BPS and pregnancy

Woman can be advised that the effect of pregnancy on the severity of BPS symptoms can be variable. ✓

BPS treatment options considered safe in pregnancy include oral amitriptyline and intravesical heparin. ✓

Although one course of DMSO may be used prior to pregnancy for symptom remission with good pregnancy outcomes (delivery at term, normal birth weight and postnatal symptom control), DMSO is known to be teratogenic in animal studies. D

1. Purpose and scope

This guideline aims to provide evidence-based information for primary and secondary care clinicians on the symptoms and treatment options for bladder pain syndrome (BPS) in women, together with an appreciation of the current uncertainties surrounding this condition.

2. Definition and epidemiology

The widespread definition for BPS is that proposed by the European Society for the Study of BPS (ESSIC) in 2008[1] as 'pelvic pain, pressure or discomfort perceived to be related to the bladder, lasting at least 6 months, and accompanied by at least one other urinary symptom, for example persistent urge to void or frequency, in the absence of other identifiable causes'. More recently, the American Urological Association[2] has described BPS as 'an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks duration, in the absence of infection or other identifiable causes'; this definition is preferable as it allows treatments to be initiated soon after symptom presentation. BPS may be associated with negative cognitive, behavioural, sexual or emotional consequences, as well as symptoms suggestive of sexual dysfunction according to the European Association of Urology.

The term BPS has been recommended rather than the previous names of interstitial cystitis (IC) and painful bladder syndrome. IC was first described in 1887 by Skene and in 1914 Hunner described the nontrigonal ulcers and bladder epithelial damage, known as 'Hunner's ulcers'.[3] More recently, these are referred to as Hunner lesions. In 1987, the National Institute of Diabetes and Digestive and Kidney Diseases,[4] one of the US National Institutes of Health, developed diagnostic criteria for the condition with the following inclusions: pain associated with bladder or urinary frequency, and glomerulations (pinpoint petechial haemorrhages) on cystoscopy or classic Hunner lesions seen after hydrodistension under anaesthesia to 80–100 cm water pressure for 1–2 minutes, where the glomerulations must be diffuse and present in at least three quadrants of the bladder at a rate of at least 10 per quadrant and not along the path of the cystoscope as this may be an artefact. Hunner lesions may be seen as inflamed friable areas or nonblanching areas in the chronic state. These strict criteria meant many patients were underdiagnosed so a new term, painful bladder syndrome, was proposed in 2002 by the International Continence Society as 'suprapubic pain related to bladder filling, accompanied by other symptoms, such as increased daytime and night-time frequency, in the absence of any identifiable pathology or infection'. The International Continence Society reserved the diagnosis of IC to patients 'with typical cystoscopic and histological features'.[5]

BPS is a chronic condition with unknown aetiology. Cystoscopic findings have been omitted from the 2008 definition, as positive findings, such as glomerulations, have been found in asymptomatic patients and inclusion of cystoscopic findings into the disease criteria runs the risk of excluding symptomatic patients. As the definition of BPS has evolved, it is seen now as a diagnosis of exclusion with no definitive diagnostic test; hence, it is difficult to estimate prevalence, which can be dependent on whether symptoms are clinician assigned or patient reported. A large American study[6] found prevalence rates of 2.3–6.5%. BPS is between two and five times more common in women than men.[7–9] A systematic review found the most commonly reported symptoms of BPS to be bladder/pelvic pain, urgency, frequency and nocturia.[10] A number of expert panels, including the ESSIC,[1] American Urological Association,[2] European Association of Urology[11] and International Consultation on Incontinence,[12] have published symptom-based diagnostic criteria for BPS. All include the symptoms of pain related to the bladder, at least one other urinary symptom, absence of identifiable causes and minimum duration of symptoms of 6 weeks[2] to 6 months. Although there are very limited data on BPS in the UK, a survey of urogynaecologists[13] has shown variable practice regarding its diagnosis and management.

3. Identification and assessment of evidence

This guideline was developed in accordance with standard methodology for producing Royal College of Obstetricians and Gynaecologists (RCOG) Green-top Guidelines. MEDLINE, EMBASE and the Cochrane Library were searched. The search was restricted to articles published between 2006 and October 2015 and limited to humans and the English language. The databases were searched using the relevant Medical Subject Headings (MeSH) terms, including all subheadings, and this was combined with a keyword search. Search terms included 'bladder pain syndrome', 'interstitial cystitis', 'painful bladder syndrome', 'pelvic pain' and 'urogynaecology'. The National Guideline Clearinghouse, National Institute for Health and Care Excellence (NICE) Evidence Search, Trip and Guidelines International Network were also searched for relevant guidelines.

Where possible, recommendations are based on available evidence. Areas lacking evidence are highlighted and annotated as 'Good Practice Points'. Further information about the assessment of evidence and the grading of recommendations may be found in Appendix I.

4. Initial presentation and assessment

4.1 What initial clinical assessment should be performed?

BPS is a chronic pain syndrome and the principles of management of chronic pain should be used for the initial assessment of this condition. C

A thorough medical history should be taken and physical examination performed. ✓

The initial consultation is aimed at generating trust between the patient and the caregiver. In chronic pain syndromes, it is well recognised that a favourable patient rating of the initial consultation is associated with greater likelihood of complete recovery at follow-up.[14] Patients should be encouraged to talk about their symptoms and any theories that they have about the origins of the pain. This allows engagement in further investigations and management of their condition.[15,16] It is important to explain that BPS is a chronic condition with periods of fluctuating symptom severity, where symptoms may be life-long.

Evidence level 3

Symptom assessment forms the basis of the initial evaluation. This is discussed in section 5.3. The location of the pain has been described in several studies and the most commonly reported sites are the bladder, urethra and vagina. The description of the pain ranges from pressure and aching to a burning sensation. A study of 565 patients with the condition was used to identify factors that can aggravate and alleviate the condition. Voiding was found to relieve the pain in 57–73% of patients. Pain was aggravated by stress (61%), sexual intercourse (50%), constrictive clothing (49%), acidic beverages (54%), coffee (51%) and spicy foods (46%). The Events Preceding IC study of 158 women with BPS[17–19] found that pain worsened with certain food or drink, and/or worsened with bladder filling, and/or improved with urination in 97% of patients.

As the diagnosis of BPS is one of exclusion, it is important to rule out other possible causes of bladder pain. The history taken should include details of previous pelvic surgery, urinary tract infections (UTIs), sexually transmitted infections, bladder disease and autoimmune disease. Other conditions commonly associated with BPS, such as irritable bowel syndrome, vulvodynia, endometriosis, fibromyalgia, chronic fatigue syndrome and autoimmune diseases like systemic lupus erythematosus and Sjögren's syndrome, should be enquired about while taking a clinical history. The location of the pain, and relationship to bladder filling and emptying should be established. The characteristics of the pain, including trigger factors and onset, correlation with other events and description of the pain, should be recorded. It should be explored whether the woman has any history of physical or sexual abuse as this can be associated with pelvic pain.[20] This can be achieved using preformed questionnaires as this can be a sensitive topic. Information should be sought about prior or current use of oral contraception, which a systematic review[21] has shown may be associated with BPS symptoms.

Evidence level 3

Physical examination should be aimed at ruling out bladder distension due to urinary retention, hernias and painful trigger points on abdominal palpation. A genital examination should be performed to rule out atrophic changes, prolapse, vaginitis and trigger point tenderness over the urethra, vestibular glands, vulvar skin or bladder. Features of dermatosis, including vulvar or vestibular disease, should be looked for. An evaluation of the introitus and tenderness during insertion or opening of the speculum should be made. Superficial/deep vaginal tenderness and tenderness of the pelvic floor muscles should be assessed during the course of the examination. Cervical pathology should be excluded. A bimanual pelvic examination is helpful to rule out abdominal, cervical or adnexal pathology.

Evidence level 4

4.2 *What baseline investigations should be performed?*

A bladder diary (frequency volume chart) should be completed. ✓

A food diary may be used to identify if specific foods cause a flare-up of symptoms. ✓

Urine should be tested to rule out a UTI as this is a prerequisite for diagnosis of BPS. Investigations for urinary ureaplasma and chlamydia can be considered in symptomatic patients with negative urine cultures and pyuria. C

In those with a suspicion of urological malignancy, urine cytology should be tested. Cystoscopy and referral to urology should be initiated in accordance with local protocols. C

A 3-day fluid diary with input and output is useful for initial assessment (for an example diary see Appendix II). Patients with BPS classically void small volumes, so this is useful to identify the severity of the storage symptoms. The first morning void is a useful guide to the functional capacity of the bladder. The bladder diary can also be used to reinforce behavioural strategies and, where necessary, pharmacological treatment. Estimation of residual urine volumes after an episode of micturition should be assessed using bladder scans as part of initial investigations if there are concerns about incomplete bladder emptying.

Maintaining a diary to record food intake and its association with pain can be useful to identify if certain types of food cause symptoms to flare up.

A dipstick should be performed and where there is a suggestion of a UTI, a culture and sensitivity test should be obtained with consideration given to testing for acid-fast bacilli where there is sterile pyuria. Other more common causes of sterile pyuria that should be considered are urinary tract stones, partially treated UTIs and carcinoma in situ of the bladder. Ureaplasma is not isolated in routine culture tests, so would need to be specifically looked for.

A study of 92 patients diagnosed with BPS[22] demonstrated that the condition itself was not associated with persistence of bacterial or viral DNA on bladder biopsy which were negative for adenovirus, cytomegalovirus, herpes simplex virus types I and II, human papillomavirus (all subtypes) and *Chlamydia trachomatis*. These findings exclude a chronic infective aetiology for the condition. A separate study,[23] looking at the clinical characteristics of 87 women with the condition, found that 12% had a past history of chlamydia and therefore, it is important to rule this out with appropriate investigations.

Evidence level 2–

In the presence of persistent microscopic haematuria, urine cytology is usually indicated and cystoscopy considered. Persistent microscopic haematuria should be managed in accordance with local protocols for investigating haematuria. In a study of 148 patients with BPS,[24] at least one episode of haematuria was reported in 41% of cases over the preceding 18 months. In this group, of those who agreed to a full evaluation, no cases of malignancy were identified. No statistically significant differences were found in age, bladder capacity, presence of Hunner lesions or glomerulations between patients with haematuria and those without.

5. Diagnosis of BPS

5.1 What are the differential diagnoses?

BPS is a diagnosis of exclusion and other conditions should be excluded.

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ESSIC has published a list of differential diagnoses, by expert consensus.[1] These include:

- malignancy, e.g. bladder carcinoma/carcinoma in situ, cervical, uterine or ovarian cancer
- infection of the urinary or genital tract
- overactive bladder
- radiation cystitis or drug-mediated cystitis, e.g. cyclophosphamide, ketamine
- bladder outlet obstruction or incomplete bladder emptying
- calculus of the bladder or lower ureter
- urethral diverticulum
- pelvic organ prolapse
- endometriosis

Evidence level 4

- pudendal nerve entrapment or pelvic floor muscle-related pain
- irritable bowel syndrome
- diverticular disease of the bowel.

Evidence level 4

Ketamine is used as a recreational drug due to its hallucinogenic effects. Unfortunately, its abuse has led to ketamine cystitis, where the bladder becomes ulcerated and fibrosed with urinary tract symptoms, such as frequency, urgency and haematuria, along with renal impairment.

5.2 *What investigations are used to diagnose BPS?*

Bladder biopsies and hydrodistention are not recommended for the diagnosis of BPS. Cystoscopy does not confirm or exclude the diagnosis of BPS, but is required to diagnose/exclude other conditions that mimic BPS. ✓

Potassium sensitivity test, urodynamic assessment and urinary biomarkers should not be used in the diagnosis of BPS. Urodynamic tests may be considered if there is coexisting BPS and overactive bladder (and/or stress urinary incontinence and/or voiding dysfunction) that are not responsive to treatment. C

Cystoscopy without hydrodistension is expected to be normal (except for discomfort and reduced bladder capacity) in the majority of patients with BPS.

Characteristic cystoscopic findings that have been ascribed to BPS include post distension glomerulations, reduced bladder capacity and bleeding. Cystoscopy may be used to aid in classifying BPS (Appendix III). However, cystoscopy findings correlate poorly with symptoms. In the IC Database Study,[25] 150 women underwent cystoscopy and hydrodistension, and there was no correlation observed between severity of symptoms and the finding of glomerulations or bleeding following hydrodistension. Pain, urgency and reduced bladder capacity were associated with the presence of Hunner lesions in 11.7% of the women. Similar findings have been reported in other studies[26,27] along with glomerulations in asymptomatic women.

Pathological features have been described in patients with BPS, including inflammatory infiltrates, detrusor mastocytosis, granulation tissue and fibrosis, but these are nonspecific. The diagnosis of BPS cannot be made or excluded on the basis of any specific finding on bladder biopsy, and these features are not required for the diagnosis. In a study of 108 people with BPS,[28] no correlation was found between histological and cystoscopic findings. In an earlier study of 50 patients,[29] there was a correlation with reduced bladder capacity, inflammation and mast cell count; however, cystoscopic and histological findings showed large variation. Bladder biopsy may be used to classify BPS (Appendix III) or may be indicated to exclude other pathologies, such as carcinoma in situ, if suspected by a focal lesion or abnormal cytology. Hunner lesions are present in type 3 BPS and can be associated with reduced bladder capacity.

Evidence level 2–

Caution should be exercised as there is the recognised risk of bladder perforation and rupture associated with cystoscopy and hydrodistension.[30]

Evidence level 3

