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Bladder Symptoms in the Early Menopausal Transition

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Abstract

Purpose: Bladder symptoms are common in women and result in use of healthcare resources and poor quality of life. Bladder symptoms have been linked to age and menopause, but controversy exists in the literature. This paper examines factors associated with bladder symptoms in late pre-menopausal and peri-menopausal reproductive stages.

Methods: We analyzed cross-sectional data from a prospective cohort study of midlife women (mean age 48, range 44- 54 years) in northern California. The sample consisted of 158 late pre-menopausal and peri-menopausal women with complete data on bladder symptoms.

Assessments included: anthropometrics, menstrual cycle lengths and symptoms, urine samples for follicular stimulating hormone level, and self-reported health perception and depressive symptoms. Analyses included descriptive bivariate statistics, group comparisons, and regression models.

Results: The most common bladder symptoms were nocturia (72%) at least once per night, and urinary incontinence (50%) at least once per week. Incontinence was less prevalent in African American women compared to European Americans and Latinas ($p=0.001$) and more prevalent in late pre-menopause than in peri-menopause ($p=0.024$). Controlling for age, late pre-menopausal women were more likely to report nocturia compared to women in peri-menopausal stage ($p=.016$), and higher BMI ($p=0.007$), and race ($p=.017$) contributed to the variance in weekly nighttime urinary frequency.

Conclusion: Bladder symptoms were associated with reproductive stage rather than chronological age. Women in late pre-menopause were more likely to experienced nocturia and incontinence than peri-menopausal women. The higher rates of nocturia and incontinence in late stage pre-menopausal women are intriguing and warrant further study.

Keywords: bladder symptoms, pre-menopause, peri-menopause, urinary frequency, nocturia, urinary incontinence, menopause stage, age, ethnicity, BMI

Introduction

Over half of women will experience bladder symptoms at some time over the course of their lives, and bladder problems are common for women regardless of age or menopause status (Cardozo & Robinson, 2002; Lin, Ng, Chen, Hu, & Chen, 2005). Bladder symptoms such as incontinence, urgency, or frequency are commonly associated with a lower quality of life and increased use of healthcare resources (Coyne, Sexton, et al., 2013; Coyne et al., 2014; Holm-Larsen, 2014; Kupelian et al., 2012; Tang et al., 2014). Bladder symptoms may be due to age-related autonomic denervation, decreased bladder muscle tone or increased bladder muscle fatigue (Chen, Chen, Hu, Lin, & Lin, 2003). Parity and medical conditions such as diabetes, obesity, and depression are associated with prevalence and incidence of bladder symptoms (Gopal et al., 2008; Hsu et al., 2015; Link, Steers, Kusek, & McKinlay, 2011; Maserejian et al., 2014; Rortveit, Hannestad, Daltveit, & Hunskaar, 2001; Weiss, 2012). Racial and gender differences in bladder symptoms, specifically symptoms of overactive bladder such as incontinence or urgency have also been reported (Coyne, Margolis, Kopp, & Kaplan, 2012; Coyne, Sexton, et al., 2013; Hsu et al., 2015).

The menopause transition is also associated with increased urinary complaints linked to the drastic reduction in endogenous estrogens yet the literature remains unclear as to whether age or menopause stage has a greater effect on bladder symptoms (Chen et al., 2003; Lin et al., 2005; Mac Bride, Rhodes, & Shuster, 2010; Portman & Gass, 2014; Robinson, Toozs-Hobson, & Cardozo, 2013). Many of these factors are interrelated and may depend on inherent personal characteristics, health conditions, or life-style situations. Therefore, the purpose of this paper is to describe factors associated with bladder symptoms in late stage pre-menopausal and perimenopausal reproductive stages. Data from a San Francisco cohort of midlife women were used to describe the experience of bladder symptoms by age, reproductive stage and ethnicity.

Based on the Symptom Management Theory (SMT), we hypothesized that age, reproductive stage and menopause transition, race/ethnicity, and childbirth history would help to explain the experience of bladder symptoms for midlife women. Symptom experience is central to this theory, which also recognizes the importance of person and environment in approaching any treatment or management of symptoms (Dodd et al., 2001; Humphreys et al., 2014). When evaluating symptoms, SMT proposes considering multiple personal and clinical factors with the goal of developing effective tailored interventions and improving health outcomes.

Methods

Design and Participants

This cross-sectional research was conducted within a prospective cohort study of midlife women in the San Francisco Bay Area who participated in the University of California San Francisco (UCSF) Women's Health Study. Assessments of bladder symptoms were added to the last three years of the study (years 5-7). Eligible participants were community-dwelling women between 40 and 50 years of age who reported still experiencing regular menstrual periods and denied using hormone replacement therapy in the past 12 months. Women who self-identified as having major health problems or who were taking hormone therapy at initiation of the study were excluded (Choi, Guterrez, Gilliss, & Lee, 2012). The parent cohort study was conducted over 7 years with assessments every 6 months through one year post-hysterectomy, one-year post-initiating hormone therapy, or one year after the last menstrual period (Gilliss et al., 2001).

At baseline, there were 347 women in the study. This sub-study of bladder symptoms is focused on the 158 participants who provided complete data for bladder symptoms. Details of recruitment and protocol were previously reported (Choi et al., 2012; Gilliss et al., 2001). The UCSF Committee on Human Research (CHR) approved the parent study and all participants provided informed consent prior to data collection.

Measures

Bladder symptoms such as day and nighttime urinary frequency, urinary incontinence, and urinary tract infections were assessed using self-report questionnaire measures adapted from other epidemiologic women's health studies focusing on urinary tract function (Bradley et al., 2011; Fitzgerald et al., 2006; Hannestad, Rortveit, Sandvik, & Hunskaar, 2000; Sandvik et al., 1995). Urinary tract infection was assessed using the question: "How many times have you been told that you had a urinary tract infection in the past 6 months?" Daytime and nighttime urinary frequencies were assessed by asking women to think about the past week and report the number of times during the day and the number of times during the night that they urinated on average during the past week. They were then dichotomized as either no nocturia (0) or having nocturia (1) at least once per night on average (Abrams et al., 2002).

Urinary incontinence was assessed by asking the women if they had leaked even a small amount of urine during the past 6 months. Their response options included 1) none, 2) less than once per month, 3) one or more times per month, 4) one or more times per week, and 5) everyday. They were then asked if they had leaked urine in the past 7 days, and if so how many times it was related to an activity (coughing, sneezing, laughing, lifting, etc.) and how many times it was related to sudden urge. Women were considered to have clinically significant urinary incontinence if they reported leakage occurring at least once per week on average and this variable was dichotomized (0 = less than once per week, 1 = at least once per week or daily).

Other participant characteristics assessed by self-report included age, race/ethnicity as African American, Latina, or European American, education (ranging less than high school equivalent to college graduate), income (ranging less than \$31,000 to over \$81,000), perceived health status (rated from 1 = excellent to 5 = poor) and parity (number of live births). Current use of diuretic medications was assessed with a yes or no response.

As part of the parent study, women provided a urine sample for assaying follicular stimulating hormone (FSH), measurement of weight and height to calculate body mass index (BMI), and measurement of waist and hip circumferences to determine waist-to-hip ratio (WHR). Reproductive stage was coded as either 'pre-menopause' or 'peri-menopause' using a combination of menstrual regularity and FSH trends based on Stages of Reproductive Aging Workshop (STRAW) criteria that provide a comprehensive characterization of hormonal and physiological changes associated with menopause in order to standardize clinical and research nomenclature (Harlow et al., 2012).

Depressive symptoms were assessed using the 20-item Center for Epidemiologic Studies Depression (CES-D) Scale that asks participants to self-rate 20 symptoms on frequency of occurrence from 0 (not during the past week) to 3 (5-7 days in the past week). Scores range from 0-60 and a score of 16 or higher indicates risk for clinical depression and need for clinical follow up (Radloff, 1977). The items were internally consistent in this sample (Cronbach alpha coefficient = 0.92).

Statistical Analysis

Descriptive statistics were used to compare demographic and bladder characteristics by race/ethnicity and by reproductive stage. Pearson correlation coefficients (r) or Spearman's ρ were used to examine relationships between continuous variables; Chi square was used to evaluate categorical associations. Independent t-tests and analysis of variance (ANOVA) were conducted to evaluate mean differences in characteristics between racial/ethnic and reproductive stage groups to better understand their bladder symptom experience. A logistic regression model was used to evaluate independent associations between participant characteristics and nocturia, focusing on characteristics reported in the literature to have the potential to influence bladder symptoms: age, race/ethnicity, income, reproductive stage, BMI, depressive symptoms, parity, diuretic usage, urinary incontinence, major illness, and perceived general health status. A logistic

regression was also used to evaluate the impact of the same variables on experience of incontinence. All analyses were performed using SPSS version 22.0 software.

Results

Demographic and Clinical Characteristics

The mean (\pm SD) age of the 158 participants was 48.1 ± 2.2 years; 72 were pre-menopausal and 86 were peri-menopausal. Over 60% of the women evaluated their health as 'very good' or 'excellent' in general. As seen in Table 1, only 8% reported having had a urinary tract infection (UTI) in the past 6 months and there was no significant difference by reproductive stage or race/ethnicity; only 6% ($n=10$) reported taking a diuretic, and the rate was significantly higher in African American women ($\chi^2 = 13.7$; $p = .001$).

[Table 1 about here]

Bladder Symptoms by Race/Ethnicity and Other Socio-demographic Characteristics

The most prevalent bladder symptom (73.2%) for participants in this sample was nocturia reported at least once per night during the past week. Frequency of nocturia was associated with BMI ($\rho = 0.293$, $p < .001$) and diuretic use ($\rho = 0.166$, $p = .039$). There was no race/ethnic difference in the prevalence of nocturia (see Table 2). Only 42 (26.8%) women reported no nocturia in the past week. These 42 women without nocturia ranged from 44 to 52 years of age, half (52%) were European American, and 28 (67%) were peri-menopausal.

Urinary incontinence was the second most common bladder symptom; only 28.5% of the sample reported no experience with incontinence in the past 6 months. Almost half (49.4%) reported that they experienced incontinence in the past week (see Table 2). Urinary incontinence was unrelated to age, BMI, parity, depressive symptoms, or diuretic use. This bladder symptom was significantly associated with race/ethnicity ($\chi^2 = 12.87$, $p = 0.001$). Despite more use of

diuretics and higher BMI, only 27% of African American women reported incontinence compared to 61% of European Americans and 56% of Latinas. Of the 78 participants who reported urinary incontinence, 32 (20%) reported urgency incontinence and 58 (37%) reported leakage related to activity (stress incontinence).

[Table 2 about here]

Bladder symptoms by reproductive stage

Nocturia, UTI, and use of diuretics were not significantly associated with reproductive stage. Peri-menopausal women had a higher BMI (29.5 ± 7.17) compared to women who were late pre-menopausal (28.2 ± 7.45). Reproductive stage was associated with urinary frequency; late pre-menopausal women reported a higher daytime frequency than peri-menopausal women ($t = 2.61, p = 0.010$), but the difference in nighttime frequency did not reach statistical significance ($t = 1.69, p = .093$). Late pre-menopausal women were also significantly more likely to report urinary incontinence ($t = 2.28, p = 0.024$), although differences between types of incontinence (urgency or stress) were not statistically significant given the small numbers for each type of incontinence (See Table 3).

[Table 3 about here]

Regression Analyses

Given the high prevalence of nocturia and urinary incontinence in this sample, logistic regression analyses were conducted to simultaneously examine potential factors that could account for each of these prominent bladder symptoms. Variables in both models included: age, race/ethnicity, income, education, depressive symptoms, diuretic use, perceived general health status, major health problem in the past year, number of live births, reproductive stage, and BMI. As seen in Table 4, the model for experiencing nocturia was significant ($\chi^2 = 29.86, p = .003$) with

the following characteristics included: age, race/ethnicity, income, education, reproductive stage, diuretic use, parity, depressive symptoms, health status, BMI and major health problem in the past year. Controlling for all other variables, BMI ($p = .007$), peri-menopausal stage ($p = 0.016$), and race ($p = .017$) made significant contributions to the overall model. The model for experiencing urinary incontinence was not significant (Table 5).

[Table 4 about here]

[Table 5 about here]

Discussion

In describing the bladder symptom experience for this female cohort of midlife women, we were able to show that the two most prevalent bladder symptoms were nocturia and urinary incontinence. We also found that reproductive stage had more influence on these bladder symptoms than age. Due to the prevalence of these bladder symptoms, it is reasonable to conclude that these women will continue to experience symptoms in the post-menopause reproductive stage (Blumel et al., 2012; Cardozo & Robinson, 2002; Chen et al., 2003; Hannestad et al., 2000). Although this sample of women was healthy when originally recruited, it is possible that developing medical conditions may have contributed to the bladder symptoms, however, developing a major health problem in the past year and general health perception were not significant predictors in the regression model

BMI was the most significant contributor to the experience of nocturia. This finding was not surprising, as obesity and weight gain have been identified as risk factors in bladder symptom occurrence (Chen et al., 2003; Coyne, Wein, et al., 2013). In addition, BMI has also been shown to influence reproductive stage (Santoro & Chervenak, 2004; Santoro et al., 2004; Thurston, Santoro, & Matthews, 2011), and peri-menopause was a significant contributor in the regression model when also controlling for age, parity, diuretic use, race/ethnicity, and BMI.

Women in this sample ranged in age from 44 to 54 years, but age was not a significant factor for the experience of bladder symptoms. Although we hypothesized that reproductive stage would be a factor in bladder symptoms, we were surprised to initially find that women in the late pre-menopause stage were more likely to report urinary incontinence and nocturia compared to women who were peri-menopausal. However, after controlling for age, parity, BMI and other relevant factors, the experience of incontinence was no longer associated with reproductive stage, and the experience of nocturia was associated with peri-menopausal stage rather than late pre-menopausal stage (Table 4). Our findings would suggest that when both age and reproductive stage are considered simultaneously, reproductive stage is more of a factor in bladder symptoms than chronological age.

Similarly, race/ethnicity was initially a factor in the experience of incontinence and nocturia (Table 2). However, after controlling for age, parity, BMI and other relevant factors, the experience of incontinence was no longer associated with race/ethnicity, and African American women remained protected against nocturia (Table 4). The reasons for this finding are not completely clear, however the African American women in this sample had higher BMIs and FSH levels in comparison to European Americans and Latinas of similar age. Race, BMI, and reproductive stage remain consistent in their influence on the experience of nocturia in this group of midlife women (Aydin, Hassa, Oge, Yalcin, & Mutlu, 2014; Cardozo & Robinson, 2002; Hsu et al., 2015). However, use of diuretics, parity, and depressive symptoms were consistent factors that did not influence bladder symptoms in this sample of women.

Although age was not a significant contributor to the experience of nocturia, there was a very narrow age range across this sample of women. The similarity in chronological age proved fortuitous, as it allowed us to see that biological age (reproductive stage) was a greater factor than chronological age. Biological age is highly variable, and can be influenced by multiple factors such as genetics, health status, race and environmental stressors.

The non-significant regression model for experience of incontinence is an interesting finding. Key variables are clearly lacking to gain a deeper understanding of incontinence in midlife women. Incontinence is greatly influenced by physiological factors and co-morbid conditions, and these factors were not fully explored in this study. Fewer variables in the regression model may allow for more statistical power to detect significance with characteristics such as race/ethnicity, reproductive stage, and BMI, and further research is needed on the experience of incontinence in midlife women.

Using Symptom Management Theory as a foundation for this analysis, we explored multiple salient factors associated with women's experience of the two most prevalent bladder symptoms: nocturia and incontinence. These factors should be considered in developing and testing interventions to manage bladder symptoms and improve quality of life for women in any reproductive stage. Symptom management strategies will be best determined by our ability to further deconstruct the bladder symptoms that are most bothersome for the individual woman and tailor appropriate interventions to their expected or desired outcomes.

Study Limitations

Our study has limitations to consider that may influence the conclusions. Given the sample size and demographics of the sample, findings cannot be generalized to all midlife women. Demographic and health data were collected every 6 months over time (Phase 1 Times 1-7, and Phase II Times 8-11), but the bladder symptom questionnaire was included only in Phase II. Data for this analysis were collected in Phase II after some participants were already excluded because of 12 consecutive months of amenorrhea, 12 months of hormone replacement therapy, or having a hysterectomy. Thus, our results are limited to only late pre- and peri-menopausal women between 44 and 54 years of age. Bladder symptom data over a longer time frame and earlier in the pre-menopausal reproductive stage could provide more insight into the onset and timing of bladder symptoms in conjunction with the onset and timing of transitions in menopause stage.

Conclusions/Recommendations

Women are at risk of bladder symptoms due to natural aging and menopause, but when they are most at risk is yet to be determined. Bladder symptoms, such as nocturia and urinary incontinence are associated with significant morbidity and lower quality of life. BMI, peri-menopause reproductive stage, and being Latina or Caucasian were the most significant factors associated with the experience of nocturia in our sample of midlife women. We found no difference in symptom reports by parity, health problems, or depressive symptoms. Further research is needed to determine why bladder symptoms are more common in women of the same age, and how race and age may impact the severity or progression of bladder symptoms.

While differences between pre- and post-menopausal symptoms have been more extensively researched, differences in specific bladder symptom experiences for late pre- and early peri-menopausal stages are less clear, particularly for incontinence. Further research about differences in urinary symptom experience based on reproductive stage, body composition, and race/ethnicity would enhance our understanding of this symptom experience and potentially decrease associated long-term morbidity and improve quality of life for all women across midlife.

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Table 1. Demographic and Clinical Characteristics (N (%) or mean \pm standard deviation)

Participant Characteristics	African American n = 46	Latina n = 41	European American n = 71	Total sample N = 158
Age (yrs)	48.02 \pm 2.24	48.01 \pm 2.61	48.04 \pm 1.94	48.05 \pm 2.20
FSH (IU/DL)	3.27 \pm 5.01	1.38 \pm 1.98	1.33 \pm 1.75	1.75 \pm 2.87*
BMI	30.54 \pm 7.49	28.95 \pm 5.89	27.05 \pm 6.06	28.41 \pm 6.43*
CES-D depressive symptoms (0-60)	10.85 \pm 10.50	9.26 \pm 9.66	11.62 \pm 9.15	10.82 \pm 9.92
Reproductive Status				
Late Pre-menopause	16 (34.8)	21 (51.2)	35 (49.3)	72 (45.6)
Peri-menopause	30 (65.2)	20 (48.8)	36 (50.7)	86 (54.4)
Parity				
0 live births	16 (32)	14 (27)	30 (41)	60 (35)*
1-2 live births	25 (57)	15 (40)	31 (45)	71 (47)
3 or more live births	5 (11)	12 (33)	10 (14)	27 (18)
Education				
< high school	2 (4.4)	4 (9.7)	0	6 (3.8)*
High school or GED	1 (2.1)	6 (14.6)	0	7 (4.4)
Some college	19 (41.3)	13 (31.7)	12 (16.9)	44 (27.8)
College graduate	24 (52.2)	18 (43.9)	59 (83.1)	101 (64.0)
Marital Status				
Married	17 (37.0)	21 (51.2)	42 (59.1)	80 (50.6)*
Living with partner	4 (8.7)	4 (9.8)	14 (19.7)	22 (14.0)
Single/Divorced	24 (52.1)	15 (36.6)	14 (19.8)	53 (33.5)
Widowed	1 (2.2)	1 (2.4)	1 (1.4)	3 (1.9)
Income				
< \$ 30,999	8 (18.7)	10 (25.0)	2 (2.8)	20 (13.0)*
\$31 – 50,999	7 (16.3)	10 (25.0)	10 (14.0)	27 (17.5)
\$51 – 80,999	13 (30.2)	10 (25.0)	13 (18.2)	36 (23.4)
> \$ 81,000	15 (34.9)	10 (25.0)	46 (64.8)	71 (46.1)
	3 missing	1 missing		
Take a diuretic	8 (17.4)	0	2 (2.8)	10 (6.3)*
Perceives general health as 'excellent' (1) or 'very good' (2)	21 (45.7)	24 (58.5)	47 (69.1)	92 (59.0)*
Major health problem in the past year	11 (23.9)	15 (21.1)	11 (26.8)	37 (23.4)

*The 3 groups differed significantly ($F_{[2, 157]} > 3.0, p < .05$)

Table 2. Bladder Symptoms by Race/Ethnicity

Participant Characteristics	African American n = 46	Latina n = 41	European American n = 71	Total sample N = 158
	N (%)	N (%)	N (%)	N (%)
Urinary infection (UTI) past 6 months	2 (4.5)	6 (16.2)	5 (7.2)	13 (8.2)
Incontinence frequency past 6 months				
none	22 (48)	12 (29)	11 (15)	45 (28.5)
about once/month	16 (35)	17 (42)	36 (51)	69 (43.7)
about once/week	6 (13)	9 (22)	19 (27)	34 (21.5)
every day	2 (4)	3 (7)	5 (7)	10 (6.3)
Incontinence last week (yes)	12 (26.1)	23 (56.1)	43 (60.6)	78 (49.4)*
Urinary Frequency	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Day time (number/day)	5.10 ± 1.95	5.66 ± 1.86	6.54 ± 2.11	5.86 ± 2.03*
Night time (number/night)	1.26 ± 0.98	1.07 ± 1.13	1.04 ± 0.99	1.11 ± 1.03

*The 3 groups differed significantly ($F_{[2, 157]} > 5.0, p < .01$)

Table 3. Bladder Symptoms by Reproductive Stage¹ (N = 158)

Bladder symptoms	Late Pre-menopause (n = 72)	Peri-menopause (n = 86)
	N (%)	N (%)
Urinary Tract Infection (UTI) in the past 6 months (yes)	6 (8.5)	7 (8.3)
Incontinence frequency past 6 months		
none	12 (17)	33 (38)
about once/month	38 (53)	31 (36)
about once/week	17 (23)	17 (20)
every day	5 (7)	5 (6)
Incontinent last week (yes)	43 (59.7)	35 (40.7)*
Stress incontinence	31	28
and/or Urge incontinence	18	15
Urinary Frequency	Mean ± SD	Mean ± SD
Day time (number/day)	6.31 ± 2.17	5.48 ± 1.84**
Night time (number/night)	1.26 ± 1.03	0.99 ± 1.01***

¹defined by Stages of Reproductive Aging Workshop criteria (STAW) (Harlow et al., 2012).

* The 2 groups differed significantly (Pearson $\chi^2 = 5.68$, $p = .017$)

** The 2 groups differed significantly ($t = 2.61$, $p = .010$)

*** The 2 groups were not significantly different ($t = 1.69$, $p = .093$)

Table 4. Logistic Regression Summary for Experiencing Nocturia

Nocturia N=158			
Explained Variance: $\chi^2 = 29.86, p = .003$			
Characteristics	Beta	p value	Exp(B)
Age	-.131	.263 (NS)	.877
Race/ethnicity			
African American (1=yes)	-1.945	.017*	.143
European American (1=yes)	-.709	.247 (NS)	.492
Income	-.019	.128 (NS)	.982
Education	.016	.942 (NS)	1.016
Menopause Status	1.272	.016*	3.568
Diuretic Use	.973	.393 (NS)	2.647
Number of Live Births	.308	.127 (NS)	1.360
CES-D (depressive symptoms)	-.005	.863 (NS)	.995
Perceived General Health Status	-.531	.131 (NS)	.588
Body Mass Index (BMI)	.150	.007*	1.162
Major health problem past year	.793	.142 (NS)	2.211

NS = not statistically significant, $p > .10$

* = statistically significant, $p < .05$

Table 5. Logistic Regression Summary Table for Experiencing Incontinence

Incontinence N=158			
Explained Variance $\chi^2 = 9.535, p = .657$			
Characteristics	Beta	p value	Exp(B)
Age	-.117	.252 (NS)	.889
Race/ethnicity			
African American (1=yes)	.981	.147 (NS)	2.667
European American (1=yes)	-.482	.385 (NS)	.618
Income	-.015	.148 (NS)	.986
Education	.074	.695 (NS)	1.077
Menopause Status	-.170	.694 (NS)	.844
Diuretic Use	-.183	.853 (NS)	.833
Number of Live Births	-.124	.430 (NS)	.883
CES-D (depressive symptoms)	-.006	.777 (NS)	.994
Perceived General Health Status	.085	.755 (NS)	1.089
Body Mass Index (BMI)	.027	.381 (NS)	1.027
Major health problem past year	-.388	.430 (NS)	.678

NS = not statistically significant ($p > .10$)