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Serum Estradiol Levels Are Not Associated with Urinary Incontinence in Mid-life Women Transitioning through Menopause

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Abstract

Objective—We evaluated the relationship between annually measured serum endogenous estradiol and the development or worsening of stress and urge incontinence symptoms over 8 years in women transitioning through menopause.

Methods—This is a longitudinal analysis of women with incontinence in the Study of Women's Health Across the Nation (SWAN), a multi-center, multi-racial/ethnic prospective cohort study of community-dwelling women transitioning through menopause. At baseline and each of 8 annual visits, SWAN elicited frequency and type of incontinence in a self-administered questionnaire and drew a blood sample on days 2-5 of the menstrual cycle. All endocrine assays were performed using a double-antibody chemiluminescent immunoassay. We analyzed data using discrete Cox survival models and generalized estimating equations with time dependent covariates.

Results—Estradiol levels drawn at either the annual visit concurrent with or previous to the first report of incontinence were not associated with the development of any (hazard ratio (HR) = 0.99, 95% CI 0.99, 1.01), stress, or urge incontinence in previously continent women. Similarly, estradiol levels were not associated with worsening of any (odds ratio (OR) = 1.00, 95% CI 0.99, 1.01), stress, or urge incontinence in incontinent women. Change in estradiol levels from one year to the next was also not associated with the development (HR = 0.98, 95% confidence interval 0.97, 1.00) or worsening (OR = 1.03, 95% CI 0.99, 1.05) of incontinence.

Conclusions—We found that annually measured values and year-to-year changes in endogenous estradiol levels had no effect on the development or worsening of incontinence in women transitioning through menopause.

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Keywords

Urinary incontinence; Estradiol; Reproductive hormones; Menopause transition; Epidemiology; Prospective cohort study

Introduction

The increasing prevalence of urinary incontinence with aging in women has traditionally been linked to declining levels of estrogen associated with the menopausal transition and post-menopause. Alpha and beta estrogen receptors exist throughout the urogenital tract and exogenous estrogen increases urethral cellular maturation¹, urethral blood flow² and urethral pressure³⁻⁵ presumed to be important to continence. However, secondary analyses of randomized clinical trials have revealed that estrogen treatment in postmenopausal women is associated with a *higher* risk of newly developing and worsening existing incontinence^{6, 7}. Less is known about how endogenous estrogen levels affect incontinence.

In our previous work, we found that advancement through the stages of the menopausal transition was not significantly associated with the development or worsening of incontinence over the first six years of the Study of Women's health Across the Nation (SWAN)^{8, 9}. But epidemiological evidence to date suggests a weak negative effect of endogenous estrogen on incontinence. Higher levels of serum estradiol (E2) have been associated with more prevalent incontinence symptoms in a cross-sectional study¹⁰. A steep decline in serum E2 levels over 11 years was associated with a decrease in incontinence symptoms compared with a more gradual decline or no change in E2 levels across this same time frame¹¹.

Our objective was to evaluate the relationship between annually measured serum endogenous E2 levels and the development or worsening of self-reported stress and/or urge incontinence symptoms across the menopausal transition in the first eight years of SWAN. We also investigated the association with other reproductive hormone levels, specifically follicle stimulating hormone (FSH), testosterone, and dehydroepiandrosterone sulfate (DHEAS). In these analyses, we accounted for other factors known to affect the development or worsening of incontinence such as high body mass index (BMI), weight gain, anxiety and diabetes.

Methods

Study Sample

SWAN is a multi-center prospective cohort study of women from five racial/ethnic groups who have been followed to characterize the menopausal transition¹². SWAN is comprised of seven clinical sites (Boston, Massachusetts; Chicago, Illinois; the Detroit area, Michigan; Los Angeles, California; Newark, New Jersey; Pittsburgh, Pennsylvania; and Oakland, California), a coordinating center, and a central endocrine laboratory. The SWAN is a community-based sample of 3302 women: the white and minority groups do not represent an underlying population distribution. All seven sites recruited white women (N=1550 white) and three sites recruited African American women (N=395). Japanese (N=281), Chinese (N=250), and Hispanic (N=286) women were recruited at one site each. Eligibility criteria for the SWAN cohort were age 42-52 years and self-identification as one of the five racial/ethnic groups. Exclusion criteria included inability to speak English, Spanish, Japanese, or Cantonese, no menstrual period in greater than 3 months before enrollment, having had a hysterectomy and/or bilateral oophorectomy prior to enrollment, and current

pregnancy or hormones use. The institutional review boards at all sites approved the SWAN protocol and all women gave informed consent to participate.

Outcome Variables

The women included in this analysis were those followed through eight annual follow-up visits (1995-2004). SWAN obtained baseline and annual information on incontinence symptoms, incontinence frequency and type through a self-administered questionnaire. Based on response to the question: "In the past year (or since your last study visit), have you ever leaked even a small amount of urine involuntarily?", we classified frequency of incontinence as "almost daily/daily" (daily), "several days per week" (weekly), "less than one day per week" (monthly), less than once a month or "none." We defined any incontinence as incontinence occurring at least monthly. We considered incontinence occurring less than once a month as clinically insignificant and subject to a higher misclassification rate and therefore combined this category with "no incontinence." We categorized type of incontinence as "stress" if participants reported leakage with "coughing, laughing, sneezing, jogging, jumping, with physical activity or picking up an object from the floor" or as "urge" if participants reported leakage "when you have the urge to void and can't reach the toilet fast enough."

Women who were continent at baseline but then reported incontinence at any of the eight annual follow-up visits were considered to have incident incontinence and were compared to women who did not develop incontinence over the same time frame. Women who reported incontinence at any time point and then reported an increase in frequency from one year to next were considered to have worsening incontinence, i.e. from no regular incontinence (after a previous report of incontinence) to monthly or more, from monthly to weekly or more or from weekly to daily. We compared women with worsening incontinence to those with no change (same frequency from one visit to the next) or improved (decreased frequency from one visit to the next) incontinence.

Hormones

Our main variable of interest was the annually measured value of E2. We also evaluated FSH, testosterone and DHEAS and the year to year changes in the values. SWAN measured these four hormones annually with the goal to standardize them from year to year by drawing blood in the early follicular phase, days 2-5 of the menstrual cycle, whenever possible. We categorized time of phlebotomy for the hormone assays as follows. For pre- and early peri-menopause, we defined phlebotomy between days 2-5 to be "in window," while we defined phlebotomy done outside of days 2-5 to be "out of window." Because late peri-menopause is characterized by long periods of amenorrhea, the number of women whose blood was drawn between days 2-5 of a menstrual cycle were too few for analysis. Thus we considered phlebotomy in late peri- or post-menopause as random annual time-points in each of these transition stages.

All endocrine assays were performed on the Automated Chemiluminescence System (ACS)-180 analyzer (Bayer Diagnostics Corporation, Tarrytown, NY) using a double-antibody chemiluminescent immunoassay with a solid phase anti-IgG immunoglobulin conjugated to paramagnetic particles, anti-ligand antibody, and competitive ligand labeled with dimethylacridinium ester¹³. The E2 assay modified the rabbit anti-E2-6 ACS-180 immunoassay to increase sensitivity, with a lower limit of detection of 1.0 pg/mL. Duplicate E2 assays were conducted with results reported as the arithmetic mean for each participant, with a coefficient of variation of 3-12%. All other assays were single determinations. The FSH assay was a modification of a manual assay kit (Bayer Diagnostics) utilizing two monoclonal antibodies directed to different regions on the beta subunit. The testosterone

assay modified the rabbit polyclonal anti-testosterone ACS-180 immunoassay. The DHEAS and sex hormone binding globulin (SHBG) assays were developed on site using rabbit anti-DHEA-S and anti-SHBG antibodies.

Covariates

SWAN classified menopausal status from menstrual bleeding patterns annually. Pre-menopause was defined by less than three months of amenorrhea and no menstrual irregularities in the previous year; early peri-menopause by less than three months of amenorrhea and some menstrual irregularities in the previous year; late peri-menopause by three to 11 months of amenorrhea; and post-menopause by 12 consecutive months of amenorrhea. Because we aimed to evaluate the effects of natural menopausal serum hormone levels on incontinence, we permanently censored women who had a hysterectomy with or without bilateral salpingoophorectomy prior to their final menstrual period (because their menopause transition stage became unclassifiable). Women who started taking systemic hormones were excluded at the time of hormone initiation (because HT use prior to the final menses obscures the classification of MT stage and also because HT use precludes the measurement of endogenous sex steroids). However, women who stopped hormones, and for whom we could determine a menopausal status, re-entered our analysis in that status after a wash out period of at least 6 months.

We calculated BMI as weight in kilograms/(height in meters)² based on measurements taken annually by certified staff who used calibrated scales and a stadiometer. As described previously, covariates were measured by mostly validated questions⁸. Socioeconomic status was approximated by level of difficulty paying for basics (food, heat and shelter) at baseline. Sensitivity to body symptoms was collected at the first annual visit¹⁴. Each year, interviewers obtained self-reported medical histories, smoking history and medication use. In annual self-report questionnaires, SWAN used the same validated questions eliciting depressive symptoms¹⁵, social support and stressors^{16,17}, and anxiety symptoms¹⁸.

Missing Data

We defined-drop outs as those who were deceased, discontinued the study voluntarily, or could not be contacted after missing two or more annual visits. When a woman was missing data on frequency and type of incontinence from one or two visits, we imputed values as follows. If the missing value occurred at year 8, we imputed the value at the previous visit. If women reported no incontinence in the years previous and subsequent to a missing incontinence report, we assumed no incontinence in those missing years. If a woman was missing incontinence data in the one to two years previous to a first report of incontinence we randomly assigned her missing values to either no incontinence or the frequency and/or type of incontinence in that subsequent year. We imputed incontinence frequency for 1018 women at 1487 visits (7.1% of all visits) and incontinence type for 1511 women at 2759 visits (13.2% of all visits). We only imputed one or two missing hormone values when they occurred between two known values measured in the same menopausal status. Additionally, for pre- and early peri-menopausal statuses, we only imputed hormone values between two known values from blood drawn in-window in the same status. In these cases the missing value(s) were randomly assigned the previous or subsequent value. We imputed 2826 hormone values for 248 women (1.9% of all values). When weight was missing for one or two visits, the values for 501 women were imputed as the mean between the two known values for 1379 visits (6.6% of all visits). Similarly, waist circumference values were imputed for 527 women at 1414 visits (6.8% of all visits). We dropped all other missing data from the analysis.

Data Analyses

We used t-, chi-square, and Kruskal-Wallis tests to compare distributions of each variable for women at baseline who remained in versus dropped out of the study by year 8. We used a discrete Cox survival model using time-dependent annual hormone values and change in values, adjusting for both time-varying and baseline co-variables to model time until incident incontinence. This model is used to analyze the effects of each unique annual hormone value, or change in value, on the hazard of incontinence, adjusted for potential confounding factors. To evaluate the association between hormone level, or change in level, and worsening incontinence, we modeled the marginal probabilities of worsening (at the time of observation compared to improving or no change in incontinence) as logistic regressions using time-dependent annual hormone values and change in values, and adjusting for both baseline and time-varying covariates. Here we used generalized estimating equations (GEEs) methodology which is designed to accommodate dependence of repeated observations on the same women.

To evaluate the association between annual hormone value and time to the development of incontinence, we ran two separate models, one using the value of E2, FSH, testosterone and DHEAS in the year of first reported incontinence, and the other in the year prior to the first report of incontinence in previously continent women. To evaluate the association between worsening incontinence and the time dependent variables, E2, FSH, testosterone and DHEAS, we again developed two models, one using these hormone values in the year of and the other using them in the year prior to the reported increase in frequency of incontinence. We also ran models with each hormone alone and with different combinations of the hormones and found no differences in the point estimates of any model variable. We ran the same models using free E2 index (total E2/SHBG $\times$ 100) and free androgen index (total testosterone/SHBG $\times$ 100) without adjusting for SHBG and found no differences in the results.

We were also interested in whether annual change in hormone level was associated with the development or worsening of incontinence. We defined change in hormone level as the difference in E2, FSH, testosterone and DHEAS value between the year of and the year prior to either the first report of incontinence in continent women or the reported increase in frequency of incontinence. In the discrete Cox survival and GEE models we included all late peri- and postmenopausal women and the pre- and early peri-menopausal women whose hormone values were in window. We excluded out of window hormone values because the meaning of annual change between out of window hormone values in women who still have some regular menstrual cycles is not interpretable.

Candidate covariates for all our models included factors found to be associated with incontinence in the literature or our previous analyses, possible confounders of the relationship between hormone level and incontinence based on *a priori* hypotheses, and those associated with our incontinence outcomes with a p-value of < 0.10 . Besides the hormone values and change in values, time-varying covariates included: menopausal status/phlebotomy window, weight change, occurrence of stressful life events, development of anxiety and depressive symptoms, social support, and general health status. We checked the proportional hazard assumptions for our baseline covariates (race/ethnicity, education level, marital status, difficulty paying for basics, baseline BMI, baseline smoking, parity, baseline diabetes, baseline hypertension, and baseline fibroids) using our previously described methods^{8,9}. To evaluate the effects of our imputation methods, we ran both types of models with and without imputed hormone and other variable values and found no appreciable differences in the model results. For all analyses, we used SAS 9.1, SAS Institute Inc., Cary, NC, USA.

Results

The baseline characteristics of women who followed up for all eight years were different than those of the women who dropped out of the study (Table 1). The 2891 women who stayed in the study were more likely to have a higher education, have better health, be married, have an easier time paying for basics, have never smoked, be white race, have a lower anxiety score, have higher levels of DHEAS and SHBG and lower levels of FSH, and have incontinence compared to the 407 women who dropped out. While these differences may limit the generalizability of this study, the small magnitude of the differences are unlikely to affect the biological relationship between endogenous hormone levels and incontinence.

Over the eight years of the study, 738 women in the follow-up cohort were censored due to starting hormones in the pre- or peri-menopause, but 70% re-entered study after stopping hormones and resuming a natural menstrual cycle for at least one year. Ninety-six women were censored after having a hysterectomy with or without oophorectomy prior to their final menstrual period. Overall, 1587 of 2891 (55%) women transitioned to natural post-menopause.

We found that annual serum reproductive hormone levels measured in women transitioning through menopause were not associated with the development or worsening of incontinence. The mean E2 and FSH levels, which change considerably across the menopausal transition, did not differ between those who developed and those who did not develop incontinence (Figure 1a). Similarly, these hormone levels did not differ between incontinent women who reported worsening incontinence compared with those who did not have worsening incontinence (Figure 1b).

In our proportional hazards models, E2, FSH, DHEAS and testosterone levels drawn at either the annual visit concurrent with or previous to each woman's first report of incontinence, were not associated with the development of any, stress or urge incontinence in previously continent women (Table 2). Similarly, in our GEE models, these hormone levels drawn in concurrent and previous years were not associated with worsening any incontinence in incontinent women (Table 3). Odds ratios for stress and urge incontinence were also close to 1.00, 95% confidence interval 0.99, 1.01.

Finally, in our models examining the change in E2, FSH, DHEAS, and testosterone from the previous to concurrent year of first report or increased frequency of incontinence we again found no association between annual change in these hormone levels and the development or worsening of incontinence. As with our other analyses, hazard and odds ratios calculated were between 0.98 (95% confidence interval 0.97, 1.00) and 1.03 (95% confidence interval 0.99, 1.05).

Discussion

We found that annually measured values and year-to-year changes in endogenous serum E2 levels had no significant relation to the development or worsening of urinary incontinence in mid-life women transitioning through menopause. These findings have at least two possible biological explanations. First, endogenous estrogens are not related to the development or worsening of incontinence. Second, and more likely based on previous work^{10, 11}, endogenous estrogens have at least a weak association with incontinence, but this relationship is not based on annual values or between year changes in isolated serum E2 levels, but rather is hidden within the complexity of estrogen action at the level of the urogenital and/or neural tissues. For example, alpha and beta estrogen receptor distribution and density can vary in different tissues depending on estrogen exposure¹⁹ and menopausal

status²⁰. Genotypic variation in estrogen receptors and in estrogen metabolism may lead to different effects of estrogen on incontinence as unique estrogen receptor and estrogen metabolic pathway single nucleotide polymorphisms have been associated with different health measures such as bone mineral density and symptoms such as depression and hot flushes²¹⁻²³.

We also found no association between FSH, testosterone or DHEAS levels and the development or worsening of incontinence. Few studies have evaluated the relationship of these hormones with incontinence. In spayed female dogs, lower FSH concentrations were associated with incontinence adjusting for body weight and time from spaying²⁴. We could not identify any studies evaluating FSH and incontinence in humans, but no direct biological action of FSH on the urogenital tissues has been identified that could explain a relationship. While androgen receptors are present in the levator ani muscles, their numbers are small compared with estrogen receptors²⁵. Women with stress incontinence have been reported to have higher levels of urine androgen metabolites compared with continent women²⁶, and higher serum testosterone levels have been associated with reduced collagen turnover in urogenital tissues of stress incontinent compared with continent women²⁷, suggesting that biologically androgens may have a protective effect against the development or worsening of stress incontinence. However, our results support the current evidence of no simple epidemiological association between testosterone and/or androstendione and incontinence¹⁰.

One main limitation of our study was that E2, FSH, DHEAS, testosterone and SHBG were measured just once per year. In most cases these were measured in days 2-5, the early follicular phase of the menstrual cycle, but in peri-menopausal women especially, cycles may vary significantly and so a single measurement may not be representative of the other cycles during that year. Additionally, one of our main outcomes, worsening incontinence, was based on self-reported incontinence frequency which may not always represent a true biological change in incontinence, but rather may represent a change in reporting behavior associated with change in other factors such as anxiety symptoms. Exactly when incontinence developed or worsened in the previous year was not certain and thus cannot be directly linked with a specific hormone measurement.

SWAN has followed almost 2900 community-based women of diverse race/ethnicity across the menopausal transition for over eight years with standardized questionnaires and annual blood draws for sensitive E2 and other reproductive hormone assays. The same incontinence questions assessing clinical type of incontinence (stress and urge) were asked on an annual basis. These questions were similar to validated questions and those that have been used widely in other epidemiological studies of incontinence^{28, 29}. The sensitivity and specificity of self-reported stress and urge incontinence is estimated at 71-85% and 60-79% respectively in validated questionnaires^{30, 31}.

Conclusions

These negative findings add a small piece to the puzzle of the relationship between estrogen and urinary incontinence. From a clinical standpoint, our findings challenge previously held beliefs about low or declining levels of estrogen being associated with incontinence. Rather, levels of and changes in E2 (or any of the other reproductive hormones examined here) have no measureable relation to the development or worsening of incontinence over time. However, because of the evidence that exogenous estrogen affects symptoms of incontinence negatively and because the action of estrogen is complex, future studies should explore whether incontinence may be associated with other facets of this complexity, such as genetic variation in estrogen metabolism and receptor expression.

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FIG. 1.

A: Mean estradiol and FSH levels in women who developed and did not develop UI across the natural menopausal transition. Number of observations in each year: -6, 365; -5, 481; -4, 522; -3, 556; -2, 557; -1, 513; 0, 442; +1, 327; +2, 245; +3, 164; +4, 109; +5, 60; +6, 24. **B:** Mean estradiol and FSH in women whose UI did and did not worsen across the natural menopausal transition. Number of observations in each year: -6, 59; -5, 117; -4, 183; -3, 237; -2, 286; -1, 336; 0, 368; +1, 320; +2, 253; +3, 177; +4, 105; +5, 54; +6, 25. FSH, follicle-stimulating hormone; UI, urinary incontinence.

Table 1

Baseline Characteristics and Differences between Women Who Followed-up and Dropped-out of SWAN over Eight Years

Baseline Characteristics	Baseline Cohort ^a N = 3301		Follow-up Cohort N = 2891		Drop out Cohort ^b N=407		p-value ^c
Age (mean ± SD)	45.8	2.7	45.8	2.7	45.7	2.7	0.488
Race (N, %)							0.001
African American	934	28.3	821	28.4	112	27.5	
White	1546	46.8	1402	48.5	143	35.1	
Chinese	250	7.6	235	8.1	15	3.7	
Hispanic	278	8.4	160	5.5	117	28.7	
Japanese	281	8.5	266	9.2	15	3.7	
Menopausal status (N, %)							0.572
Pre-menopausal	1726	52.3	1521	52.6	203	49.9	
Early peri-menopausal	1498	45.4	1311	45.3	186	45.7	
Baseline Reproductive Hormones (mean ± SD)							
Estradiol (pg/mL)	76.8	80.4	76.1	80.3	80.8	81.2	0.271
DHEAS (ug/dL)	129.7	79.0	131.0	80.1	121.4	69.7	0.012
FSH (mIU/mL)	24.4	26.5	24.1	26.0	27.1	29.6	0.048
Testosterone (ng/dL)	46.9	29.1	47.0	29.3	46.9	27.4	0.983
SHBG (nM)	45.3	24.6	45.0	24.4	47.7	26.2	0.048
Free estradiol index	8.1	14.5	8.1	15.1	7.7	9.4	0.412
Free androgen index	5.2	7.6	5.2	7.7	4.9	7.1	0.345
Education (N, %)							0.001
High school or less	819	24.8	655	22.7	163	40.0	
College or higher	2451	74.3	2213	76.5	236	58.0	
Marital status (N, %)							0.001
Single	439	13.3	389	13.5	49	12.0	
Married	2148	65.1	1914	66.2	232	57.0	
Separated/Divorced/Widowed	660	20.0	549	19.0	111	27.3	
Social Support (N, %)							0.005

Baseline Characteristics	Baseline Cohort ^a N = 3301		Follow-up Cohort N = 2891		Drop out Cohort ^b N=407		p-value ^c
> 25 th percentile	2214	67.1	1965	68	248	60.9	
≤ 25 th percentile	1087	32.9	926	32	159	39.1	
General Health Status (N, %)							0.001
Excellent	694	21.0	632	21.9	62	15.2	
Very good	1179	35.7	1058	36.6	119	29.2	
Good	945	28.6	808	27.9	136	33.4	
Fair	368	11.1	302	10.4	66	16.2	
Poor	62	1.9	53	1.8	9	2.2	
Difficulty paying for basics (N, %)							0.001
Very hard	306	9.3	241	8.3	65	16.0	
Somewhat hard	1005	30.4	842	29.1	161	39.6	
Not at all hard	1968	59.6	1793	62.0	174	42.8	
Body Mass Index (mean ± SD)	28.3	7.2	28.2	7.3	28.8	6.7	0.097
Waist-hip ratio (mean ± SD)	0.8	0.1	0.8	0.1	0.8	0.1	0.035
Parity	2	1.4	2	1.4	2.2	1.5	0.006
Smoking History (N, %)							0.001
Never smoked	1872	56.7	1677	58.0	194	47.7	
Past only	798	24.2	708	24.5	89	21.9	
Current	557	16.9	449	15.5	107	26.3	
Diabetes	163	4.9	139	4.8	24	5.9	0.289
Hypertension	642	19.4	558	19.3	83	20.4	0.850
Fibroids	670	20.3	600	20.8	70	17.2	0.118
Depressive symptoms	804	24.4	684	23.7	118	29.0	0.015
Anxiety symptoms	749	22.7	649	22.4	98	24.1	0.460
Life events (mean ± SD)	3.4	2.5	3.5	2.5	2.9	2.6	0.001
Symptom sensitivity (mean ± SD)	10	4.6	10.1	4.4	9.1	7.1	0.086
Incontinence Frequency (N, %)							0.001
None	1806	54.7	1477	51.1	329	80.8	
Monthly	997	30.2	946	32.7	51	12.5	

Baseline Characteristics	Baseline Cohort ^a N = 3301		Follow-up Cohort N = 2891		Drop out Cohort ^b N=407	p-value ^c
Weekly	321	9.7	308	10.7	11	2.7
Daily	175	5.3	159	5.5	16	3.9
Incontinence Type (N, %)						0.095
Stress	775	23.5	737	25.5	36	8.8
Urge	253	7.7	245	8.5	8	2.0
Mixed	420	12.7	389	13.5	31	7.6
Missing or none	1853	56.1	1520	52.6	332	81.6

N = number, SD = standard deviation

FSH = follicle stimulating hormone, DHEAS = dehydroepiandrosterone, SHBG = sex hormone binding globulin

Due to missing data, numbers may not add to column total and percentages may not add to 100%

^aBaseline cohort does not include three women who were missing incontinence data at baseline

^bDrop out cohort: those deceased, who voluntarily withdrew or could not be contacted for 2 or more visits by year 6.

^cComparison between follow-up and drop-out cohorts using t-test and chi-squared test

Adjusted Hazard Ratios for Developing Monthly or More Urinary Incontinence in Continent Women by Annual Serum Hormones

Table 2

Hormones Measured in Same Year as First Reported Incontinence						
	Any ^a 3763 observations		Stress ^b 3472 observations		Urge ^c 3346 observations	
	HR	95% CI	HR	95% CI	HR	95% CI
Estradiol per 10 pg/ml	0.99	0.99, 1.00	0.99	0.98, 1.01	1.00	0.99, 1.00
FSH per 10 mIU/ml	0.99	0.99, 1.00	0.99	0.95, 1.03	1.00	0.99, 1.00
Testosterone per ng/dl	0.99	0.99, 1.00	0.99	0.99, 1.00	1.00	0.99, 1.00
DHEAS ug/dl	0.99	0.99, 1.00	0.99	0.99, 1.00	1.00	0.99, 1.00
Hormones Measured in the Year Previous to First Reported Incontinence						
	Any ^d 4064 observations		Stress ^e 3746 observations		Urge ^f 3616 observations	
	HR	95% CI	HR	95% CI	HR	95% CI
Estradiol per 10 pg/ml	1.00	0.99, 1.01	1.00	0.99, 1.02	0.99	0.99, 1.00
FSH per 10 mIU/ml	0.98	0.95, 1.03	0.97	0.94, 1.01	1.00	0.99, 1.00
Testosterone per ng/dl	0.99	0.99, 1.00	0.99	0.99, 1.00	0.99	0.99, 1.00
DHEAS per ug/dl	1.00	0.99, 1.00	1.00	0.99, 1.00	0.99	0.99, 1.00

FSH = Follicle stimulating hormone, DHEAS = dehydroepiandrosterone

HR = Hazard Ratio, 95% CI = 95% Confidence Interval

^a All hormones in model and adjusted for the following time-varying covariates: serum hormone binding globulin, menopausal status/window of phlebotomy, weight gain, and the following baseline covariates: diabetes at baseline, parity, race/ethnicity, baseline body mass index and baseline educational level.

^b Comparison group: all women who did not develop stress incontinence. All hormones in model and adjusted for the following time-varying covariates: serum hormone binding globulin, menopausal status/window of phlebotomy, weight gain, and the following baseline covariates: parity, race/ethnicity, baseline body mass index.

^c Comparison group: all women who did not develop urge incontinence. All hormones in model and adjusted for the following time-varying covariates: serum hormone binding globulin, menopausal status/window of phlebotomy, weight gain, change in life events, change in anxiety score, and the following baseline covariates: baseline body mass index, baseline hypertension, parity, race/ethnicity, baseline educational level, baseline level of difficulty paying for basics.

^d All hormones in model and adjusted for the following time varying covariates: serum hormone binding globulin, menopausal status/window of phlebotomy, weight gain, and the following baseline covariates: baseline diabetes, parity, race/ethnicity, baseline body mass index, and baseline educational level.

^e All hormones in model and adjusted for the following time-varying covariates: serum hormone binding globulin, menopausal status/window of phlebotomy, weight gain, and the following baseline covariates: smoking status, baseline body mass index, parity, race/ethnicity.

^fAll hormones in model and adjusted for the following time-varying covariates: serum hormone binding globulin, menopausal status/window of phlebotomy, weight gain, change in life events, symptom score, and the following baseline covariates: baseline body mass index, baseline hypertension, parity, race/ethnicity, baseline educational level, and baseline level of difficulty paying for basics

Table 3

Adjusted Odds Ratios for Worsening Monthly or More Urinary Incontinence in Incontinent Women by Annual Serum Hormones

	Hormones in Same Year as Worsening Any Incontinence N = 8851 observations		Hormones in Year Previous to Worsening Any Incontinence N = 9247 observations	
	OR	95% CI	OR	95% CI
Estradiol per 10 pg/ml	1.00	0.99, 1.01	0.99	0.99, 1.01
FSH per 10 mIU/ml	1.00	0.98, 1.02	0.99	0.98, 1.01
Testosterone per ng/ml	1.00	0.99, 1.00	1.00	0.99, 1.01
DHEAS per ug/ml	1.00	0.99, 1.00	1.00	0.99, 1.00

FSH = Follicle stimulating hormone, DHEAS = dehydroepiandrosterone

OR = Odd Ratio, 95% CI = 95% Confidence Interval

Comparison group: all women whose incontinence improved or did not change.

All hormones in both models and adjusted for the following time-varying covariates: serum hormone binding globulin, menopausal status/window of phlebotomy, weight gain, waist gain, change in social support, change in life events, current anxiety, current depression symptoms, and the following baseline covariates: marital status, parity, smoking status, symptom sensitivity score, baseline age, baseline body mass index, baseline hypertension, baseline education, baseline diabetes, baseline difficulty paying for basics, race/ethnicity, baseline health status, fibroids at baseline, and first reported frequency of incontinence.