SEXUAL MEDICINE REVIEWS REVIEWS

Interstitial Cystitis/Bladder Pain Syndrome Treatment: A Systematic Review of Sexual Health Outcomes

Andrew Chen, MD,[1] Robert H. Shahiyan, BA,[2] and Jennifer T. Anger, MD[1]

ABSTRACT

Introduction: Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic condition with highly prevalent negative consequences on sexual health and quality of life. However, there is a lack of consensus regarding treatment options that improve sexual function in this population. This study aims to review the current literature on sexual health outcomes in patients treated for IC/BPS.

Methods: We conducted a systematic review of the literature on sexual health outcomes after treatment of IC/BPS. PubMed, MEDLINE, EMBASE, CINHAL, and Google Scholar were queried, and results were screened using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Inclusion criteria for this review were: IC/BPS was clearly defined in the cohort, sexual health outcomes were measured as the primary or a secondary outcome, manuscript was written in English from January 2000 to April 2020. Studies on cystectomy were excluded as radical surgery is a confounding factor for sexual dysfunction.

Results: We identified 1611 items with our search algorithm and determined that 10 studies ultimately met inclusion criteria. 4 of 10 studies reported improved sexual function after treatment. 4 of 10 studies were randomized control trials and reported no improvement in sexual function in each of the therapies that were investigated. Data were conflicting regarding the effect of intravesical hyaluronic acid.

Conclusion: This systematic review demonstrates the lack of focus on sexual health outcomes in studies of the IC/BPS. There was no strong evidence that any modality used to treat IC/BPS also improves sexual function despite the higher prevalence in this population. **Chen A, Shahiyan RH, Anger J. Interstitial Cystitis/Bladder Pain Syndrome Treatment: A Systematic Review of Sexual Health Outcomes. Sex Med Rev 2021;xx:xx–xx.**

INTRODUCTION

Interstitial cystitis (IC) and bladder pain syndrome (BPS) are chronic debilitating conditions that affect both women and men with a frequency of 5:1.[1] The current definition accepted by the American Urological Association (AUA) and the Society for Urodynamics and Female Urology (SUFU) is: "An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks duration, in the absence of infection or other identifiable causes."[2] While other societies have variations on the definition, most agree that it is a diagnosis of exclusion after ruling out other pelvic pain etiologies.[3-7] Prevalence studies for IC/BPS have been difficult to conduct due to variable presentation of the disease, but is estimated to be between 0.83% and 6.5% for women.[8-10] In men, the prevalence rates are even less clear as chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) can be difficult to delineate from IC/BPS. Suskind et al. reported an estimate of 1.9% to 4.2% in men and that 17% of men met the definition for both IC/BPS and CP/CPPS.[11]

In addition to a constellation of bladder and voiding symptoms, interstitial cystitis has also been associated with significant sexual health consequences that can lead to reduced quality of life.[12,13] However, diagnosis and evaluation of sexual health is complex and often incomplete. Sexual dysfunction is multifactorial and involves multiple domains such as hypoactive sexual desire disorder, sexual aversion disorder, female sexual arousal disorder, lubrication difficulties, female orgasmic disorder, and pain disorders.[14] While validated questionnaires such as the Female Sexual Function Index (FSFI) have been established as quantifiable measures of sexual dysfunction, they are often insufficient for diagnosis without evaluation of psychological distress.[15] Furthermore, studies often report total questionnaire scores without domain scores (eg. desire, arousal, orgasm, pain).[16]

Current literature reports that women with IC/BPS have been found to have increased rates of dyspareunia, altered desire, reduced lubrication, and reduced orgasm frequency in comparison to the rest of the population.[17-19] In the RAND Interstitial

Received June 15, 2020. Accepted December 21, 2020.

[1]Department of Urology, Cedars-Sinai Medical Center, Los Angeles, CA, USA;

[2]UCLA David Geffen School of Medicine, Los Angeles, CA, USA

https://doi.org/10.1016/j.sxmr.2020.12.005

Cystitis Epidemiology (RICE) study, 61% of women reported problems with sexual arousal and 64% reported lack of desire. Prevalence of dyspareunia is estimated to be between 49% to 90% of patients and is likely related to bladder contact during intercourse. Severity of deep dyspareunia in women with endometriosis was found to be associated with the diagnosis of IC/BPS; furthermore, irritation during intercourse has been reported to exacerbate other IC/BPS symptoms.[20] Another study by Bogart et al. estimated the overall prevalence of sexual dysfunction in any domain to be as high as 88%.[17] FSFI scores in IC/BPS patients were also found to be significantly lower than controls, and highly correlated to severity of symptoms.[19,21,22]

The AUA offers a stepwise approach in treating interstitial cystitis. First-line therapy includes general relaxation, education, and behavioral modification while second-line therapy includes oral and intravesical agents. Utilization of hydrodistension or treatment of Hunner's lesions is third-line therapy. After failure of less invasive options, fourth-line therapy such as intradetrusor botulinum toxin A or neuromodulation can be performed. Finally, fifth-line treatment involves use of cyclosporin A while the most invasive sixth-line treatment is urinary diversion with or without cystectomy.[4] Often times patients undergo multimodal treatment as symptom profiles can differ significantly between individuals.[23]

Given that IC/BPS is associated with an increased prevalence of sexual dysfunction, we aim to review the current literature on sexual health outcomes in patients treated for IC/BPS.

METHODS

Search Strategy

We performed a systematic review of the literature based on the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Framework.[24] We established a review strategy to identify studies that differentiated ICS/BPS patient as a study cohort and evaluated sexual dysfunction following IC/BPS treatment. The primary source of information was PubMed, MEDLINE, EMBASE, CINHAL. The search algorithms were defined in MeSH and is found in Table 1. We also queried peer-reviewed studies in Google Scholar based on the search phrase in Table 1. The queried results were screened according to the following criteria: a clearly defined cohort of IC/BPS patients, studies must have been written in English from January 2000 to April 2020, and sexual function/dysfunction must have been evaluated as either a primary or secondary outcome.[25,26] Studies on cystectomy for IC/BPS were excluded due to the confounding variables on sexual function after radical surgery. Incomplete trials were also excluded from analysis. Duplicate search results were screened out. The remaining studies were then read in full text to ensure they met inclusion and exclusion criteria for analysis. Two independent reviewers evaluated each study in detail, and a third reviewer was used if there were any uncertainties regarding whether a study met inclusion criteria.

Table 1. Database search terms utilized

Database Search		
Source	Search Algorithm	N=
Pubmed, MEDLINE, EMBASE, CINAHL	(interstitial cystitis OR "bladder pain syndrome") AND (sexual function OR sexual dysfunction OR dyspareunia)	1143
Google Scholar	"interstitial cystitis" AND "sexual function" AND "treatment"	468

Data Collection

The studies included for qualitative synthesis were reviewed to determine the study design and IC/BPS treatment modality assessed. The following data fields were collected for each study: authorship, year published, study design type, sample size of study cohort, sex of study cohort, therapy evaluated, questionnaire or method used to evaluate sexual function, statistical significance of change in sexual function outcomes, and whether there was improvement in sexual function. A meta-analysis of quantitative data was unable to be performed as sexual function was evaluated differently across studies examining the same treatment.

RESULTS

Our search algorithm returned with 1611 results (See PRISMA Flowchart, Figure 1). After removing duplicates and screening all searches, 10 studies met the inclusion criteria listed previously for this systematic review (Table 2). Four of the included studies were randomized controlled trials (RCT), two were retrospective cohort studies, and four were prospective cohort studies. The four RCTs examined non-invasive or minimally invasive therapies.

Non-Pharmacological Therapy

Both studies that examined the effect of non-pharmacologic treatments were RCTs and had cohorts consisting of female participants exclusively.[27,28] They both utilized the FSFI questionnaire as their method of evaluating sexual health outcomes in their patients. Kanter et al. randomized IC/BPS patients to Mindfulness-Based Stress Reduction (MBSR) or usual care (UC). In the experimental arm, patients were provided 8 weekly sessions of MBSR. The authors found no difference in FSFI scores at 8 weeks post-treatment (P = 0.6).[27] FitzGerald et al. conducted a multicenter RCT that aimed to compare Global Therapeutic Massage (GTM) to pelvic floor myofascial physical

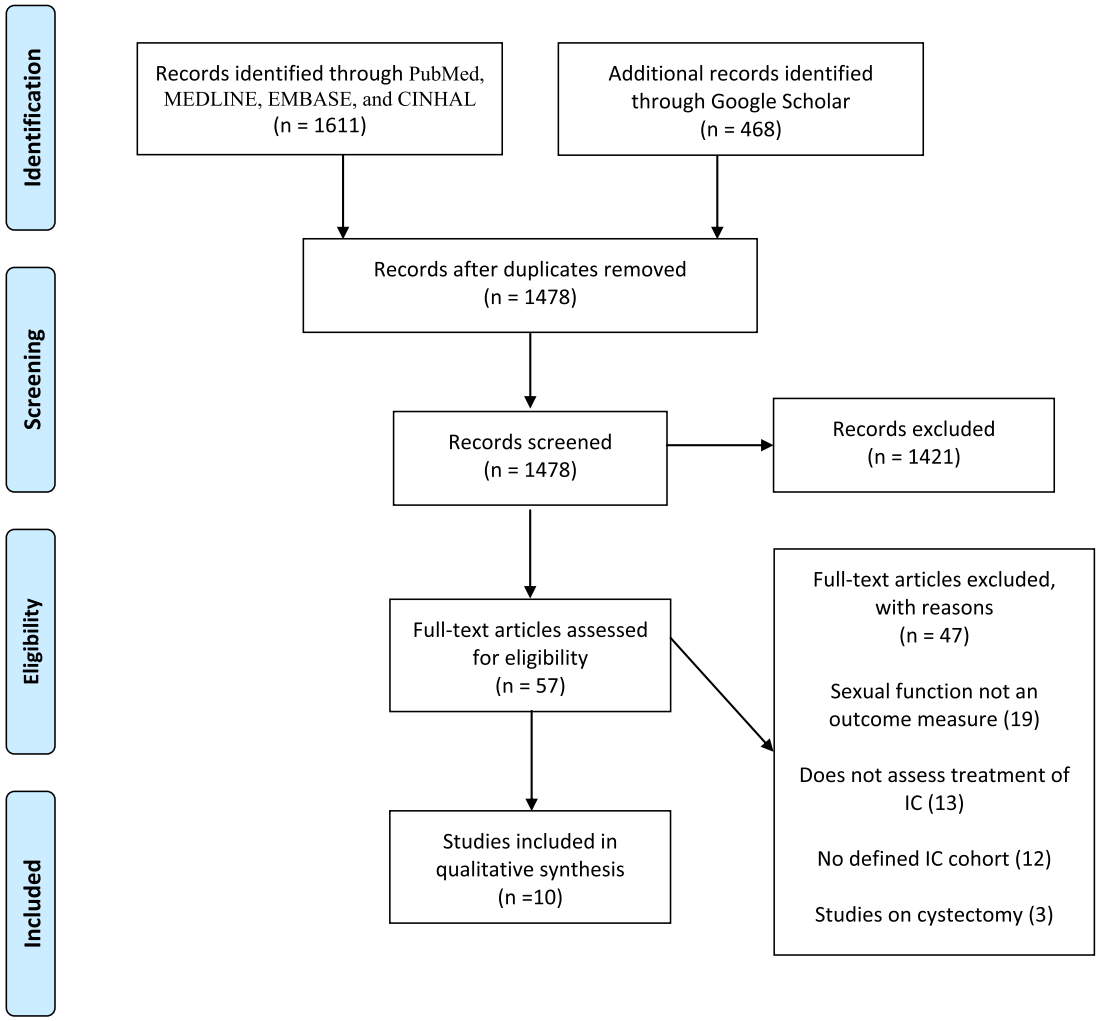

Figure 1. PRISMA flow diagram

therapy (MPT) for the treatment of women with newly symptomatic IC/BPS.[28] 42 patients were randomized to GTM and 39 were randomized to MPT. This study also did not show any statistically significant improvement in FSFI scores for either treatment group during follow ($P = 0.67$).[28]

Oral and Intravesical Therapy

Eight of the 10 studies examined pharmacological and minimally invasive treatment options. Of these 8, 4 studies reported an improvement in sexual function measures. Foster et al. studied the use of amitriptyline in treatment naïve patients with IC/BPS.[29] They randomized 231 patients, both male and female participants, to treatment and placebo groups but did not find any difference in sexual function outcomes utilizing FSFI and SHIM scores. Nickel et al. studied pentosan polysulfate sodium (PPS) and found a mean increase of 8.9 in Medical Outcomes Sexual Functioning Scale (MOS-SFS) scores in their cohort ($P = 0.005$).[30] Additionally, there was a significant correlation between both symptom index scores and mental quality of life components with sexual function scores.

Multiple studies evaluated the use of intravesical instillation therapies. The majority (n=4) utilized hyaluronic acid. The results of the studies were conflicted as two reported improvement in sexual function outcomes while two reported no significant change.[31-34] Hung et al. found an improvement in the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ)-9 scores for their female patients up to 6 months after treatment ($P < 0.0001$), while Arslan et al. reported significant improvement in FSFI score at 6 months for both combined hyaluronic acid/chondroitin sulfate and chondroitin sulfate alone in comparison to prior to treatment.[33,34] However, Kim et al. and Liang et al. reported no significant changes in Pelvic Pain and Urgency/Frequency Patient Symptom Scale scores pertaining to sexual function or PISQ-12 scores, respectively, from pretreatment baseline in women.[31,32]

The effect of intravesical chondroitin sulfate alone on sexual function is also conflicted in the included samples. While Arslan

Table 2. Summary of Reviewed Studies (n=10)

Author	Year	Therapy	Type of Study	N =	Sexual Function Assessment Method	*p*-value	Outcome
Kanter et al.	2016	Mindfulness	RCT	20	FSFI	0.6	Not Improved
Fitzgerald et al.	2012	Myofascial PT	RCT	81	FSFI	0.67	Not Improved
Foster et al.	2010	Amitriptyline	RCT	231	FSFI, IIEF	N/A	Not Improved
Nickel et al.	2008	Pentosan polysulfate sodium	Prospective	128	MOS-SFS	0.005	Improved
Hung et al.	2014	Intravesical HA	Prospective	103	PISQ9	<.0001	Improved
Welk et al.	2008	Intravesical Lidocaine/ Bicarbonate/Heparin	Prospective	23	FSFI	<0.001	Improved
Kim et al.	2014	Intravesical HA	Retrospective	33	PUF	0.77	Not Improved
Nickel et al.	2010	Intravesical CS	RCT	65	FSFI	N/A	Not Improved
Liang et al.	2018	Intravesical HA	Prospective	22	PISQ12	0.16	Not Improved
Arslan et al.	2019	Intravesical CS and HA/CS	Retrospective	68	FSFI	0.03 CS, 0.035 HA/CS	Improved

RCT: randomized controlled trial, FSFI: Female Sexual Function Index, PT: physical therapy, IIEF: International Index of Erectile Function, MOS-SFS: Medical Outcomes Sexual Functioning Scale, HA: hyaluronic acid, PUF: Pelvic Pain and Urgency/Frequency, PISQ: Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire, CS: chondroitin sulfate, GRA: Global Response Assessment

et al. reported a statistically significant benefit, a prospective, randomized, double-blind, inactive vehicle study did not report similar findings.[34,35]

Welk et al. treated their cohort of IC/BPS patients who were experiencing dyspareunia with an intravesical solution of lidocaine, bicarbonate, and Heparin. They enrolled a total of 23 sexually active patients and reported an overall improvement in their patients FSFI score from a mean of 1.9 pre-treatment to 3.7 post-treatment at 3 weeks follow-up ($P < 0.01$).[36]

DISCUSSION

The goal of this study was to provide a comprehensive review and analysis of the current literature on how treatments for IC/BPS affect sexual function. We did not find strong evidence that any one treatment modality for IC/BPS significantly improves sexual dysfunction.

Assessing sexual outcomes is especially difficult in the ICS/BP population for several reasons. Firstly, there is a wide variety of national and international guidelines on the nomenclature, diagnosis, and treatment of IC/BPS. As demonstrated by this systematic review, sexual function is also measured with a multitude of different questionnaires and scoring systems. This prevents accurate comparison of outcomes across studies examining the same treatment option. Patients are also often treated with multimodal therapies and have differing treatment histories, which are major confounders in cohort studies.

The literature screened into this systematic review examined a variety of treatment options defined by the AUA.[4] First-line treatment options were ineffective for improving sexual function in outcomes analysis of the two RCTs. However, the longest duration of follow-up in these studies was 12 weeks and could be an inadequate duration to observe the effects of conservative strategies. Kanter et al. also mentioned this as a possible reason for why they did not observe a difference in their cohort.[27]

Evidence was highly conflicting regarding the efficacy of intravesical hyaluronic acid on improving sexual dysfunction in IC/BPS; two studies reported improvement and two did not. Kim et al. found no improvement in sexual function after instillations, but the cohort was heterogenous and included patients with symptoms refractory to previous treatments. The sample included women who had failed hydrodistention, pentosan polysulfate, and/or transurethral cauterization.[31] Liang et al. also reported negative sexual function findings, but pretreatment included hydrodistention prior to intravesical instillation.[32] It is possible that failure of previous targeted bladder interventions such as hydrodistention is associated with failure of intravesical hyaluronic acid in improving sexual function. Intravesical hyaluronic acid may only be efficacious in a subset of IC/BPS patients.

Studies included in our review also tended to utilize questionnaire scores that aggregated sexual dysfunction domains. It is possible that IC/BPS treatment improves only specific sexual dysfunction domains with being reflected in the overall questionnaire score.

CONCLUSION

There is a lack of strong evidence that any treatment modality studied thus far improves sexual dysfunction in the IC/BPS population. While sexual dysfunction is more prevalent in IC/BPS patients than controls, the results of our systematic review underscores that treatment of the disease itself may be insufficient to

address the multifactorial contributors of sexual dysfunction. Future studies are needed to not only better characterize the nature of sexual dysfunction in IC/BPS but also to target it for improvement as a component of treatment.

Corresponding Author: Jennifer T. Anger, MD, Department of Urology, Cedars-Sinai Medical Center, Los Angeles, CA, USA; E-mail: Jennifer.anger@cshs.org

Conflict of Interest: The authors report no conflicts of interest.

Funding: None.

REFERENCES

1. Jones CA, Nyberg L. Epidemiology of interstitial cystitis. **Urology 1997;49:2–9.**
2. Hanno P, Dmochowski R. Status of international consensus on interstitial cystitis/bladder pain syndrome/painful bladder syndrome: 2008 snapshot. **Neurourol Urodyn 2009;28:274–286.**
3. Homma Y, Ueda T, Tomoe H, et al. Clinical guidelines for interstitial cystitis and hypersensitive bladder updated in 2015. **Int J Urol 2016;23:542–549.**
4. Hanno PM, Erickson D, Moldwin R, Faraday MM. American urological a. diagnosis and treatment of interstitial cystitis/bladder pain syndrome: AUA guideline amendment. **J Urol 2015;193:1545–1553.**
5. Wein AJHPM, Gillenwater JY. Interstitial Cystitis: An Introduction to the Problem. In: Hanno PMSDR, Krane RJ, Krane RJ, Wein AJ, editors. Interstitial Cystitis. London: Springer; 1990.
6. van de Merwe JP, Nordling J, Bouchelouche P, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. **Eur Urol 2008;53:60–67.**
7. Daniels AM, Schulte AR, Herndon CM. Interstitial cystitis: an update on the disease process and treatment. **J Pain Palliat Care Pharmacother 2018;32:49–58.**
8. Clemens JQ, Link CL, Eggers PW, et al. Prevalence of painful bladder symptoms and effect on quality of life in black, Hispanic and white men and women. **J Urol 2007;177:1390–1394.**
9. Berry SH, Bogart LM, Pham C, et al. Development, validation and testing of an epidemiological case definition of interstitial cystitis/painful bladder syndrome. **J Urol 2010;183:1848–1852.**
10. Konkle KS, Berry SH, Elliott MN, et al. Comparison of an interstitial cystitis/bladder pain syndrome clinical cohort with symptomatic community women from the RAND Interstitial Cystitis Epidemiology study. **J Urol 2012;187:508–512.**
11. Suskind AM, Berry SH, Ewing BA, et al. The prevalence and overlap of interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome in men: results of the RAND Interstitial Cystitis Epidemiology male study. **J Urol 2013;189:141–145.**
12. Nickel JC, Tripp D, Teal V, et al. Sexual function is a determinant of poor quality of life for women with treatment refractory interstitial cystitis. **J Urol 2007;177:1832–1836.**
13. Sacco E, D'Addessi A, Racioppi M, et al. Bladder pain syndrome associated with highest impact on sexual function among women with lower urinary tract symptoms. **Int J Gynaecol Obstet 2012;117:168–172.**
14. McCool ME, Zuelke A, Theurich MA, et al. Prevalence of female sexual dysfunction among premenopausal women: a systematic review and meta-analysis of observational studies. **Sex Med Rev 2016;4:197–212.**
15. Meston CM, Freihart BK, Handy AB, et al. Scoring and Interpretation of the FSFI: What can be Learned From 20 Years of use? **J Sex Med 2020;17:17–25.**
16. Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. **J Sex Marital Ther 2005;31:1–20.**
17. Bogart LM, Suttorp MJ, Elliott MN, et al. Prevalence and correlates of sexual dysfunction among women with bladder pain syndrome/interstitial cystitis. **Urology 2011;77:576–580.**
18. Gupta P, Gaines N, Sirls LT, et al. A multidisciplinary approach to the evaluation and management of interstitial cystitis/bladder pain syndrome: an ideal model of care. **Transl Androl Urol 2015;4:611–619.**
19. Peters KM, Killinger KA, Carrico DJ, et al. Sexual function and sexual distress in women with interstitial cystitis: a case-control study. **Urology 2007;70:543–547.**
20. Orr N, Wahl K, Joannou A, et al. Deep dyspareunia: review of pathophysiology and proposed future research priorities. **Sex Med Rev 2020;8:3–17.**
21. Ottem DP, Carr LK, Perks AE, et al. Interstitial cystitis and female sexual dysfunction. **Urology 2007;69:608–610.**
22. Yoon HS, Yoon H. Correlations of interstitial cystitis/painful bladder syndrome with female sexual activity. **Korean J Urol 2010;51:45–49.**
23. Dell JR, Butrick CW. Multimodal therapy for painful bladder syndrome/interstitial cystitis. **J Reprod Med 2006;51:253–260.**
24. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. **PLoS Med 2009;6:e1000097.**
25. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. **J Sex Marital Ther 2000;26:191–208.**
26. Rosen RC, Cappelleri JC, Smith MD, et al. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. **Int J Impot Res 1999;11:319–326.**
27. Kanter G, Komesu YM, Qaedan F, et al. Mindfulness-based stress reduction as a novel treatment for interstitial cystitis/bladder pain syndrome: a randomized controlled trial. **Int Urogynecol J 2016;27:1705–1711.**

28. FitzGerald MP, Payne CK, Lukacz ES, et al. Randomized multicenter clinical trial of myofascial physical therapy in women with interstitial cystitis/painful bladder syndrome and pelvic floor tenderness. **J Urol 2012;187:2113–2118.**
29. Foster Jr. HE, Hanno PM, Nickel JC, et al. Effect of amitriptyline on symptoms in treatment naive patients with interstitial cystitis/painful bladder syndrome. **J Urol 2010;183:1853–1858.**
30. Nickel JC, Parsons CL, Forrest J, et al. Improvement in sexual functioning in patients with interstitial cystitis/painful bladder syndrome. **J Sex Med 2008;5:394–399.**
31. Kim A, Lim B, Song M, et al. Pretreatment features to influence effectiveness of intravesical hyaluronic Acid instillation in refractory interstitial cystitis/painful bladder syndrome. **Int Neurourol J 2014;18:163–167.**
32. Liang CC, Lin YH, Hsieh WC, et al. Urinary and psychological outcomes in women with interstitial cystitis/bladder pain syndrome following hyaluronic acid treatment. **Taiwan J Obstet Gynecol 2018;57:360–363.**
33. Hung MJ, Su TH, Lin YH, et al. Changes in sexual function of women with refractory interstitial cystitis/bladder pain syndrome after intravesical therapy with a hyaluronic acid solution. **J Sex Med 2014;11:2256–2263.**
34. Arslan B, Gonultas S, Gokmen E, et al. Outcomes of intravesical chondroitin-sulfate and combined hyaluronic-acid/chondroitin-sulfate therapy on female sexual function in bladder pain syndrome. **Int Urogynecol J 2019;30:1857–1862.**
35. Nickel JC, Egerdie RB, Steinhoff G, et al. A multicenter, randomized, double-blind, parallel group pilot evaluation of the efficacy and safety of intravesical sodium chondroitin sulfate versus vehicle control in patients with interstitial cystitis/painful bladder syndrome. **Urology 2010;76:804–809.**
36. Welk BK, Teichman JM. Dyspareunia response in patients with interstitial cystitis treated with intravesical lidocaine, bicarbonate, and heparin. **Urology 2008;71:67–70.**