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International Journal of Surgery

journal homepage: www.theijs.com

Review

The ‘evil twin syndrome’ in chronic pelvic pain: A systematic review of prevalence studies of bladder pain syndrome and endometriosis

S.A. Tirlapur^{a,c,*}, K. Kuhrt^b, C. Chaliha^c, E. Ball^c, C. Meads^{a,d}, K.S. Khan^{a,c}^a Women's Health Research Unit, Queen Mary, University of London, Turner Street, London E1 2AB, United Kingdom^b Barts and The London School of Medicine and Dentistry, London E1 2AB, United Kingdom^c Barts Health NHS Trust, The Royal London Hospital, Whitechapel Road, London E1 1BB, United Kingdom^d Health Economics Research Group, Brunel University, Uxbridge, Middlesex UB8 3PH, United Kingdom

ARTICLE INFO

Article history:

Received 6 October 2012

Received in revised form

11 January 2013

Accepted 6 February 2013

Available online 15 February 2013

Keywords:

Chronic pelvic pain

Bladder pain syndrome

Painful bladder syndrome

Interstitial cystitis

Endometriosis

Prevalence

ABSTRACT

Background: Chronic pelvic pain (CPP), a common gynaecological presentation, may be due to bladder pain syndrome (BPS) or the co-existence of BPS and endometriosis, known as the ‘evil twins syndrome’.

Objectives: To estimate the prevalence of BPS and the co-existence of BPS and endometriosis in women with CPP.

Data sources: We searched until March 2012: The Cochrane Library, DARE (1997–2012), EMBASE (1980–2012), Medline (1950–2012), PSYCHINFO (1806–2012), Web of knowledge (1900–2012), LILACS (1982–2012) and SIGLE (1990–2012) with no language restrictions. We manually searched through bibliographies and conference proceedings of the International Continence Society.

Study selection: Observational studies of women suffering from CPP, who were not pregnant or suffering from cancer, who underwent a laparoscopy and cystoscopy to investigate their symptoms. Study selection, data extraction and quality assessment was performed independently by two reviewers. Statistical analysis was performed to estimate prevalence and confidence intervals (CI).

Results: Nine studies were included with 1016 patients with CPP. Study quality and diagnostic assessment varied. The mean prevalence of BPS was 61% (range 11–97%, CI 58–64%, $I^2 = 98%$). The mean prevalence of endometriosis was 70% (range 28–93%, CI 67–73%, $I^2 = 93%$) and co-existing BPS and endometriosis was 48% (range 16–78%, CI 44–51%, $I^2 = 96%$).

Conclusion: Almost two thirds of women presenting with CPP have BPS. Large variations in prevalence may be due to variable study selection and quality. Clinicians need to actively investigate patients for BPS, a condition that appears to co-exist with endometriosis.

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1. Background

The diagnosis and treatment of chronic pelvic pain (CPP) has a large financial burden on health care economies. Bladder pain syndrome (BPS) is a recognised cause of CPP. It can have a huge impact on quality of life and sexual function.¹

Abbreviations: BPS, bladder pain syndrome; CI, confidence interval; CPP, chronic pelvic pain; ESSIC, European Society for the Study of Interstitial Cystitis/Painful Bladder Syndrome; IC, interstitial cystitis; NIDDK, National Institute of diabetes and digestive and kidney diseases; OLS, O’Leary-Sant; PBS, painful bladder syndrome; PRISMA, preferred reporting items for systematic reviews and meta-analyses; PUF, pelvic pain urgency/frequency; SD, standard deviation.

* Corresponding author. Women’s Health Research Unit, Queen Mary, University of London, 58 Turner Street, London E1 2AB, United Kingdom. Tel.: +44 207 882 5883; fax: +44 207 882 2552.

E-mail address: s.a.tirlapur@qmul.ac.uk (S.A. Tirlapur).

BPS is defined as the symptoms of CPP, bladder pressure or discomfort along with at least one other urinary symptom in the absence of any identifiable pathology or infection.^{2,3} This definition was proposed by the European Society for the Study of Interstitial Cystitis/Painful Bladder Syndrome (ESSIC) in 2008. The condition can be further classified by cystoscopy grading and biopsy results. BPS was formerly known as interstitial cystitis (IC) and painful bladder syndrome (PBS). It has an unknown aetiology with a reported prevalence between 5 and 16 per 100,000 of the population.^{4,5} The prevalence of BPS amongst women with CPP is unknown. The co-existence of diseases in CPP, such as BPS and endometriosis, described by Chung et al. as the ‘evil twins syndrome’^{6,7} can make management very difficult.⁸ While the term ‘the evil twin syndrome’ is not a medical definition, it conveys the misery of the co-existence of these two chronic pain conditions.

The purpose of this systematic review was to estimate the prevalence of BPS in women suffering from CPP. Secondly we

estimated the prevalence of endometriosis and the co-existence of BPS and endometriosis within this group of women.

2. Methods

Our systematic review was conducted and reported in accordance with the PRISMA statement.⁹

3. Data sources

A search through the following databases was performed until March 2012: The Cochrane Library, DARE (1997–2012), EMBASE (1980–2012), Medline (1950–2012), PSYCHINFO (1806–2012), Web of knowledge (1900–2012) and LILACS (1982–2012). Grey literature was searched through SIGLE (1990–2012). There were no language restrictions.

3.1. Search strategy

We used MeSH headings and keywords for ‘chronic pelvic pain’ and ‘chronic pain’ combined using the Boolean operator ‘and’ with the terms ‘interstitial cystitis’ or ‘painful bladder syndrome’ or ‘bladder pain syndrome’ or ‘urinary frequency’ or ‘urinary urgency’. The search was restricted to those studies involving female patients. A hand search of bibliographies from relevant articles and conference proceedings of the International Continence Society was performed to identify articles not electronically cited, as prevalence studies are not well indexed in database searches.

3.2. Study selection

Relevant studies on CPP were identified which met the following criteria:

3.3. Participants

Women suffering from chronic pelvic pain with, or without, urinary symptoms suggestive of IC, PBS or BPS, who were not pregnant or suffering from cancer, who underwent a laparoscopy and cystoscopy to investigate their symptoms. Patients diagnosed solely on intravesical potassium sensitivity test (PST) were excluded. CPP was defined as intermittent or constant pain in the lower abdomen or pelvis of at least 6 months duration, not occurring exclusively with menstruation or intercourse and not associated with pregnancy.¹⁰

3.4. Outcome

Most of the studies were performed prior to introduction of the BPS disease nomenclature, but for the purpose of this review all those with IC were considered to have a symptom based diagnosis of BPS, as this would logically happen under the new disease classification. BPS was defined according to the 1987 National Institute of diabetes and digestive and kidney diseases (NIDDK) criteria. The patient needed to have glomerulations on cystoscopy or a classic Hunner’s ulcer, and either pain associated with the bladder or urinary urgency. Glomerulations are punctuate petechial hemorrhages on the bladder wall.¹¹ These were diagnosed after two minutes of bladder distension under anaesthesia. At least ten glomerulations were needed in at least three quadrants of the bladder.¹²

3.5. Study selection

A systematic review was performed on the prevalence of BPS in women with chronic pelvic pain. This included cross-sectional studies, which are neither prospective nor retrospective but

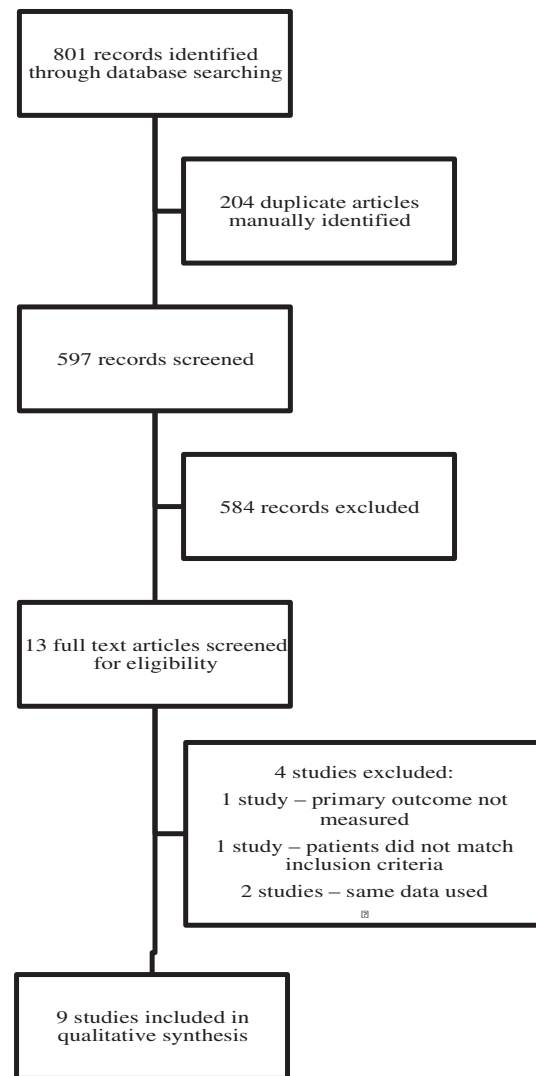


Fig. 1. Study selection for a systematic review on prevalence of bladder pain syndrome amongst women with chronic pelvic pain.

measure the given condition at one point in time. Cohort studies were also included as it is possible to get prevalence figures from the baseline data collection phase.

3.6. Data extraction and quality assessment

The data were independently extracted by two reviewers (SAT, KK) using a pre-designed data collection form. Data were collected for patient characteristics (number of participants, age and ethnicity), study details (study design, location, setting, and participant recruitment as part of the study quality assessment to assess possible selection bias) and outcomes assessed (diagnostic tools and rates of BPS, endometriosis and co-existing pathology).

Quality assessment was performed to assess the overall quality of the studies used in this systematic review. It was carried out by one reviewer and checked by a second reviewer. Studies not published in English were translated by individuals with command of the relevant language.¹³ Data from one study was extracted from a conference abstract¹⁴ where the full article could not be obtained. A quality assessment checklist was developed to evaluate internal validity using the following characteristics^{15,16}: (a) Study design to determine if BPS assessment had been performed prospectively to

Table 1
Study characteristics for papers included in the systematic review of bladder pain syndrome and endometriosis.

Study	Country	Mean age in years (age range)	Ethnicity	Number of patient	Duration of study (months)	Source of recruitment
Cheng 2012	Australia	30	Not documented	150	29	Specialist clinic
Chung 2002	USA	19–62	Not documented	60	12	Specialist clinic
Chung 2005	USA	18–60	Not documented	178	24	Specialist clinic
Clemons 2002	USA	35.2 (20–53)	73% Caucasian, 16% Hispanic, 2% African American, 9% other	45	7	Operating list
Paulson 2011	USA	Not documented	Not documented	284	72	Operating list
Rackow 2009	USA	13–25	96% Caucasian, 4% African-American	28	168	Operating list
Shahmohamady 2005	USA	36 (20–60)	Not documented	92	Not documented	Specialist clinic
Stanford 2005	USA	32.7	Not documented	64	12	Community gynaecology clinic
Villegas 2011	Columbia	32.6 (17–53)	Not documented	115	26	Specialist clinic

minimise recall bias; (b) Adequacy of sampling by assessing whether participant recruitment was random or consecutive; (c) Sufficiently high response rate (>80%); (d) Use of diagnostic criteria to diagnose BPS to ensure participants response rates are a true representation of the underlying condition; (e) Sample size calculation so as to ascertain prevalence reliably. A study was considered 'high quality' if it complied with 3/5 quality criteria.¹⁷ External validity was considered separately as the representativeness of the sample for the general population (source of sample).⁸

3.7. Data synthesis

The prevalence and 95% confidence interval (CI) was computed for each study. Heterogeneity was assessed using I² using the Metadisc statistical software package.¹⁸ Pooled results were given for information only as the results of individual studies were too heterogenous to be used as combined results. Results with I² > 50% are considered highly heterogenous.

4. Results

The search identified 801 citations (Fig. 1). After removal of duplicates there were 597 citations, of which 13 were deemed relevant and their full papers were retrieved. Four studies were excluded; in one only the secondary outcome of co-existing BPS and endometriosis was measured, in another the presenting condition was BPS rather than CPP and two studies reported the same patient population, as confirmed by the corresponding author. Nine studies were included in the systematic review.

4.1. Study characteristics

The nine included observational studies were performed between 1990 and 2011 and included 1016 patients in total. The study characteristics are summarised in Table 1.

In all the studies, even though the disease nomenclature may have varied, the diagnosis was defined using the NIDDK criteria. The diagnosis of BPS ranged from 11%¹⁹–97%,⁷ with a mean prevalence of 61% (58–64%). Five of the studies were prospective in design. Only one study performed sample size calculations using Piface software.¹⁷ There was a lack of reporting about whether participants were randomly or purposefully recruited, making it difficult to assess external validity, although, in three studies participants were recruited retrospectively from theatre operating lists. Seven studies were considered 'high quality' (Fig. 2). In one study routine bladder biopsies were performed when glomerulations were seen on cystoscopy.²⁰ In 44% of these patients, normal histopathology was noted. In two studies bladder biopsies

were performed; one to rule out carcinoma and in the other where no cause was identified on cystoscopy.

The prevalence of endometriosis was given in all nine studies. It ranged from 28%¹⁹–93%,⁷ with a mean prevalence of 70% (CI 67–73%) (Fig. 3). It was diagnosed by visual inspection on laparoscopy with biopsy confirmation of disease performed in 3 studies.^{6,7,19} In 2 other studies^{20,21} biopsies were obtained to confirm the diagnosis of endometriosis where possible. The co-existence of endometriosis and BPS was given in seven studies. The prevalence ranged from 16%²²–78%,⁷ with a mean prevalence of 48% (CI 44–51%) (Fig. 3).

In five (45%) studies the affected patient group was identified through their symptoms and clinical examination. In the other four studies (44%) validated questionnaires were used; one used the IC symptom index problem index (O'Leary Sant questionnaire, OLS) which correlated with the diagnosis of BPS in 94% of patients, two used the pelvic pain urgency/frequency (PUF) questionnaire, showing higher PUF scores in the BPS patients, and one used both questionnaires to assess the degree of BPS, showing higher scores in the BPS patients (mean PUF score of 8.6 and OLS score of 7.5).²⁰ Three studies (33%) used the visual analogue scale questionnaire to assess pain. The mean pain score for CPP ranged from 5.3–8, and 5.4–7 for BPS.^{20–22}

5. Discussion

A range of prevalence rates for BPS were reported in the literature. The large variation in rates observed in this paper may be explained by the variable study quality and sample selection. The highest prevalences were noted in patients recruited from specialist clinics and operating lists. From the nine studies, in 4 studies patients suffered from CPP and urinary symptoms and notably, some of the highest prevalences of BPS were seen in these

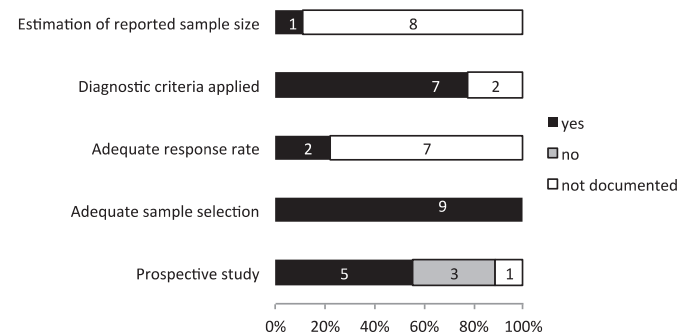
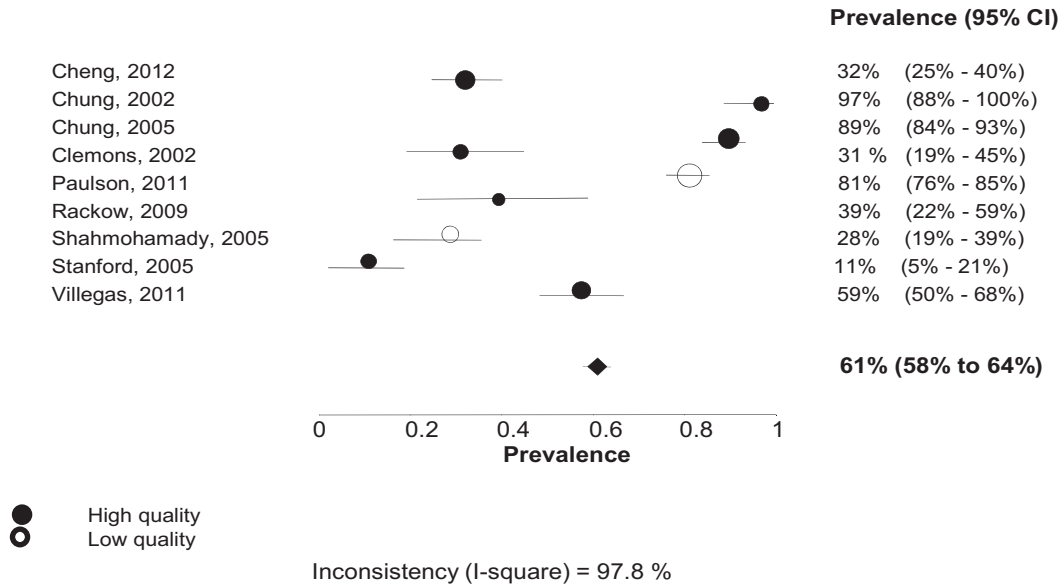
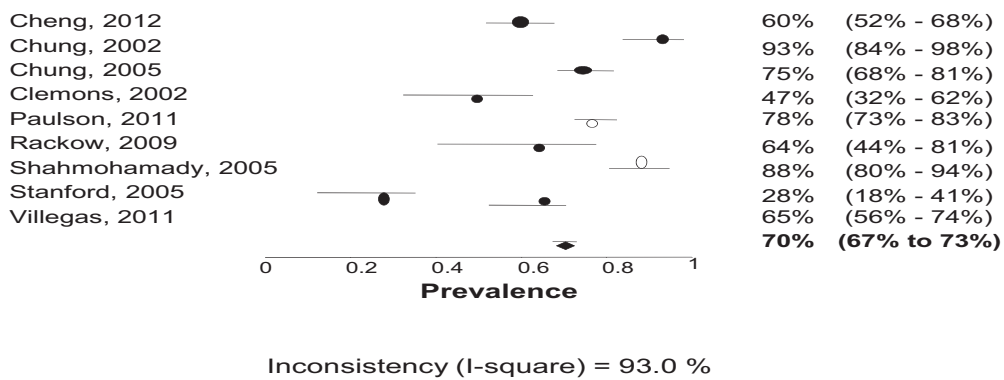


Fig. 2. Quality of studies included in the systematic review of the prevalence of bladder pain syndrome and endometriosis.

3a: Prevalence of BPS amongst women with CPP



3b: Prevalence of endometriosis amongst women with CPP



3c: Prevalence of BPS and endometriosis amongst women with CPP

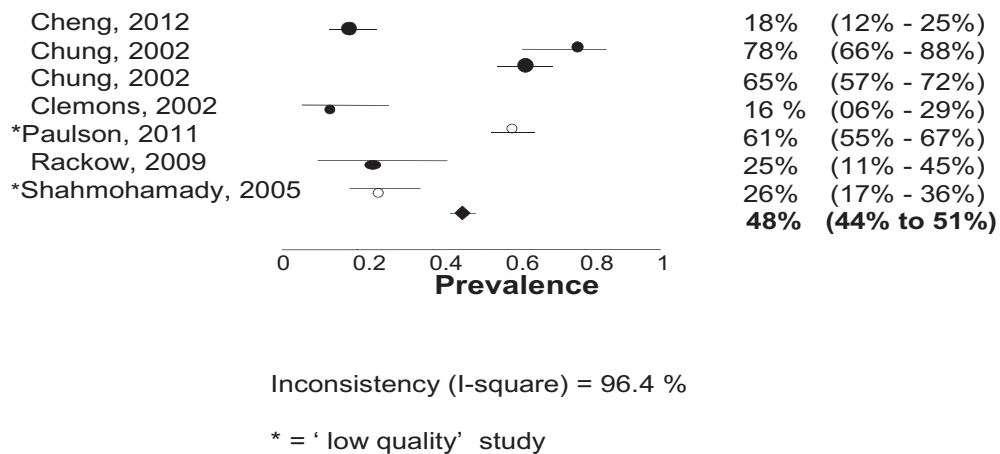


Fig. 3. Prevalences of bladder pain syndrome (BPS), endometriosis and co-existing BPS and endometriosis amongst women with chronic pelvic pain (CPP).

patients.^{6,7,14,21} In 6 (67%) of the studies, the authorship team had a special interest in urogynaecology.

We complied with PRISMA, searched comprehensively, selected studies and extracted data in duplicate, and synthesised results appropriately. This systematic review highlights the fact that almost two thirds of patients presenting with CPP have BPS, a finding that merits consideration. In all the studies, the diagnosis was made by the presence of urinary symptoms and positive cystoscopy findings. A limitation is that both cystoscopic normality and bladder lesions are poorly correlated with histopathology,²³ leading to the risk of misdiagnosis of patients. BPS has a wide symptom spectrum with imprecise clinical characterisation. Bladder pain or bladder filling pain is not captured in the commonly used questionnaires like OLS and PUF. The value of these questionnaires as a diagnostic tool is debatable.²⁴ There was limited information about the ethnicity of the participants in the included studies, which makes it difficult to apply the results of this review internationally. Literature shows that the prevalence of BPS does not vary with ethnicity although minority women appear to be symptomatic for longer than Caucasian women, while the prevalence of endometriosis appears to be higher in Asian women than other ethnicities.^{25–27}

Identification of BPS is challenging, as the clinical presentation can be similar to several other conditions, which can lead to delays in diagnosis and inappropriate treatment. In 2011 the American Urological Association published guidelines for the diagnosis and management of IC and BPS, which recommended diagnosis by clinical history and physical examination, with cystoscopy only used as a diagnostic tool in complex presentations. Thus allowing initiation of conservative treatments, such as pain relief, behavioural modification and stress management.²³ We found an overlap between BPS and endometriosis. Clinicians need to be aware of the existence of co-existing pathology and actively investigate urinary symptoms and BPS as a cause of CPP and commence active management early.

Ethical approval

Not needed.

Funding

None.

Author contribution

SAT – Conception, design, search, study selection, data extraction, data synthesis and writing and revising the manuscript.

KK – Data extraction.

CC – Revising manuscript.

EB – Revising manuscript.

CM – Advice on search strategies, quality assessment, data analysis and presentation and revisions to manuscript.

KSK – Conception, design, data synthesis, writing and revising the manuscript.

Conflict of interest

None.

Acknowledgements

Ana Gutierrez for her help with translation of a foreign manuscript.

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