

DISCUSSION

The most important finding of this study is that women with recurrent UTIs have greater urinary frequency and increased perceived bladder sensation in the absence of an active infection than control women. The significantly greater total number of daily voids in the bladder diary in women with recurrent UTI cannot be explained by their larger fluid intake alone nor by selection bias in obtaining bladder diaries and urodynamics only in recurrent UTI patients who complained of increased urinary frequency. In the bladder diary, women with recurrent UTI had significantly smaller average voided volume and significantly greater number of voids per litre of fluid intake than controls. These bladder diary findings are supported by filling cystometry data that showed earlier first desire to void and significantly earlier strong desire to void and smaller maximum cystometric capacity in women with recurrent UTI than controls. The increased bladder sensation on filling cystometry was noted in the absence of any rise in detrusor pressure and in the absence of active UTI as documented by a negative urine dipstick immediately prior to the cystometry. Therefore, based on the criteria established by the International Urogynecological Association and the International Continence Society [9] recurrent UTI have increased bladder sensation or bladder oversensitivity compared with controls.

In an ideal case-control study exploring the hypothesis that women with recurrent UTI have bladder oversensitivity, cases should be women with recurrent UTI and controls should be healthy women with no bladder disorders. Given the difficulty of performing invasive tests such as filling cystometry in healthy women, using our electronic medical records and careful inclusion and exclusion criteria, we identified women with 'pure' stress urinary incontinence to serve as controls. Dikono *et al.* [16] have previously reported that the mean maximum cystometric capacity in women with stress urinary incontinence (493 mL, range 120–1245 mL) is similar to that of healthy controls (531 mL, range 300–780 mL). The number of daytime voids in the control group of our study (median 6.5, range 5–9) is identical to values previously reported in asymptomatic women (6.5,

range 4–8) [15]. These findings suggest that the presence of stress incontinence in the control group did not have any significant effect on micturition variables and bladder function. Therefore, our selection of women with stress urinary incontinence as controls, although not ideal, probably does not affect the validity of our findings.

Since women with recurrent UTI had bladder oversensitivity, we considered the possibility that these women had coexistent IC/PBS. As per the most recent recommendations [17], the diagnosis of IC/PBS is based on clinical criteria (painful symptoms that are perceived to originate from the bladder and associated with frequency or urgency). A clinical diagnosis of IC/PBS was not made by the treating clinicians (first and second authors) for women in the case group. In a previous study, an Interstitial Cystitis Symptom Index score of 5 or greater had 95% sensitivity and 93% negative predictive value for the diagnosis of interstitial cystitis [18]. The median Interstitial Cystitis Symptom Index score for women with recurrent UTI in this study was 4 (range 0–5) and only 4% of women had a score of 5. Additionally the Interstitial Cystitis Problem Index score was low for cases. These findings suggest that women in our case group probably did not have coexistent interstitial cystitis.

The underlying cause of bladder oversensitivity in women with recurrent UTI is not clear, although a neurogenic mechanism seems likely. Visceral pain is transmitted centrally for processing via the spinothalamic tract via 'silent' unmyelinated C-fibres [19]. C-fibres are abundant in the bladder [20] and may undergo electrophysiological changes that result in

the perpetuation of an acute insult into chronic symptoms [19]. During an acute episode of UTI, inflammation of bladder mucosa and underlying nerves results in symptoms of urgency and frequency [20]. It is conceivable that in some women with recurrent UTI, repeated inflammation of the bladder and its mucosa gradually result in hypersensitivity of the nerves of the bladder. Therefore an initial pattern of episodes of UTI and associated symptoms that responds promptly to antibiotics is gradually transformed into a more chronic pattern of persistent symptoms even in the absence of bacteriuria.

Using three different diagnostic methods (urinary nitrites, urine culture and urinary symptoms), Warren *et al.* [1] have shown that a proportion of patients with IC/PBS have an episode of UTI at the onset of disease. Our case-control study suggests that women with recurrent UTI have bladder oversensitivity. Ness *et al.* [5] have reported that women with interstitial cystitis have bladder oversensitivity and decreased threshold of pain stimulation. Prospective studies will be required to determine if bladder oversensitivity can lead to the development of interstitial cystitis in women with recurrent UTI.

Limitations of our study are that although we used validated questionnaires women may have reported symptoms only from episodes of infection. Misclassification bias should also be considered. Women in the control group did not undergo cystoscopy. However, the mean voided volume in women with stress urinary incontinence (195 mL) in our study was similar to reported values (190 mL [20] and 200 mL

TABLE 3 Bladder sensation during filling cystometry and postvoid residual volume in women with recurrent UTI and controls

	Recurrent UTI, N = 41,	Controls, N = 41,	P*
First desire to void (mL)	125 (50–250)	175 (60–264)	0.06
Strong desire to void (mL)	193 (75–350)	289 (255–359)	0.03
Maximum cystometric capacity (mL)	275 (175–359)	392 (166–625)	0.004
Postvoid residual volume (mL)	12 (0–19)	15 (0–22)	0.8

*Wilcoxon rank-sum test.