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Association of Change in Estradiol to Lower Urinary Tract Symptoms During the Menopausal Transition

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Abstract

Objective: To estimate the relationship between changes in estradiol levels over time and lower urinary tract symptoms in premenopausal women as they transition to menopause.

Methods: A self-administered validated questionnaire to measure lower urinary tract symptoms was administered to 300 women at the 11th assessment period on an ongoing longitudinal Penn Ovarian Aging cohort study. The association between the change in estradiol over time through the menopausal transition and lower urinary tract symptoms (urinary incontinence, filling symptoms, voiding dysfunction) was determined. Risk factors associated with lower urinary tract symptoms were determined by univariable analysis and multivariable linear regression.

Results: Estradiol levels and menopausal stage at one point in time were not associated with lower urinary tract symptoms. Women with a sharp decline in estradiol levels over time had significantly lower urinary incontinence scores in comparison to women without a change in estradiol levels through the study period (3.11 ± 2.86 vs 2.08 ± 2.43 , adjusted mean difference = -0.93 , 95% CI: $-1.8, -0.02$). Women between the ages of 45 to 49 had significantly higher urinary incontinence scores than women woman age > 55 (1.59 ± 1.86 vs 3.04 ± 2.93 , adjusted mean difference = 1.0 , 95% CI: $0.01, 2.1$). Women with a BMI greater than 35 also had significantly higher urinary incontinence scores than women in the normal weight range, (3.53 ± 3.16 vs 1.98 ± 2.52 , adjusted mean difference = 1.5 , 95% CI: $0.59, 2.3$) after adjusting for changes of estradiol through the menopausal transition. High anxiety was associated with worsening scores in all three lower urinary tract symptoms domains (incontinence, filling, voiding).

Conclusion: Women with a sharp decline in estradiol through the menopausal transition have significantly lower urinary incontinence scores. Urinary filling symptoms and voiding dysfunction were not associated with changes in estradiol through the menopausal transition.

Introduction

The prevalence of lower urinary tract symptoms (LUTS) increases with advancing age, and particularly, by the time a women enters the perimenopausal years and into menopause.¹⁻³ However, it remains unclear whether the increasing prevalence of urinary tract symptoms is due to the hormonal changes that occur during the menopausal transition, or advancing age. It has been shown that a hypoestrogenic state is associated with thinning of the urethral mucosa, changes in urethral closure pressure from loss of urethral sphincter tone and alteration of the

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urethrovesical angle.⁴ These physiologic changes that occur in the urogenital tissue are factors that have been shown to affect the severity of urinary incontinence. Studies⁵⁻⁷ exploring the relationship between hormonal status and incontinence have been limited by the inadequate assessment of estradiol levels, menopausal status and severity of lower urinary tract symptoms, including incontinence. Our aim was to estimate the relationship between changes in estradiol levels over time and lower urinary tract symptoms in premenopausal women as they transition to the different stages of menopause. We hypothesized that declining estradiol levels during the perimenopause transition to menopause correlates with an increase of lower urinary tract symptoms and more specifically incontinence.

Material and Methods

The proposed investigation was conducted as part of the Penn Ovarian Aging Study. The Penn Ovarian Aging Study is a prospective longitudinal cohort of women enrolled to evaluate the relationship between changes in reproductive hormone levels and various symptoms associated with the menopausal transition. Women were recruited from Philadelphia County from 1996-1997 and identified by random digit dialing. Women were initially enrolled between the ages of 35-47 if they had menstrual cycles in the normal range (22-35 days) and an intact uterus with at least one ovary. Exclusion criteria included use of current hormonal medications, oral contraceptive pills within the last three months and use of psychotropic medications. Women were also excluded if there was a history of alcohol or drug abuse in the past year, pregnancy or breast feeding, a serious medical problem that could compromise ovarian function or major psychiatric disorder that would interfere with their ability to complete the study. In this cohort, none of the women had a history of prior incontinence surgery. Written informed consent was obtained from all subjects and the Institutional Review Board at the University of Pennsylvania approved the study.

As part of this study, subjects were assessed initially at 8-month intervals until assessment period 6 and then yearly for a total of 11 assessments over 10 years. At each assessment, subjects were seen on two separate visits one month apart during the first six days of the menstrual cycle. Blood specimens, anthropometric measures, and extensive questionnaires were obtained from the subjects at each visit. Repeat blood samples one month apart were collected in order to ensure reliable point estimates of hormone measurements. Estradiol hormone levels, body mass index, psychosocial and demographic variables were measured at each visit. At the latest assessment period, the Bristol Female Lower Urinary Tract Symptoms (BFLUTS-SF) questionnaire was also administered to the participants. Using the combination of previously collected and prospectively collected measures, there will be ten years of estradiol hormone measurements and recent data on lower urinary tract symptoms to analyze.

Blood samples were centrifuged and frozen in aliquots at -80°C . Assays were conducted in the laboratory of the General Clinical Research Center of the Hospital of the University of Pennsylvania. Estradiol levels were measured by radioimmunoassay using Coat-A-Count commercial kits (Diagnostic Products, Los Angeles, CA). Estradiol assays were timed to the subject's early follicular phase, repeat measurements were taken to ensure reliable point estimates and assays were repeated if values differed by more than 15%. The intra- and inter-assay coefficients of variation were as consistently less than 5% for all hormones measured.

Trained research interviewers conducted the interviews in-person with the study participants and performed the data collection. Self-report questionnaires were also utilized. In the latest assessment period, the BFLUTS-SF was added to the various self-report questionnaires given to the study population to investigate the association between lower urinary tract symptoms and estradiol change through the menopausal transition. The BFLUTS-SF⁸⁻⁹ questionnaire has been shown to be a valid and reliable instrument that can be utilized to ascertain a woman's

lower urinary tract symptoms and its effect on her quality of life and sexual function. This questionnaire is a 19-item, multidimensional self-report instrument assessing key dimensions of lower urinary tract symptoms, sexual function, and quality of life. There are five subscales within the questionnaire. Three subscales focus on incontinence symptoms (BFLUTS-IS), voiding symptoms (BFLUTS-VS) and filling symptoms (BFLUTS-FS). The remaining two focus on sexual function (BFLUTS-sex) and impact on a woman's quality of life (BFLUTS-QoL). Responses range from none to always, no problem to serious problem, and '0' to '4' with 4 representing the most severe symptom. No cutoff values have been established in the literature; therefore, the domain scores were analyzed as continuous measures. Subscore changes have been shown to be more sensitive than a single combined score for lower urinary tract symptoms.⁹ For our analysis we focused on the domain scores (cumulative summary score of all questions in a particular domain) specifically addressing lower urinary tract symptoms (BFLUTS-IS, BFLUTS-VS, BFLUTS-FS).

At each assessment period the participants current menstrual dates and 2 prior menstrual periods were ascertained by interview and the by each woman's daily symptom diary. With the menstrual information given, each woman was assigned a hormonal status based on the Stages of Reproductive Aging Workshop consensus statement.¹⁰ The stages are as follows: Premenopausal, regular menstrual cycles in the 22-35 day range; early transition, change in cycle length of 7 days or longer in either direction from the participant's own baseline for at least 2 cycles; late transition, 3 to 11 months of amenorrhea; and menopause, 12 months or more of amenorrhea without hysterectomy.

Anxiety was assessed using the Zung Anxiety Index.¹¹ Established score ranges for the Zung Anxiety Index include: normal anxiety (20-35), moderate anxiety (36-47) and high anxiety (48-60). Demographic information including, race, parity, history of hysterectomy, tobacco use and body mass index was also obtained.

Means and standard deviation of estradiol levels were calculated. Because of the skewed distributions, hormones values were analyzed on the log scale and reported as geometric means. We explored the association between the changes in estradiol levels that occurred from the starting point of entry for each woman in the Penn Ovarian Aging cohort to the current assessment period and the LUTS domains of the BFLUTS-SF. Participants were categorized by the direction of change of hormone levels over time which reflects the transition into menopause. Values obtained through the 11 assessment periods, over 10 years of evaluation (a maximum of 22 hormone values per woman) were then plotted. A regression coefficient (slope) corresponding to the overall trend of change in hormone values was obtained. These regression coefficients were used to summarize each participant's hormonal trend into four different estradiol quartiles. The four estradiol quartiles were: increase, slight decrease, sharp decrease and no significant change. The distribution of each participant's current menopausal stage by estradiol quartiles was compared as well as the BFLUTS-SF domain scores. A univariable analysis was performed to assess the association between BFLUTS-SF domain scores and known risk factors (age, race, BMI, parity, anxiety, smoking and history of prior hysterectomy) of LUTS utilizing non-parametric testing such as Kruskal-Wallis or the rank sum test. A multivariable linear regression model was used to estimate the association between trend of estradiol change through the menopausal transition and urinary symptoms, adjusting for potential confounders. A variable was considered a confounder, and included in the model, if the estimated associations of interest change by 15% or if the variable is associated with the outcome (BFLUTS-SF subscale scores) with a $p < 0.2$.¹² Data analysis utilized STATA version 9.2 software (College Station, TX), with a two-tailed interpretation of tests and a P-value less than 0.05 considered statistically significant.

We defined a clinically meaningful difference in BFLUTS-SF's sub-domain scores as 1/2 standard deviation that corresponded to a difference in severity of 1 level on a single question in the BFLUTS-SF questionnaire. Sample size calculations were performed utilizing a 2 group comparison of the difference in mean BFLUTS-SF incontinence domain scores between two of the four estradiol quartile groups. We determined at a two-sided alpha error of 0.05, power 80%, and a mean incontinence subscale score of 2.66 ± 2.81 in our cohort that 64 patients will be needed in each group of categorized overall estradiol change to detect a difference of 1/2 standard deviation in mean BFLUTS-SF incontinence subscale scores.

Results

Of the 436 women originally enrolled in the Penn Ovarian Aging Study, 311 participated at assessment period 11. During that assessment, 300 women completed the BFLUTS-SF questionnaire and therefore were eligible for inclusion into this sub-study. Demographic characteristics of the study cohort and mean domain scores are displayed in Table 1. Overall the mean BFLUTS-SF score for the study participants was 8.38 (SD 2.81). The mean age of the cohort was 50.6 (3.52) years with a mean parity of 3.2 (2.1). Forty-six percent of the women in this cohort had stress incontinence.

Univariable associations between risk factors and the continuous outcome incontinence, filling and voiding dysfunction scores are displayed in Table 2. African American women had higher scores in all 3 domains in comparison to Caucasian women and had a statistically significant increase in filling symptoms ($p=0.002$). Smokers had a significantly higher urinary filling symptoms score ($p=0.001$). Menopausal stage and age were not associated with the 3 BFLUTS-SF domains. Women with a BMI >35 reported an increase in incontinence ($p=.002$) and urinary filling ($p=0.008$) symptoms. Women with moderate and high anxiety had a statistically significant increase in lower urinary tract symptoms scores through all 3 domains of the BFLUTS-SF. No correlation was seen between estradiol levels at assessment period 11 and the incontinence scores ($\rho=0.06$), filling scores ($\rho=0.04$) and voiding scores ($\rho=0.03$). A moderate correlation was seen between parity and incontinence scores ($\rho=0.20$) while a weak correlation was seen between parity and urinary filling ($\rho=0.15$) symptoms and voiding ($\rho=0.14$) symptoms. The estradiol quartiles were not associated with urinary filling and voiding dysfunction scores. However, women with decreasing estradiol quartiles had lower urinary incontinence symptom scores that approached significance ($p=0.09$).

The regression coefficients describing each participant's estradiol trend was categorized based on quartiles into 4 categories: sharp decrease ($n=75$), slight decrease ($n=75$), no change ($n=75$) and increase ($n=75$). These groups characterized the change in measured estradiol levels observed over the 10 year study period and was reflective of their current menopausal status ($p<0.001$). Seventy-three percent of the women in the sharp decrease group were in menopause. The women in the slight decrease category were almost equally distributed between early transition (33%), late transition (30%) and menopause (37%). The majority of women in the no change group were in the early transition (46%), followed by late transition (22%), menopause (21%) and premenopause (11%). The distribution of women in the increase group was similar to the no change group with the majority of women in early transition (51%), followed by menopause (27%) and late transition (15%). Because the changes in estradiol over time as represented by the estradiol quartiles and current menopausal stage were collinear, menopausal stage was not included in the final linear regression model.

Table 3 represents the multivariable models assessing the association between the trend of change in longitudinally measured estradiol levels and the 3 BFLUTS-SF domains evaluated at assessment 11. Women with a sharp decline in estradiol over the 9 years had significantly lower incontinence scores (-0.93 , 95% CI: $-1.8, -0.02$) compared to women in the 'no change'

estradiol quartile group. This decrease represents a change in severity by one level on a single question in the incontinence domain of the BFLUTS-SF questionnaire. The 'slight decrease' and 'increase estradiol' quartile groups were not associated with incontinence scores. Women between the ages of 45 to 49 had a significant increase in incontinence score compared to women aged < 45 after adjusting for changes of estradiol through the menopausal transition. To further determine if a specific form of urinary incontinence was associated with the estradiol quartiles, the final models were repeated utilizing the individual question pertaining to stress incontinence and urge incontinence within the BFLUTS-SF incontinence domain as the outcome. We found that women in the sharp decrease estradiol quartile had a significant reduction in stress incontinence symptoms (-0.48 , 95% CI: $-0.80, -0.16$ $p=0.003$). Urge incontinence was not associated with the change in estradiol levels though the menopausal transition. When examining the relationship between estradiol quartiles and the remaining BFLUTS-SF domain scores (urinary filling symptoms and voiding dysfunction) no significant change in domain scores was seen. High anxiety was associated with worsening scores in all three domains (incontinence, filling, voiding).

Discussion

Our goal was to identify risk factors for lower urinary tract symptoms and to determine if the change in estradiol level through the menopausal transition significantly affected a woman's LUTS. Unexpectedly, we found that women with a sharp decline in estradiol levels through the menopausal transition have significantly decreased urinary incontinence symptoms. Furthermore, we found that increasing parity, age between 45-49 years, a BMI > 35 and high levels of anxiety were associated with an increase in urinary incontinence symptoms. While several studies^{5-7,13-14} have examined the relationship between urinary incontinence and menopausal stage, very few¹³ have investigated the relationship between serum estradiol change through the menopausal transition and urinary incontinence.

The most important finding of our study was that women who had a sharp decline of estradiol levels from premenopause to menopause had a clinically significant decrease in overall incontinence symptom scores. Notably, mean levels of estradiol at one point in time were not associated with LUTS. These findings were surprising because it has been generally accepted that a woman's urinary symptoms increase with menopause due changes in the pelvic floor from estrogen decline.^{4,15} Schaffer et al. demonstrated that a hypoestrogenic state is associated with thinning of the urethral mucosa, changes in urethral closure pressure from loss of urethral sphincter tone and alteration of the urethrovesical angle.⁴ These physiologic changes that occur in the urogenital tissue are factors that have shown to affect the severity of urinary incontinence. While these findings were unexpected, they are supported by recent observational^{5,7} studies. In another large prospective cohort study, Waetjan et al.⁷ reported that women who transitioned from premenopause to menopause had improved overall urinary incontinence. Although not statistically significant, they also reported similar trends in the reduction of stress and urge incontinence. While we could not assess the change in LUTS over time since the BFLUTS-SF questionnaire was not administered at each assessment period, we found that women with a sharp decline in estradiol levels indicative of a transition from premenopause to menopause, had a statistically significant decrease in the severity of urinary incontinence and more specifically stress incontinence. We did not however see a similar reduction in the severity of urge incontinence. Furthermore, no association was seen between the change in estradiol levels through the menopausal transition with voiding and filling urinary symptoms. Slight differences in the results of these studies likely stem from the use of different questionnaires. We should also note that the reduction in stress incontinence score seen in our cohort was below our a priori defined clinical meaningful change in symptom score of one point, therefore whether this finding is clinically important warrants further investigation.

When adjusting for the effect of the menopausal transition, age was an independent risk factor for incontinence symptoms. In particular, we found women between the ages of 45-49 had a clinically significant increase in incontinence symptoms. In our study, this age group remained an independent risk factor for worsening urinary incontinence when controlling for estradiol hormone change through the menopausal transition. We believe this change in score is clinically significant because a change in level of symptom severity by one response category can have a clinically meaningful impact on a women's quality of life. Other studies have supported this finding, since women between the ages of 45-49 years have been found to have the highest prevalence rates of urinary incontinence in comparison to other decades of life. 23-16 Sampsel et al. ⁶ reported a similar increase in the odds of urinary incontinence by 18% for women between the ages of 48-52 in comparison to younger women in the late reproductive years (age 42-47).

The effect of estradiol on target tissues in the bladder and pelvic floor remain unclear. Multiple studies have investigated the effect of exogenous estrogen hormonal therapy with conflicting results. Some studies have demonstrated improvements in LUTS ¹⁷⁻¹⁹ symptoms with treatment while others have demonstrated worsening urinary symptoms. ²⁰⁻²¹ A possible explanation for these clinical findings could be that the distribution of estrogen receptors in the bladder and pelvic floor changes during the different menopausal stages. ²²⁻²⁴ This change in distribution of estradiol receptors could explain the different clinical responses to estrogen therapy seen in women of varying age and menopausal stages. It might also explain our finding that decreased endogenous estradiol improves incontinence symptoms. In our cohort of women, we excluded women who were receiving exogenous estrogen supplementation. Hence, we were able to investigate how the natural change in estradiol levels through the menopausal transition affect LUTS. Further research is needed to determine the specific relationship between estradiol hormone levels, advancing age and lower urinary tract symptoms.

We also found that a BMI > 35, increasing parity and anxiety were independently associated with an increase in urinary incontinence symptoms. A BMI > 35 and moderate to high anxiety was also associated with an increase in urinary filling symptoms. These findings are consistent with those reported in previous studies. 25-26 Dwyer et al. ²⁶ has reported that obesity was significantly more common in women with stress and urge incontinence. The excess weight in these individuals has been thought to create excess strain on the pelvic floor muscles and nerves resulting in these urinary symptoms. Anxiety has been previously associated with a many types of incontinence (stress, mixed, urge) and LUTS. ²⁵ In this study we found an association between high anxiety and LUTS. It is not clear whether women with anxiety simply are more likely to report LUTS, whether LUTS causes more anxiety, or whether anxiety somehow worsens LUTS. Due to the small number of women with high anxiety (n=10) in our study cohort, a longitudinal assessment of anxiety and LUTS would help to further clarify this relationship.

Our study has a number of strengths. This study is unique in that we have the ability to investigate the relationship between the changes in estradiol levels over time in premenopausal women as they transition to the different stages of menopause. Furthermore, the focus of our study was to investigate not only urinary incontinence but also the full spectrum of LUTS such as bladder filling and voiding dysfunction symptoms. None of the prior longitudinal studies have utilized a validated questionnaire (BFLUTS-SF) that focuses on urinary incontinence and LUTS. Additionally, ten years of longitudinal data on estradiol hormone level change through the menopausal transition is rare. By investigating estradiol change during the menopausal transition, we hope to provide some insight into the relationship between estradiol levels and LUTS. This may help generate further investigations that explore a biologically plausible mechanism for the conflicting results of multiple trials examining the effect of hormonal therapy and urinary incontinence.

Our study also has a number of limitations. We do not have information available on LUTS from the earlier assessment points as the BFLUTS-SF was added to the latest assessment period of the Penn Ovarian Aging Study. Therefore we were unable to assess change in LUTS during the menopausal transition. However, by using a regression coefficient (slope) to describe the trend of change in a woman's estradiol levels through the menopausal transition, we were able to investigate the relationship between estradiol change over time and LUTS. Currently, only 71% of the study participants remained active in the parent Penn Ovarian Aging study at assessment period 11 and therefore were eligible for inclusion into this study. It is possible that this loss to follow-up may introduce selection bias and affect the generalizability of the results. However, a prior comparison of baseline values between active and inactive subjects in this cohort study found no differences in estradiol levels, racial and demographic characteristics.²⁷ It is also possible that some of our significant findings may be due to chance as there were multiple endpoints used in this study design.

Severity of urinary incontinence symptoms has been found to be strongly associated with a decline in estradiol levels and ages between 45–49. Unlike previously held viewpoints that both age and the menopausal transition worsen incontinence symptoms, we found that a sharp decline in estradiol, reflective of the progression through the menopausal transition to be protective. Further investigations are needed to elucidate the impact of estradiol change, advancing age and severity of LUTS symptoms.

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Table 1

Study Variables at Assessment 11

	N=300 (%)		N=300 (%)
Age	Body Mass Index		
<45	34 (11)	< 25	63 (21)
45-49	133 (44)	25-30	86 (29)
50-54	121 (41)	30-35	53 (18)
>55	12 (4)	> 35	98 (32)
Race	Anxiety		
African American	142 (47)	Normal	215 (72)
Caucasian	158 (53)	Moderate	75 (25)
Smoking		High	10 (3)
No	203(68)		
Yes	95 (32)		
Menopausal stage			
Premenopause	15 (5)	Incontinence*	2.66 (2.81) [†]
Early transition	106 (35)	Filling*	3.35 (2.35) [†]
Late transition	62 (21)	Voiding*	0.99 (1.48) [†]
Postmenopausal	117 (39)		
Hysterectomy			
No	283 (94)		
Yes	17 (6)		
Estradiol(pg/mL)	40.92 ±36.7 (range 1-260.1)		

* BFLUTS-SF Domain scores

[†] mean (SD)

Table 2

Analysis of Association Between BFLUTS-SF Domains and Study Covariates

Variable	Incontinence Score	P-value	Filling Score	P-value	Voiding Score	P-value
Estradiol Quartiles#						
Sharp dec	2.08 (2.42)		3.36 (2.58)		0.98 (1.41)	
Slight dec	2.93 (3.01)		3.35 (2.34)		1.09 (1.68)	
No change	3.11 (2.85)		3.69 (2.36)		1.09 (1.63)	
Increase	2.48 (2.78)	0.09	3.09 (2.12)	0.55	0.88 (1.18)	0.83
Race						
African American	2.78 (2.83)		3.81 (2.51)		1.13 (1.64)	
Caucasian	2.58 (2.81)	0.56	2.94 (2.11)	0.002	0.87 (1.31)	0.38
Smoking						
No	2.59 (2.82)		3.13 (2.37)		0.92 (1.34)	
Yes	2.71 (2.67)	0.46	3.80 (2.26)	0.001	1.12 (1.73)	0.76
Menopausal stage						
Premenopause	3.33 (3.74)		3.33 (2.44)		0.55 (0.88)	
Early transition	2.92 (2.89)		3.12 (2.13)		1.14 (1.70)	
Late transition	3.01 (3.12)	0.23	4.00 (2.70)	0.18	0.67 (0.97)	.25
Menopause	2.37 (2.58)		3.20 (2.32)		1.10 (1.54)	
Hysterectomy						
No	2.83 (2.85)		3.36 (2.35)		0.98 (1.48)	

Variable	Incontinence Score	P-value	Filling Score	P-value	Voiding Score	P-value
Yes	1.47 (1.70)	0.08	3.23 (2.44)	0.89	1.06 (1.56)	0.77
BMI						
< 25	1.98 (2.52)		2.87 (1.97)		1.02 (1.52)	
25–30	2.57 (2.81)		3.09 (2.27)		1.16 (1.56)	
30–35	2.05 (2.07)		3.06 (2.29)		0.58 (0.88)	
> 35	3.52 (3.16)	0.001	4.05 (2.55)	0.008	1.09 (1.62)	0.24
Age						
<45	1.59 (1.86)		2.64 (2.33)		0.62 (1.18)	
45–49	3.03 (2.93)		3.56 (2.51)		1.04 (1.51)	
50–54	2.53 (2.81)		3.29 (2.30)		1.07 (1.56)	
>55	3.00 (3.27)	0.04	3.75 (1.91)	0.09	0.75 (0.86)	0.39
Anxiety						
Normal	2.31 (2.57)		2.87 (2.08)		0.76 (1.20)	
Moderate	3.42 (2.97)		4.41 (2.43)		1.49 (1.74)	
High	4.70 (4.59)	0.002	5.80 (3.15)	0.001	2.20 (2.93)	0.002

Data are presented as mean (standard deviation). BFLUTS-SF: Domain maximum scores are 20 for incontinence, 12 for voiding symptoms, and 15 for filling symptoms. Anxiety was assessed using the Zung questionnaire: normal anxiety (score 20–35), mild to moderate anxiety (score 36–47), and high anxiety (score 48–60). Domain Scores were not normally distributed and analyzed as continuous variables. Nonparametric testing was used for statistical comparisons and a P-value of <0.05 was considered statistically significant.

Estradiol quartiles represent the categorized equivalent of the overall trend of estradiol level change over the 10-year study period.

Table 3

Linear Regression of Lower Urinary Tract Symptoms and Estradiol Quartiles

BFLUTS-SF Domains	Incontinence Score	Filling Score	Voiding Score
Estradiol Quartiles [#]			
Sharp dec	-.93(-1.8, -.02)[†]	-.23(-.98, .51)	-.19(-.68, .30)
Slight dec	-.28(-1.1, .58)	-.31(-1.0, .40)	.03(-.44, .50)
No change	Reference	Reference	Reference
Increase	-.44(-1.3, .43)	-.47(-1.2, .25)	-.23(-.71, .25)
Parity	.21(.06, .36)[†]	.09(-.02, .22)	.06(-.02, .15)
Anxiety			
Normal	Reference	Reference	Reference
Moderate	.66(-.07, 1.4)	1.3(.77, 1.9)[‡]	.74(.32, 1.1)[‡]
High	2.4(.67, 4.1)[*]	2.9(1.5, 4.4)[‡]	1.3(.33, 2.2)[‡]
BMI			
<25	Reference	Reference	Reference
25-29	.49(-.38, 1.4)	.34(-.39, 1.0)	.09(-.39, .57)
30-34	.23(-.76, 1.3)	.43(-.39, 1.3)	-.38(-.93, .16)
>35	1.5(.59, 2.3)[‡]	1.1(.45, 1.9)[‡]	-.01(-.48, .46)
Age			
<44	Reference	Reference	Reference
45-49	1.0(.01, 2.1)[†]	.73(-.18, 1.6)	.20(-.36, .76)
50-54	.32(-.76, 1.4)	.45(-.54, 1.4)	.25(-.33, .84)
>55	.70(-1.1, 2.5)	.64(-.99, 2.3)	-.30(-1.3, .69)

[#] Estradiol quartiles represent the categorized equivalent of the overall trend of estradiol level change over the 10-year study period; [†]A change in score by 1 unit represents a change in level of severity by 1 choice in any question of the particular BFLUTS- SF domain; Adjusted for race, smoking, hysterectomy; Bolded values are statistically significant;

[†] ≤.05

^{*} <.02

[‡] <.001