Serum estradiol does not differentiate stress, mixed and urge incontinent women around menopause. A report from the Women's Health in the Lund Area (WHILA) study.

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Serum estradiol does not differentiate stress, mixed and urge incontinent women around menopause. A report from the Women´s Health in the Lund Area (WHILA) study.

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Conflict of interest

None

Condensation:

Serum estradiol levels in 369 perimenopausal women reporting urinary incontinence were not significantly different in subjects with stress, mixed or urge incontinence.

Abstract

Objective:

To outline serum estradiol levels in perimenopausal women with stress, mixed or urge incontinence. We believe the majority of urgency symptoms in perimenopausal women to be caused by a pelvic floor dysfunction and a hypermobility of the bladder neck. If this is the case, there would be no difference in estradiol levels between the groups.

Study design:

Setting: university hospital. In the observational Women´s Health In the Lund Area study, a subset of 400/2221 women reporting urinary incontinence completed a detailed questionnaire regarding lower urinary tract symptoms and had their serum steroid hormone levels measured. Statistical analyses were made by Chi-square test, nonparametrical tests, ANOVA, multi- and univariate logistic regression analysis.

Results:

Stress incontinence was reported by 196, mixed incontinence by 153 and urge incontinence by 43 women. Serum estradiol did not differ significantly between stress incontinent (median 49.5 pmo/l, range 2.63-875.4), urge incontinent (median 31.6 pmol/l, range 2.63-460.7) or mixed incontinent women (median 35.5 pmol/l, range 2.63-787.9, $p = 0.62$). Logistic regression analysis correcting for age, parity, hormonal status, smoking, hysterectomy and BMI also failed to show any difference in estradiol levels between the groups ($p=0.41-0.58$).

Conclusion:

No significant differences in serum estradiol levels between stress, mixed or urge incontinent perimenopausal women could be demonstrated .

Keywords:

Female urinary incontinence; mixed urinary incontinence; serum estradiol; stress urinary incontinence; urge urinary incontinence.

Introduction

Estrogen plays an important role in the function of the female lower urinary tract throughout adult life. Estrogen receptors have been identified in areas of the brain involved in micturition control as well as in the bladder, urethra and pelvic floor. Fluctuation in circulating estrogen and progesterone levels are conceivably linked to changes in the prevalence of urinary symptoms and for urodynamic changes [1]. Animal studies have shown that ooforectomy alters the pressure flow characteristics of micturition in rats [2].Van Geelen et al. found an increase in the urethral functional length during mid-cycle in healthy nulliparous women that could be correlated with changes in the circulating levels of estradiol [3].

The influence of hormonal therapy (HT) on urinary tract symptoms including urinary incontinence (UI) is a source of discrepancy. Salomon reported in 1941 the successful use of estrogen to treat UI [4]. More recently, both a Cochrane review from 2003 [5] and a study from Fantl et al. [6] report improvement of urinary tract infections as well as urge and stress incontinence symptoms from HT when compared to placebo. However, other studies show no improvement [7, 8], worsening of preexisting incontinence or even de novo incontinence when HT was introduced [9-12]. The WHI study found that HT users ran a higher risk of developing stress incontinence (SUI) than mixed (MUI) or urge incontinence (UUI), and that hormonal supplementation with estrogen alone led to a higher risk for developing UI than an estrogen/progestin combination [9].

There are few studies that relate the prevalence of UI to serum estradiol rather than usage of HT and they report contradictive results. We have been unable to find any studies on estradiol levels and different subtypes of UI. We have formerly reported that urinary incontinence seemed to be associated with higher levels of serum estradiol in perimenopausal women participating in the Women´s Health in the Lund Area (WHILA) study [13]. In this study we postulated that one of the reasons for UI could be due to higher serum estradiol levels

contributing to a more elastic collagen/connective tissue, leading to a more mobile pelvic floor/bladder neck. This would lead to a higher prevalence of SUI but could also result in urgency symptoms due to a triggering of the bladder emptying reflex by urine coming down into the bladder neck and proximal urethra.

The primary aim of this study was to further investigate a subset of the women reporting UI in the WHILA study regarding possible differences in serum estradiol levels between the different incontinence types. Our hypothesis was that we would not find a difference in estradiol levels between the incontinence groups.

Methods

Clinical as well as laboratory data were collected from the observational population-based "Women's Health in the Lund Area" (WHILA) study. The WHILA study invited all women (*n* = 10,766) living in the Lund area of Southern Sweden by 1995, who were born between 1935 and 1945, of whom 6917 accepted to participate in the study. The main reasons for not participating were foreign nationality, having moved out of the community, refusal and death. The health screening program included a validated postal questionnaire concerning medical history, drug treatment, family history of diabetes and hypertension, menopausal status, smoking and alcohol habits, education, household, working status, physical activity, quality of life as well as subjective physical and mental symptoms [14]. The participants ran through the questionnaire together with a specially trained research nurse-midwife and misunderstandings were corrected when they arrived for their visit where laboratory tests were taken. Of the 6917 women, 6440 contributed to the hormonal determinations. The most common reason for missing results was that the blood sample collected was too small for a complete hormonal analysis (also testosterone, androstenedione, and cortisol were analyzed). In those cases the woman was excluded from hormonal analysis altogether. Women with regular bleedings were categorized as premenopausal. Menopause was defined as bleed-free interval of at least 12 months. Postmenopausal women with hormonal treatment (HT) were defined as those on systemic, not local treatment only.

Thirty-two percent (*n*=2221) of the participating women reported UI according to the 1988 ICS definition valid at the time of the survey, i.e. involuntary urinary leakage causing a social or hygienic problem [15]. Of these, one third (11%) were considered as needing professional help for their incontinence because of their degree of bother (more than 2 on a visual analogue scale from 0-10).

One part of the WHILA study aimed at evaluating the effect of a limited training programme

performed in primary care for incontinent women. Due to the limited resources for primary health care centers to take care of these subjects, a total of 400 women reporting urinary incontinence were recruited during two periods of the entire study, one at the start and one at the end of the study. During these two periods, all women with urinary incontinence stating a bother of 2 or more on the VAS scale were asked to participate. Thus, the sample was not calculated primaily for evaulation of serum estradiol levels in relation to incontinence types. The 400 women answered a more detailed questionnaire. It comprised 19 questions regarding duration and type of urinary incontinence, urgency, frequency, nocturia, dysuria, use of protective pads, pelvic floor exercising, possible medical treatment for incontinence or urinary infections and impact on daily activities. Stress urinary incontinence was identified as urinary leakage during sneezing, coughing, lifting and/or during fast walking or walking in stairs, urge urinary incontinence as having urgency before urinary leakage at all and/or during the night. Mixed urinary incontinence was defined as having one or more symptom of both stress and urge incontinence. Amount of leakage was divided into three categories: mild ("just a few drops"), moderate ("small quantities") and severe ("the whole bladder content.").

Blood samples were processed as following: serum was separated and stored at -70 degrees C. All analyses were then made at the same time using the same batch. KRYPTOR ®- Estradiol 17B (B.R.A.H.M.S. Ag., Heningsdorf, Germany) was used for automated immunofluorescent assay of estradiol in serum. ELISA techniques were used for determination of serum hormone binding globulin (SHBG) and cortisol levels using commercial monoclonal antibodies (DRG Instrument GmbH, Marburg,Germany). Detection limits and coefficient of variations were for estradiol 3.5 pmol/l and 7.1 % and for SHBG 0.2 nmol/l and 3.0%. An ad hoc value of 2.63 pmol/l was used for the cases with an estradiol level beneath the detection limit of 3.5 pmol/l. Statistical analyses were carried out using Gauss (Gauss™, Aptech Systems Inc., Maple Valley, WA, USA). Frequencys were compared using chi square tests, and binary outcomes

were analysed using univariate- and multivariate logistic regression analyses correcting for possible confounding factors as specified, respectively. Continuous outcome measurements were analyzed using non-parametric tests (Kruskal-Wallis), or ANOVA when specified. The Wilk–Shapiro test was used to test for normal distribution of estradiol values. Due to the test results, all ANOVA analyses were performed using logarithmized estradiol values. A p value of < 0.05 was considered significant.

A post hoc power analysis was performed, which indicated that it was possible by an 80% power, to detect a serum estradiol difference of 0.31 of the SD (supposed to be 40 pmol/l) when comparing stress incontinent women to women with mixed incontinence, and a difference of 0.49 of the SD (=60 pmol/l) when comparing the stress incontinent group to the urge incontinent group.

Results

Eight women stated neither SUI nor UUI, leading to a total of 392 women reporting type of incontinence. Estradiol values were missing in 23 women, leaving 369 women with complete data for analysis. The clinical characteristics of the 392 women and their lower urinary tract symptoms are presented in Table1. The age of the women ranged between 51 to 63 years. The amount of leakage was graded as mild by 115 women (28.8%), moderate by 258 (64.8%) and severe by 25 (6.3%), two were missing. There were no differences in distribution of incontinence types in the premenopausal, postmenopausal with no HT or postmenopausal receiving HT respectively (Table 2).

Estradiol levels showed a wide distribution in all incontinence types and hormonal status groups (Table 3). For all three groups, Wilk-Shapiro tests for Gaussian distribution for estrogen levels showed p-values $<10^{-6}$. When the estradiol levels were logarithmized, the distribution of estrogen levels were somewhat more close to normal distribution, especially in premenopausal women (p for normal distribution=0.06). There were no significant differences between the groups of women with SUI, MUI and UUI (p = 0.652, Kruskal-Wallis). A univariate logistic regression analysis found no association between UUI and logarithmized estradiol levels, as compared to SUI, when logarithmized estradiol levels was entered as a continuous independent variable (p=0.47). When parity, age, BMI, smoking, hysterectomy, and hormonal status were adjusted for, the association between UUI and logarithmized estradiol levels was even less discernible (p=0.58). The corresponding p-values for an association between estradiol levels obtained by logistic regression analyses, MUI versus SUI were p=0.46 for crude results, and p=0.41 for adjusted estimates, respectively.

Comments

This population-based study of perimenopausal women failed to find any correlation between serum estradiol levels and type of incontinence.

The sample size and the fact that some of the questions in the study form were not formulated according to the current ICS definitions may be considered as the main limitations of our study. It was not possible, due to the design of the WHILA study, to perform specific clinical or laboratory tests to refine the diagnosis of incontinence (i.e.pad-test, voiding diary or urodynamics) or menopausal status (i.e. serum FSH determinations) on the participants. However, we believe that data are reliable as patient's answers were double-checked between the subject and a specially trained nurse in order to avoid misunderstandings and errors and that it was possible to outline the questions stating SUI and UUI respectively.

Compared to the whole incontinent group in the WHILA study, the 392 women did not differ regarding age, smoking or previous hysterectomy, but had a slightly lower parity and a higher BMI. These women had actively consented to taking part in this study regarding treatment of their condition and stated more severe leakage which could partly be related to their higher BMI. That could however not explain the lower parity.

Our material has a similar prevalence for type of incontinence related to age as the one reported by Hannestad et al. [16] and by the WHI report for the cohort at baseline [9]. Studies analysing older populations (> 60 years) reveal an increased prevalence of UUI [17-20] with a higher prevalence rate among HT users [21].

Higher estradiol levels may be associated to a higher risk for developing urinary incontinence, SUI more than MUI or UUI. Waetjan et al. reported that women who transitioned from premenopause to menopause improved their urinary incontinence symptoms, mainly SUI. (22) Gopal et al. have shown that women having a sharp decline of estradiol levels, indicative

of a transition from premenopausal to postmenopausal state, had a significative decrease in overall incontinence symptoms scores, especially SUI. (23) Furthermore, Teleman et al. found that perimenopausal women reporting urinary incontinence symptoms had significantly higher serum estradiol levels compared to continent ones.(13)

The role of estradiol in target tissues in the lower urinary tract remains unclear. It has been postulated that estrogen may increase loose connective tissue and/or stimulate collagen degradation in the pelvic and urethral tissue [17, 24, 25]. It could be speculated that this could result in an increased hypermobility of the bladder neck and the paraurethral tissue leading to an impaired urethral closure function [13]. Hvidman et. al. found a limited correlation between alterations in the menstrual cycle and urinary incontinence, as well as a moderate increase of urinary incontinence at the time of ovulation, and it has been suggested by Chen et al. that gene expression of the estrogen receptor may vary during the menstrual cycle in incontinent women (26-28) As no information regarding menstrual cycle/ HT ingestion was recorded at the time when blood samples were retrieved during the WHILA study, we could not draw any conclusions on this point. However, as only 8% of the women in our sample were premenopausal, we do not believe that ovulation-realted incontinence influenced our results

We believe that pelvic floor disfunction was the main etiology for the urgency symptoms among the majority of the women reporting such in our study, rather than a neurological or a bladder condition. This concurs with the lack of differences in serum estradiol among the three incontinence groups.

We are aware that women in the menopausal transition conform a heterogeneous group from a hormonal point of view, and it was in a way expected that serum estradiol level would not follow a normal distribution. However, we believe it is important to further study this particular subset of women (those experiencing incontinence around menopause) as an entity,

rather than dividing them in pre- or postmenopausal, as the diagnosis of menopause itself is difficult in common clinical practice, and women in their fifties are well represented among those seeking help for incontinence problems. The results in these women may well differ from those in elderly women, where other etiologies of urgency such as neurological disease and/or urogenital atrophy, leading to dysuria and urinary tract infections, are more common.

Conclusion

Our study failed to show a statistically significant difference in serum estradiol levels between peri- and postmenopausal women with different types of urinary incontinence.

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Table 1.

Characteristics of the 392 women compared to the whole material of incontinent WHILA women and between the incontinence groups. Analyses made by chi-square and ANOVA.

	WHILA incontinent N=2221	The 392 group N=392	p-value	SUI N=196	UUI N=43	MUI N=153	p-value
Age (years)	56.4 ± 2.97 range	56.3 ± 2.83 range 51-63	0.34	56.07 ± 2.83	56.26 ± 2.87	56.49 ± 2.84	0.39
Parity mean Median (range)	2.25 ± 0.90 2 (0-9)	2.14 ± 1.01 2 (0-5)	0.02	2.18 ± 0.98 2 (0-5)	1.70 ± 0.96 2 (0-4)	2.19 ± 1.00 2 (0-5)	0.009
Hysterectomy *n* (%)	287 (12.9)	61 (15.6)	0.17	26 (13.3)	8 (18.6)	27 (17.6)	0.46
BMI (kg/m^2)	26.08 ± 4.46	26.8 ± 4.8	0.002	26.49 ± 4.35	26.86 ± 5.36	27.27 ± 5.11	0.30
Smoking *n* (%)	406 (18.7)	75 (19.7)	0.67	32 (17)	13 (30.2)	30 (20.0)	0.14
Frequency > 8 times/day n(%)		52 (13.3)		21 (10.8)	9 (20.9)	22 (14.4)	0.18
Nocturia >1 time/night n(%)		111 (28.4)		40 (20.5)	18 (41.9)	53 (34.6)	0.0016

Table 2

The distribution of incontinence types in the three hormonal status groups. Chi-squared test.

	Premenopausal	Postmenopausal No HT	Postmenopausal On HT	p-value
Total	32 (8.0%)	174 (44.5%)	185 (47.5%)	
SUI	19 (9.7%)	87 (44.6%)	89 (45.6%)	0.491
UUI	3 (7.0%)	19 (44.2%)	21 (48.8%)	0.968
MUI	10 (6.5%)	68 (44.4%)	75 (49.0%)	0.708

Table 3.

Serum estradiol levels (missing in 23 women) in relation to hormonal status and related to type of incontinence also with the ratio to serum hormone binding globulin analyzed by Kruskal-Wallis .

Hormone	Incontinence type			p-value	Hormonal status (n)			p-value
	SUI (N=186)	UUI (N=40)	MUI (N=143)		Premenopausal (30)	Postmenopausal (166)	Postmenopausal on HT (181)	
Estradiol pmol/l median (range)	49.5 (2.63 – 875.4)	31.6 (2.63 – 460.7)	35.5 (2.63 – 787.9)	0.65	170.9 (2.63 – 875.4)	15.31 (2.63 – 622.1)	78.21 (2.63 – 787.9)	<0.001
Estradiol pmol/l Quantiles% 25-50-75	9.9-49.5-128.1	14.8-31.6-98.7	13.6-35.5-105.0		52.61-170.9-246	2.63-15.31-40.79	28.84-78.21-137.7	
SHBG (nmol/l) Mean ± SD	64.5 ± 42.5	58.3 ± 30.8	61.0 ± 40.0	0.98				
Estradiol/SHBG Mean ± SD	1.7 ± 2.4	1.4 ± 1.6	1.4 ± 2.1	0.40				