15}$ It is believed that stimulation of sensory nerves could lead to the release of neuropeptides and mediators from mast cells. This concept could explain inflammation limited to the bladder without direct damage to or infection of the bladder.$^{16}$

It has been demonstrated that mast cells in the bladders of mice can only provoke antigen-induced inflammation in the presence of neurokinin-1.$^{17}$

**Infection**

One condition for the diagnosis of IC/BPS is the exclusion of any urinary tract infection. However, certain bacteria such as *Ureaplasma urealyticum* and *Mycoplasma hominis* require special culture methods and are therefore easily missed. There are various publications on the positive effects of antibiotics in some IC/BPS patients.$^{18,19}$ A possible role of bacteria in initiating and perpetuating IC/BPS cannot be entirely excluded since the relationship between diseases and microorganisms is a complex one, for example because the consequence of an infection depends on the genetic properties of individuals.

**Toxins in the urine**

In some patients, bladder symptoms may improve following surgical diversion of urine so that the urine no longer enters the bladder. This has led to the theory that the urine of IC/BPS patients contains toxic substances that cause inflammation. Support has been found for this hypothesis in animal experiments.$^{20}$ The improvement after urinary diversion could also be due to the absence of the mechanical effects of bladder volume changes due to filling and emptying of the bladder.

**Urinary markers**

The antiproliferative factor (APF) is a peptide secreted by bladder epithelial cells from patients with IC/BPS.$^{76}$ APF inhibits bladder cell proliferation by means of regulation of cell adhesion protein and growth factor production. It has been detected in 86% of women with IC/BPS, compared with 8% of asymptomatic control women, 12% of women with bacterial cystitis, and 0% of women with vulvovaginitis, yielding sensitivity and specificity values of 91.4% and 90.6%, respectively. The test is advocated as a useful noninvasive means for diagnosing IC/BPS in women.$^{21,77}$ However, no data on the clinical value of the APF test for the diagnosis of IC/BPS are available to support this claim. Moreover, the test is not yet widely available, so it cannot be recommended as a diagnostic tool to date.

Erickson et al measured several urine markers in 24-hour specimens from IC/BPS patients and healthy age-matched controls.$^{79}$ Certain markers were significantly increased in IC/BPS, including APF, epidermal growth factor (EGF), insulin-like growth factor (IGF) binding protein-3 and IL-6. Markers significantly decreased in IC/BPS were heparin-binding EGF-like growth factor, cyclic guanosine monophosphate and methylhistamine. Other markers were not significantly different in the IC/BPS and control groups, including total glycosaminoglycans, epitectin, hyaluronic acid, IL-8, IL-1 and nitrates plus nitrites. Of all markers studied, APF had the least overlap in IC/BPS and control groups. The only significant association of marker with symptom score was a positive correlation of IL-6 with nocturia.

Lamale et al examined histamine, methylhistamine (MH), and IL-6 in the 24-hr urine of IC/BPS patients and healthy controls.$^{80}$ IL-6 and histamine levels were significantly higher in IC/BPS patients than in the controls. MH levels were also higher in IC/BPS patients, but the results were not statistically significant. Of these three markers, no marker alone was able to distinguish as effectively between the patient and the control group.

Boucher et al investigated the number of tryptase positive bladder mast cells and the level of urine tryptase in IC/BPS patients.$^{81}$ Tryptase was measured in
urine samples collected immediately (spot) and during a period of 24 hours. The patients’ spot urine sample tryptase levels were indistinguishable from those of controls. However, the tryptase levels in 24-hour urine samples were greatly elevated only in patients with IC/BPS.

Okragly et al found higher tryptase levels in urine samples of IC/BPS and bladder cancer patients compared to controls. Histological evaluation of tissue from bladder cancer patients confirmed the presence of numerous and degranulated mast cells releasing tryptase into the milieu. This finding suggests that urinary tryptase levels correlate with mast cell degranulation occurring in the bladder.

El-Mansoury et al found that in IC/BPS patients the histamine levels were slightly increased in the spot and 24-hour urine collections. MH, on the other hand, a major metabolite of histamine, was greatly elevated in spot and 24-hour urine samples.

Erickson et al did not find significant associations between urine MH and symptom scores, response to bladder distension, cystoscopic findings or bladder biopsy features, including mast cell count by tryptase staining.

Studies comparing several urinary markers between IC/BPS patients and healthy controls failed to show that urinary markers are useful for discrimination between these groups. But even if parameters that could distinguish IC/BPS patients from healthy subjects were found, these were not of much interest as the distinction between IC/BPS patients and healthy subjects is never a relevant clinical question in patient care. More interesting is the question whether urinary markers correlate with disease activity, disease damage or long-term prognosis in individual patients when measured longitudinally. No such markers have been found to date.

Nitric oxide
See back under Hunner’s lesions for further information on nitric oxide in the bladder lumen.

Phenylacetylglutamine
Fukui et al analyzed urine samples from 10 patients with BPS/IC, 10 with bacterial cystitis and 10 healthy subjects using a non-targeted quantitative analysis of tissue and bio-fluids for low molecular mass organic endogenous metabolites. A urinary marker of IC/BPS was identified as phenylacetylglutamine (PAGN). The urinary level of PAGN measured relative to creatinine (Cr) was significantly elevated in IC/BPS patients (mean 0.25mg/mg Cr) and healthy subjects (mean 0.11mg/mg Cr). Urinary PAGN/Cr ratios in patients with mild and moderate IC/BPS were higher than for patients with severe IC/BPS.

PAGN is a normal constituent of human urine and is formed in the liver from the condensation of glutamine with phenylacetyl-CoA. Urinary levels may be influenced by medications and/or ingestion of materials with a structure similar to that of phenylalanine. The sweetener aspartame, which contains phenylalanine in its structure, may be metabolized to PAGN. PAGN detected in this study was considered to not have been influenced by medication and/or food, because of the analyzed urine specimens were collected in the morning before medication and/or breakfast.

The reason for IC patients excreting increased PAGN into their urine is not clear. The investigators suggest that urinary PAGN/Cr ratio is a potential marker of IC and that it may indicate an underlying pathological condition in early IC patients, e.g. an abnormal amino acid metabolism.

This is an interesting finding but awaits confirmation in larger patient populations and the reproduction in other laboratoria around the world.

Genetic factors
In a study with 8 monozygote twins and 26 dizygote twins, concordance was found in the monozygote twins varying from 37.5% (confirmed IC/BPS in the co-twin) to 62.5% (probable IC/BPS in the co-twin). In the dizygote twins, concordance was 0%.

The prevalence of IC/BPS among first-degree relatives (parent, brother, sister, or child) of patients with IC/BPS was subsequently compared with the prevalence of IC/BPS in the general population. It was found that adult female first-degree relatives of patients with IC/BPS may have a prevalence of IC/BPS 17 times that found in the general population. This, together with the previously reported evidence showing a greater concordance of IC/BPS among monozygotic than dizygotic twins, suggests a genetic susceptibility to IC/BPS.
Association of IC/BPS with other diseases

IC/BPS often occurs in association with other diseases (table 12.4). This concerns allergies, fibromyalgia, irritable bowel syndrome, inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis and Sjögren’s syndrome.

**Allergy**

In a survey study in the United States, 40.6% of the patients with IC/BPS stated that they suffered from allergy and in a Swedish study 41-47%. In a Japanese study, young IC/BPS patients (20-39 years) were studied in more detail and compared with an older IC/BPS group (50-69 years). The study looked at the number of allergies, the type of IC/BPS symptoms (“painful type” or “frequency and urgency type”), skin tests, blood tests and the course of the IC/BPS following hydrodistension. In two patients from the young group, IC/BPS was considered to be part of generalised allergic diseases. In 25 patients an association was assumed between IC/BPS and the allergy and in 15 of these the symptoms of allergy and IC/BPS alternated or ran parallel. Eleven patients had multiple allergies. In the young patients, 86% had one or more allergies, in the older patients this was 19%.

**Irritable bowel syndrome**

Irritable bowel syndrome (IBS) is a disorder of the function of the intestines and not an inflammatory condition. In questionnaires, 25-43% of IC/BPS patients mentioned they had IBS, 2-4x more than the normal prevalence. IBS is clinically important as abdominal bloating may be responsible for pressure on the stomach (dyspepsia) and bladder. Inflammation is not part of IBS and this is a marked difference with IC/BPS. Further information can be found in the chapter on gastrointestinal disorders.

**Fibromyalgia**

Fibromyalgia occurs in 3% of the population and more commonly in women than in men. The main symptom is pain all over the body, followed by fatigue, morning stiffness and sleep disturbances. In the USA survey 12.8% of IC/BPS patients stated that they suffered from fibromyalgia, 4x more frequent than in the general population. See the chapter on fibromyalgia for further information.

**Crohn’s disease and ulcerative colitis**

Crohn’s disease and ulcerative colitis are inflammatory bowel diseases of unknown cause. Some consider them to be autoimmune diseases. They are often combined under the term inflammatory bowel disease (IBD). This was also the case in the USA survey where 7.3% of IC/BPS patients stated that they suffered from IBD. This is 100x more frequent than in the general population. Further information on Crohn’s disease and ulcerative colitis can be found in the chapter on gastrointestinal disorders.

**Rheumatoid arthritis**

Rheumatoid arthritis (RA) is a systemic disease characterised by the specific way in which joints are affected by chronic inflammation. The disease is associated with systemic lupus erythematosus and particularly with Sjögren’s syndrome. RA occurs in 1-2% of the population. Peek et al mentioned that RA occurred in 13% of their classic IC patients (with “ulcers”) and in 4% of IC patients without ulcers. This is about 10x more frequent than in the general population.

**Systemic lupus erythematosus**

Systemic lupus erythematosus (SLE) is the autoimmune disease which has been known for many years to have a relationship with IC/BPS. IC/BPS in SLE patients was often called lupus cystitis.

In the USA survey 1.7% of IC/BPS patients stated that they suffered from SLE, this is 34x more frequent than in the general population. SLE is a generalised autoimmune disease that occurs more frequently in women (10x) and nonwhites.
100 patients with IC/BPS who were investigated for the presence of Sjögren’s syndrome. The IC/BPS patients had characteristic irritative urinary voiding symptoms, no evidence of infection or other bladder disease, typical cystoscopic appearance demonstrable with maximal bladder distension, bladder biopsies ruling out other diseases and showing inflammation in the mucosa and submucosa with lymphocytic infiltrate and increased numbers of mast cells.

The diagnosis of Sjögren’s syndrome was made according to the recent version of the American-European criteria for Sjögren’s syndrome. These consist of six defined items and can be summarized as follows:

1. ocular symptoms
2. oral symptoms
3. ocular signs
4. salivary gland histopathology
5. salivary gland involvement demonstrated by radiology, scan or salivary flow
6. auto-antibodies to SSA/Ro and/or SSB/La

The criteria allow a diagnosis of Sjögren’s syndrome if four out of items 1-6 (one of which must be 4 or 6) or three out of items 3-6 are present. This latter situation did not occur in our patient group as we did not further investigate patients for Sjögren’s syndrome if both ocular and oral symptoms were absent. Item 3 was only tested if item 1 was present, item 4 was only tested if item 2 was present. Item 5 was never tested because of lack of reproducibility or sensitivity.

Table 12.5 Summary of the criteria for the diagnosis of systemic lupus erythematosus (American Collega of Rheumatology 1997)

<table>
<thead>
<tr>
<th>Item</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>malar rash</td>
<td>68</td>
</tr>
<tr>
<td>discoid rash</td>
<td>60</td>
</tr>
<tr>
<td>photosensitivity</td>
<td></td>
</tr>
<tr>
<td>oral/nasopharyngeal ulcer</td>
<td></td>
</tr>
<tr>
<td>arthritis</td>
<td></td>
</tr>
<tr>
<td>pleuritis or pericarditis</td>
<td></td>
</tr>
<tr>
<td>proteinuria &gt; 0.5 g/day</td>
<td></td>
</tr>
<tr>
<td>neurologic/psychiatric disorder</td>
<td></td>
</tr>
<tr>
<td>haematologic disorder</td>
<td></td>
</tr>
<tr>
<td>anti-DNA, anti-Sm, or antiphospholipid antibodies</td>
<td></td>
</tr>
<tr>
<td>antinuclear antibodies (ANA)</td>
<td></td>
</tr>
</tbody>
</table>

Table 12.6 Prevalence of separate items of the American-European criteria for Sjögren’s syndrome in 100 patients with IC/BPS

<table>
<thead>
<tr>
<th>Item</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ocular symptoms</td>
<td>68</td>
</tr>
<tr>
<td>oral symptoms</td>
<td>60</td>
</tr>
<tr>
<td>abnormal ocular test</td>
<td>16</td>
</tr>
<tr>
<td>abnormal salivary histology</td>
<td>16</td>
</tr>
<tr>
<td>antibodies to SSA/Ro or SSB/La</td>
<td>12</td>
</tr>
</tbody>
</table>

Sjögren’s syndrome

In 1992, as a consequence of the similarity observed between IC/BPS and Sjögren’s syndrome, we began a clinical study of IC/BPS patients to investigate whether the presence of a second autoimmune disease could be demonstrated. We recently presented data on
We concluded that in 8% of our patients with IC/BPS a diagnosis of Sjögren’s syndrome according to the American-European classification criteria could be made. In addition, 20% of the patients had three items of these criteria and no other disease was found that could account for the present items. In a clinical situation, a diagnosis of Sjögren’s syndrome (Sjögren’s-like syndrome or incomplete Sjögren’s syndrome) is justified in these 20% too.27,29

This finding of a relationship between IC/BPS and Sjögren’s syndrome has led to a hypothesis in which autoantibodies against the muscarinic M3-receptor, which is present on exocrine cells and the detrusor muscle, play a role in causing early symptoms as well as causing local inflammation later on.31 Unfortunately, it is not yet possible to reliably demonstrate M3-receptor stimulating and blocking auto-antibodies.

Several authors have also studied the relationship between IC/BPS and Sjögren’s syndrome. Peeker et al surveyed the clinical records of 222 patients with IC/BPS for diagnoses of autoimmune disorders. 43% of the IC/BPS patients had some type or degree of hypersensitivity/allergy. Rheumatoid arthritis occurred in 10% and inflammatory bowel disease (Crohn’s disease and ulcerative colitis) in 1% but no diagnoses of Sjögren’s syndrome were found.24

Using a questionnaire, Leppilahti et al, on the other hand, recently found IC/BPS-like urinary symptoms in 5% of 870 patients with Sjögren’s syndrome.32

**Conclusion**

The clinical relevance of the findings is that a high index of suspicion for Sjögren’s syndrome is indicated in IC/BPS patients and vice versa. The findings also support the possibility of a common pathogenic mechanism such as has recently been proposed.31

### 3. Non-bacterial prostatitis

The prostate is the target of many pathological conditions affecting men of all ages. These conditions range from infections, chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) of a still unknown etiology to benign hyperplasia and cancer. CP/CPPS is one of the most prevalent diseases in the urologic clinic and affects men younger than 50 years old. An autoimmune response against prostate antigens has been suggested in patients with CP/CPPS.46

The author has seen a high prevalence of nonbacterial prostatitis in male patients with Sjögren’s syndrome. This may be less surprising as the lacrimal glands, salivary glands, pancreas and prostate have many properties in common. Definite associations have been found between autoimmune lacrimal gland and salivary gland inflammation (Sjögren’s syndrome) and autoimmune pancreatitis (see chapter on liver and pancreatic disorders).

Yasuda et al 44 described a case of non-bacterial prostatitis in a patient with Sjögren’s syndrome complicated by primary biliary cirrhosis. Histologically, the distribution and subpopulation of infiltrating lymphocytes were similar in the salivary gland, liver, and prostate. Treatment with steroids was successful. Uehara et al 45 described six patients with autoimmune pancreatitis with lower urinary tract symptoms and prostate enlargement in four. Their lower urinary tract symptoms (LUTS) improved after steroid therapy.

It is concluded that there is limited and indirect evidence for an association between non-bacterial inflammatory prostate disorders and Sjögren’s syndrome. Clinical studies are needed to clarify the association.

### 4. Vulvodynia (vulvar pain syndrome)

Vulvodynia or vulvar pain syndrome is defined as a chronic discomfort in the vulva, often described as a burning pain, without objective findings or specific signs of a neurological disorder. Pain in the urogenital area has major effects on women’s daily lives, relationships, sex lives, quality of life and psychological wellbeing.

Vulvodynia is classified according to the localization of the pain in the vulva, whether it is generalized or localized and to whether it arises on provocation of the area or is unprovoked. The pain may also be found in a mixed form.53

Several common and many rare disorders may cause vulval burning and/or pain. Common disorders may be due to irritants, allergy or infection.

Irritant dermatitis is common as affected women may have used topical agents on the vulva. Irritants include soap, panty liners, synthetic underwear, moistened wipes, deodorants, douches, lubricants, spermicides, topical medication, urine, faeces, and excessive vaginal discharge.58 Allergic contact dermatitis may be related to topical medication or sanitary napkins.

Vaginal candidiasis causes vulval burning and itching. Other causes include vulvovaginal atrophy (oestrogen deficiency), recurrent herpes simplex infection, herpes zoster and post-herpetic neuralgia, lichen sclerosus, erosive lichen planus, Behçet’s syndrome, cicatricial pemphigoid, Sjögren’s syndrome, vulval intraepithelial neoplasia, and carcinoma.58
Terminology
The localized, provoked form was previously termed vulvar vestibulitis, as clinical examination of these patients confirmed vestibular erythema and inflammatory cells in skin biopsies from the vestibule. Vestibulodynia, the type of vulvodynia that is localized only in the vestibule, is classified as primary or secondary. Primary vestibulodynia has been present since first tampon use or intercourse. Secondary vestibulodynia develops after a time without pain on intercourse or on insertion of a tampon.

Women who present with a history of pain characterized by a generalized, diffuse distribution arising spontaneously without demonstrable cause were previously given the diagnosis dysesthetic vulvodynia. This term has been replaced by generalised, unprovoked vulvodynia.

Epidemiology
The reported prevalence of a disorder strongly depends on the criteria used for the diagnosis and the population studied. Prevalence estimates suggest that women suffering from vulvodynia make up about 4% of the general population, and about 15% of gynecologic clinic populations. A survey of 994 women using stricter criteria suggested that 1.3% of women had ongoing vulvodynia and 1.7% reported past symptoms.

The cause
The cause of vulvodynia is believed to be a condition with a multifactorial etiology, with organic or functional components. A possible explanation is an increased number of C-afferent nociceptors in the skin. This suggests a change in the nerve supply to the affected area, which could be a possible pathophysiological basis for increased pain sensitivity on touch or even constant pain. An increase has also been found in the number of mast cells.

A chronic inflammatory process in the mucosa has been suggested to underly the local proliferation of nerves as described above with central pain sensitization as a result.

A correlation between HPV infection and vulvodynia has also been suggested but is not confirmed.

Theories focusing on vulvodynia as a functional disorder are based on the documented effect of treatment by cognitive therapy as well as pelvic floor awareness training and stretching exercises. However, hypertonicity and spasms in the pelvic floor musculature may be secondary to the chronic changes in the mucosa.

The evidence that women with vulvodynia present psychopathological traits to a greater degree than women without vulvodynia seems to be growing. Many diseases, however, with known causes today, were once falsely considered to result from psychopathology. The lesson is that an unknown cause of a disease should not be interpreted as a psychosomatic cause if real evidence is lacking.

Diagnosis
Vulvodynia is a diagnosis that can be made after the exclusion of all known possible causes such as infection (candidiasis, herpes), inflammation (e.g. lichen planus), neoplasia (Paget’s disease, planocellular carcinoma) or a neurological disorder (herpes neuralgia, spinal nerve compression).

Vulvodynia and associated disorders
Fibromyalgia and irritable bowel syndrome were found to occur 3-4x more often in patients with vulvodynia than in a control group. Vulvodynia patients were also found to have more often a history of chronic yeast vaginitis and urinary tract infections.

Peters et al found that almost 60% of women with IC/BPS had vulvodynia.

Treatment
Many treatment regimes are employed throughout the world in the treatment of vulvodynia. Randomized clinical studies exist and are increasing in numbers on the efficacy of treating vulvodynia with topical applied lidocaine gel, biofeedback, surgery and cognitive behavioral therapy. The evidence behind treatment with antidepressive medicine, local botox injection or local lidocaine injection is based on retrospective cohort studies. It is recommended that the patient initially be encouraged to follow general advice, despite the lack of evidence, on hygiene and then later to try local treatment regimes or systemic treatment regimes.

General hygiene advice includes the wearing of cotton underwear, no underwear at night, avoidance of allergenic irritants (e.g. perfumes, toiletries, soap) in the vulvar region, application of oil to the vestibule before bathing, application of moisturising cream to the affected area of the vulva after bathing and avoiding the use of panty-liners.
CHAPTER 12 UROGENITAL DISORDERS

JOOP P VAN DE MERWE - SJÖGREN’S SYNDROME: INFORMATION FOR PATIENTS AND PROFESSIONALS

Prognosis

Vulvodynia was traditionally considered a chronic pain disorder, with symptom remission considered rare. Recent surveys of non-clinic-based populations show that in a substantial proportion of women who reported past vulvodynia symptoms the symptoms have resolved. Reed et al.\(^5\) found that during a 2-year follow-up, each year about one in 50 women developed symptoms of vulvodynia, and one in 10 women with vulvodynia reported remission of symptoms.

5. Dyspareunia

Dyspareunia is defined as painful sexual intercourse and is mainly attributed to pelvic disorders, such as vaginal dryness or vaginal infection. Vaginal lubrication is not related to the production of fluids from the local glands but is mostly a transudate through the vaginal walls and is also derived from the cervical mucous. Insufficient vaginal lubrication has usually multifactorial causes but is most commonly related to an oestrogen deficiency, lack of adequate sexual stimulation or both.

It is well known that dyspareunia is common in patients with Sjögren’s syndrome. Skopouli et al.\(^5\) found that 40% of their premenopausal Sjögren’s patients had dyspareunia. An obvious cause was found in half of their patients, although in some patients with normal cytological findings dyspareunia was also reported. Despite the normal vaginal mucosa observed in premenopausal patients with dyspareunia, all patient tissues showed focal perivascular infiltrates in the dermis, a finding which was not seen in the dermis of the normal controls. This lymphocytic perivasculitis could be involved in the pathogenesis of dyspareunia through impaired transudate and inadequate lubrication during sexual intercourse.

Possibly, the vaginal tissues may be affected by an inflammatory process as in other organs, such as the exocrine glands or kidney interstitium.\(^5\)

Dyspareunia in patients with Sjögren’s syndrome may also be related to associated disorders such as IC/BPS.\(^6\)

References

mast cell activation may be used as histopathologic diagnostic


17.  http://www.nice.org.uk/CG040


86. Association of Reproductive Health Professionals (ARHP); http://www.arhp.org

Latest additions or modifications (date: dd.mm.yyyy)

date | addition/modification
--- | ---
23.01.2009 | Information on genetics added (ref 43)
10.02.2009 | Paragraph added on non-bacterial prostatitis title of chapter changed
26.02.2009 | Minor corrections
15.10.2009 | Information on history of disease definition (references 63-69); Information of potassium sensitivity test (PST) and the antiproliferative factor (APF); ref 70-77. Other markers: ref 78-85.
31.03.2010 | Inclusion of table 12.3